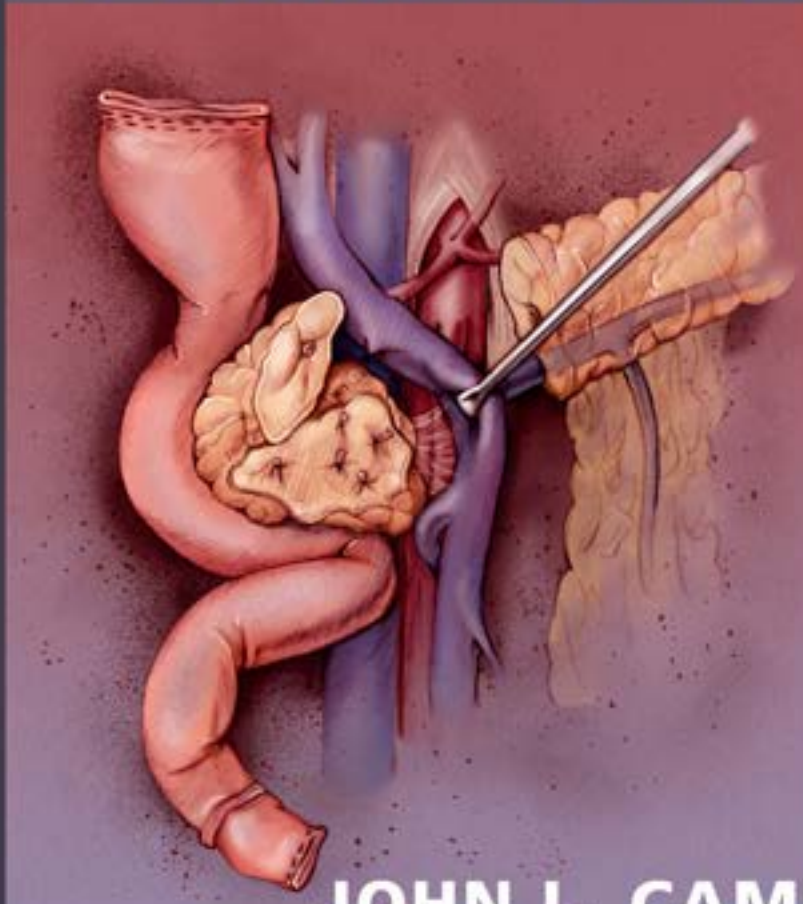
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FOURTEENTH EDITION



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Preface

The first edition of *Current Surgical Therapy* was published in 1984. The textbook has thus been in existence for almost 40 years, and this is the fourteenth edition. In each edition, we have updated the material to reflect the continuing evolution of the field of general surgery. The textbook continues to be perhaps the most popular surgical book in the field, and as long as it fulfills a need, we plan to continue the publication every 3 years. It has been a special privilege and honor for the two editors to be able to review contributions from surgeons around the country and, indeed, from around the world, on what they believe is the current surgical therapy for essentially all common general surgical topics. It is an enjoyable task and keeps two surgeons who care for surgical patients current on all general surgical topics.

As with prior editions, nearly every chapter has been written by a new author. All authors have contributed their specific and personal thoughts on the current surgical therapy of the disease about which they are experts. Therefore, to obtain a broad view of the topic, the reader may want to review the contributions of the other experts in the past two or three editions of *Current Surgical Therapy.*

As with the past editions, disease presentation, pathophysiology, and diagnosis are discussed only briefly, with the emphasis on current surgical therapy. When an operative procedure is discussed, an effort has been made to include brief and concise descriptions with figures and diagrams when possible. *Current Surgical Therapy* is written for surgical residents, fellows, and fully trained surgeons in private practice or in an academic setting. Many have told us that it is an excellent textbook to review before taking the general surgical boards or recertifying. Medical students have also given us feedback that they believe the text is of value to them. However, *Current Surgical Therapy* is not written principally for medical students. We believe a more classic surgical textbook with substantial sections on disease presentation, diagnosis, and pathophysiology is more appropriate for medical students.

We remain grateful to the many surgeons throughout the country, as well as to the international surgeons, who participated in creating this textbook. Most of the potential authors whom we solicit respond enthusiastically to the opportunity to present their expert views. Their efforts obviously are what make this textbook a success. In addition, we could not have compiled this textbook without the herculean efforts of Ms. Irma Silkworth, who has been involved with virtually all of these editions. Ms. Katie DeFrancesco at Elsevier has also has been a terrific help and stands out in the publishing industry.

Both editors continue to enjoy and thrive in our chosen profession of general surgery. In recruiting medical students into our specialty over the past 40 years, we have used the statement, "If you pick a profession you love, you never have to work the rest of your life." In our view, that profession is surgery.

Finally, we would like to dedicate this edition, as with the others, to the surgical house staff and fellows at Johns Hopkins Hospital, who are "the best of best."

Andrew M. Cameron, MD
John L. Cameron, MD



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The American Board of Surgery Certifying (Oral) Examination

The American Board of Surgery Certifying (Oral) Examination

Jo Buyske, MD, and Daniel L. Dent, MD

PRINCIPLE

The American Board of Surgery (ABS) was founded in 1937, with a mission to protect the public and enhance the profession. At the time, the standards for becoming a surgeon were vague and inconsistent. Some people did a Halstedian residency. Some apprenticed themselves to surgeons. Others did internships and then were self-taught, or they skipped formal training altogether. The public had no way to distinguish the training or skill of these practitioners. The ABS and the certification process was a way to set standards for the profession and to provide a testimonial to patients that their surgeon was qualified.

Certification by the ABS is the culmination of surgical training. It is a testimonial to quality, knowledge, and judgment based on several distinct components. First, training in an Accreditation Council for Graduate Medical Education (ACGME)-accredited training program is a prerequisite for certification in nearly all cases. Second, candidates must meet the standards of training as set by the ABS, including things like passing knowledge and skills tests in laparoscopy (FLS), endoscopy (FES), trauma (ATLS), and cardiovascular events (ACLS). Candidates must meet case minimums both in the early years of training to "prepare the soil" and also during the chief year to demonstrate maturation. There are time requirements, and required observations of both clinical and operative skills. Third is a knowledge exam, the Qualifying Examination. The Qualifying or written examination is a 300-plus question, computer-based multiple choice exam designed to test foundational knowledge.[1] Finally, after all of these other qualifications have been met, the Certifying, or oral examination, is a test of judgment and applied knowledge. The two tests measure different assets, and candidates' performance is not predictable across the two exams. That is to say, doing well on one exam does not predict doing well on the other exam. They measure different attributes, and each one is important to fulfill the ABS mission of serving the public and the profession.[2]

The Certifying Examination consists of a series of carefully created scenarios. The scenarios are the tool that supports the examiners in their charge, which is to "evaluate a candidate's clinical skills in organizing the diagnostic evaluation of common surgical problems and determining appropriate therapy. Emphasis is placed on candidates' ability to use their knowledge and training to "safely, effectively and promptly manage a broad range of clinical problems." Additionally, "Technical details of operations may also be evaluated, as well as issues related to a candidate's ethical and humanistic qualities."[3]

CONTENT

The content of the Certifying Examination is generally aligned with the ABS SCORE Curriculum Outline. The majority of the exam will focus on topics that are listed among the core content of the curriculum. The remainder of the exam will be on complications of these basic scenarios or may be taken from the advanced portion of the curriculum.[4] While each exam roster contains 12 cases, the content for the exam comes from 13 question-writing committees. There is some overlap of the content between committees. For example, a case of septic shock secondary to a colonic perforation from an incarcerated hernia could have been put forward as content from the colorectal, hernia, or critical care committees. Each roster of cases is reviewed for breadth of content and consistency of difficulty relative to historical performance of the individual questions so exam difficulty is consistent across all rosters. Because the candidate will also be tested as to baseline surgical knowledge on the qualifying (written) exam, it is not generally expected that the candidate will be asked to regurgitate basic surgical facts. With that said, the candidate can expect that some questions may include a list of questions asking how the candidate's management plan might change in the face of variations of patient presentation or pathologic findings, or in the setting of intraoperative or postoperative complications. This should not necessarily be interpreted as meaning that the candidate is off track, but rather is a way of probing the candidate's skill and judgment in managing a variety of situations.

PROCESS

The Certifying Examination consists of three exam sessions that each last 30 minutes. In each session, the candidate will be presented with four case scenarios. Two examiners are used in each session to help ensure the validity of the exam. All examiners are in active practice, currently certified by the ABS, and participating in the ABS Continuous Certification Program. All of the examiners have taken the certifying exam themselves, some of them more than once. Examiners are all volunteers, and they do not receive any financial compensation for their service.[5–7]

The examiners will typically alternate in presenting the case information to the candidate. In presenting the case scenarios, the goal of the examiners is to provide a clear description of each case. It is the intent of the examiners to provide sufficient information at each step in the case so the candidate may make pertinent decisions on how to progress in the workup and treatment of the patient.

The COVID-19 pandemic presented a new challenge for the administration of the Certifying Examination. The inability to administer the exam in person created a need to administer the exam in a virtual format. In the 2020–2021 academic year, the exam was administered with all candidates and examiners participating virtually. This necessitated some modifications to the timing of the exam, specifically that each room was given an extra 5 minutes in case of

technical difficulties. The time allotted to answering questions did not change; if the extra time was not needed, then there was simply a short break between sessions. The candidates found the experience to be fair and the vast majority support keeping the exam in a virtual format going forward.[8]

PREPARATION

The ideal preparation for the Certifying Examination is to have successfully provided evidence-based care for each condition that will be covered during the exam. Surgical residency, as currently structured by the parameters of the ACGME, Residency Review Committee (RRC), and ABS, provides strong foundation for the exam. Given the breadth of general surgery, however, it is likely that candidates will encounter scenarios they have not seen in training. Before taking the exam, candidates are encouraged to practice taking oral exams with colleagues who have successfully completed the examination process as the concise oral presentation of decision making benefits from repetition and practice. In doing so, the candidate should practice case scenarios over a wide range of pathologic conditions. Specific recommendations for preparing for the exam include the following:

- Practice clarity of communication with regard to explaining the decision-making process.
- Practice anatomic descriptions of common procedures (e.g., inguinal herniorrhaphy) as verbalizing operative anatomy can be challenging in a high-stakes setting.
- Recognize that the goal of the exam is to convey how one would actually safely manage a patient, not to try to guess what the examiners want to hear.
- Plan for management of complications and consequences of treatment decisions. For example, in appropriately selected patients with colon pathology, it may be appropriate to perform primary anastomosis. However, the candidate should also know how to handle the potential consequence of an anastomotic leak. Conversely, if the candidate initially chooses to manage the patient with a colostomy, it is reasonable to expect that the candidate can also manage ostomy ischemia and parastomal hernia.
- Recognize that the exam is not a multiple-choice exam and that each case discussion is an ongoing conversation. As the case evolves, the optimal management evolves with it. For example, it may be appropriate to initially manage a patient nonoperatively but then convert to operative management if the patient's condition changes.

ASSESSMENT

Examiners receive standardized training before giving an exam. This includes practice scoring, implicit bias training, and team review of the scenarios. In addition, examiners routinely get formative feedback from observers and their co-examiners. Finally, examiner scoring patterns are evaluated from a psychometric perspective, looking at patterns of consistency and severity as well as any evidence of bias.[9]

- Each examiner records a score for each case to maximize the number of independent observations that contribute to the candidate's total score. A total score that reflects the ability to safely care for the broad array of cases that are presented over the course of the exam is considered a passing grade. There is no preset pass or fail rate for the exam. On each scenario, candidates may be given a passing grade, a failing grade, or an equivocal grade. The equivocal grade is given when the examiners do not have enough information to give a passing grade, such as when the candidate spends more time asking questions than answering them, or when the candidate makes multiple noncritical errors while also making a number of correct management choices. The examiners are charged with assessing the following characteristics of the candidate's performance:

- Demonstrates an organized approach and solid rationale for planned actions.
- Rapidly determines and interprets key findings in a clinical presentation.
- Effectively and efficiently uses clinical knowledge to solve clinical problems; effectively addresses key management points.
- Avoids errors and critical fails (omission and commission) associated with the case.
- Recognizes personal limitations in knowledge and expertise when diagnosing and treating clinical problems.
- Reacts in a prompt but flexible manner to alterations in the patient's course (e.g., disease or treatment complications).
- Overall, demonstrates appropriate surgical judgment, clinical reasoning skills, and problem-solving ability.[2,3]

In answering the examiners' questions, candidates should be able to not only state what they would do, but also concisely explain how and why they would provide the stated care.[5]

SUMMARY

The ABS Certifying Examination is an assessment of a surgeon's thought processes in managing surgical conditions. Board certification is the culmination of targeted training in accredited programs, meeting specific training requirements in order to be eligible for the exam process, and then passing a written foundational knowledge exam and an oral exam of judgment delivered by trained surgical examiners. The process serves as a testimonial that board-certified surgeons have met the standards established by the profession.

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Esophageal Function Tests

Wasay Nizam, MBBS, Hamza Khan, MD, and Malcolm V. Brock, MD

The esophagus is a muscular, tubelike structure located in the posterior mediastinum. It spans from the posterior oropharynx to the cardia of the stomach with three functional regions: the upper esophageal sphincter (UES), esophageal body, and lower esophageal sphincter (LES). With the aid of peristalsis and coordinated relaxation/contraction of sphincters, the esophagus allows the transport of food boluses to the stomach and prevents the reflux of corrosive stomach contents. Assessment of esophageal motility requires evaluating its structural integrity, peristalsis, and synchronized pressure changes of the sphincters. The diagnostic tools assessing these functions are termed *esophageal function tests.* Utilizing pressure sensors, these tests provide a dynamic demonstration of esophageal motility and an assessment of alternating pressures within the LES.

Patients presenting with dysphagia, reflux, or non-cardiac chest pain should undergo endoscopic or radiologic examination first to rule out structural lesions such as malignancy. Once these are ruled out, functional disorders secondary to esophageal dysmotility are considered (Box 1). This chapter will review commonly used tests, such as manometry and esophageal pH monitoring. Esophageal integrity may be evaluated both directly and indirectly by endoscopy or radiologic tools, respectively. These modalities will also be discussed in depth in subsequent chapters along with details on management of esophageal dysmotility disorders such as achalasia.

ESOPHAGEAL MANOMETRY

Esophageal manometry remains the gold standard for assessing esophageal motility. This test permits evaluation of the contractility and coordination of esophageal muscles. It measures a series of pressure events along the esophageal length and presents them as curves of amplitude over time. Originally developed in the 1950s, esophageal manometry underwent numerous modifications before becoming the state-of-the-art diagnostic tool it is today. Briefly, all versions of the manometer contain a series of sensors placed on a thin catheter that transduce intraluminal esophageal pressure into electrical signals that are then displayed as pressure waves. The original version was based on a pneumo-hydraulic system that has since been replaced by a solid-state catheter that provides a faster response and requires less technical expertise.

Conventional manometry utilizes information from sensors placed at fixed locations (~5 cm) along the length of the catheter. This catheter is placed transnasally into the esophagus with its distal tip in the stomach. Characteristics of the pressure waveform after a swallowing event allow for the recognition of the UES, the esophageal body, the LES, and the gastric cardia (Fig. 1). However, conventional manometry has several limitations including: (1) widely spaced sensors that preclude information on motor activity less than 5 cm apart, (2) unidirectional sensors unable to record pressures accurately in an asymmetrical lumen, and (3) false pressure readings during swallowing because of the tendency of the sphincters to move cephalad, dislodging the catheter.

To overcome these challenges, manometry systems have evolved to utilize more sensors (20–36) placed 1 cm apart that also record circumferentially. As a result, data on various pressure points are gathered and plotted using computer software as a smooth contour plot giving a high-resolution manometry (HRM) image. Readings are presented in color-coded spatiotemporal pressure graphs called *esophageal pressure topography* (EPT) or *Clouse plots,* named after Ray Clouse, who established the technique. These topographical plots represent time on the *x*-axis, location of the pressure wave on the *y*-axis, and color denoting pressure (Fig. 2). With the advent of HRM, a smooth continuous pressure wave along the esophagus in real-time is now available. This led to advances in our understanding of many esophageal motor diseases that were previously puzzling, such as achalasia.

A standard protocol for esophageal manometry conduction has been outlined in version 4.0 of the Chicago Classification. The original classification scheme, proposed in 2009 by the International HRM Working Group, was in response to rapid advances in HRM technology. But the scheme became so clinically useful that

BOX 1 Indications and Contraindications for Esophageal Function Tests

Indications

- Noncardiac chest pain or heartburn with no improvement from acid suppression and no explanation on radiologic or endoscopic examination
- Nonobstructive dysphagia or odynophagia that is unexplained
- Evaluating esophageal peristalsis before foregut surgery
- Localizing LES to place impendence probe in preparation of pH monitoring study
- Evaluating dysphagia after foregut surgery
- Workup of scleroderma

Contraindications

- Esophageal mass causing obstruction
- Abnormal nasal-oropharyngeal anatomy precluding catheter placement
- Nonresponsive patients unable to follow commands
- Patients on anticoagulation with high risk of bleeding

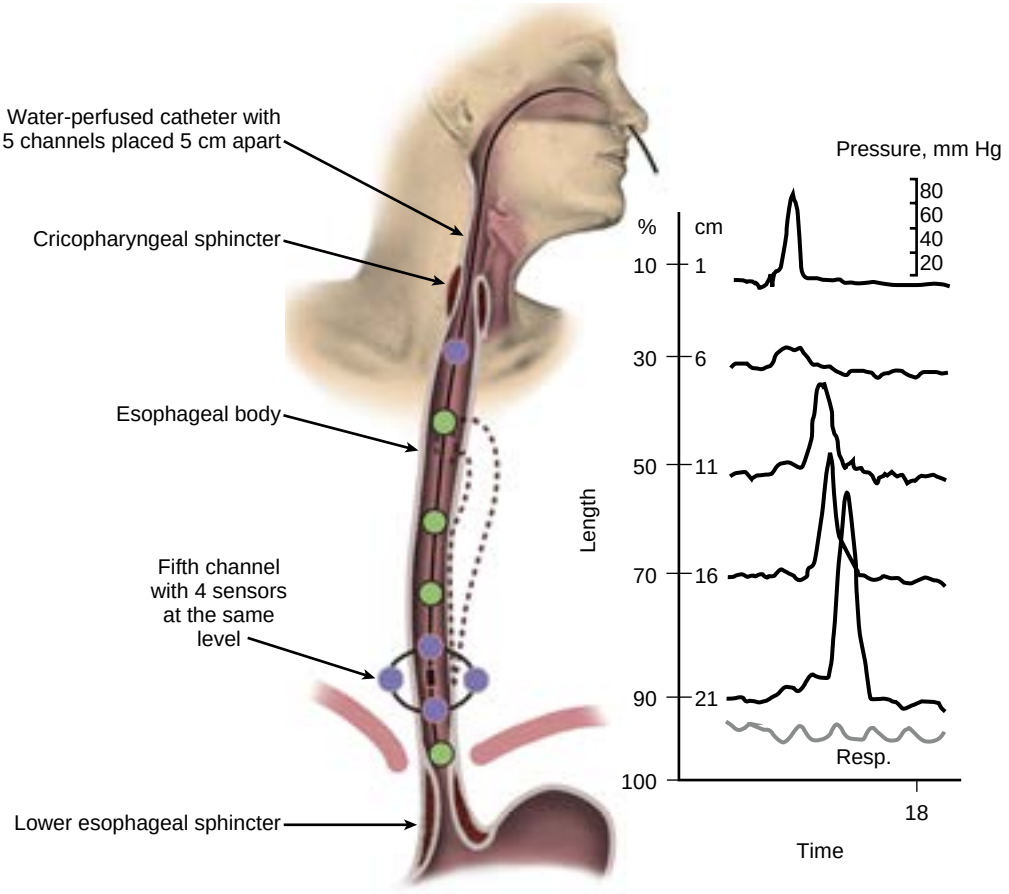


FIG. 1 Esophageal manometry showing a transnasally placed catheter that records a normal waveform progression. Newer solid-state catheters have sensors placed 1 cm apart.

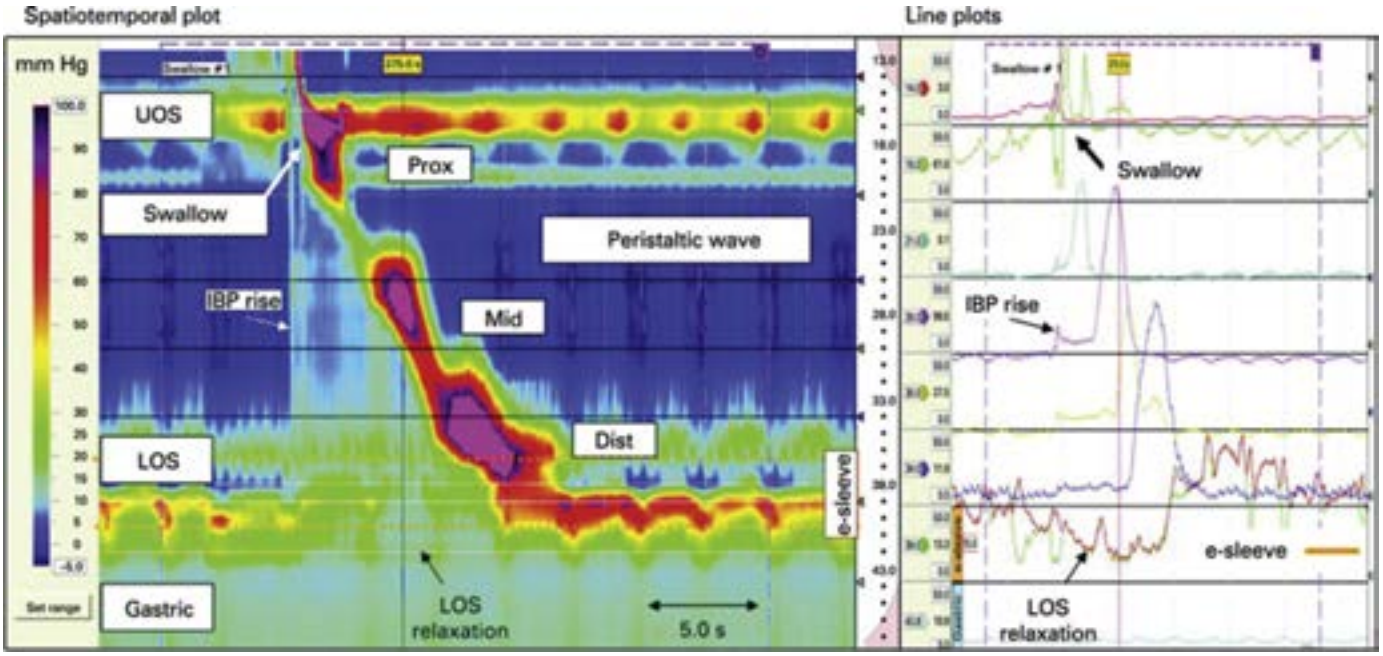


FIG. 2 Clouse plot showing a peristaltic wave after swallowing in a healthy individual. *(From Baldwin D, Puckett Y. Esophageal manometry. Updated Sep 28, 2021. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK559237/.)*

it helped accelerate esophageal HRM's current position as the state-of-the-art diagnostic tool that has thoroughly replaced conventional line tracing. Before the procedure, patients are obliged to fast for a minimum of 4 hours, and then the procedure begins with patients in the supine position for 10 wet (5-mL) swallows spaced 30 seconds apart. This is followed by a single multiple rapid swallow sequence (five 2-mL swallows, 2–3 seconds apart) that can be repeated up to three times. Following this, the patient is placed upright and given

five additional wet swallows and one rapid drink challenge (200 mL of water ingested as fast as possible). More provocative testing may include the utilization of a solid swallow test, a solid test meal, or even pharmacologic provocation. Pressure sensors within the body of the catheter then record intraluminal pressure that is transmitted to an external recording device. Clouse plots generated from HRM are interpreted with consideration of the following five metrics:

1. Integrated relaxation pressure (IRP): the average deglutitive relaxation pressure in a 4-second window beginning at UES relaxation
2. Distal contractile integral: the product of amplitude, duration, and length of the distal esophageal contraction
3. Distal latency: the interval between UES relaxation and the contractile deceleration point
4. Peristaltic breaks
5. Pressurization patterns

Information from these indices may be applied toward the diagnoses of esophageal motility disorders. The Chicago Classification broadly divides these disorders into disorders of esophagogastric junction (EGJ) outflow or of peristalsis. A useful algorithm presented in the classification then allows for the delineation of specific disorders, based on manometry findings (Fig. 3).

HRM is the preferred diagnostic tool when evaluating esophageal motor function, especially when radiologic or endoscopic studies are unable to explain the patient's symptoms. It is safe, with a low-risk profile of complications that is similar to those of nasogastric tube placement, namely, gagging, oropharyngeal discomfort, epistaxis, and rarely aspiration or perforation. Diet can be resumed immediately following removal of the catheter because only topical nasal anesthesia is used. It is an outpatient procedure requiring no sedation, and patients can drive home afterward. It is important, however, that patients stop H_2-blockers, proton pump inhibitors, opioids, nitrates, and calcium channel blockers before the study to avoid any interference with testing. Furthermore, it must be remembered that patients with a history of esophageal surgery, peptic stricture, or those with a current hiatal hernia are prone to false readings.

ESOPHAGEAL pH MONITORING

Acid reflux into the esophagus may be assessed with intraluminal pH monitoring. This can be performed with catheter-based devices or a wireless device (Bravo probe, Medtronic, Minneapolis, MN). Catheter-based devices are inserted transnasally, with the distal pH probe located approximately 5 cm above the LES. This device is then left in situ for 24 hours with patients instructed to record meals, symptoms, and periods of sleep by pressing buttons on a recorder. A wireless device is placed endoscopically in the distal esophagus and attached to the esophageal mucosa with a clip. This device then transmits information to a recorder. As there is no external component to this method, patient activities, dietary patterns, and comfort levels are more natural. Furthermore, because this is a single device, pH levels are only assessed at a single level, rather than across the length of the esophagus.

pH monitoring is used to determine whether or not acid exposure to the esophagus is physiologic. Data gathered from the probe are correlated with symptoms, patient positioning, and relation to meals. The information from the device is then used to calculate a composite pH or DeMeester score. Scores of 14.72 (95th percentile of normal) or greater are considered abnormal. The components of the DeMeester score include the following:

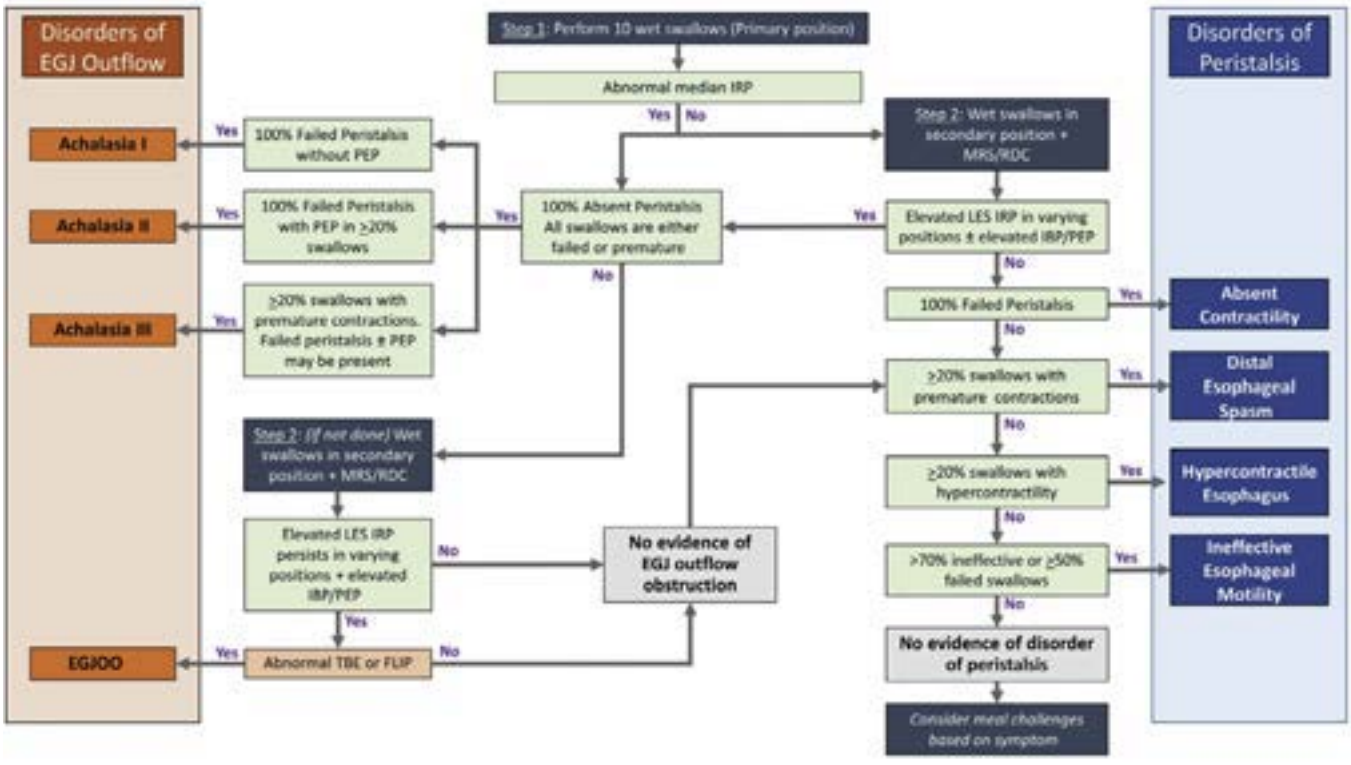


FIG. 3 Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0 Hierarchical Classification Scheme. *EGJOO*, Esophagogastric junction outflow obstruction; *FLIP*, functional lumen imaging probe; *IBP*, intrabolus pressurization; *IRP*, integrated relaxation pressure; *LES*, lower esophageal sphincter; *MRS*, multiple rapid swallows; *PEP*, pan-esophageal pressurization; *RDC*, rapid drink challenge; *TBE*, timed barium esophagram. *(From Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0.* Neurogastroenterol Motil. *2021;33:e14058.)*

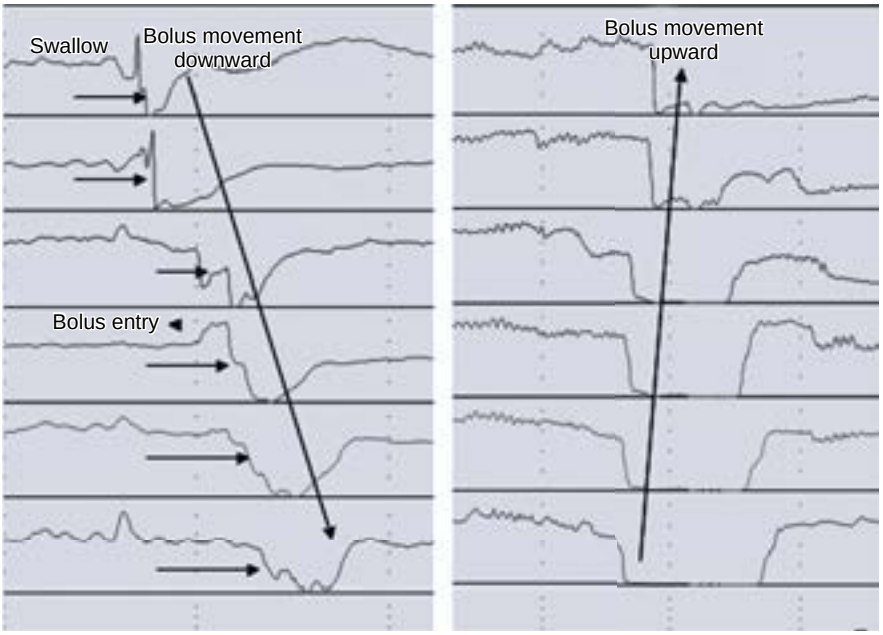


FIG. 4 Impedance testing showing **(A)** normal downward movement of the bolus after swallowing and **(B)** reflux of the swallowed bolus.

1. Percent total time pH <4
2. Percent upright time pH <4
3. Percent supine time pH <4
4. Number of reflux episodes
5. Number of reflux episodes ≥5 minutes
6. Longest reflux episode (in minutes)

IMPEDANCE TESTING

Impedance testing utilizes the principles of current resistance. A long flexible catheter with 6 to 8 sensors is placed transnasally for 24 hours, with patients instructed to proceed with normal activity. The tube is connected to a small receiver for data recording. A small voltage is applied between two electrodes. In principle, at resting state, an electrical charge within the esophageal mucosa carries current between the catheter sensors. Because liquids permit faster ion conductivity, a liquid bolus will be sensed as a rapid decrease in impedance (resistance) between the sensors. In contrast, air is a poor conductor, and swallowed air boluses will be detected as increased impedance. Based on the direction of change, this can assess both antegrade and retrograde movement (normal peristalsis or gastroesophageal reflux). Data on change in impedance gathered from multiple electrodes along the catheter is then used to determine the position of a bolus after swallowing and whether there is reflux back into the esophagus after it has entered the stomach (Fig. 4). Special impedance catheters are also available that combine impedance testing with assessment of esophageal pH sensors and manometry testing (high-resolution impedance manometry [HRIM]), allowing for improved diagnosis.

FUNCTIONAL LUMINAL IMAGING PROBE PANOMETRY

Functional luminal imaging probe (FLIP) panometry is an emerging technology in esophageal function testing used in concert with endoscopy. It is performed with a catheter possessing a distal overlying balloon. The tip of the catheter functions as an imaging probe, and within the balloon, electrodes are present, enabling the detection of impedance. The balloon may be inflated with saline in 10-mL increments up to 70 mL. The data from the sensors are then converted in real time to allow for assessment of the various metrics such as wall stiffness, pressure changes, diameter, volume, and EGJ dynamics. FLIP panometry may be used as a complementary tool in diagnosing esophageal motility disorders as well as intraoperatively during antireflux procedures to assess the adequacy of esophageal wraps.

CONCLUSION

Esophageal function testing can provide valuable information regarding the biomechanics of esophageal motility. The practicing surgeon must be well aware of the utility of these tests and be able to interpret them in light of the patient's symptoms. Optimal outcomes require close collaboration between the radiologist, gastroenterologist, and surgeon within the clinical realm to treat these complex patients. As technology evolves, newer testing techniques may improve our understanding of complicated esophageal disease and assist with intervention.

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Surgical Management of Gastroesophageal Reflux Disease

Jay Zhu, MD, and Brant K. Oelschlager, MD

Gastroesophageal reflux occurs when the contents and secretions of the stomach flow retrograde into the esophagus across an inappropriately relaxed or compromised lower esophageal sphincter. Although nearly everyone experiences symptomatic episodes of reflux to some degree in their lifetime, gastroesophageal reflux disease (GERD) is a condition characterized by chronic symptoms or complications related to gastroesophageal reflux. GERD is a common diagnosis, affecting up to 20% to 30% of the US population and costing an estimated $12 billion to $20 billion in direct healthcare expenditure annually. The high incidence of GERD in the United States and other Western countries is also thought to be the primary reason behind the rising incidence of esophageal adenocarcinoma over the past four decades. In this chapter, we discuss the surgical evaluation and technical approach to gastroesophageal reflux disease.

PRESENTATIONS OF GERD

Symptoms related to GERD can be divided into typical, atypical, and alarm symptoms (Box 1). Typical symptoms of GERD are the classic esophageal manifestations of gastroesophageal reflux, which include heartburn and regurgitation. Atypical symptoms encompass the extraesophageal manifestations of reflux such as cough, dysphonia, sore throat, globus sensation, and noncardiac chest pain. Although GERD can be clinically diagnosed in patients presenting with typical symptoms, patients presenting primarily with atypical symptoms require further investigation to rule out other causes. For surgeons, distinguishing typical from atypical symptoms is useful in assessing the likelihood that a patient's symptoms are attributable to GERD and thus will respond to surgical intervention. Patients with heartburn and regurgitation tend to be more responsive to acid suppression therapy and experience higher rates of symptom resolution after antireflux surgery (ARS) when compared with those presenting with atypical symptoms.

Alarm symptoms are ones that raise suspicion for malignancy and other complications of GERD. These include weight loss, early satiety, dysphagia, odynophagia, and signs of gastrointestinal bleeding. Alarm symptoms should never be attributed solely to uncomplicated GERD, and patients presenting with these symptoms require further workup. The chronic inflammation and irritation associated with reflux can lead to intraesophageal complications such as peptic stricture, Barrett's metaplasia, and esophageal adenocarcinoma. Less commonly, reflux can also lead to extraesophageal complications such as laryngopharyngeal reflux and lung injury from aspiration. Exacerbations of asthma or interstitial lung diseases are unusual manifestations of GERD but clear reasons to consider surgical intervention. It is important to mention that decisions regarding ARS in patients with complications of GERD are often shared across disciplines. When treating patients with GERD-related complications, we often work closely with colleagues in gastroenterology, otolaryngology, or pulmonology depending on the specific complication.

BOX 1 Presenting Symptoms of Gastroesophageal Reflux

Typical Symptoms

Heartburn (also known as *pyrosis*)
Regurgitation
Acid brash

Atypical Symptoms

Cough
Wheezing
Dyspnea/shortness of breath
Voice changes
Sore throat
Globus sensation

Alarm Symptoms

Dysphagia
Odynophagia
Anorexia/early satiety
Weight loss
Gastrointestinal bleeding

DIAGNOSIS AND PREOPERATIVE EVALUATION

The primary purpose of preoperative of testing in the surgical evaluation of GERD is to (1) confirm the correct diagnosis, (2) evaluate the anatomy (e.g., the presence of a hiatal hernia), and (3) rule out concurrent esophageal or gastric pathology before surgery. We routinely obtain the following tests before surgical consultation for GERD.

- **pH testing:** Ambulatory pH monitoring in patients off acid suppression therapy is the gold standard for diagnosing GERD. This is accomplished using either a 24-hour dual-probe catheter system placed transnasally or a 48-hour wireless capsule placed endoscopically. Both tests rely on correct spacing above the lower esophageal sphincter and generate a composite score based on the frequency and duration of distal esophageal acid exposure (i.e., pH below 4). A DeMeester composite score above 14.72 or total distal esophageal acid exposure time greater than 5% to 6% are commonly used thresholds indicative of pathologic reflux.
- **Upper endoscopy:** The presence of LA Grade C or D esophagitis (Table 1; Fig. 1), Barrett's metaplasia, or a peptic stricture on

TABLE 1 The Los Angeles Classification of Esophagitis

Grade	Lesion
A	One (or more) mucosal break <5 mm long that does not extend between the tops of two mucosal folds
B	One (or more) mucosal break >5 mm long that does not extend between the tops of two mucosal folds
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves <75% of the circumference
D	One (or more) mucosal break that involves at least 75% of the esophageal circumference

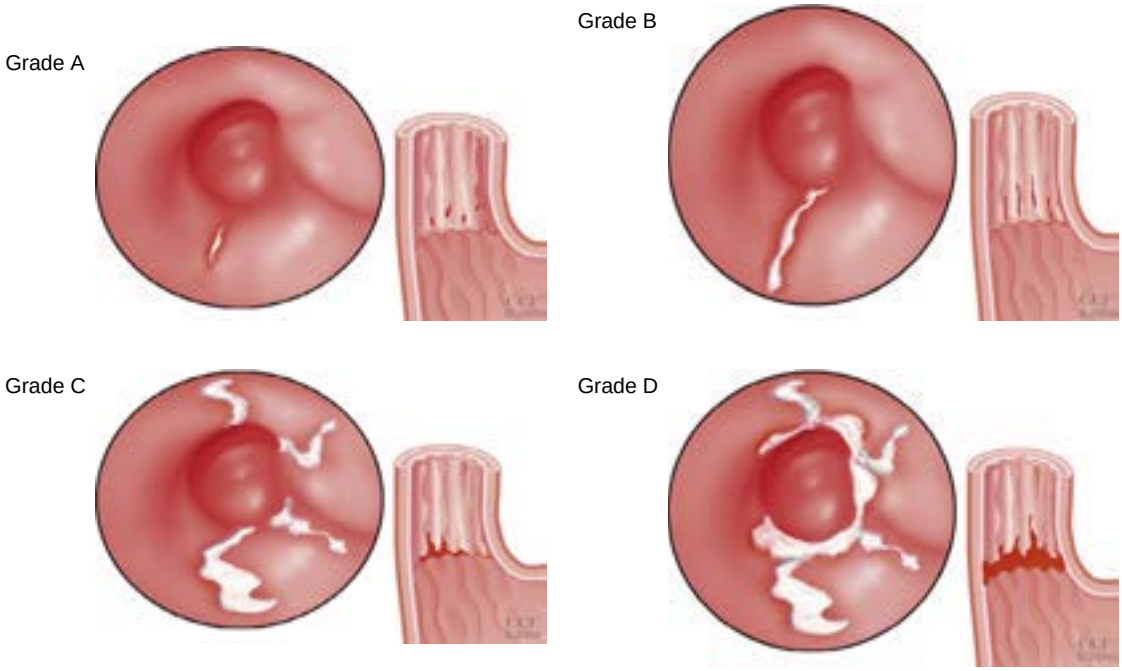


FIG. 1 The Los Angeles classification of esophagitis. Grades A to D are illustrated as described in Table 1. *(From Nayar DS, Vaezi MF. Classifications of esophagitis: Who needs them?* Gastrointest Endosc. *2004;60[2]:253–257.)*

endoscopy are all findings that confirm the diagnosis of GERD. In the case of peptic strictures, serial endoscopic dilations can provide therapy before ARS. Furthermore, endoscopic examinations are useful in identifying hiatal hernias, retained food suggestive of delayed gastric emptying, and other gross pathology involving the esophagus and stomach.

- **Manometry:** We use esophageal manometry in the setting of GERD primarily to help determine the type of fundoplication to perform. Our preference is to perform a complete 360-degree posterior (Nissen) fundoplication for patients who exhibit normal esophageal motility as this is likely the most durable treatment for reflux. For patients who have ineffective esophageal motility according to Chicago Classification version 4.0 (updated in 2020), we consider performing a partial 270-degree posterior (Toupet) fundoplication to avoid issues with postoperative dysphagia. Obtaining a manometry study also serves to rule out achalasia and other named esophageal motility disorders, which can sometimes present with symptoms that overlap with GERD.
- **Barium Esophagram:** Combined with the aforementioned studies, an upper GI barium esophagram increases the sensitivity of diagnosing a hiatal hernia or identifying other anatomic abnormalities such as an esophageal diverticulum. This is especially relevant when the treating surgeon is not the one performing the preoperative endoscopy. Furthermore, a high-quality barium esophagram is particularly useful in understanding the anatomy and geometry of a previously constructed wrap in patients with postoperative concerns or complications.

INITIAL MANAGEMENT AND INDICATIONS FOR SURGERY

With rare exception, all patients should be on acid suppression therapy with a proton pump inhibitor (PPI) before being considered for ARS. It is important to ensure that patients are taking PPIs consistently and correctly (usually 40 mg daily) to maximize the drug's efficacy and assess for a clinical response in symptoms. In general, PPIs are well-tolerated, and adverse reactions or side effects such as nausea, diarrhea, constipation, and abdominal discomfort are rare. Patients who report preoperative issues with bloating may be evaluated for delayed gastric emptying and should be counseled on the risk of worsening gas bloat when weighing the risks and benefits of ARS.

Indications for Surgical Management of GERD

The primary reason to perform ARS is for symptomatic control to reduce suffering and improve patients' quality of life. Fundoplication has not been shown to reduce rates of esophageal adenocarcinoma or improve survival outcomes. Accordingly, the most common indication for ARS is the presence of persistent symptoms that affect quality of life despite maximal medical therapy. As previously discussed, patients who exhibit atypical or alarm symptoms should undergo appropriate workup and/or interdisciplinary consultation as indicated. In patients with atypical symptoms and objectively confirmed reflux, we estimate that approximately one-third of these patients may not see improvement in their symptoms following ARS. Thus, it is important to counsel such patients carefully when weighing the risks and benefits of an operation. In general, patients presenting with typical GERD symptoms that are partially mitigated with acid suppression (or worsen when stopping acid suppression) are most likely to experience significant improvement following ARS.

Although the inability to tolerate acid suppression therapy is an indication for surgical management, true medication intolerance in the treatment of GERD should be rare. More commonly, patients will present with hesitancy or concerns surrounding long-term acid suppression therapy, with many seeking a definitive solution to their reflux. In patients who have well-controlled symptoms on a PPI, we typically advise against surgical intervention because the risks and side effects of ARS outweigh the risks of regular acid suppression therapy. Stated differently, it is very difficult to improve upon medically well-managed symptoms through an operation.

Finally, some patients with interstitial lung disease and objective findings of GERD may benefit from ARS. Data suggest that ARS can slow the deterioration of pulmonary function in these patients,

which can be particularly relevant for patients who are either being considered for lung transplantation or have already undergone transplantation. The decision and timing of ARS in this setting should be made in discussion with the patient's pulmonologist.

Contraindications to Antireflux Surgery

Patients with a normal DeMeester score and normal distal acid exposure on ambulatory pH testing should not be considered for ARS. Symptomatic patients who do not demonstrate objective findings of abnormal reflux should undergo further workup to identify an alternative diagnosis. The use of impedance or pharyngeal pH monitoring to confirm pathologic GERD is controversial and should be evaluated with caution. On the other hand, patients may have abnormal ambulatory pH monitoring, but complete preoperative workup demonstrates another diagnosis altogether such as achalasia, esophageal cancer, or a large paraesophageal hernia. In these cases, the primary diagnosis is not GERD, and patients should be treated appropriately for these other disorders. Finally, obesity is a relative contraindication for ARS. Patients with a BMI >40 should be referred for bariatric surgery evaluation to be considered for Roux-en-Y gastric bypass, as this procedure addresses the broader spectrum of obesity-related health problems, which includes GERD.

SURGICAL TECHNIQUE

In 1937, Rudolf Nissen performed the first known fundoplication in which he wrapped the stomach to buttress an esophagogastric anastomosis as part of the repair for a penetrating esophageal ulcer. Later in the 1950s, he utilized this technique for the first time as a treatment for reflux. Since then, the eponymous 360-degree wrap has become the gold standard in ARS. Although advances in technology have introduced laparoscopic and robotic-assisted approaches to ARS, the surgical principles remain the same with the goal of restoring intraabdominal esophageal length, closing the hiatal defect, and creating a one-way flap valve. Newer endoscopic approaches such as the transoral incisionless fundoplication only accomplishes one of these three goals, and long-term outcomes are still unknown. Here, we describe a laparoscopic Nissen fundoplication, which continues to be our favored procedure for GERD, and a laparoscopic Toupet fundoplication, which we perform in patients with ineffective esophageal motility (Fig. 2).

Steps of the Procedure: Initial Setup, Hiatal Dissection, and Closure of the Crura

The initial steps in performing a laparoscopic fundoplication are similar, regardless of whether a partial or complete fundoplication is being constructed. We use the same instruments (Box 2), patient positioning, and port placement (Fig. 3) for both a Nissen and a Toupet fundoplication. Although the hiatal dissection can begin on either side of the gastroesophageal junction, we prefer to first expose the left crus and then enter the mediastinum starting on the left, as follows.

1. Patient positioning and port placement
   a. The patient is positioned supine in the split leg position with padded straps secured around both thighs (some prefer lithotomy). The surgeon stands between the patient's legs while the assistant stands on the left side of the patient. Before draping, the operating table should be tested in the steep reverse Trendelenburg position in which the procedure is performed to ensure that the patient is secure and not at risk of shifting or sliding during the operation.
   b. A Veress needle is used to access and insufflate the abdomen, and the ports are placed as shown in Figure 3. The patient is then placed in steep reverse Trendelenburg before elevating the left lateral segment of the liver using a liver retractor (we use a Nathanson retractor). We typically use a 5-mm 30-degree scope.
2. Exposing and opening the hiatus on the left side (note that some prefer to start on the right)
   a. The fundus is retracted caudally to expose the membranous avascular phrenogastric attachments between the fundus and the diaphragm. These attachments are divided to begin exposure of the left crus.
   b. The gastrosplenic ligament is divided near the inferior pole of the spleen to enter the lesser sac. The gastrosplenic ligament and the associated short gastric vessels are then divided with a vessel-sealing energy device to mobilize the fundus. The posterior attachments of the stomach are divided to ensure that the fundus is completely mobilized.
   c. With the fundus retracted medially, the left crus should be clearly exposed. Additional medial traction on the gastroesophageal junction places the phrenogastric ligament on tension, exposing this white membranous connection between the medial border of the left crus and the intraabdominal esophagus. This membrane is carefully divided at the posterior base of the left crus, opening a space to the left of the esophagus. The correct mediastinal plane contains thin areolar connective tissue that can typically be easily developed with blunt dissection using the tip of a suction device or other instrument. Once the correct plane is identified, the left phrenoesophageal membrane is continually placed on stretch as it is divided, progressing anteriorly and sweeping tissue away from the membrane toward the esophagus to avoid injury to the anterior vagus nerve. Care is taken not to denude the peritoneum off the crus, as this can weaken the crural closure.
   d. A blunt instrument can then be inserted behind the esophagus to create a retroesophageal window from the left side.
3. Exposing and opening the hiatus on the right side
   a. The gastrohepatic ligament is divided starting at the pars flaccida and continuing cephalad toward the anterior aspect of the esophageal hiatus to expose the right crus. If a sizeable accessory or replaced left hepatic artery is encountered, this should be preserved.
   b. The retroperitoneal fat attached to the right crus above the left gastric artery can be retracted toward the patient's left to expose the right phrenoesophageal membrane. This should be divided to enter the same mediastinal plane that was developed on the left. The dissection can then be carried out circumferentially in similar fashion as on the left side, following the same principles of preserving the peritoneal covering over the right crus while bluntly sweeping tissue toward the esophagus to identify and preserve both anterior and posterior vagal nerves (Fig. 4).
   c. Once the phrenoesophageal membrane has been circumferentially opened around the esophagus, a ½-inch Penrose drain is inserted and encircled around the gastroesophageal junction, and then secured to itself using either suture or clips. This provides the assistant a handle to retract the esophagus during mobilization of the distal esophagus.
4. Distal esophageal mobilization
   a. The dissection is carried circumferentially around the esophagus, identifying and preserving both vagal nerves as the dissection progresses up into the mediastinum. Direct arterial branches from the aorta to the esophagus can be ligated using a vessel-sealing energy device. Care should be taken to avoid dissecting into the retroperitoneal fat overlying the aorta, as this is where the thoracic duct resides.
   b. The parietal pleura when identified should be swept laterally to avoid injury and creation of a capnothorax. If the pleura is entered inadvertently, it is important to communicate this finding with the anesthesia provider. If the opening in the pleura is easily identified, we typically choose to close this defect in an effort to limit the temporary physiologic

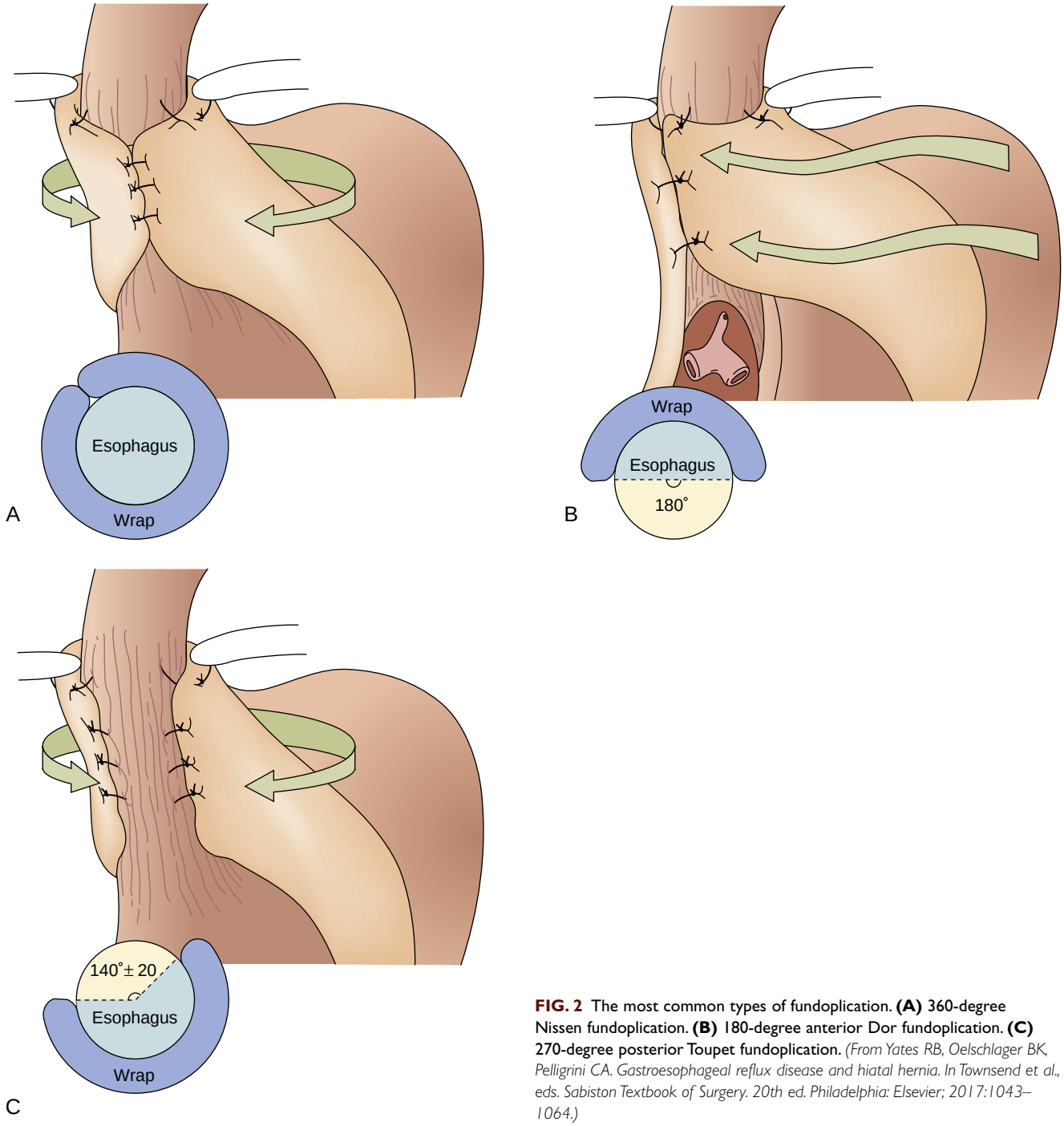


FIG. 2 The most common types of fundoplication. **(A)** 360-degree Nissen fundoplication. **(B)** 180-degree anterior Dor fundoplication. **(C)** 270-degree posterior Toupet fundoplication. *(From Yates RB, Oelschlager BK, Pelligrini CA. Gastroesophageal reflux disease and hiatal hernia. In Townsend et al., eds. Sabiston Textbook of Surgery. 20th ed. Philadelphia: Elsevier; 2017:1043–1064.)*

derangements associated with a capnothorax. However, when closure of a pleural defect is not easily achievable, expectant management and lowering of the intraabdominal insufflation pressure will typically suffice as this allows the patient to compensate physiologically for the carbon dioxide introduced into the hemithorax. Usually after a few minutes, parameters such as decreased blood pressure, increased ventilatory pressure, and increased end-tidal CO_2 will stabilize, allowing the surgeon to proceed with the operation.

c. The lower esophagus should be mobilized to achieve 3 to 5 cm of intraabdominal length without tension.

5. Closure of the crura
   a. Nonabsorbable suture is used to reapproximate the crura posterior to the esophagus. We prefer to use interrupted 2-0 silk without pledgets. This closure is performed until the esophageal hiatus approximates the diameter of the esophagus without any notable gaps. At the same time, the hiatal closure should not apply any external compression on the esophagus.
   b. On rare occasion, we will place a single anterior suture to close the anterior hiatus if there is concern that the posterior closure is bringing the esophagus so far anterior that it may be creating an angle as the esophagus exits the chest.

BOX 2 Equipment for Laparoscopic Antireflux Surgery

Basic Laparoscopic Supplies

0- and 30-degree laparoscope, camera, and video equipment
5- and 12-mm ports
Veress needle
Suction-irrigation device

Laparoscopic Energy Devices

Hook electrocautery
Bipolar or ultrasonic vessel-sealing device

Specialized Equipment

Liver retractor (e.g., Nathanson)
52-Fr Bougie (optional for partial fundoplication)
Laparoscopic suturing supplies
½-inch Penrose drain
Equipment for upper endoscopy

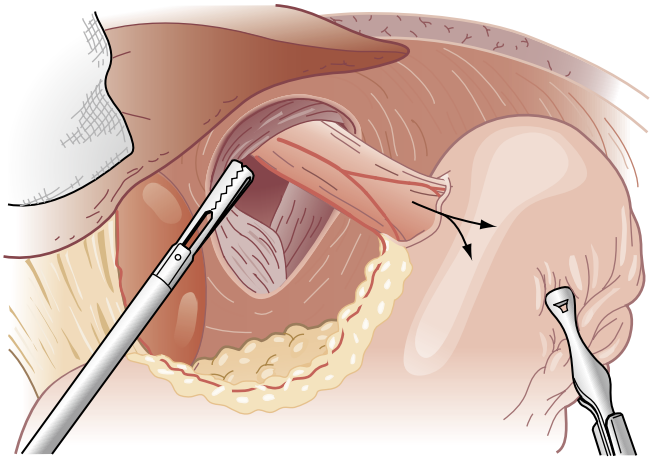


FIG. 4 Completion of the circumferential crural dissection. This illustration depicts the view immediately before insertion of the Penrose drain. *(From Yates RB, Oelschlager BK, Pelligrini CA. Gastroesophageal reflux disease and hiatal hernia. In: Townsend et al., eds. Sabiston Textbook of Surgery. 20th ed. Philadelphia: Elsevier; 2017:1043–1064.)*

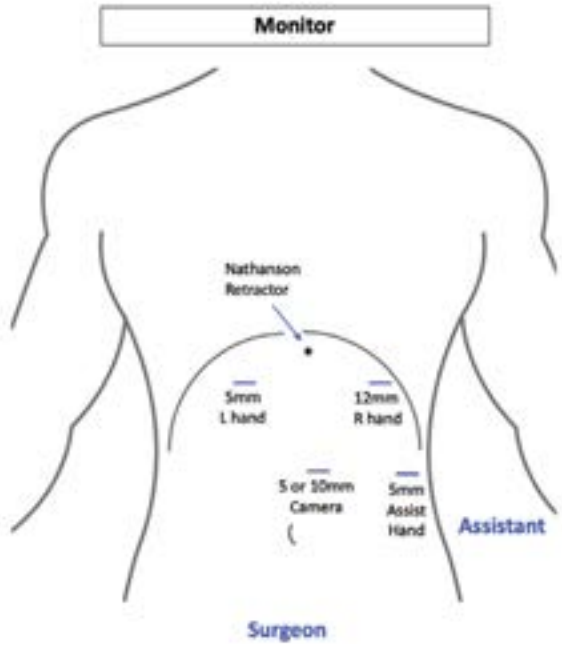


FIG. 3 Port placement for laparoscopic antireflux surgery. The camera port is positioned approximately 15 cm below the left costal margin, 2 cm to the left of midline. The Nathanson liver retractor is inserted through a stab incision in the epigastrium to the left of midline.

Steps of the Procedure: Creating a 360-Degree Nissen Fundoplication

As previously discussed, we prefer to perform a complete fundoplication in patients with normal esophageal motility. We believe this provides a more durable repair, and we find that the geometry of a complete fundoplication lends itself to greater reproducibility from a technical standpoint.

1. Orientation of the wrap
   a. The fundus and greater curve of the stomach is retracted medially, and a marking stitch is placed on the posterior fundus approximately 3 cm below the angle of His and 2 cm inside the greater curve.
   b. The posterior fundus is passed behind the esophagus, and the point on the stomach where the marking stitch was placed is lifted anteriorly against the right side of the esophagus.
   c. A point on the anterior fundus is identified that mirrors the location where the marking stitch was placed posteriorly (approximately 3 cm away from the angle of His and 2 cm from the greater curvature of the stomach). This point on the stomach is pulled up along the left side of the esophagus.
   d. A "shoe-shine" maneuver is performed to assess the symmetry of the fundoplication before bringing the two sides of the fundus together anterior to the esophagus (Fig. 5). With this construction, the greater curve of the fundus should run longitudinally posterior and to the left of the esophagus (and thus is no longer visible when suturing the fundoplication).
2. Suturing the fundoplication
   a. The first stitch is placed, bringing the anterior and posterior fundus together at the points identified in the previous steps. The marking stitch and Penrose drain are then removed. A 52F bougie is then passed down the esophagus and into the stomach.
   b. The remaining two or three sutures are placed with the bougie in place to complete the fundoplication. The bougie is then removed (see Fig. 5).
   c. We place a coronal suture on each side of the wrap that incorporates the top of the fundus/wrap, a partial thickness bite of the esophagus, and the ipsilateral crus. This helps fix the orientation of the fundoplication in the abdomen (see Figs. 2A and 5).
   d. We also typically place a suture between the posterior aspect of the fundoplication and where it naturally rests against the crural closure as an additional fixation point.
   e. We perform routine upper endoscopy upon completion of the fundoplication to evaluate and document the appropriate appearance of the newly augmented flap valve.

Steps of the Procedure: Creating a 270-Degree Posterior Toupet Fundoplication

In patients with manometric evidence of ineffective esophageal motility, we typically recommend a partial fundoplication. When

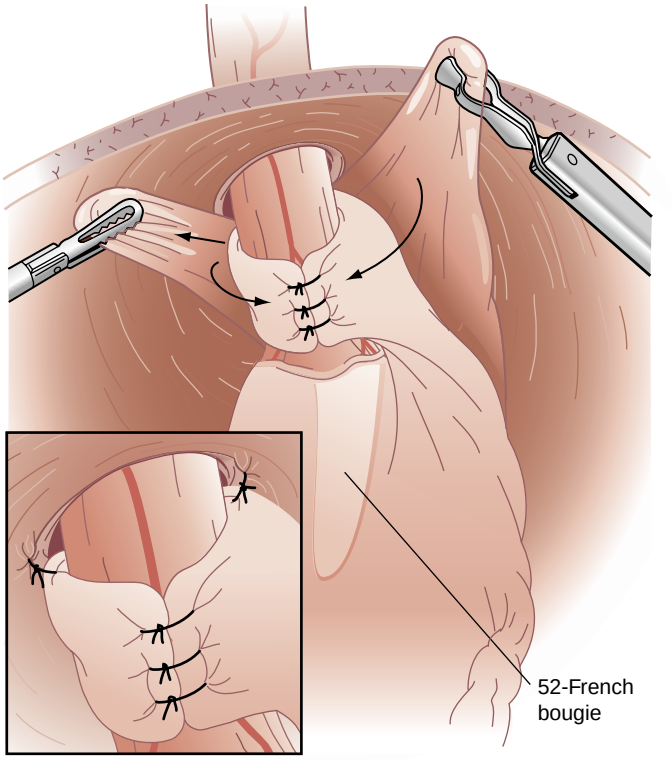


FIG. 5 Creating a 360-degree Nissen fundoplication. The "shoe-shine" maneuver is performed by grasping the posterior and anterior fundus with the left and right hand, respectively, 3 cm from the angle of His, and 2 cm from the greater curvature of the stomach. *(From Oelschlager BK, Eubanks TR, Pellegrini CA. Hiatal hernias and gastroesophageal reflux disease. In: Townsend CM, Beauchamp RD, Evers MB, et al., eds. Sabiston Textbook of Surgery. 19th ed. Philadelphia: Elsevier; 2012.)*

considering the geometry of a 270-degree (Toupet) fundoplication, the inner circumference of the fundoplication should approximate that of the esophagus, while the outer circumference should be appropriately redundant, resembling a crescent with rounded corners in cross-section. This geometry provides volume to the fundoplication, which supports the intended flap-valve effect. The constructed geometry should be very similar to that of a Nissen, just without bringing the stomach together, thus the following description is very similar. Of note, we do not routinely use an esophageal bougie when performing a partial fundoplication.

1. Orienting and creating the right half of the wrap.
   a. The fundus and greater curve of the stomach is retracted medially, and a marking stitch is placed on the posterior fundus approximately 3 cm below the angle of His and 2 cm inside the greater curve.
   b. The posterior fundus is passed behind the esophagus, and the point on the stomach where the marking stitch was placed is lifted anteriorly against the right side of the esophagus.
   c. A coronal suture is placed on the right side, incorporating the posterior fundus, a partial thickness bite of the esophagus, and the right crus (just like in a Nissen).
   d. A posterior stitch is placed to fixate the wrap to where it naturally lies against the crural closure.
   e. Two additional sutures are placed between the esophagus (to the right of the anterior vagus nerve) and posterior fundus, completing the right side of the fundoplication (see Fig. 2C).
2. Completing left side of the fundoplication
   a. The anterior fundus is pulled laterally to remove the redundant stomach from behind the esophagus.
   b. A left coronal suture is placed, incorporating the anterior fundus, a partial bite of the esophagus, and the left crus (again, just like the Nissen orientation).
   c. Two additional sutures are placed between the esophagus (to the left of the anterior vagus nerve) and posterior fundus, completing the left side of the fundoplication (see Fig. 2C).
   d. We routinely perform an upper endoscopy upon completion of the fundoplication to evaluate and document the appropriate appearance of the newly augmented flap valve.

POSTOPERATIVE CARE, SURGICAL COMPLICATIONS, AND OUTCOMES

Postoperatively, acid suppression therapy is routinely discontinued, and all medications are administered in either crushed or liquid form for 4 weeks. We typically admit patients to the hospital on a liquid diet and monitor for appropriate pain control and PO intake before discharge the following day. Although some surgeons routinely obtain a barium esophagram on the first postoperative day, we have not adopted this practice. Instead, patients who are able to tolerate a liquid diet without issue are advanced to a soft esophageal diet upon discharge on the first postoperative day, and this diet is maintained for 4 weeks.

Mild dysphagia is very common following ARS, and patients should be counseled to expect this during their preoperative and postoperative diet education. Similarly, patients are typically unable to belch or vomit following ARS, and many patients may experience mild bloating discomfort, abdominal distention, or epigastric pain. For most patients, both dysphagia and gas bloat should improve after 6 to 8 weeks. If these symptoms persist beyond this timeframe, endoscopic dilation of the wrap may be considered.

Long-term outcomes associated with laparoscopic ARS can be measured by examining patient-reported symptoms, objective measures of distal esophageal acid exposure, resumption of PPI use, complications of GERD, or rates of reoperation. Thus, depending on the primary outcome examined, definitions of success and failure vary across studies. In general, available studies demonstrate a 15% to 30% recurrence rate for GERD at 10 years in patients following laparoscopic ARS. Most patients with recurrent GERD are medically managed with acid suppression therapy, while a minority (less than 5%–10%) undergo reoperation. As mentioned previously, ARS is associated with higher complication rates compared with acid suppression therapy. In studies that focus on patient-reported outcomes, ARS generally outperforms medical therapy when patients are surveyed on GERD-related symptoms and quality of life. Patient-reported satisfaction following ARS consistently approaches 90% or higher.

SPECIAL CONSIDERATIONS

It is important to distinguish ARS from paraesophageal hernia repairs as the surgical evaluation and approach to GERD differs from that of paraesophageal hernias. This can be confusing because fundoplications are often performed in conjunction with paraesophageal hernia repairs, thus the anatomic result following completion of both procedures is essentially identical. However, in the absence of a paraesophageal hernia, adequate circumferential mobilization of the distal esophagus should almost always provide enough intraabdominal length to obviate the need for an esophageal lengthening procedure. When performing ARS in patients with a small- to moderate-sized sliding hiatal hernia, the lower esophageal sphincter should (by definition) reach the intraabdominal cavity. Thus, we reserve the discussion of Collis gastroplasty and esophageal lengthening procedures for chapters focused on paraesophageal hernia repair. In the same vein, although the use of absorbable mesh has

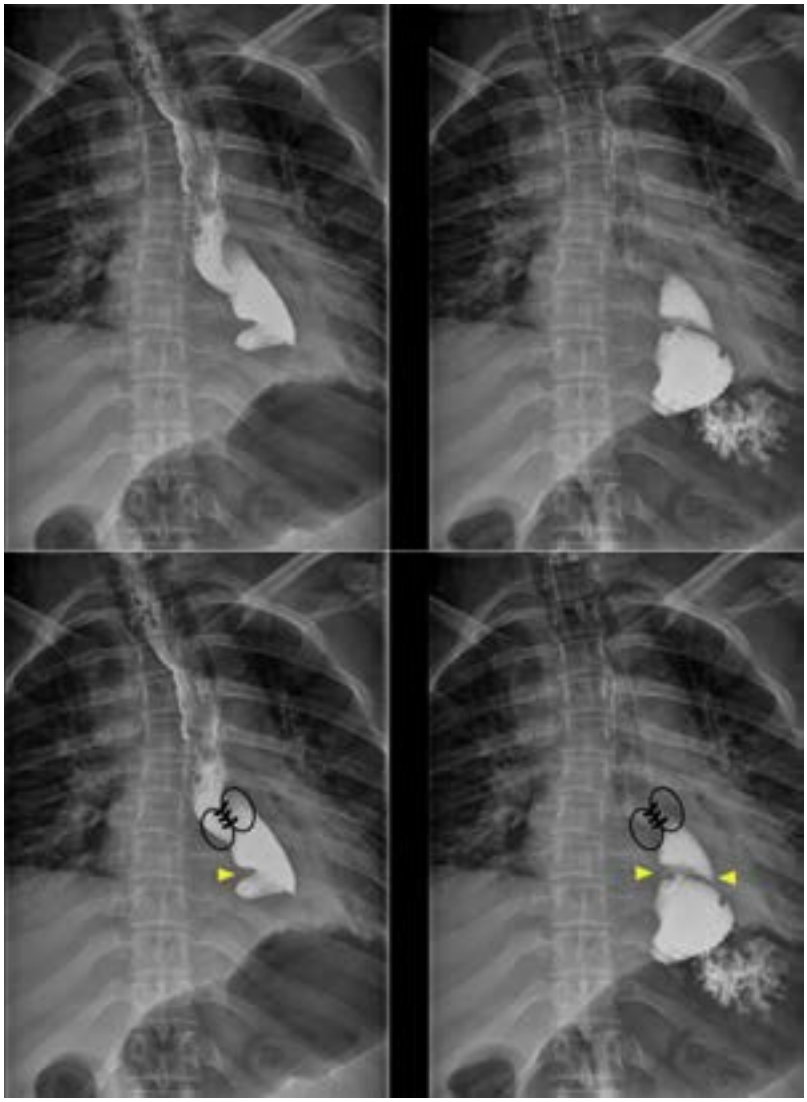


FIG. 6 Upper gastrointestinal barium esophagram depicting herniated fundoplication. Original radiographs *(top)*. Herniated position of fundoplication is outlined in *black (bottom)*. *Yellow arrowheads* depict diaphragmatic impression.

been studied and debated in the context of paraesophageal hernia repairs, there is no real indication for mesh use in laparoscopic ARS for GERD.

In patients who develop recurrent GERD symptoms following ARS, it is important to review the prior operative records and obtain a complete workup as described earlier in this chapter. Herniation of the wrap cephalad into the mediastinum is the most common cause of anatomic failure in patients with a previous fundoplication (Fig. 6). Failure can also result from an inappropriately constructed fundoplication that incorporates the body of the stomach (Fig. 7) or simply from loosening of the wrap over time. Anatomic failures can lead to recurrent GERD and new symptoms of dysphagia, odynophagia, or epigastric pain. Just as in the initial management of GERD, patients presenting with typical reflux symptoms following ARS can often be managed medically. In patients with persistent dysphagia, epigastric pain, or poorly controlled reflux symptoms despite medical therapy, surgical revision may be considered after careful evaluation to identify anatomic causes of failure while ruling out other possible etiologies. In general, caution should be exercised when considering a surgical revision as the complication rates associated with revisional surgery are higher than for first-time ARS.

When approaching a revisional operation, the surgeon should always plan to take down the prior fundoplication as this is the only way to evaluate the construction of the prior wrap and ensure the correct construction of a new fundoplication. After both halves of the fundoplication have been dissected free, the right half should be passed behind the esophagus to restore the normal orientation of the stomach and confirm that the wrap has been completely taken down before creating a new fundoplication. Importantly, we have encountered many barium esophagrams with radiology reports suggesting complete dehiscence of a previous fundoplication. In our institution's collective experience performing revisions, we have never encountered a complete dehiscence in the operating room. There is always a wrap that needs to be properly identified and taken down. Finally, when evaluating patients who have failed two prior antireflux procedures, we generally do not consider a third attempt to redo the wrap. If indications arise to consider another revision after multiple prior failures, a revision may be considered, but the surgeon and patient should be prepared for the possibility of a partial gastrectomy and Roux-en-Y reconstruction with either a gastrojejunostomy or potentially an esophagojejunostomy. This is, of course, is a major operation, and the associated risks and lifelong dietary modifications

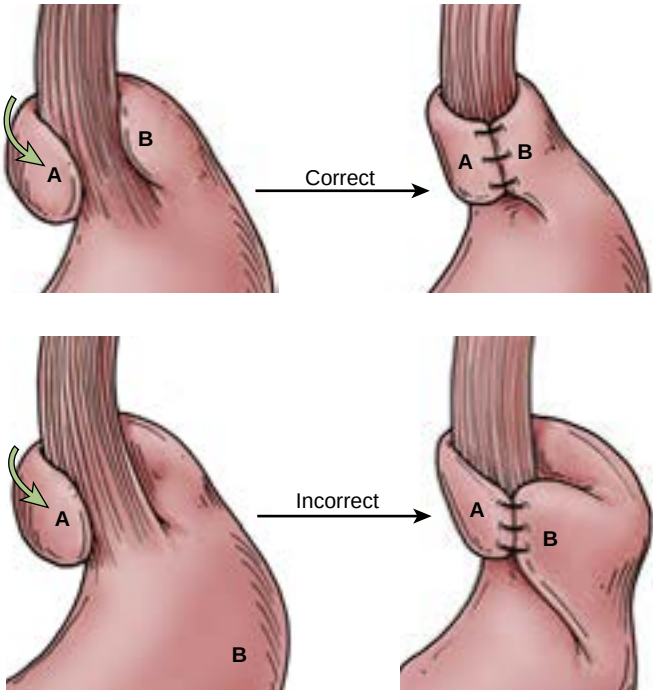


FIG. 7 A wrap can be incorrectly constructed by suturing the fundus to the body of the stomach. *(From Smith CD, McClusky DA, Rajad MA, Lederman AB, Hunter JG. When fundoplication fails: redo? Ann Surg. 2005;241[6]:861–869.)*

should be weighed against the severity of the patient's symptoms when counseling patients who have failed multiple attempts at ARS.

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New Approaches to Gastroesophageal Reflux Disease (LINX)

Tom R. DeMeester, MD

Between the early 1960s and early 1970s, Drs. Rudolf Nissen, Ronald Belsey, and Lucius Hill introduced the golden era of antireflux surgery. These physicians designed procedures that took down a hiatal hernia, altered the anatomy of the gastroesophageal junction with a fundoplication of various degrees, and stopped reflux of gastric juice into the esophagus. In 1975, the first randomized controlled study confirmed the superiority of surgical over medical therapy with antacids. Surgery was off and running.

All came to a dramatic halt when the Nobel Prize was awarded to Sir James W. Black in 1988. He discovered an approach to drug development called *rational drug design structure*. Simply stated, if the pathophysiology of a disease is properly understood, a specific drug could be synthesized to interrupt key points in the pathogenesis and cure the disease. He used this concept to discover the beta and H_2 receptor antagonists, propranolol and cimetidine. Cimetidine became the first drug ever to exceed $1 billion per year in sales. The methodology eventually led to the development of proton pump inhibitors (PPIs), which block the secretion of acid by the parietal cells. The aim of these drugs is to increase the pH of the gastric juice, which, along with the lower esophageal sphincter, contribute to gastroesophageal reflux disease (GERD). By the 1980s, the clinical benefits of PPIs were demonstrated dramatically by the abolishment of GERD symptoms and the virtual elimination of acid-induced reflux esophagitis, strictures, and giant Barrett's ulcers. Now medicine was off and running.

WHY A NEW SURGICAL ANTIREFLUX PROCEDURE?

After 35 years of experience with more than 20 million GERD patients on prescribed PPIs, physicians have developed some concerns. Despite the introduction and use of the new powerful acid-suppression drugs over this period, the incidence of GERD continues to increase by 30% every 10 years, and 30% to 40% of patients on PPI therapy have only partial relief of their symptoms. Between 2% and 3.5% of the 20 million patients with GERD receiving PPI therapy develop Barrett's esophagus every year, of which 0.5% to 1% progress to esophageal adenocarcinoma. Despite this high percentage of patients with a partial response and disease progression on PPI therapy, less than 1% seek surgical therapy. These concerns have given rise to the thought that the time has come for a change in the treatment strategy of GERD. The current treatment strategy focuses only on one of the two determinants of the disease, the acid composition of the gastric juice, whereas the other determinant, failure of the lower esophageal sphincter (LES), is ignored. This focus on PPIs and disregard for the LES is likely the result of a historical misunderstanding that GERD is primarily an acid peptic disease. The primary abnormality in GERD is the loss of an effective LES to keep the gastric juice in the stomach. This was pointed out in 2003 in a publication by Dr. G. Wetscher and colleagues

from Innsbruck, Austria. They showed that the recurrence of reflux symptoms and/or endoscopic esophagitis in patients on PPIs was related to the functional status of the LES and esophageal body. Patients with both a defective LES and esophageal contractions had an 80% recurrence rate compared with 39% in those patients with a defective LES and normal esophageal body contractions, or 8% in those with both a normal LES and normal esophageal contractions. They concluded that the status of the LES is a critical factor in the effectiveness of PPI therapy. The medication works well in patients with a normal LES and not so well in patients who have a defective LES. In the latter situation, reflux episodes continue at the same frequency whether the patient is off or on the medication. The only difference is a change in the pH of the refluxed gastric juice. As a consequence, 85% of patients on PPIs still experience GERD-related symptoms, and in 35% the symptoms have reached the level to cause dissatisfaction with PPI therapy. In an effort to improve symptom control, the prescriptions for double-dose PPIs have increased by 50% in the past 7 years, and 42% of patients supplement their prescription with other acid-suppression medication in an effort to gain relief. Of greatest concern is that 10% to 15% of patients have disease progression while on PPI therapy, and the longer the disease persists, the greater the number of patients who progress.

Over the past 35 years, antireflux surgery has not fared much better. Even though the surgery can be performed through a laparoscope and achieve effective control of reflux symptoms and heal esophagitis, the outcomes vary in their effectiveness and durability, and the early surgical revision rate is too high. The procedures have significant side effects in that patients are unable to belch or vomit, risk having increased flatulence and postprandial bloating, and have a small possibility of bothersome dysphagia. When performed by the occasional surgeon, only 61% of patients are completely satisfied with their operation. These results discourage patients against antireflux surgery, and at present less than 1% of GERD patients have surgical therapy. Unless there are some fundamental improvements in surgical therapy, it appears that the use of surgery for the treatment of GERD will reach a standstill.

NEW SURGICAL APPROACH TO GERD

The ideal surgical procedure to improve the function of the LES in a patient with GERD would be a minimally invasive, short, outpatient procedure that augments the LES function without causing anatomic alterations. Based on the effectiveness of the Nissen fundoplication, it should have a greater than 80% probability of normalizing esophageal acid exposure and a 90% probability of eliminating GERD-related symptoms. It should allow an unrestricted diet and cause no long-term side effects such as persistent dysphagia, symptomatic bloating, increased flatus, or the inability to belch or vomit. Further, it must be reversible without sequelae.

Over the past 10 years, studies on the pathophysiology of the LES have opened the door for technology to design a new device that meets the ideal requirement for a new surgical procedure for the treatment of GERD. These studies have shown that gastric distension or dilation after meals can cause effacement of the LES, resulting in progressive shortening of its length and, as a consequence, loss of its competency (Fig. 1). This process exposes the effaced squamous mucosa of the distal esophagus and the underlying muscle of the LES to gastric juice. The inflammatory injury that occurs destroys the squamous mucosa, heals by the induction of metaplastic cardiac mucosa, and induces permanent damage to the muscle of the LES, resulting in a loss of its abdominal length, overall length, and pressure. The resulting structurally defective LES allows repetitive LES effacement to occur with ease, resulting in escalation of the degrees of esophageal exposure to acidic bile containing gastric juice. Placing a loose ligature or ring around the inferior border of the LES can stop the effacement and has formed the basis for the design of new devices to augment LES function.

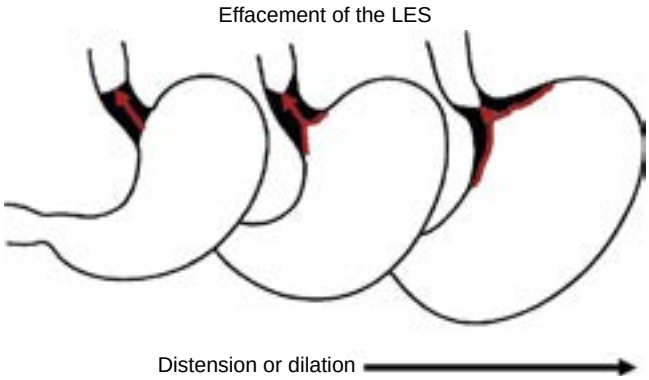


FIG. 1 Effacement and shortening of the length of the lower esophageal sphincter *(LES)* that occurs with gastric distension or dilation after meals and, as a consequence, loss of its competency. The process exposes the effaced squamous mucosa of the distal esophagus *(red line)* and the underlying muscle of the LES *(black area below the red line)* to gastric juice.

LINX ANTIREFLUX DEVICE

One of the new devices is the LINX Reflux Management System (Torax Medical, St. Paul, MN). It is a simple procedure, performed laparoscopically, that does not alter gastric or gastroesophageal junctional anatomy, augments the LES as a functional barrier to reflux, and can be reversed easily if necessary, thereby preserving the option for fundoplication or other therapies in the future. The LINX procedure is designed to limit technical variability, which will result in more standardization of antireflux surgery and more consistent clinical outcomes. The LINX device consists of a series of titanium beads with magnetic cores hermetically sealed inside (Fig. 2). The beads are interlinked with independent titanium wires to form a dynamic ring designed to conform to the changing physiologic movements of the esophagus during swallowing. The device was designed to use the magnetic attraction between adjacent beads to prevent the opening of the LES by distal to proximal effacement and shortening of its length caused by episodes of gastric distension or postprandial gastric dilation secondary to adaptive relaxation. The device is sized to fit around the external circumference of the esophagus at the distal end of the LES without compressing the esophageal musculature. The beads separate to allow the transport of a food bolus into the stomach, to relieve gastric distension by belching or nausea by vomiting (Fig. 3).

The LINX device was not designed to deter reflux episodes caused by pressure challenges that affect the whole abdominal environment. To deter these challenges requires sufficient esophageal length in the abdominal domain to allow the LES to be compressed by changes in the abdominal environmental pressure that occur with daily living and working. For this reason, it is recommended that, if possible, the LINX device be implanted with minimal disruption of the phrenoesophageal ligament to preserve sufficient length of esophagus in the abdominal domain.

LINX IMPLANTATION PROCEDURE

The LINX magnetic sphincter augmentation device is implanted laparoscopically under general anesthesia. Surgical ports are placed similar to the pattern used for the laparoscopic Nissen fundoplication with one exception. The dissection port in the patient's right upper quadrant is placed far laterally to optimize the visualization and sizing of the esophagus at the gastroesophageal junction. A limited focus dissection is ideal for implantation of the LINX device in a patient without a hiatal hernia. When performing a limited focus

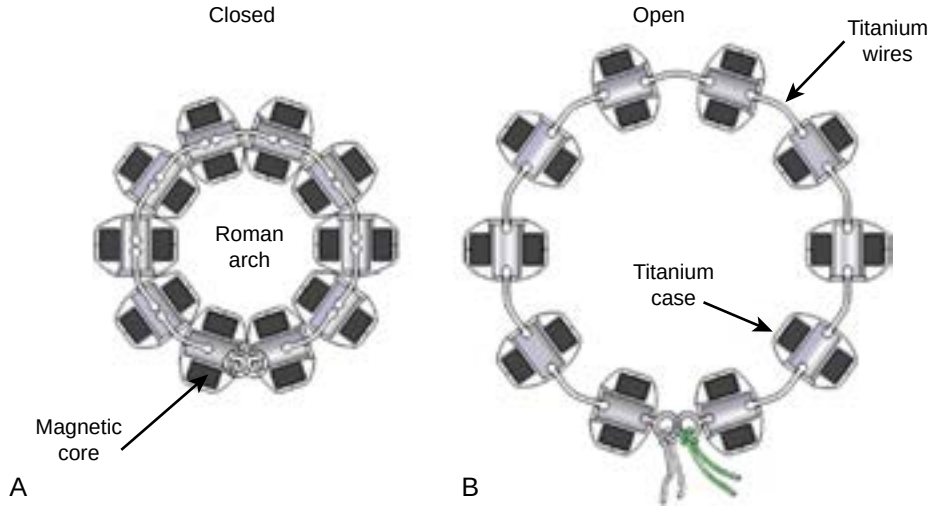


FIG. 2 Engineering schematic of the magnetic sphincter augmentation device. The device consists of an expansible bracelet of magnetic beads designed to be placed surgically around the exterior surface of the distal end of the lower esophageal sphincter *(LES)*. Each bead is composed of a titanium case containing a magnetic core of small disk-shaped magnets. The beads are connected by titanium wires of specific lengths that limit the distance any two individual beads can move apart. When the device is closed **(A)**, the magnetic force is sufficient to prevent effacement and opening of the LES yet is weak enough to allow the device to open **(B)** with esophageal peristalsis. When the device is closed, the Roman arch construction prevents compression of the esophageal tissues.

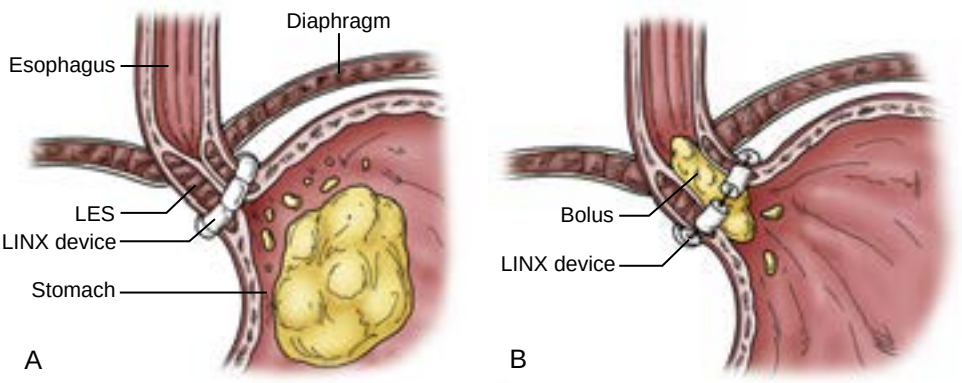


FIG. 3 The LINX magnetic sphincter augmentation device is implanted around the inferior border of the lower esophageal sphincter *(LES)*, as shown. **(A)** The magnetic device is shown in the closed position, which prevents effacement and opening of the LES and subsequent reflux. Each magnetic bead rests on the adjacent beads to prevent compression of the esophageal tissues. **(B)** The device is shown in the open position, which allows transport of food by esophageal peristalsis, belching of an overdistended stomach, and vomiting when necessary.

dissection, the surgeon must preserve and not dissect the phrenoesophageal ligament.

The surgical dissection begins by mobilizing the posterior gastric fundic wall off the lateral surface of the left crus to expose the caudal anterior edge of the left crus. In doing so, as few short gastric vessels as possible are divided. A 1-cm segment along the anterior margin of the left crus just above the crural decussation is identified. At this location, a medial dissection is performed just beneath the esophagus to form a pocket target for the right-sided tunnel dissection. In performing this dissection, care is taken not to enter the mediastinum. After the pocket target is made, the dissection is switched to the right side of the esophagus. The gastrohepatic ligament is opened by making two windows, a small one just superior to the hepatic branch of the anterior vagal nerve and a larger one inferior to the hepatic branch. The inferior window allows access to construct a retroesophageal tunnel through a 1- to 2-cm incision in the peritoneum along the anterior edge of the right crus just above the crural decussation. Using a dissector placed through the far lateral right upper quadrant port and the inferior window in the gastrohepatic ligament, a gentle dissection is made toward the left crus just to identify the posterior vagal nerve as it leaves the esophagus and drops posterior to the celiac plexus (Fig. 4A). Bleeding from the small vessels can obscure the dissection and is controlled with judicial use of cautery. Delicately, a tunnel is dissected in a right-to-left direction, between the posterior vagal nerve and the posterior esophageal wall, to connect with the previously constructed pocket target on the anterior margin of the left crus. Entering the mediastinum during the tunnel dissection should be avoided. The dissector is passed through the pocket target and into the left upper quadrant. The dissector is removed from the left upper quadrant, drawing a ¼-inch Penrose drain through the tunnel and securing its right and left ends for retraction. In line with the expected position of the device, the fibroareolar tissue from the right and left lateral esophageal surfaces is removed, and a trench is constructed through existing fat on the anterior surface of the esophagus below the inferior leaf of the phrenoesophageal ligament. The circumference of the esophagus then is measured to choose the proper size of the LINX device to be implanted. The sizing tool is a laparoscopic instrument with a soft, circular curved tip that is actuated by coaxial tubes through a handset. The handset contains a numerical indicator that corresponds to the size range of the LINX

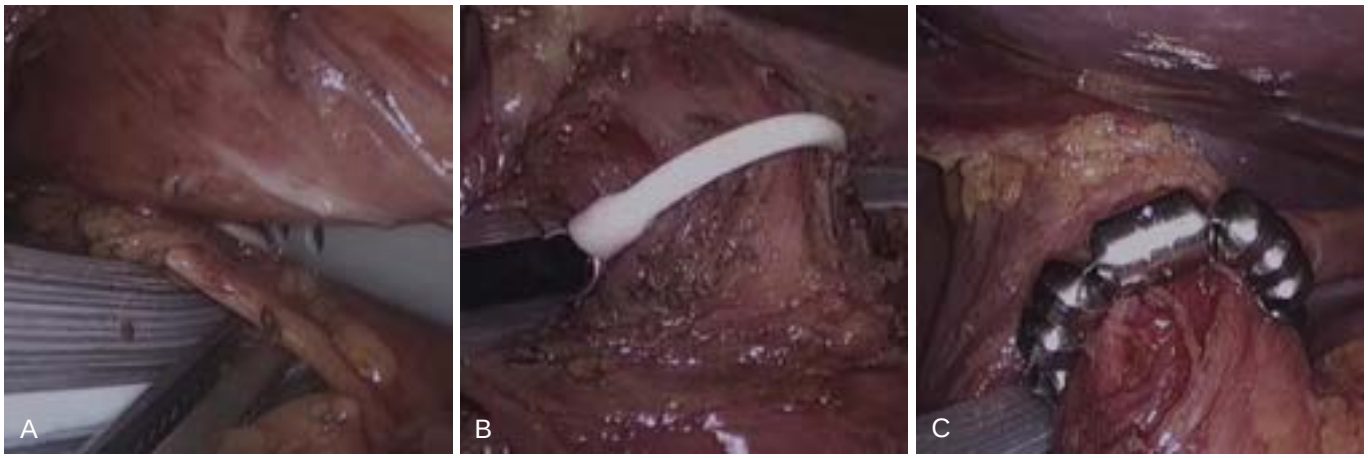


FIG. 4 Intraoperative images. **(A)** Dissection of the tunnel between the posterior vagal nerve and the posterior esophageal wall at the inferior border of the lower esophageal sphincter *(LES)*. **(B)** The position of the sizing tool to measure the circumference of the esophagus at the lower border of the LES. **(C)** Completed implantation of the LINX device around the lower border of the LES with the clasps connected.

device. The sizing tool is inserted through the far-lateral placed right upper quadrant port and then passed through the dissected tunnel between the posterior vagal nerve and esophageal wall and around the esophagus (see Fig. 4B). Anterior retraction on the previously placed Penrose drain simplifies this maneuver. When making the measurement, the surgeon must not intubate the esophagus or compress its muscular wall by the measuring device. Two measurements should be taken. If the measurement is between two sizes, the larger size is selected. The most common size is 14, and smaller sizes should be used sparingly and with caution. The appropriate size of device is selected and pulled through the tunnel in a left to right direction. Again, anterior retraction of the Penrose drain simplifies this maneuver. The ends of the device are brought anteriorly around the esophagus, the left end around the Angle of His and the right end over the gastrohepatic branch of the anterior vagal nerve. The clasps are connected, and the anterior portion of the device is placed in the trench if present (see Fig. 4C). If the right and left crura appear to diverge from one another above the crural decussation, one or two figure-of-8 sutures can be placed to approximate them, provided no further dissection is required. A small hiatal hernia less than 3 cm in size can be effectively repaired by this maneuver. The surgical time is usually less than 1 hour. The patient is discharged the same day or, if an afternoon procedure, the next morning. The patient is instructed to slowly return to a normal diet over the next week and discontinue the use of acid-suppression medication.

For patients with a hiatal hernia greater than 3 cm, a more extended and less focused dissection can be done to allow dissection and reduction of the hernia into the abdomen, approximation of the crura around a 2- to 3-cm length of abdominal esophagus, and implantation of the LINX device. An extended dissection also provides a fallback solution when greater exposure is necessary to implant the LINX device for reasons other than a hiatal hernia. Normalization of esophageal acid exposure is similar in patients after a limited focus or extended dissection (Fig. 5). Again, when doing an extended dissection, it is important to approximate the crura around the esophagus in a manner that maintains 2 to 3 cm of esophagus in the abdominal environment. When this is not done, the ability to deter the reflux of gastric juice into the esophagus caused by episodes of increased abdominal environmental pressure is compromised.

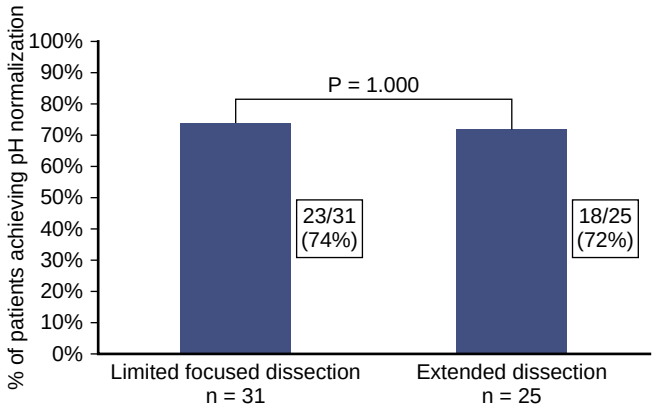


FIG. 5 The degree of dissection necessary to implant the LINX antireflux device and normalization of esophageal acid exposure. With either dissection (limited focus or extended), the esophageal acid exposure was normalized in more than 70% of patients. The durability of competency with a limited focus dissection is beyond 5 years. The durability of competency with an extended dissection is unknown.

LONG-TERM CLINICAL OUTCOMES OF THE LINX MAGNETIC SPHINCTER AUGMENTATION DEVICE

Long-term outcomes of patients who had the LINX magnetic sphincter augmentation device implanted for GERD have been reported recently. The final 5-year results of the US Food and Drug Administration's approved trial provides a careful analysis of the safety and effectiveness of the LINX device. The studied population consisted of 100 adults who had GERD for at least 6 months or longer, were partially responsive to daily PPIs, and had abnormal esophageal acid exposure on 24-hour pH testing. The LINX device was placed using standard laparoscopic techniques. In this study, 85 subjects were followed for 5 years and evaluated for quality of life (GERD-HRQL score), reflux control (postoperative 24-hour pH testing at 1 year), use of PPIs, and side effects. A quality of life questionnaire was administered at baseline to patients on and off PPIs and after placement of the LINX device yearly for 5 years. Over the follow-up period, no device erosions, migrations, or malfunctions occurred. At baseline, the median GERD-HRQL scores were 27 when patients were not taking PPIs, 11 when taking PPIs, and decreased to 4 at 5 years after LINX placement (Fig. 6). All patients were taking daily PPIs at baseline, and this decreased to 15.3% at 5 years (Figs. 7 and 8). Moderate to severe heartburn occurred in 89% of patients at baseline but only 11.9% at 5 years (see Fig. 7). Moderate to severe regurgitation occurred in 57% of patients at baseline, but only 1.2% at 5 years

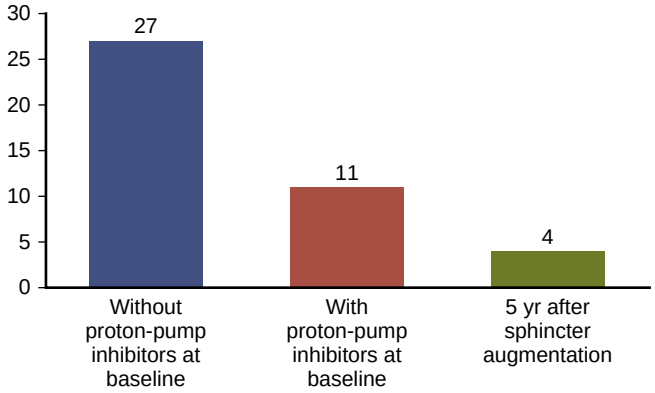


FIG. 6 Median total GERD-HRQL scores measured at baseline without and with proton pump inhibitors, as compared with 5 years after implantation of the LINX sphincter augmentation device. Higher scores indicate worse symptoms. $P < 0.001$ for all comparisons with baseline.

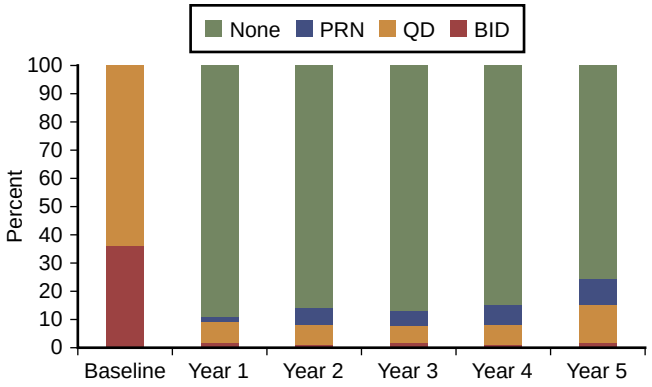


FIG. 8 The use of PPIs at baseline and yearly throughout the 5 years. PPI use was categorized as none, as needed *(PRN)*, once a day *(QD)*, and twice a day *(BID)* at each yearly visit based on the prior 30 days. Patients who required BID PPIs decreased from 36% at baseline to 2.4% at 5 years.

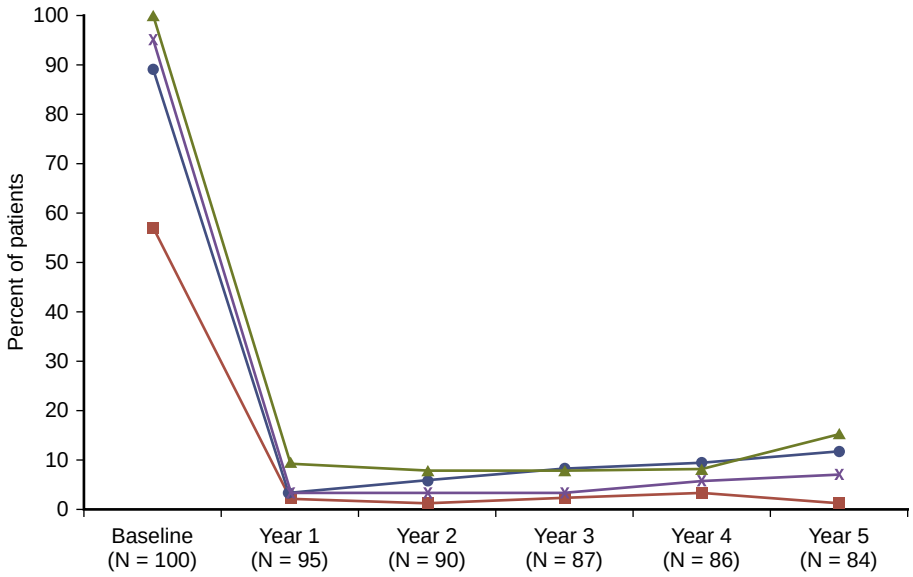


FIG. 7 Reflux control of moderate-severe heartburn, moderate-severe regurgitation, PPI dependency, and dissatisfaction with therapy. P < 0.001 between baseline and yearly follow-up evaluation out to 5 years for all comparisons. Of the six patients who were dissatisfied at 5 years, five reported daily use of PPIs.

(see Fig. 7). All patients reported the ability to belch and vomit if needed. Bothersome dysphagia was present in 5% at baseline and in 6% at 5 years (Fig. 9). Bothersome gas bloat was present in 52% at baseline and decreased to 8.3% at 5 years (see Fig. 9). No significant complications occurred. No new safety risks emerged over the 5 years of follow-up. On the basis of this and other reported studies, LINX is an effective fundic-sparing, antireflux procedure with minimal side effects. It is applicable to patients who have a partial response to PPIs, a desire to be off PPIs, or endoscopic/histologic signs of progression while on PPI therapy. A hiatal hernia is likely not a contraindication to the use of the LINX device, but long-term results regarding the recurrence rate of the hiatal hernia are needed.

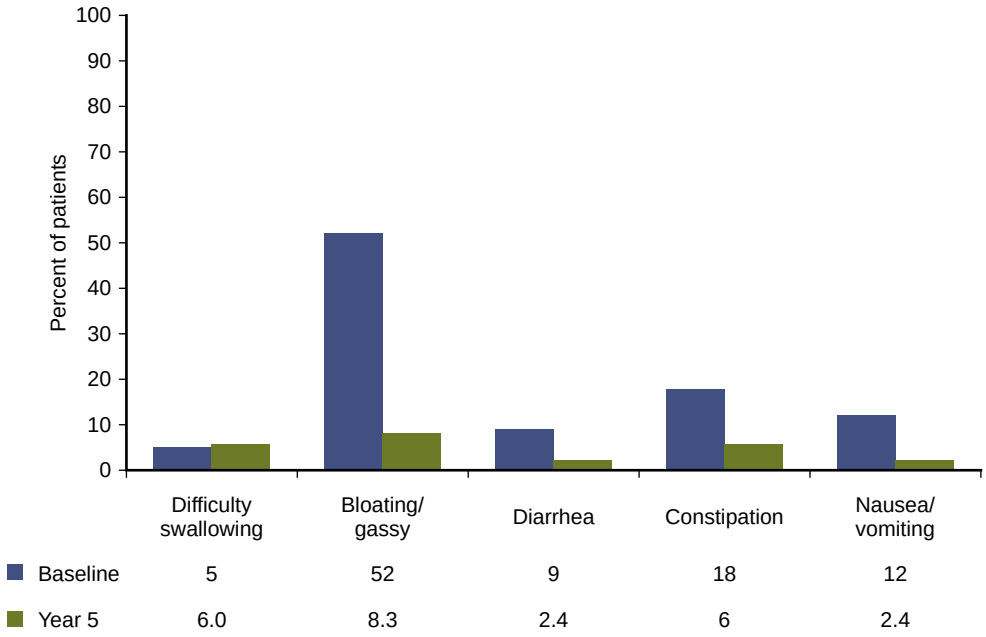


FIG. 9 Potential side effects of LINX magnetic sphincter augmentation at 5 years when compared with the same symptoms at baseline. $P = 0.739$ for difficulty swallowing, $P < 0.001$ for bloating/gassy feeling, $P = 0.103$ for diarrhea, $P = 0.008$ for constipation, and $P = 0.003$ for nausea and vomiting.

Suggested Readings

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Management of Barrett's Esophagus

Stephen R. Broderick, MD, MPHS

DEFINITION OF BARRETT'S ESOPHAGUS AND TREATMENT OBJECTIVES

Barrett's esophagus (BE) is defined as metaplastic change of the epithelial lining of the distal esophagus from normal stratified squamous epithelium to intestinal columnar epithelium containing goblet cells. The diagnosis of BE must be made endoscopically with a visible change in the lining of the distal esophagus and biopsy demonstrating columnar epithelium with goblet cells (Fig. 1). BE results from chronic injury to the esophageal mucosa secondary to long-standing gastroesophageal reflux disease (GERD). Population-based estimates of the prevalence of BE range from 0.4% to 2%, with higher rates (5%–15%) among patients with GERD. BE is the major risk factor

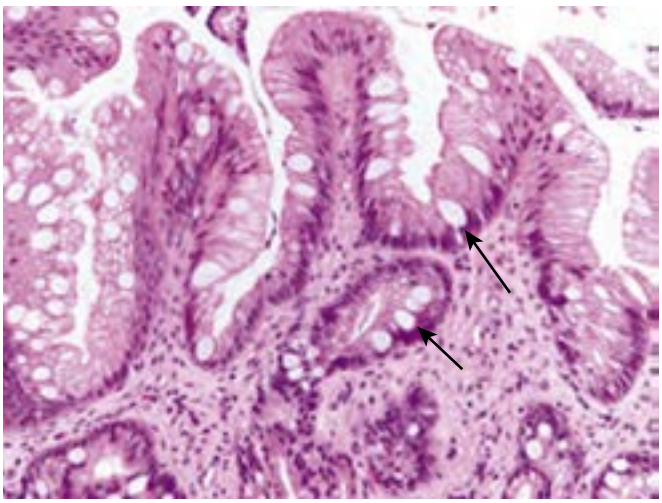


FIG. 1 Intestinal metaplasia with goblet cells *(arrows)*.

for esophageal adenocarcinoma (EAC). Therefore, the objectives of treatment are to treat the underlying reflux disease, prevent progression of BE, and treat BE with dysplasia before progression to EAC.

CLINICAL EFFECT AND FEATURES OF BARRETT'S ESOPHAGUS

The primary clinical implication of BE is the risk of progression to EAC. Rates of EAC in Western populations have been increasing over recent decades, and overall survival remains poor despite improvements in early diagnosis and treatment. Estimates of risk of EAC in patients with BE range from 30 to 125 times that of the general population. Progression from BE to EAC generally takes place in a stepwise manner over time from normal squamous epithelium to non-dysplastic BE, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and finally EAC. LGD and HGD are determined by the degree of distortion in the architecture of dysplastic cells. This distinction can be subtle with a high degree of interobserver variability.

In addition to GERD, a number of other risk factors have been associated with the development of BE and subsequent EAC. These include family history, age older than 50 years, male sex, central obesity, white race, presence of hiatal hernia, and tobacco use.

SCREENING AND EVALUATION OF BARRETT'S ESOPHAGUS

Screening

Given the low background prevalence of BE, routine endoscopic screening is not recommended. Various society guidelines exist supporting screening in patients with risk factors. The American College of Gastroenterology (ACG) Clinical Guidelines support screening for males with chronic GERD, defined as symptoms for 5 or more years with at least weekly symptoms and two or more additional risk factors (age >50, white race, central obesity, current or past smoking, family history in a first-degree relative). Screening is not recommended in women but may be considered on an individual basis if risk factors are present.

Evaluation

The initial evaluation for BE consists of white light endoscopy. BE should be suspected when salmon pink mucosa is identified proximal to the gastroesophageal junction (GEJ). The endoscopist should inspect for areas of columnar metaplasia as well as irregularities in the mucosal surface. These may signify areas of dysplasia or invasive adenocarcinoma. The Prague classification is the most commonly used standardized reporting mechanism which identifies the proximal extent of circumferential BE as well as the maximal extent of any tongues of BE. The presence and size of any hiatal hernia should also be noted.

Biopsies should be taken of the distal esophagus in four quadrants from the GEJ at 1- to 2-cm intervals through the proximal extent of suspected BE (the Seattle protocol). Biopsies of the gastric mucosa for comparison purposes and of any areas with mucosal irregularity should also be taken. Narrow band imaging (or another form of chromoendoscopy) should be employed to enhance visualization of mucosal surface vascular patterns and irregularities (Fig. 2). The finding of BE with dysplasia requires confirmation by a second pathologist with gastrointestinal (GI) expertise.

SURVEILLANCE

Current practice guidelines from both medical and surgical societies universally recommend endoscopic surveillance once BE is identified. The goal of surveillance is to identify progression to dysplasia or EAC at an early, treatable stage. There is some degree of variation in the details of surveillance protocols. Areas of consensus and debate include the following:

1. White light endoscopy is the preferred method of surveillance with or without the addition of narrow band imaging.
2. There is near consensus that the Seattle protocol consisting of four-quadrant biopsies is the optimal biopsy strategy, with some debate over a 1-cm versus 2-cm interval between biopsies. All nodular lesions should be biopsied and sent separately for pathologic evaluation. Some guidelines recommend against biopsies in areas of active esophagitis, favoring repeat endoscopy after a period of suppressive therapy.
3. There is unanimity that dysplasia should be confirmed by a second pathologist with expertise in GI pathology.
4. Guidelines are consistent regarding a surveillance interval of 3 to 5 years for nondysplastic BE. There is variation in the impact of the length of the BE segment on the recommended surveillance interval, with some guidelines suggesting shorter intervals for patients with longer-segment BE.



FIG. 2 Barrett's esophagus seen on endoscopy under both white light endoscopy **(A)** and narrow band imaging **(B)**.

5. There is no consensus regarding when to stop surveillance. Cessation is recommended when patients are no longer candidates for endoscopic or surgical therapy or cannot tolerate repeat endoscopic procedures.

MANAGEMENT OF BARRETT'S ESOPHAGUS WITHOUT DYSPLASIA

The overriding principle in managing a patient with non-dysplastic BE is treatment of underlying GERD. This will accomplish not only symptom control but also protect the esophageal mucosa from repetitive reflux injury. Medical therapy with once-daily dosing of proton pump inhibitors (PPIs) is the recommended first-line therapy in addition to diet and lifestyle modifications. Escalation to twice-daily dosing is recommended only when symptom control on daily dosing is inadequate.

Antireflux surgery is an adjunct to medical therapy for GERD. Data supporting the role of surgery in preventing progression to EAC are weak. Therefore, surgery is recommended for failure of medical therapy to control symptoms or impaired quality of life. The role or benefit of mucosal ablation with radiofrequency or other modalities is unproven in patients with non-dysplastic BE. There may be a role for ablation in patients with ultralong segment (>8 cm) BE to reduce the complexity of biopsy procedures.

Regardless of the approach to treat GERD (medical therapy or surgery), surveillance endoscopy is necessary to evaluate for progression to dysplasia.

MANAGEMENT OF BARRETT'S ESOPHAGUS WITH LOW-GRADE DYSPLASIA

LGD is associated with an increased risk of progression to adenocarcinoma compared with nondysplastic BE. The presence of LGD on any biopsy necessitates thorough evaluation with four-quadrant biopsies every 1 to 2 cm over the entire area of BE if not already performed. The presence of dysplasia should be confirmed by an expert GI pathologist, as the distinction of LGD from inflammatory atypia can be subtle. Patients with LGD should then be initiated on PPI therapy with repeat endoscopic evaluation in 6 months. LGD will often regress to nondysplastic BE with PPI therapy. Antireflux surgery should be considered at the identification of LGD or if LGD persists despite initiation of PPIs. Nissen fundoplication has demonstrated superior rates of regression of LGD compared with PPI therapy alone.

Persistent dysplasia despite control of GERD with PPI and/or antireflux surgery is an indication for mucosal ablation. Radiofrequency ablation has been shown to reduce the risk of progression to adenocarcinoma compared with surveillance alone.

MANAGEMENT OF BARRETT'S ESOPHAGUS WITH HIGH-GRADE DYSPLASIA

Given the proven high risk for progression to EAD, the presence of BE with HGD is an indication for intervention in most patients. If initial endoscopic evaluation identifies HGD, a careful repeat endoscopy is performed to thoroughly map areas of HGD and identify any areas of nodularity or ulceration in the metaplastic columnar mucosa. Both white light and narrow band imaging (or another form of chromoendoscopy) should be employed to aid in identification of mucosal lesions.

Endoscopic mucosal resection (EMR) should be used to remove any small, discrete nodules. In EMR, a cap is attached to the tip of the endoscope, the target lesion is suctioned into the cap, and a band is applied to the base, creating a "pseudopolyp." This is then snared and sent for pathologic evaluation. In lesions 1 cm or larger, endoscopic ultrasound (EUS) is employed to assess for invasion into the esophageal wall and presence of periesophageal lymphadenopathy. EUS is not useful for very small lesions or HGD in which no mucosal abnormality is identified. In the event that an EMR specimen demonstrates adenocarcinoma, the depth of invasion (Tis vs. T1a vs. T1b) is critical in determining the next steps in evaluation and treatment. Thus, a good EMR specimen will contain mucosa and submucosa, leaving muscularis at the base of the resection site. The ER specimen can also be evaluated for other high-risk features including degree of differentiation or lymphovascular invasion, which may prompt more aggressive management. Invasion into the submucosa (T1b), a poorly differentiated lesion, and lymphovascular invasion increase the likelihood of occult lymph node metastases. Thus, these features should prompt further staging investigations and consideration of esophagectomy in appropriate surgical candidates.

Patients found to have HGD alone or adenocarcinoma confined to the mucosa (T1a) without high-risk features are candidates for endoscopic interventions to ablate the lesion(s) and preserve the esophagus. The goal of endoscopic therapy should be resection of all raised or suspicious mucosal lesions. This can be accomplished with in one or multiple sessions over a 6- to 8-week period until all documented areas of dysplasia are removed. Oftentimes ablation of the residual metaplastic mucosa is then performed to reduce the risk of progression to further areas of dysplasia.

After complete eradication of both dysplasia and intestinal metaplasia, ongoing surveillance is essential. Surveillance endoscopy after ablation of HGD should be performed every 3 months for the first year, every 6 months for the second year, and annually thereafter if no recurrent areas of dysplasia are identified. It is also critical that patients with documented HGD achieve long-term control of underlying GERD with medical therapy or antireflux surgery.

Esophagectomy in High-Grade Dysplasia

Although endoscopic therapies are now the standard of care, there remains a role for esophagectomy in select patients in whom BE with HDG is identified. Esophagectomy provides the most thorough eradication of the diseased esophagus but carries the significant potential morbidity and mortality of surgery. Operative mortality associated with esophagectomy for HGD is less than 1% at experienced centers. Esophagectomy is considered in patients with the following characteristics:

- High-risk features: length > 2 to 3 cm, lymphovascular invasion, multifocality, poorly differentiated lesion
- Patient with preference for surgery or inability to attend repeat surveillance or procedural endoscopies
- Inability to eradicate areas of HGD with endoscopic therapies
- Evidence of progression despite endoscopic ablation
- Technically insufficient endoscopic ablation
- End-stage esophageal function (secondary to motility disorder, stricture, hernia)

CONSIDERATIONS REGARDING ANTIREFLUX SURGERY IN BARRETT'S ESOPHAGUS

GERD that leads to BE is associated with a higher degree of reflux, incompetent lower esophageal sphincter (LES), esophageal dysmotility, and hiatal hernia. These factors lead to lower likelihood of control of GERD with medical therapy alone. Antireflux surgery has several theoretical benefits in the management of GERD, including the control of both acid and biliopancreatic substrates that are contributing to mucosal injury and restoration of the hiatus and incompetent LES. More complete control of reflux into the distal esophagus has been

associated with more frequent regression of BE and reduced rates of progression to EAC.

Antireflux surgery in the setting of esophageal dysmotility or hiatal hernia can be more challenging than routine fundoplication. Fundoplication is more likely to fail in patients with BE, and failure is associated with progression of BE. Thus, patients who undergo antireflux procedures still require frequent surveillance endoscopy.

In addition to endoscopy, evaluation of the patient with BE for consideration of antireflux surgery consists of contrast esophagram and high-resolution manometry. Preoperative and postoperative pH testing can assist in determining which patients can discontinue PPI therapy following fundoplication. Consideration to the type of fundoplication (complete vs. partial) should be given based on the patient's esophageal motility.

CONCLUSION

Management of the patient with BE is closely associated with management of the patient's underlying GERD. There are two intertwined objectives of therapy: (1) identification, treatment, and surveillance of intestinal metaplasia and (2) treatment of the underlying GERD. Combined, these strategies serve to reduce the risk of progression from nondysplastic BE to dysplasia or adenocarcinoma. In addition, treatment of GERD reduces symptomatology and improves dietary quality of life. Antireflux surgery can be beneficial to eradicate GERD symptoms, induce regression of dysplasia, and reduce the chance of progression. Patients should be carefully selected for surgery as those with BE are commonly associated with hiatal hernia and esophageal dysmotility, putting them at higher risk for failure of fundoplication. Endoscopic therapies are now the standard of care for patients with dysplasia and

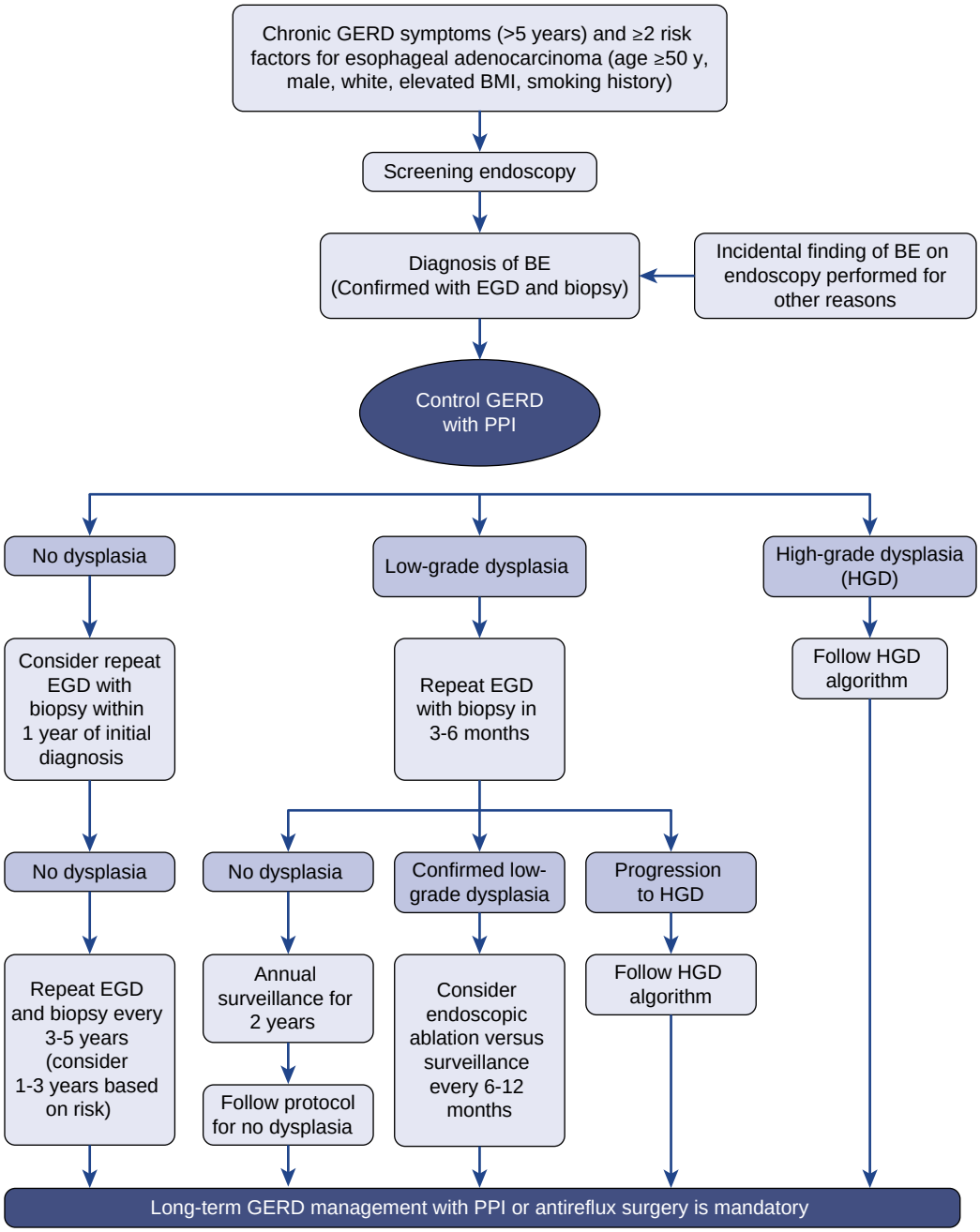


FIG. 3 Management of Barrett's esophagus. *BE,* Barrett's esophagus; *BMI,* body mass index; *EGD,* esophagogastroduodenoscopy; *GERD,* gastroesophageal reflux; *PPI,* proton pump inhibitor.

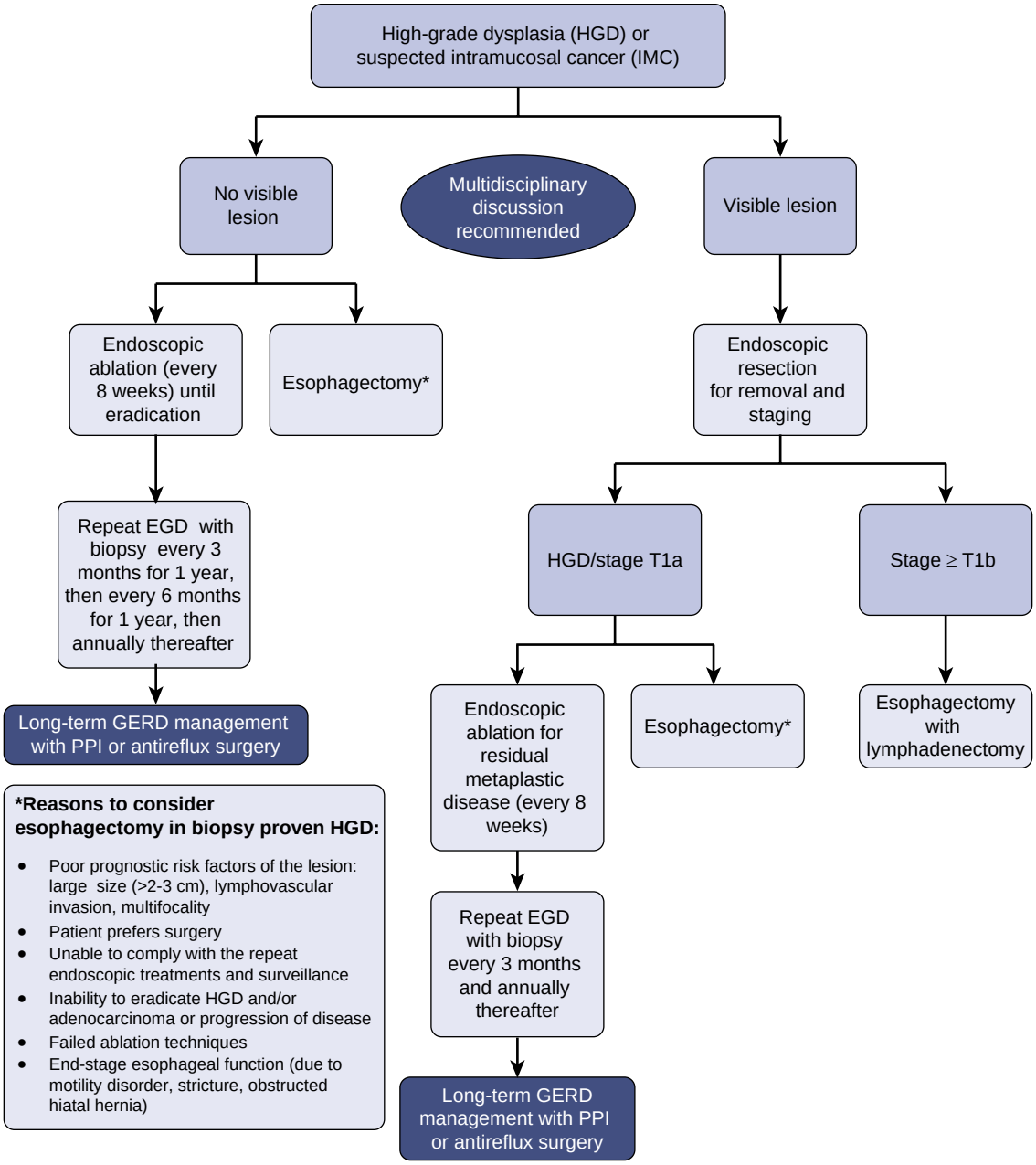


FIG. 4 Management of high-grade dysplasia and intramucosal cancer *(IMC). EGD*, Esophagogastroduodenoscopy; *GERD,* gastroesophageal reflux; *PPI,* proton pump inhibitor.

allow for preservation of the esophagus. However, there remains a role for esophagectomy in select patients with BE (Figs. 3 and 4).

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Endoscopic Treatment of Barrett's Esophagus

Anne P. Ehlers, MD, MPH, and Brant K. Oelschlager, MD

Barrett's esophagus (BE) is a disease characterized by the gradual replacement of the normal stratified squamous epithelium of the esophagus with columnar, intestinal metaplasia (Figs. 1 and 2). This transformation is due to chronic exposure to gastric contents, often within the context of gastroesophageal reflux disease (GERD). Patients at risk for BE are screened with endoscopy and biopsy. The major concern with BE is that it is a precursor lesion for esophageal adenocarcinoma (EAC), a disease with poor prognosis and poor long-term survival. In addition, EAC is a disease that continues to increase in incidence. Given this, identifying and eradicating BE before progression to adenocarcinoma is a top priority. In the past, patients with BE often were recommended for esophagectomy. More recently, evolving endoscopic techniques have replaced esophagectomy for many of these patients, allowing for eradication of BE with less morbidity and fewer complications.

SURVEILLANCE AND MANAGEMENT ALGORITHM

Screening

The primary risk factor for BE is longstanding GERD, along with male sex, age older than 50 years, and central obesity. Patients with GERD have a 10% to 15% risk of BE; increasing age and long-segment BE (>3 cm) are risk factors for progression to dysplasia. Overall, the rate of progression from BE to esophageal adenocarcinoma is low, perhaps as low as 0.12% per year. Other evidence suggests that for patients with nondysplastic BE, the annual risk of progression to EAC is 0.33% per year among all patients with BE and 0.19% per year among patients with short-segment BE (<3 cm). For patients with low-grade dysplasia (LGD), this risk increases to 0.5% per year. The risk increases substantially among those with high-grade dysplasia (HGD), up to 19% in some studies. Early detection of invasive cancer is important because patients detected at an early stage have a much higher 5-year survival rate (83%–90%) compared with patients who present symptomatically with more advanced disease (10%–30%).

Identifying the most appropriate pool of patients for screening is an area of active debate, especially with the large number of adults who have GERD. Because only a minority of patients with GERD will ever develop BE, screening every patient with GERD is neither feasible nor efficient. However, evidence suggests that surveillance of BE is associated with diagnosis of EAC at an earlier stage, which may be associated with improved outcomes. For these reasons, accurately identifying the population of patients with BE is critical. Current guidelines from the American College of Gastroenterology (ACG) recommend screening male patients with 5 or more years of GERD symptoms AND two or more risk factors for BE or EAC (age >50 years, white race, central obesity, history of smoking, family history of BE or EAC). Screening for female patients is generally not recommended, except for patients with multiple risk factors, as outlined previously.

Screening is generally undertaken using high-resolution endoscopy with liberal use of narrow band imaging and biopsy, but as previously stated this can be very labor and time intensive. Several novel screening modalities have been proposed to reduce this burden. One alternative is transnasal esophagoscopy, which is an office-based procedure that uses topical anesthetic to pass an endoscope through the nares and into the esophagus. Compared with traditional high-resolution endoscopy, the image quality is reduced and the biopsies are smaller but often are sufficient for histologic analysis to allow a diagnosis of BE to be made without a formal endoscopy. A second option for screening is the Cytosponge, which is a gelatin-coated capsule attached to a string that is then swallowed by the patient. Once in the stomach, the gelatin coating dissolves leaving behind a sponge that is then retrieved by pulling on the string. As the sponge comes back through the esophagus, it picks up cells that can then be examined for abnormalities. It currently holds promise as a screening tool for BE but is not adequate to screen for EAC. Because transnasal esophagoscopy and Cytosponge are still relatively new, high-resolution endoscopy is still the gold standard for diagnosis of BE.

Surveillance

Patients with confirmed BE in the absence of dysplasia or EAC should be regularly surveilled to detect disease progression. A challenge in the past has been lack of universal criteria for describing the extent of disease. To address this challenge, the Prague Criteria are a set of endoscopic data developed and validated by a working group specifically focused on esophagitis using standardized videos of endoscopies. The purpose was to improve on the previously used vague descriptions of "long" versus "short" segment disease and to facilitate communication between providers. The Prague Criteria measures the extent of disease based on circumference and maximum extent (C&M) criteria, with C being the maximum circumferential extent of disease and M the maximum length, including any isolated tongues of disease.

Once a patient has been diagnosed with BE, the next step is to evaluate for any dysplasia or invasive cancer. The current recommendation is to evaluate the patient with high-resolution or high-definition white light endoscopy followed by meticulous inspection of the esophageal lumen, after both insufflation and desufflation, including inspection of the gastroesophageal junction in the retroflexed view. Some data suggest that longer inspection time is associated with better detection of dysplasia or EAC. Suspicious lesions such as erosions, ulcerations, nodules, plaques, and other mucosal or luminal abnormalities should be selectively sampled. Random biopsies are not recommended. Suspicious lesions in patients with known dysplasia are best removed via endoscopic mucosal resection (EMR), which will be described later in the chapter. Additionally, the ACG recommends against taking biopsies in areas of active, erosive esophagitis and instead suggests waiting until the patient has been treated with antisecretory agents to allow the inflammation to subside.

Ongoing surveillance is dependent on the pathology determined at the time of biopsy. For patients who have BE without evidence of dysplasia, the recommendation is that they undergo repeat endoscopic surveillance every 3 to 5 years, as described previously. In cases in which biopsies are inconclusive for dysplasia, patients should be placed on an acid suppression regimen for 3 to 6 months, after which repeat endoscopy should be performed. If the biopsies are still inconclusive at that time, repeat endoscopy should be performed 12 months later. If dysplasia is diagnosed (LGD or HGD), the biopsies should be reviewed by two separate pathologists, one of whom is an expert in gastrointestinal pathology because there is a high level of interobserver variability when it comes to dysplasia.

Once dysplasia is confirmed, the next steps depend on the degree of dysplasia. For LGD, endoscopic therapy is preferred for patients without significant comorbidity; however, repeat endoscopy in 12 months is acceptable in these cases. For HGD, endoscopic therapy is recommended except in the case of life-limiting comorbid conditions. Patients with a diagnosed cancer should undergo further staging workup to determine whether the cancer is resectable, and some early adenocarcinomas can be managed endoscopically. For certain young patients with long-segment multifocal HGD, recurrent HGD, or

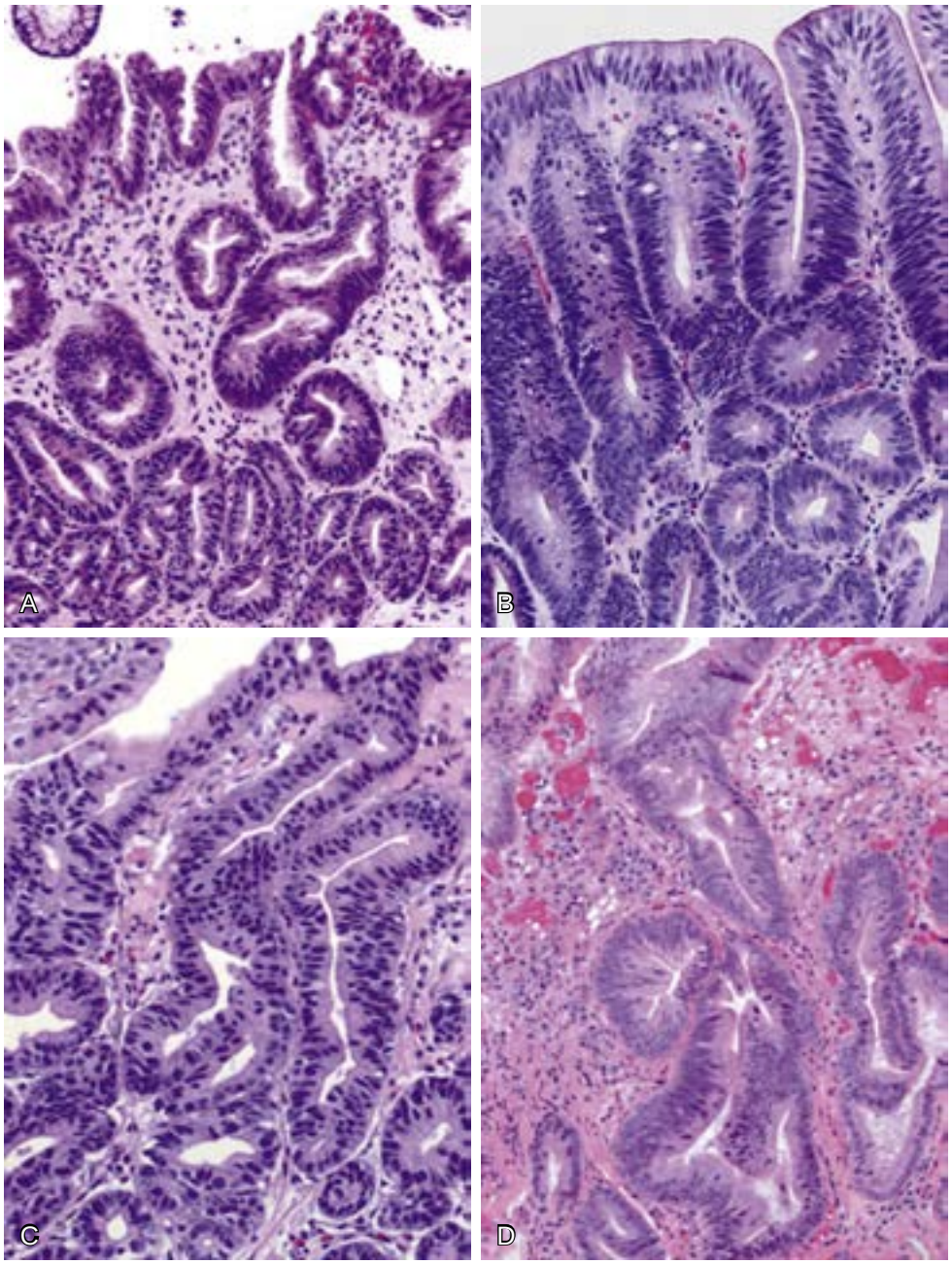


FIG. 1 Spectrum of dysplasia grading. **(A)** Negative for dysplasia. Although some nuclear hyperchromasia is noted, it is limited to the normal proliferative zone with evidence of surface maturation. **(B)** Low-grade dysplasia shows basally oriented, hyperchromatic nuclei with pseudostratification. Crypt architecture is preserved. **(C)** High-grade dysplasia demonstrates prominent mitotic activity, enlarged nuclei, and loss of nuclear polarity with evidence of glandular crowding. **(D)** This lesion shows cytoarchitectural atypia, equivalent to that of low-grade dysplasia, in the deep glands. However, given the presence of surface maturation and the stromal changes suggestive of a reparative process, it is best classified as indefinite for dysplasia. *(From Hagen CE, Lauwers GY, Mino-Kenudson M. Barrett esophagus: diagnostic challenges. Semin Diagn Pathol. 2014;32:100–113.)*

intramucosal cancer, surgery should be considered. A summary of the surveillance and treatment algorithm is provided in Figures 3 and 4.

PRINCIPLES OF ENDOSCOPIC THERAPIES

The current evidence suggests that endoscopic therapy should be used for patients with BE who have LGD, HGD, and for some patients with early intramucosal (T1a) EAC because the risk of lymph node metastasis is nonexistent for LGD and HGD and is low for intramucosal EAC. Endoscopic techniques work by either removing it before development of invasive disease or destroying abnormal tissue (ablative techniques). The intestinal metaplasia is then replaced with normal appearing squamous epithelium (Fig. 5).

ENDOSCOPIC RESECTION TECHNIQUES

Endoscopic Mucosal Resection

EMR is a technique that allows removal of lesions within segments of BE for complete histologic analysis, including dysplasia and superficial T1a adenocarcinoma. It offers an advantage over ablative techniques because it allows for examination of tissue specimens, rather than just destroying them. The ACG recommends EMR as the initial treatment modality for patients with nodular BE. For patients

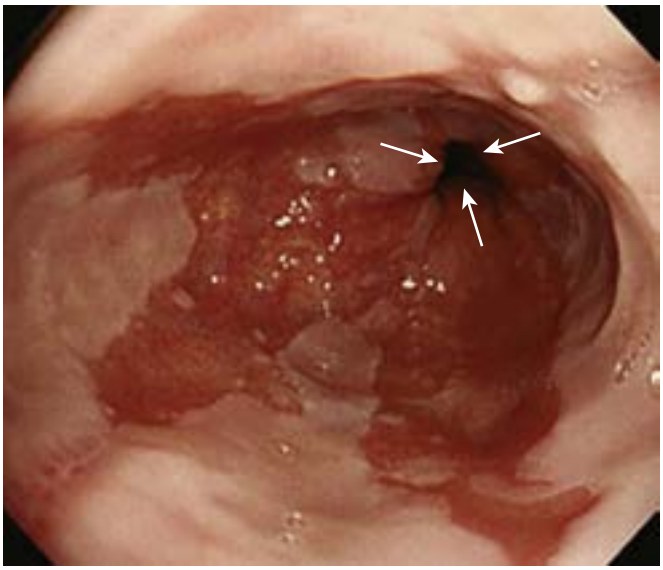


FIG. 2 Endoscopic image of Barrett's esophagus. The arrows mark the esophagogastric junction, which is identified endoscopically as the most proximal extent of the gastric folds. The reddish color and velvet-like texture of the Barrett's epithelium contrast sharply with the pale and glossy appearance of the esophageal squamous epithelium. Note that the Barrett's columnar epithelium extends well above the esophagogastric junction to line the distal esophagus. *(From Spechler SJ, Souza RF. Barrett's esophagus. In: Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: Elsevier; 2016.)*

without high-risk features (submucosal invasion, poor differentiation, or lymphatic vascular invasion), EMR has 98.8% eradication rate of BE; in patients with high-risk features, the rate is 80.6%. For T1a tumors, EMR has a 91% to 98% eradication rate.

There are several methods used for EMR. In the cap-assisted method, the endoscope is fitted with a transparent cap. Once located, the target lesion is sucked into the cap and a specialized electrocautery snare is used to resect the lesion. A submucosal injection can be performed to facilitate this. In the ligation-assisted method, lesions are removed using a band-ligation device attached to the tip of the endoscope. Once identified, the target lesion is again sucked into the endoscope and the band is applied around the lesion to create a pseudopolyp. Electrocautery is then used to remove the pseudopolyp. In the injection-assisted technique, the submucosal space is injected to lift the lesion and allow it to be snared and cut.

One of the primary side effects of EMR is esophageal stricture, which occurs in up to 40% of patients. Typically, these lesions can be managed with endoscopic dilation or stents. EMR is often used in conjunction with radiofrequency ablation (RFA) with good effect. In a recent systematic review, EMR alone had a 33.5% risk of stricture, 7.5% risk of bleeding, and 1.3% risk of perforation compared with 10.2%, 1.1%, and 0.2%, respectively, in patients undergoing EMR in conjunction with RFA.

Endoscopic Submucosal Dissection

Endoscopic submucosal dissection (ESD) is a technique that allows for complete, en bloc resection of suspicious lesions to allow for thorough histologic evaluation. When compared with EMR, it also

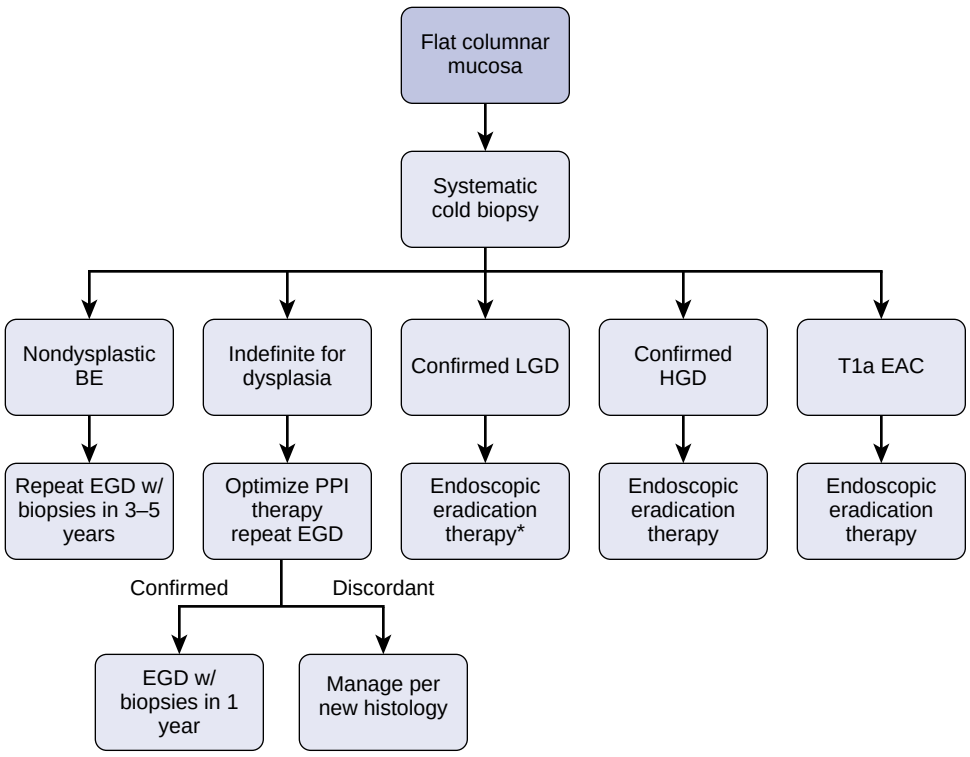


FIG. 3 Management of nonnodular Barrett's esophagus (BE). *Although endoscopic eradication therapy is associated with a decreased rate of progression, surveillance upper endoscopy at 1-year intervals is an acceptable alternative. This algorithm assumes that the T1a esophageal adenocarcinoma (EAC) displays favorable characteristics for endoscopic therapy, including well-differentiated histology and lack of lymphovascular invasion. *HGD,* High-grade dysplasia; *LGD,* low-grade dysplasia; *PPI,* proton pump inhibitor. *(From Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus.* Am J Gastroenterol. *2016;111:30–51.)*

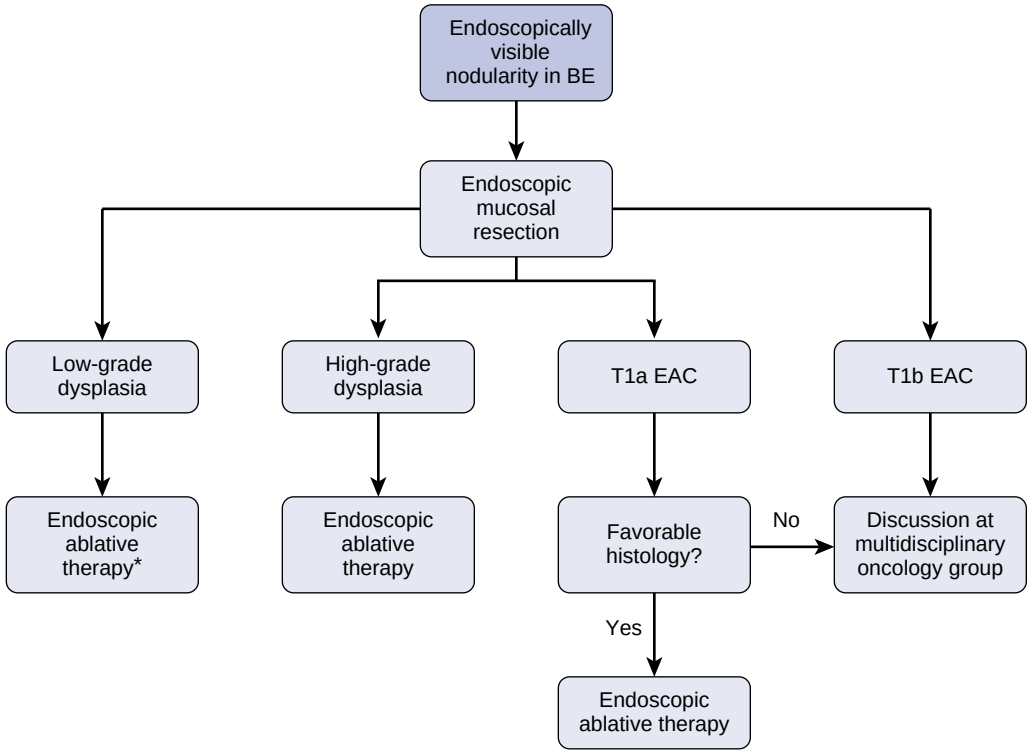


FIG. 4 Management of nodular Barrett's esophagus (BE). *Little data exist on the clinical course of patients with low-grade dysplasia (LGD) managed by endoscopic surveillance following endoscopic mucosal resection (EMR), although this is an alternative treatment strategy. Endoscopic submucosal dissection is an alternative to EMR. Favorable histology consists of no lymphatic or vascular invasion and moderate to well-differentiated disease. *EAC*, Esophageal adenocarcinoma. *(From Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus.* Am J Gastroenterol. *2016;111:30–51.)*

allows for complete resection of lesions, rather than having to resect lesions in a piecemeal fashion, especially for larger lesions (>1.5–2 cm). The primary indication for ESD is resection of nodular lesions within a segment of BE to allow for complete histologic evaluation. Given the relative technical difficulty of this procedure, as well as the concern for significant adverse events, it is not as widely used. The ACG recommends that ESD only be performed in centers of clinical expertise.

The technique of ESD involves first marking the area of resection with coagulation. The submucosal space of the marked area is then injected with a saline solution to lift the area, and finally ESD resection knives are used to incise the mucosa and perform the submucosal dissection.

Most of the available data on ESD is from Europe or Asia, but a recent multicenter study performed in the United States showed that en bloc resection occurred in 95.7% of patients with a median resection size of 45 mm. Nearly half of patients required admission after the procedure, either for routine observation or for pain control. An R0 resection was achieved in 76.1%, and the overall cure rate was 69.6%. More than two-thirds of patients in this study were found to harbor EAC in the resected specimen, resulting in histologic upstaging in more than half of all patients. Adverse events occurred in 23.9% of patients, including bleeding (6.5%), perforation (2.2%), and esophageal stricture (15.2%). All adverse events were managed endoscopically.

These results were confirmed by a recent meta-analysis demonstrating that ESD has a 92.9% success rate of achieving en bloc resection, a 74.5% rate of achieving an R0 resection, and a 64.9% rate of achieving curative resection. Bleeding occurred in 1.8% of patients, and 1.5% of patients sustained esophageal perforation. Both the bleeding and perforation events were managed endoscopically. Overall esophageal stricture rate was 11.6%; these were managed with endoscopic dilation. The total rate of immediate and delayed adverse events was 4.95%.

ENDOSCOPIC ABLATION TECHNIQUE

Photodynamic Therapy

Photodynamic therapy (PDT) involves administration of a systemic photosensitizing agent that is taken up preferentially by neoplastic tissues. The photosensitizing agent then produces cytotoxicity after exposure to an appropriate wavelength and power of light, specific to the photosensitizing agent. The two most widely available photosensitizing agents are Photofrin and 5-aminolevulinic acid. Randomized trial data indicate that complete ablation of HGD can be achieved in 77% of patients with PDT, and 52% of patients had complete replacement of all BE tissue with normal squamous epithelium.

There is a relatively high complication rate associated with PDT. Because of its systemic administration, the photosensitizing agents can predispose to cutaneous photosensitivity similar to a sunburn in more than two-thirds of patients. Other complications include odynophagia, constipation, vomiting, noncardiac chest pain, dehydration, dysphagia, and stricture formation (up to 36% in some studies). This was the first effective ablation technique, but because of the relatively high complication rate, PDT is no longer widely used.

Argon Plasma Coagulation

Argon plasma coagulation (APC) uses a beam of argon gas to conduct an electrical current, resulting in a noncontact form of thermal electrocoagulation. The depth of necrosis is relatively shallow (2–3 mm) and can be useful in conditions such as BE that involve the mucosa. In the initial randomized controlled trial (RCT) conducted by Ackroyd et al., after a median of three treatments, patients treated

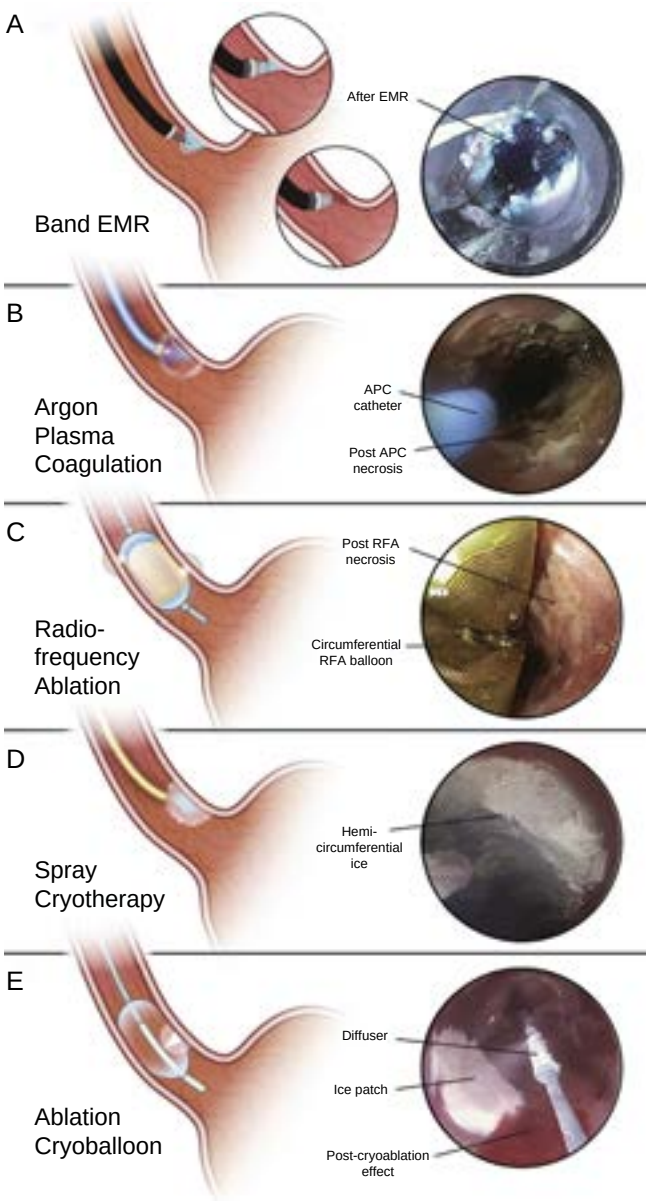


FIG. 5 Endoscopic techniques for eradication of esophageal early neoplasia. **(A)** Band endoscopic mucosal resection involves suction and ligation (banding) of a target lesion, with or without prior submucosal injection, followed by resection using snare polypectomy technique. Endoscopic photo shows the endoscopic view of the submucosa through the banding device after complete resection of well-differentiated adenocarcinoma. **(B)** Argon plasma coagulation (APC) involves conduction of heat energy with argon gas to the mucosa. Endoscopic image shows the APC catheter and white coagulation necrosis of treated BE mucosa. **(C)** Radiofrequency ablation (RFA) involves the application of a preset amount of heat energy (12 J) through electrodes on a circumferential (Halo 360) ablation catheter inflated to make contact with the esophageal mucosa. Endoscopic image of post-RFA necrosis. **(D)** Liquid nitrogen spray cryotherapy involves release of liquid nitrogen that expands to gas and freezes large areas of tissue to −196°C. The dosing of liquid nitrogen cryogen has varied from 15 to 20 seconds of ice, followed by a timed minimum 45 seconds of thaw, and repeated for three cycles. Endoscopic image of a hemicircumferential patch of ice on the esophageal mucosa. **(E)** The cryoballoon ablation system includes a portable handheld reusable controller that delivers nitrous oxide gas into a low-pressure compliant, 30 mm, oval-shaped balloon at the end of a disposable balloon catheter passed through the endoscope channel. The balloon at the end of the catheter is inflated and simultaneously cooled by the gas expansion. The cryogen is directed toward a specific location by rotation of the diffuser. Endoscopic image shows the endoscopic view through the cryoballoon with a focal ice patch and thawed treated mucosa with post cryotherapy red color change. *EMR,* endoscopic mucosal resection. *(From di Pietro M, Canto MI, Fitzgerald RC. Endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus: screening, diagnosis, and therapy.* Gastroenterology. *2018;154:421–436.)*

with APC achieved complete macroscopic ablation 60% of the time, with the remaining patients achieving a significant decrease in the size of their BE. At the 1-year follow-up, 58% of patients had no macroscopic evidence of disease compared with only 15% in the surveillance group. At 5-year follow-up, 70% of patients in the APC group had sustained at least a 95% reduction in the surface area of BE, and 40% had no histologic or macroscopic disease compared with only 25% and 15%, respectively, in the surveillance group.

There were no early complications, and long-term complications included strictures that were managed with endoscopic dilation.

Other reported complications include chest pain, odynophagia, ulceration, bleeding, perforation, and death. One advantage of APC is that the equipment is widely available and is relatively inexpensive. However, as noted in the RCTs, it often requires multiple treatments over time to achieve regression of disease.

Cryotherapy

Cryotherapy directly destroys tissue by freezing it, resulting in both immediate and delayed tissue destruction. There are several cryotherapy systems available, but the most widely studied is liquid nitrogen. In a retrospective study of patients treated with liquid nitrogen, Shaheen et al. found that after an average of four treatments, 97% of patients had resolution of HGD, 87% had resolution of intestinal dysplasia, and 57% had resolution of intestinal metaplasia. There were no serious complications, but 3% of patients developed strictures that were managed with endoscopic dilation.

At the 5-year follow-up, 93% of patients had complete resolution of high-grade dysplasia, 88% had resolution of dysplasia, and 75% had resolution of intestinal metaplasia, although some of these patients underwent "touch-up" therapy after the initial round of treatment. As with other endoscopic methods of treatment, ongoing endoscopic surveillance is required.

One advantage of cryotherapy is that it can be used both as a first-line treatment for BE with dysplasia and as a second-line treatment in patients who have failed other treatments. As with other therapies, however, it often requires multiple treatments to completely eradicate disease. In a recent review of liquid nitrogen cryotherapy, the complication rate ranged from 0% to 3% with the most frequent complication being pain requiring narcotics (10% of patients), followed by stricture requiring dilation (up to 9%), then bleeding and perforation.

Radiofrequency Ablation

The most commonly used ablative technique is RFA. Using either a balloon catheter or a focal catheter, a generator and a bipolar electrode array deliver a fixed amount of thermal energy, resulting in a uniform burn to a depth of 0.5 mm. RFA can be performed in the outpatient setting and is targeted as either a circumferential ablation (using the balloon catheter) or a focal ablation (using the focal catheter). Circumferential ablation is for circumferential segments of BE that are longer than 2 cm, whereas focal ablation is for shorter segments, or tongues, of BE. After treatment, follow-up is recommended in approximately 2 months, and often multiple sessions of RFA are required to achieve complete eradication of dysplasia, with close follow-up following eradication.

In an RCT comparing RFA with sham endoscopy, complete eradication of LGD occurred in 90.5% of patients and complete eradication of HGD occurred in 81% of patients following RFA, compared with only 22% and 19% in the sham group, respectively. Among all patients, RFA completely eradicated evidence of intestinal metaplasia in 77.4%, compared with only 2.3% in the control group. All these results were statistically significant. There is a known rate of progression to esophageal cancer, and in this study 19% of patients with HGD progressed to cancer over a 1-year timeframe. At 2-year follow-up, these results were found to be durable: complete eradication of dysplasia occurred in 95% of patients, and complete eradication of intestinal metaplasia occurred in 93% of patients; results were similar at 3-year follow-up.

The primary side effects of RFA are chest pain and dysphagia lasting up to 4 days, and strictures occur in up to 8% of patients. Bleeding is rare. No deaths have been reported following RFA. RFA is the preferred therapy for nonnodular BE.

CONCLUSION

The management of BE continues to evolve as new technology and more effective treatments become available. Compared with esophagectomy, endoscopic techniques have the advantage of being less invasive with fewer complications; however, in all cases, it is important to ensure that the correct technique is being used, which requires a baseline understanding of each technique. In general, patients with nodular disease should have this resected, and patients with early esophageal cancer should be referred for discussion at a multidisciplinary cancer group or tumor board to discuss alternative therapies to endoscopic ones.

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Management of Paraesophageal Hernia Repair

Richard J. Battafarano, MD, PhD

The most common acquired diaphragmatic hernia is the hiatal hernia. Widening of the esophageal hiatus and weakening of the phrenoesophageal ligament is associated with herniation of the stomach and other intraabdominal organs through the hiatus and into the mediastinum. Many patients are noted to have hiatal hernias with minimal symptoms. However, the most common symptoms associated with hiatal hernia are gastroesophageal reflux disease (GERD) and early satiety. Patients who develop abdominal pain after eating or who present with anemia in the setting of a hiatal hernia often have larger paraesophageal hernias with at least partial organo-axial volvulus of the stomach. Patients with these symptoms are at greater risk for the potentially lethal consequences of complete volvulus, strangulation, incarceration, and perforation. Paraesophageal hernias are classified into four types (Box 1) based on the location of the esophagogastric junction (EGJ) and the herniated abdominal contents. Type I hiatal hernias are the most common; they account for 90% to 95% of all hernias and most frequently present with GERD. Patients with type II, type III, and type IV paraesophageal hernias often present with the additional symptoms of early satiety, anemia, and postprandial abdominal or chest pain, vomiting, dysphagia, and weight loss.

BOX 1 Classification of Paraesophageal Hernias

Type I: The esophagogastric junction (EGJ) herniates above the diaphragm into the mediastinum ("sliding hernia").
Type II: A portion of the stomach is herniated into the mediastinum alongside a normally positioned (i.e., intraabdominal) EGJ.
Type III: The EGJ is above the hiatus, and a portion of the stomach is folded alongside the esophagus.
Type IV: An intraabdominal organ other than the stomach also is herniated through the hiatus.

SURGICAL INDICATIONS AND PREOPERATIVE EVALUATION

The indications for surgery in patients with paraesophageal hernia depend on the severity of the patient's symptoms and the patient's other comorbid medical conditions. Patients with paraesophageal hernias whose symptoms are well controlled on acid suppression medications and who do not have dysphagia, weight loss, or pain may be followed closely and do not require immediate repair of the paraesophageal hernia. However, patients with other symptoms should be thoroughly evaluated before proceeding with paraesophageal hernia repair. As part of the evaluation for patient's symptoms, many will have either a contrast esophagram (Fig. 1) or a computed tomography (CT) scan (Fig. 2) at the time of presentation. Although these two radiographic studies often complement one another, the current thin-cut CT scans, with coronal and sagittal reconstructions, are quite helpful for delineating the anatomy of the paraesophageal hernia and for determining if additional organs have also herniated into the mediastinum (type IV paraesophageal hernia). An upper endoscopy is important to determine the presence of esophagitis, gastritis, Cameron ulcers, and peptic ulcer disease and to rule out malignancy. Esophageal manometry is very important in patients with type I and type II paraesophageal hernias to assess esophageal motility, which will guide the decision for the appropriate fundoplication at the time of the paraesophageal hernia repair. The use of esophageal manometry in patients with large type III or type IV paraesophageal hernias is often quite difficult to accurately perform because the catheters often curl in the esophagus or herniated stomach, limiting the data that can be obtained. In these patients, a partial fundoplication should be performed. The use of pH testing in patients with paraesophageal hernia does not usually add significant information in patients whose EGJ is above the diaphragm. However, pH monitoring is critically important in patients who have significant symptoms of gastroesophageal reflux disease without the presence of a paraesophageal hernia.

SURGICAL TECHNIQUE

Type I and type II paraesophageal hernias can almost always be successfully repaired using the laparoscopic technique. Laparoscopic repair of these hernias has been associated with decreased operative morbidity, especially when compared with thoracotomy. However, the choice of operation for large type III and type IV paraesophageal hernias is somewhat more controversial. Patients with more advanced type III and type IV paraesophageal hernias often develop dense adhesions between the hernia sac and the pericardium, lung, and even the airway itself. Dissecting the sac and its contents away from these structures often results in pneumothorax with subsequent loss of pneumoperitoneum and subsequent visualization. In addition, visualizing the structures above the level of the inferior pulmonary veins becomes much more difficult using a laparoscopic approach. In these large paraesophageal hernias, open repair using either an upper midline laparotomy or a left thoracotomy may be more efficacious. Other relative indications for open repair rather than laparoscopic repair of paraesophageal hernias include a previous paraesophageal hernia repair (especially if mesh was used at the hiatus), extension of the paraesophageal hernia into one or both pleural spaces, and proximal extension of the paraesophageal hernia to the level of the carina.

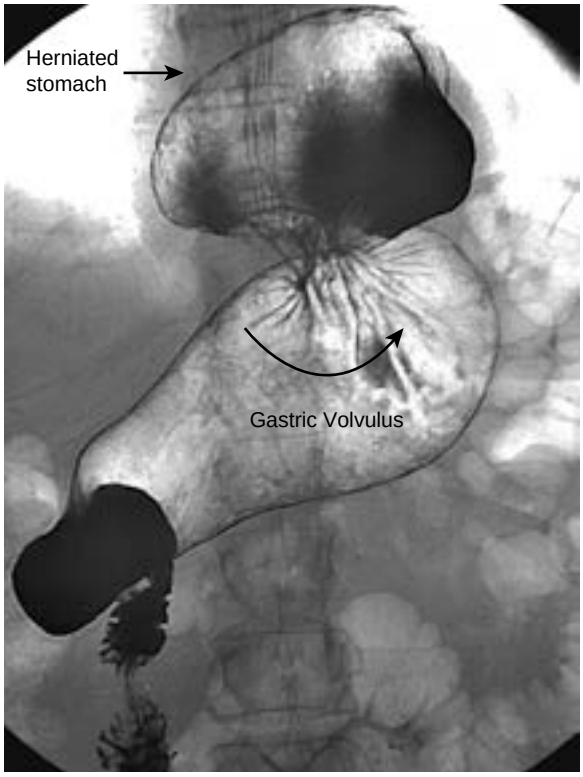


FIG. 1 Barium esophagram showing a large paraesophageal hernia with a gastric volvulus.

Laparoscopic Repair of Paraesophageal Hernias

Positioning of the Patient and Placement of Ports

After adequate general anesthesia has been performed, a nasogastric tube is placed to decompress the stomach. Although many surgeons utilize the low lithotomy position for this procedure, we have chosen to keep the patient in the supine position with a footboard to allow the steep reverse Trendelenburg position. A total of five ports are used for the procedure: one for the camera (port 1, 10 mm); two for the operating surgeon (port 4, 10 mm; port 5, 5 mm); one for the assistant (port 2, 5 mm); and one for the liver retractor (port 3, 5 mm). The first port is usually placed in the midline approximately 14 cm below the xiphoid process and is utilized for the camera. We prefer to place this port via an open technique to minimize the risk of injuring any intraabdominal contents upon entry. The remaining ports are all carefully placed under direct vision (Fig. 3). At the completion of the procedure, the fascia around each of the two 10-mm ports is closed with absorbable suture to decrease the risk of port site hernias.

Dissection and Reduction of the Hernia Sac

We begin by opening the gastrohepatic ligament up to the level of the right crus of the diaphragm. Great care is taken to identify the presence of a replaced or accessory left hepatic artery. If one of these is identified during this portion of the dissection, they are encircled

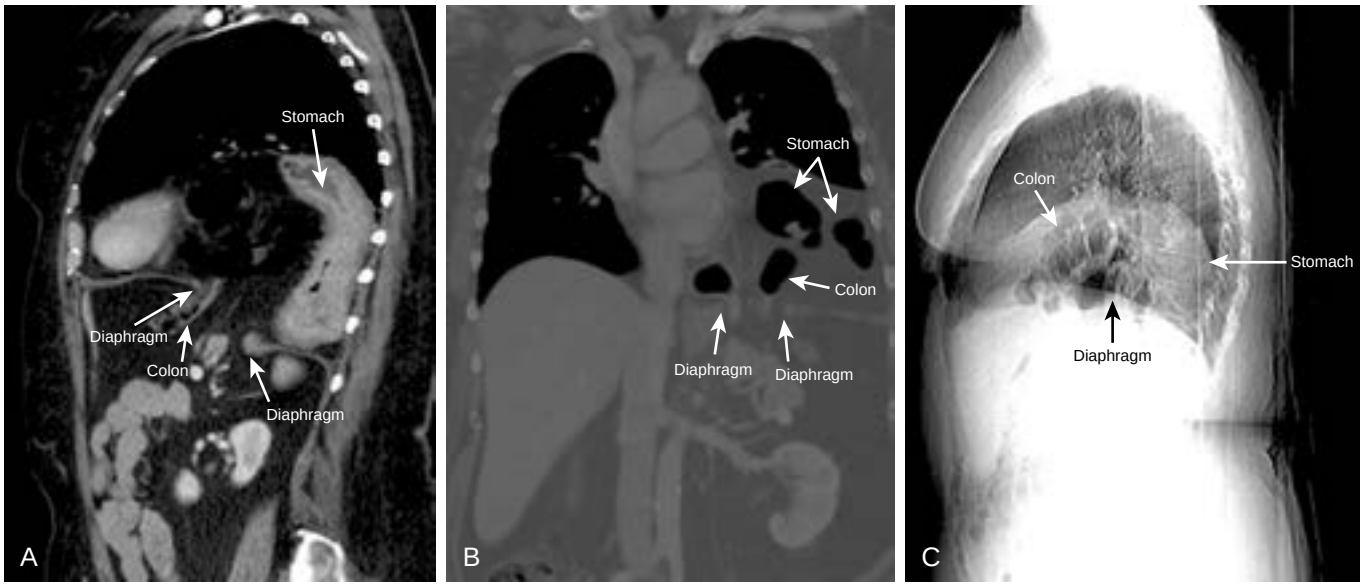


FIG. 2 CT scans showing a type IV paraesophageal hernia.

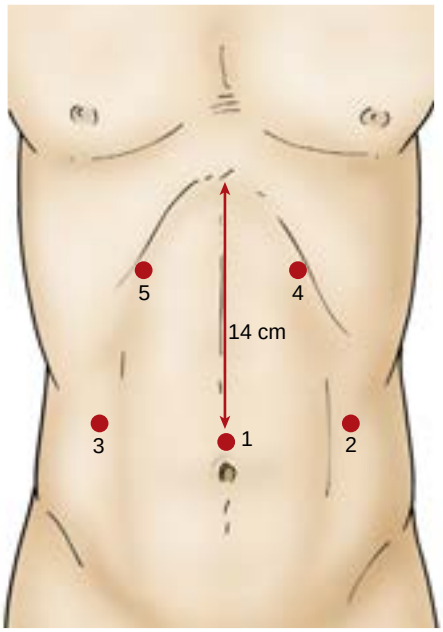


FIG. 3 Port placement for laparoscopic paraesophageal hernia repair. *(From Patti MG, Fisichella PM. Laparoscopic paraesophageal hernia repair. How I do it.* J Gastrointest Surg. *2009;13:1728-1732.)*

with a vessel loop and gently retracted during the remainder of the dissection and creation of the fundoplication. The periesophageal tissues are then dissected away from the right crus, and the anterior and posterior vagus nerves are identified. This dissection is then continued anteriorly to dissect the sac away from the pericardium and extended to the left crus of the diaphragm. The hernia sac is then dissected away from the left crus of the diaphragm exposing the posterior aspects of both the right and left crura just above the aorta. The posterior dissection is completed allowing the herniated stomach and the hernia sac to be reduced into the abdomen, and the esophagus is encircled in the lower mediastinum with a Penrose drain. Mobilization of the hernia sac and its contents in this manner decreases the amount of force applied to the stomach during this step of the procedure and greatly reduces the risk for gastric injury or perforation. With the stomach reduced into the abdomen, we mobilize the greater curvature of the stomach, dividing all of the short gastric vessels using a harmonic scalpel. Our focus on removing the entire hernia sac during the procedure often results in small tears in the pleura, creating capnothorax with associated hypotension or increased airway pressure. Reduction of the insufflation pressure and close cooperation between the surgical and anesthesia teams almost always allows completion of these procedures laparoscopically without conversion to laparotomy.

Esophageal Mobilization and Lengthening

The hernia sac is then resected taking great care to preserve both vagus nerves, and the EGJ is identified. The mediastinal dissection is extended proximally by dividing the small esophageal arterial branches using the harmonic scalpel. The dissection is continued up into the mediastinum to achieve at least 3 cm of intraabdominal esophagus. It is quite helpful to decrease the insufflation from 15 mm Hg to 8 mm Hg and to not utilize any caudal traction of the stomach at this time so an accurate measurement of intra-abdominal esophagus can be achieved. Once an accurate measurement of intra-abdominal esophagus has been made, the insufflation is returned to 15 mm Hg, and attention is directed toward posterior approximation of the right and left crura.

Closure of the Esophageal Hiatus

Retraction of the esophagus upward and toward the patient's left with the Penrose drain optimizes visualization of the posterior right and left crura. Interrupted 0 Ethibond sutures are placed to reapproximate the posterior right and left crura just above the aorta using a laparoscopic needle driver through the left upper quadrant 10-mm port. Although many surgeons perform intracorporeal knot tying, we prefer to utilize the Ti-KNOT. It is important to accurately space these posterior crural sutures on each crus because the left crus is often much longer than the right crus. In addition, it is important for the surgeon to carefully place these sutures, being mindful that both the aorta and inferior vena cava are in close proximity to the posterior crura. Before the last crural sutures are tied, a 52F or 56F bougie is carefully inserted down the esophagus, and there should be room for a closed grasper to easily slide between the esophagus and crura. Although there was initial enthusiasm for the use of biologic mesh for reinforcement of the crural closure, more recent studies have demonstrated that the long-term recurrence rates are

similar between cruroplasty alone versus cruroplasty with biologic mesh. However, the overall morbidity seems to be higher in patients repaired with nonabsorbable mesh.

Creation of the Fundoplication

For a Nissen (360-degree) fundoplication, the 56F bougie remains in the lumen of the esophagus, and the fundus of the stomach is passed behind the esophagus, taking great care to ensure sufficient mobilization to avoid having part of the gastric fundus above the wrap. A total of three 2-0 Ethibond sutures are used to create the Nissen fundoplication. Each stitch is placed through the seromuscular wall of the stomach on the left side of the fundus, the muscular wall of the esophagus, and the right side of the fundus at 1-cm intervals. At the completion of the fundoplication, the anterior portion of the fundoplication should be approximately 2 cm in length and should sit comfortably below the hiatus. Many surgeons place sutures between the superior aspect of the wrap and the right and left sides of the crural closure, creating a gastropexy to anchor the wrap below the hiatus (Fig. 4). It is critical that the wrap is not created under tension.

When the patient's esophageal motility will not allow a Nissen fundoplication, a Toupet fundoplication (posterior 240-degree fundoplication) is created by placing a total of six 2-0 Ethibond sutures. Three are placed through the seromuscular right and left sides of the fundus and are separately sutured to the right and left sides of the muscular wall of the esophagus, leaving 120 degrees of the anterior esophageal wall uncovered (Fig. 5).

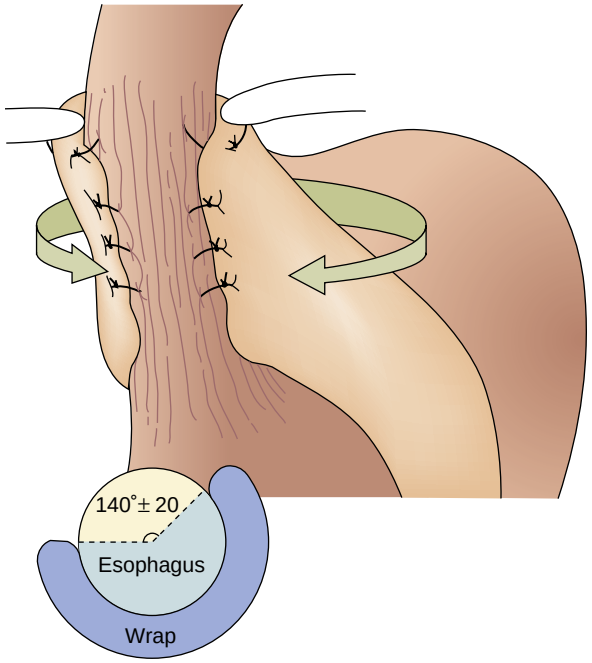


FIG. 5 Crural repair and partial posterior fundoplication. *(From Townsend CM, Beauchamp RD, Evers BM, Mattox KL.* Sabiston Textbook of Surgery. *20th ed. Philadelphia: Elsevier; 2017.)*

Open Repair of Large Paraesophageal Hernias

Repair through an Upper Midline Laparotomy

Although a number of surgeons will repair large paraesophageal hernias (type III and type IV) and reoperative paraesophageal hernias using laparoscopic and/or a combination of laparoscopic and thoracoscopic techniques, operative times are longer, and the risk for complications such as gastric or esophageal perforation is higher. For this reason, we often repair large paraesophageal hernias and reoperative paraesophageal hernias through a limited upper midline laparotomy. The postoperative morbidity of an upper midline laparotomy is minimal and offers a number of advantages over a difficult laparoscopic dissection. First, without utilizing insufflation, entrance into either the left or right pleural space as part of resection of the sac does not negatively affect or limit the ability to complete the procedure. Reduction of the sac and its contents from the mediastinum or the pleural space can often be performed more gently with one's hands in comparison with using Babcock or other laparoscopic clamps, and complete resection of the sac can be accomplished in all cases. Because large paraesophageal hernias are more likely to be associated with an EGJ that does not comfortably sit 3 cm below the hiatus despite extensive proximal mobilization of the hiatus, accurate assessment of esophageal length and the creation of esophageal lengthening procedures such as a Collis gastroplasty or a fundic wedge gastroplasty are more easily performed. In reoperative cases, takedown of the adhesions from the previous repair can be more safely achieved, especially when mesh was utilized at the time of the primary repair. CT images of a representative large type III paraesophageal hernia performed through an upper midline laparotomy are shown (Fig. 6).

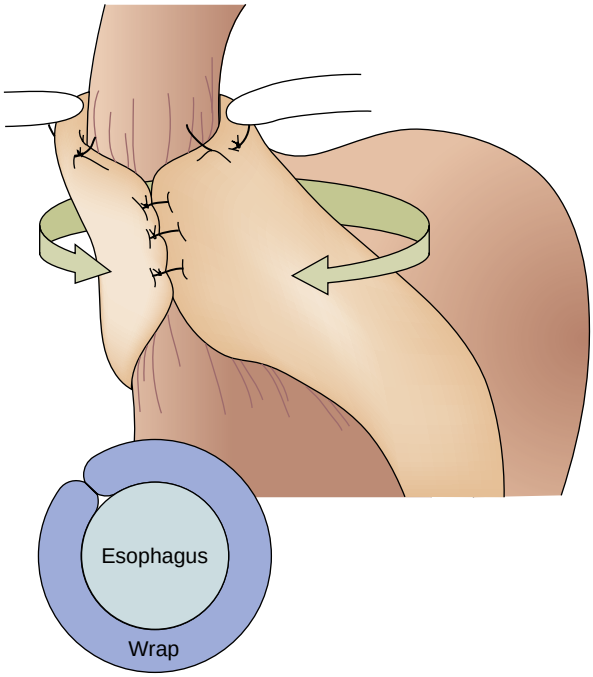


FIG. 4 Crural repair and total 360-degree fundoplication. *(From Townsend CM, Beauchamp RD, Evers BM, Mattox KL.* Sabiston Textbook of Surgery. *20th ed. Philadelphia: Elsevier; 2017.)*

Upper abdominal exposure is achieved using a standard bookwalter retractor system, and the steps of the operation are performed exactly as described earlier. When an esophageal lengthening procedure is necessary, it is performed over a 56F bougie using an endoscopic stapler with a closed staple height of 2 mm. A Toupet fundoplication is performed (instead of a Nissen fundoplication) to prevent postoperative dysphagia.

Repair through a Left Thoracotomy

Historically, the transthoracic repair of paraesophageal hernias was the standard approach for patients with this disease led by Dr. David Skinner and Dr. Ronald Belsey. Because of the increased postoperative pain associated with a thoracotomy, procedures performed using laparoscopy or through an upper midline laparotomy are currently preferred. However, transthoracic repair of large paraesophageal hernias still has a role in the care of patients with this disease (Fig. 7).

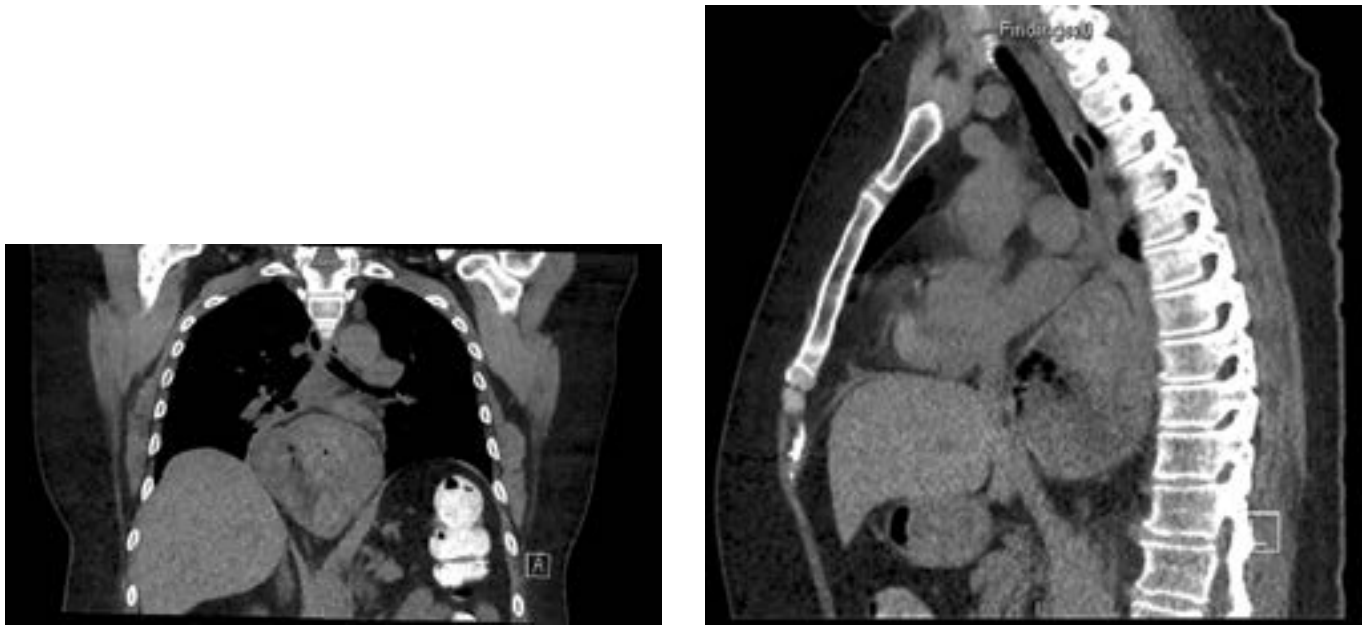


FIG. 6 Coronal and sagittal images of a large type III paraesophageal hernia extending up proximally in the mediastinum up to the level of the pulmonary veins.

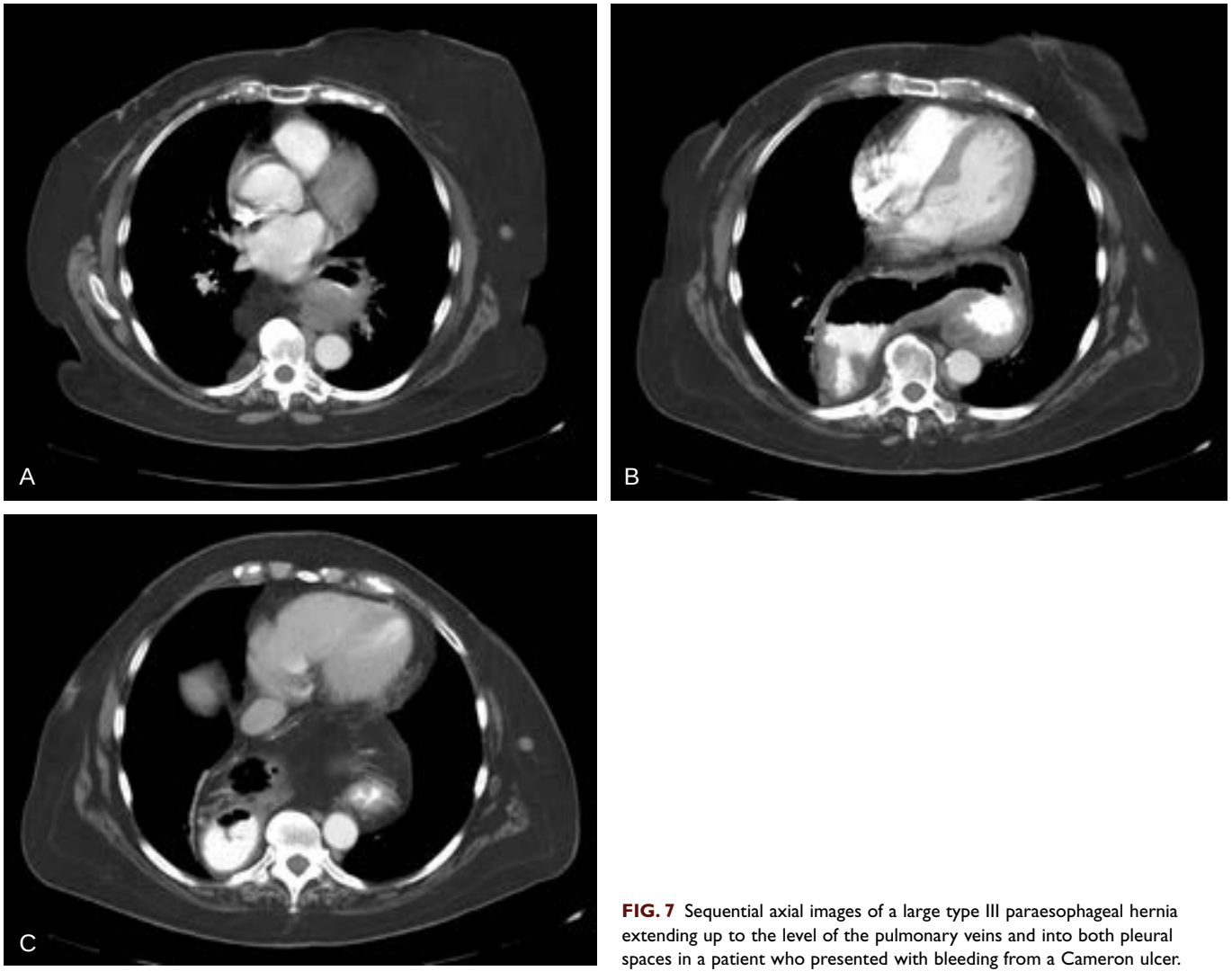


FIG. 7 Sequential axial images of a large type III paraesophageal hernia extending up to the level of the pulmonary veins and into both pleural spaces in a patient who presented with bleeding from a Cameron ulcer.

Transthoracic repair allows the surgeon to more easily divide dense adhesions between the hernia sac and its contents from the lungs and pericardium. It also allows the esophagus to be mobilized up to the level of the aortic arch behind the carina, generating maximal tension-free esophageal length. In the rare cases in which this degree of esophageal mobilization does not achieve enough length to allow the EGJ to sit comfortably below the hiatus, a Collis gastroplasty can be easily performed. Although the traditional fundoplication utilized by Skinner and Belsey was the Belsey Mark IV repair (270-degree fundoplication), this procedure can be conceptually more difficult to understand and to teach to others. Therefore, a standard Toupet fundoplication can be created in the left chest and then returned to the abdomen before tying the final two posterior crural approximation stitches to complete the repair.

POSTOPERATIVE CARE

No matter which surgical approach is utilized, patients are extubated immediately after the completion of the procedure. Nasogastric tubes are not necessary for patients with type I or type II paraesophageal hernias. However, patients with type III and type IV paraesophageal hernias often have significant gastric distension and benefit from tube decompression. I obtain a contrast esophagram on the first postoperative day to ensure flow of contrast through the fundoplication and to ensure gastric emptying. Patients are discharged on full liquids and a limited soft diet until they are seen at follow-up in approximately 2 weeks. Although patients whose repair was performed through a midline laparotomy or a left thoracotomy initially have more incisional pain, complete recovery and return to work is achieved in approximately 4 weeks.

OUTCOMES

Laparoscopic and open repair of paraesophageal hernias is associated with excellent recovery and long-term symptom relief. The choice between laparoscopic and open repair depends on the paraesophageal type and the patient's previous surgical history. Many series have demonstrated a relatively high radiographic recurrence rate. However, the need for reoperation remains quite low, especially in patients initially treated for type I and type II paraesophageal hernias.

ACKNOWLEDGMENTS

I recognize the authors of this chapter in the previous editions, as I have revised and updated their excellent work.

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MANAGEMENT OF ZENKER'S DIVERTICULUM

Fernando A.M. Herbella, MD, Riccardo Rosati, MD, and Marco G. Patti, MD

GENERAL CONSIDERATIONS

Zenker's diverticulum is a rare disease that occurs in the pharyngoesophageal area. It is a pulsion pseudodiverticulum because it is composed of mucosa only and not all wall layers. A large proportion of patients with esophageal diverticula are asymptomatic. Dysphagia is the most common symptom, but regurgitation, weight loss, chest pain, halitosis, and aspiration are also common complaints.

PATHOPHYSIOLOGY

Pharyngoesophageal diverticulum occurs in areas of muscular gap at the transition of the cricopharyngeal, inferior constrictor of the pharynx and esophageal intrinsic muscles. Three separate weak areas have been described (Laimer's, Killian's, and Killian-Jamieson's triangles); however, even though there are different eponyms for the diverticula in each area, they are usually collectively called *Zenker's diverticulum* and are similarly treated because of their proximity and pathophysiology (Fig. 1).

An altered motility of the upper esophageal sphincter is necessary to create a high-pressure zone and force the mucosa through these areas of weakness. Gastroesophageal reflux disease (GERD) is associated in up to 95% of patients, and this association may be related to esophageal longitudinal muscles reflex contraction and consequent widening of the gap between pharyngeal constrictors and cricopharyngeal muscles, or upper esophageal sphincter spasm. The incidence of cancer in a diverticulum is almost negligible.

DIAGNOSIS

Upper digestive endoscopy is usually performed to diagnose the diverticulum and to rule out malignancy and associated diseases. Endoscopists should be aware of the possibility of this diagnosis to prevent missing small diverticula or causing perforation of large diverticula misdiagnosed as the esophageal lumen (Fig. 2).

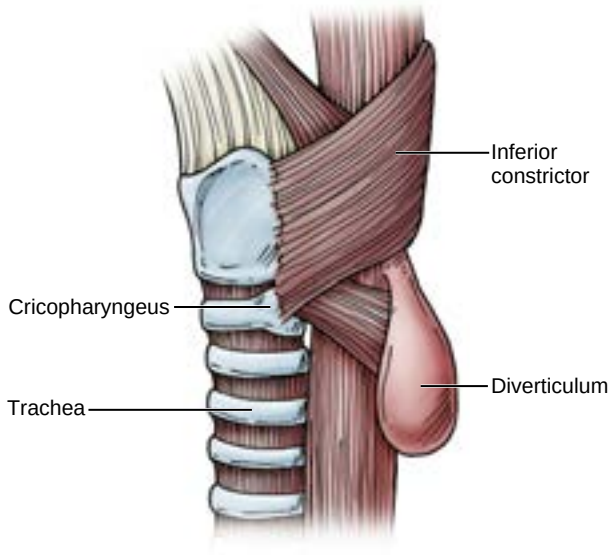


FIG. 1 Zenker's diverticulum at the pharyngoesophageal area.



FIG. 2 Zenker's diverticulum at upper digestive endoscopy.



FIG. 3 Barium swallow disclosing a Zenker's diverticulum *(arrow)*.

Barium swallow allows estimation of the size and location better than the endoscopy because the contrast distends the diverticulum (Fig. 3). Esophageal manometry may be used to diagnose the upper sphincter dysfunction, even though most experts believe that a motor disorder is always present and esophageal manometry is no more than an academic curiosity. Ambulatory pH monitoring may be indicated in patients with suspected GERD to allow planning of a combined procedure or guide medical therapy.

TREATMENT

Some propose treating only symptomatic diverticula, while others advise treatment to prevent complications such as aspiration, even in the absence of symptoms. The diverticulum may be treated by: (1) myotomy of the cricopharyngeal muscle alone; (2) myotomy plus diverticulectomy; (3) myotomy plus diverticulopexy; or (4) endoscopically by division of the septum between the diverticulum and the esophagus (diverticulo-esophagostomy [Dohlman's procedure]) (Fig. 4).

SURGICAL MANAGEMENT

Surgical Anatomy and Access

Most surgeons prefer a left cervical incision following the medial border of the sternocleidomastoid muscle, while others opt for a bilateral arciform incision. The layers to be dissected are: (1) skin; (2) subcutaneous tissue that is conjoined with the platysma muscle; and (3) superficial cervical fascia. After these planes are dissected, the infrahyoid muscles will be exposed. Usually there is no need to divide muscles. The sternohyoid muscle can be retracted medially and the omohyoid superiorly. The diverticulum is usually located below the omohyoid muscle. After the muscles are retracted, the esophagus is exposed. There is no need for circumferential dissection of the esophagus as it increases the risk of damage to the left recurrent laryngeal nerve located in the groove between the esophagus and the trachea. If the diverticulum is not yet identified, the esophagus should be rotated to expose the posterior side. Sometimes esophageal intubation by the anesthesiologist or intraoperative endoscopy is necessary to identify the diverticulum.

Dysmotility Treatment

The myotomy of the cricopharyngeal muscle must always be performed based on the assumption that an upper esophageal sphincter dysfunction is part of the pathophysiology of the disease. If the neck of the diverticulum is properly dissected, the myotomy is easily performed because the diverticulum is composed entirely of mucosa,

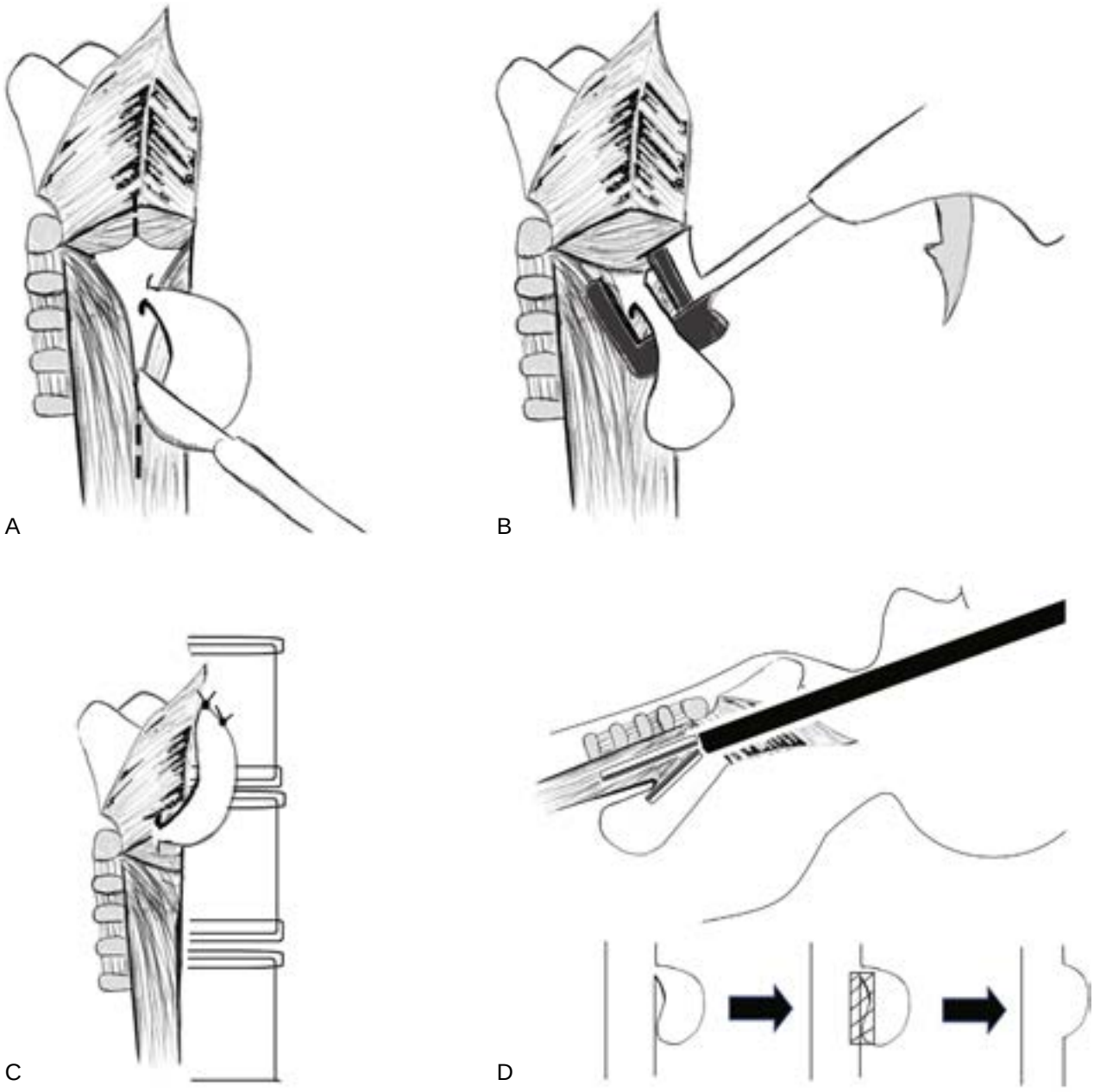


FIG. 4 Treatment options for Zenker's diverticulum. (A) Myotomy of the cricopharyngeal muscle. (B) Stapled diverticulectomy. (C) Diverticulopexy. (D) Endoscopic diverticulo-esophagostomy. *(From Herbella FA, Patti MG. Modern pathophysiology and treatment of esophageal diverticula.* Langenbecks Arch Surg. *2012;397:29–35.)*

and the interface between the muscular and mucosa layers can be effortlessly found. The myotomy must be extended about 3 cm downward onto the esophageal wall.

Diverticulum Treatment

There is no need to resect small diverticula (<2 cm) because of the low risk of complications and cancer. Larger diverticula may be resected or fixed upward to the prevertebral fascia (diverticulopexy). Resection may be performed with manual sutures or staplers. Before transecting the neck of the diverticulum, it is important to place a bougie (36Fr–40Fr) inside the esophagus to avoid pulling too much mucosa and causing narrowing of the esophageal lumen.

Some authors adopt a tailored approach choosing among the previous modalities based on the size of the diverticulum.

Outcome

Symptomatic relief is obtained in over 90% of patients. Complications may occur in up to 15% of cases and usually present as leakage and vocal cord paralysis.

ENDOSCOPIC TREATMENT OF ZENKER'S DIVERTICULUM

The treatment of Zenker's diverticulum has evolved over the past two decades from an invasive surgical procedure to an endoscopic approach that achieves favorable results in terms of symptom relief with a low complication rate, short hospital stay, and prompt return to an oral diet. Another factor in favor of the endoscopic approach is the possibility of a second attempt in cases of failure of primary treatment or recurrence of symptoms, without increasing the risk of complications such as nerve palsy.

Two different approaches can be used: rigid endoscopy or flexible endoscopy. To date, no controlled trials have been performed to demonstrate the superiority of one technique over the other, and consequently there are no accepted guidelines for patient management. The ability to access the diverticular common wall endoscopically may be limited by the patient's anatomy; therefore, a careful evaluation of the dimension of the diverticulum and its septum, clinical examination with evaluation of the anatomy of the oral cavity, and head hyperextensibility at the cervical spine level are mandatory to decide which technique is best.

Rigid Endoscopic Technique

Endoscopic diverticulostomy was first described by Mosher in 1917 using a cold knife. After initial success, the technique was abandoned and did not gain popularity until the 1960s, when Dohlman and Mattson described with success the endoscopic use of electrocautery to divide the common wall in a series of 100 patients. Since the 1990s, the endoscopic stapled-assisted diverticulostomy has become the standard approach to Zenker's diverticulum because of its low morbidity rate and excellent outcomes.

The procedure is performed with the patient under general anesthesia, lying supine with a fully extended neck. Under direct view, the Weerda diverticuloscope (Karl Storz, Tuttlingen, Germany) is carefully introduced through the mouth with the inferior blade into the pouch and the superior blade into the esophageal lumen (Fig. 5A). When a good view of the septum is achieved, the diverticuloscope is secured. To expose the diverticular septum and pouch and allow the insertion of the stapler, the two blades are gently opened. Any undigested food, saliva, or pills are aspirated. Two stay sutures (Endo Stitch 10-mm suturing device) are positioned on each side of the septum to maximize exposure and obtain traction (see Fig. 5B), therefore allowing insertion of the stapler deeper in the diverticular pouch. A modified linear stapler (AutoSuture Endo GIA 3.5, 30 mm) is introduced through the diverticuloscope with the jaws across the septum (see Fig. 5C) that is sealed and cut by firing the stapler, thus creating a common cavity between the esophagus and the diverticular sac (see Fig. 5D). A modification of the anvil by cutting the edge of the jaw (Fig. 6) introduced in the diverticular sac is mandatory to obtain the full-length division of the septum. In cases of big diverticula, more than a cartridge can be used to complete the section (see Fig. 5E, F). The residual millimeters of uncut staple line are sectioned with scissors or a coagulating hook;

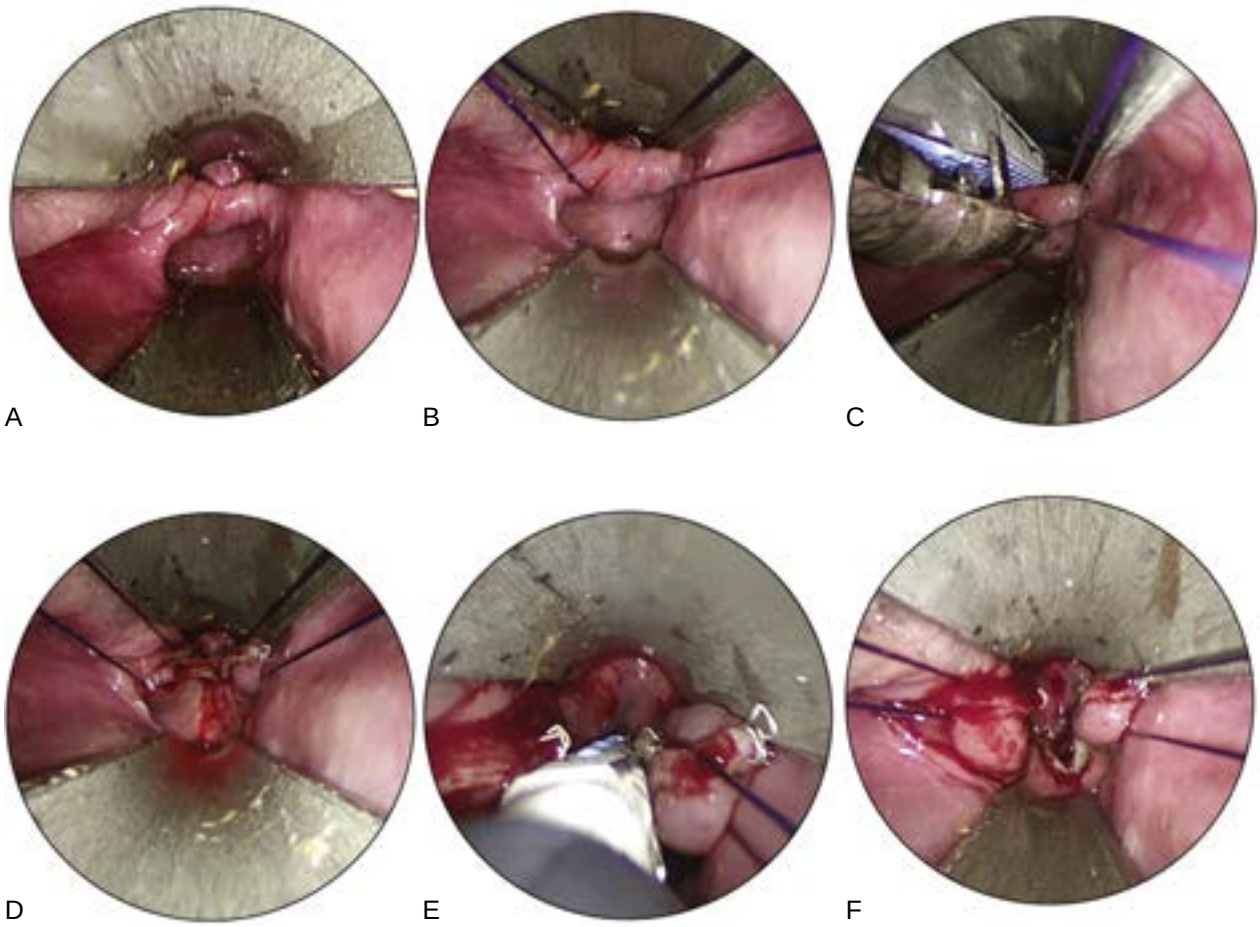


FIG. 5 Endoscopic therapy for Zenker's diverticulum. (A) Exposure of septum by the Weerda diverticuloscope. (B) Positioning of two anchoring stitches (Medtronic Endo Stitch 10-mm suturing device) at both septum sides. (C) Introduction of the linear stapler (AutoSuture Endo GIA 3.5, 30 mm) with the modified jaw into the diverticulum pouch. (D) Partial dissection of the septum after one stapler suture. (E) Further introduction of the linear stapler to obtain the full-length dissection of the septum. (F) Final appearance of the complete dissection of the septum and pouch obliteration.

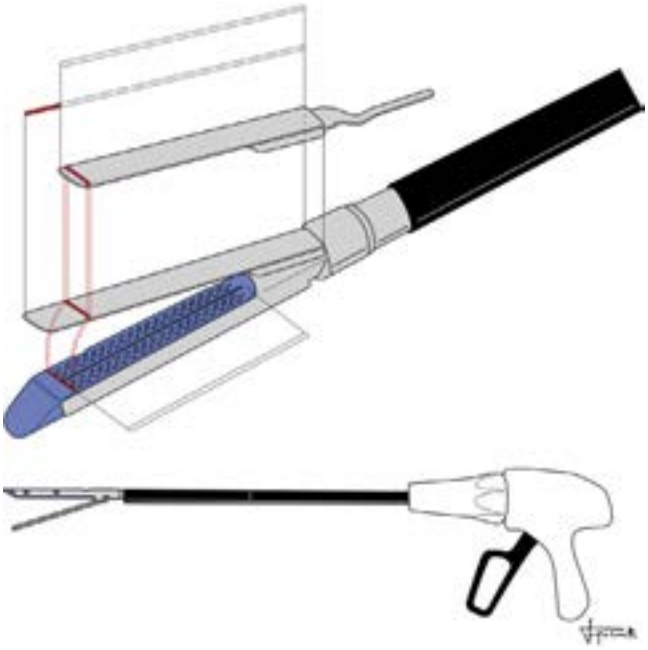


FIG. 6 Design of the modified anvil of the AutoSuture Endo GIA linear stapler, by Riccardo Rosati, and comparison with the traditional one.

any bleeding is controlled by electrocautery. In some series, division of the septum was performed using CO_2 laser, a Harmonic scalpel, or other devices as alternatives to the stapler (see Fig. 6).

This procedure is very effective, with an overall success rate of more than 90% in all large published series and a complication rate around 7.0%. The most common complications were dental injuries (2%) and esophageal mucosal perforation (1.6%).

Inability to access and fully divide the diverticular septum is a concern of this procedure. Data in the literature have shown a rate of procedure abandonment resulting from incomplete visualization that ranges between 3% and 26%. The reasons for this problem are a small oral inlet, limited neck extension, presence of osteophytes, a very small diverticular pouch, or concern regarding dental injuries. In addition, limited experience in the insertion of the diverticuloscope plays a major role.

Historically, diverticula smaller than 2 to 3 cm have not been amenable to the endoscopic technique because of the risk of a too-short myotomy length, but use of the stay sutures facilitates anchoring of the stapler in the diverticular pouch. Furthermore, a higher success rate using sutures with a single session has been achieved than without stay sutures (87.3% vs. 65.3%, respectively).

Flexible Endoscopic Technique

The rigid endoscopic approach has some limitations such as the need for general anesthesia, the inability of neck hyperextension, and anatomic problems such as a diverticulum less than 3 cm (not suitable for correct positioning of the stapler). Flexible endoscopic techniques have been proposed to overcome such difficulties. They vary from the "classic" flexible endoscopic septum division to the most cutting-edge third-space approaches. In every case, the procedure is done under direct vision of the cricopharyngeal muscle fibers. All of the procedures are performed with the patient in the left decubitus, with the patient either under conscious sedation or under narcosis.

Endoscopic Septum Division

The first technique proposed in the mid-1990s was endoscopic septum division, which shares the same principles of rigid endoscopy and involves a full-thickness incision of the mucosa, submucosa, and muscular fibers of the septum to obtain a common cavity with the esophageal lumen.

Before performing the procedure, a nasogastric tube is inserted into the esophagus as a guide to recognize the lumen. Since its introduction, many tools have been proposed, and the technique has improved: some endoscopists use a soft rubber diverticuloscope as overtube (Zenker's Diverticulum Overtube, Cook Endoscopy, Winston-Salem, NC) to obtain a better view and set the surgical field, or a short cap on the tip that also improves visibility and stabilizes the endoscope. Septotomy is performed with no need of submucosal injection. The most common devices used are the needle-knife and the hook-knife, but others can be used such as monopolar forceps or argon plasma coagulation, depending on the endoscopist's preference and personal experience. After the septotomy is completed, one or more endoclips are placed to close the incision to reduce the likelihood of a leak or bleeding. Outcomes of the septotomy are similar to the previous technique, with nearly 90% symptom relief and a recurrence rate of 11%. A retrospective comparative review showed that both rigid endoscopy septotomy and the flexible endoscopic technique have similar results and provide symptom control comparable with open surgery, with a decreased risk of serious complications.

Z-POEM

Recent advances in natural orifice transluminal endoscopic surgery (NOTES), especially for treatment of achalasia, have given rise to novel myotomy techniques for the treatment of Zenker's diverticulum. In 2016, the first septum division via a submucosal tunneling approach was reported, later called *Z-POEM*.

The advantage of this approach is that it is easier to perform a complete transection of the entire muscular septum by operating within a submucosal tunnel, thus maintaining mucosal integrity and lowering recurrence of symptoms because of incomplete transection of the muscle.

The procedure starts with submucosal injection and mucosotomy nearly 3 cm proximal to the septum. This is very difficult because the area involved as muscular spasm and anatomic limitations of the upper esophageal sphincter may reduce the ability to properly manage the mucosal incision. Then a submucosal tunnel is created along both sides of the septum, ending in the normal esophagus, 1 to 2 cm distally to the end of the septum. The muscular fibers are at this point clearly visible and can be safely transected. After removal of the endoscope, the mucosotomy site is closed with clips. It is a technically challenging procedure, but the success rate is comparable with other endoscopic approaches, with 92% achieving favorable results and 6.7% experiencing complications such as bleeding or perforation. As it is a new procedure, long-term results and comparative studies are lacking as well as the rate of recurrence.

Suggested Readings

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Achalasia of the Esophagus

T. Robert Qaqish, MD, and Mark Katlic, MD

Achalasia is a rare (US prevalence: 10 per 100, 000) neurodegenerative disorder that results in the inability of the lower esophageal sphincter (LES) to relax in combination with an aperistaltic esophagus. All age groups are affected without predilection to race or sex. There is a peak incidence of those manifesting the disease between 30 and 60 years of age. Although not completely understood, there may be a genetic predisposition to individuals with achalasia. Moreover, environmental factors may play a role, and lastly, autoimmune destruction of the underlying myenteric plexus of the esophagus may also serve as an explanation with a viral infection as the inciting agent.

The spectrum of manifestations of the disease includes regurgitation of food, retrosternal chest pain, and dysphagia. Advanced forms of disease may manifest with recurrent aspiration pneumonia, weight loss, and failure to thrive. The Eckardt score (Table 1) can be used to evaluate the severity of symptoms associated with achalasia.

TABLE 1 The Eckardt Scoring System*

Score	Weight Loss (kg)	Dysphagia	Retrosternal Chest Pain	Regurgitation
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5–10	Daily	Daily	Daily
3	>10	With each meal	With each meal	With each meal

*The Eckardt scoring system allows clinicians to assess the severity of symptoms associated with achalasia and the effectiveness of any therapeutic intervention.

Moreover, the adequacy and effectiveness of treatment can also be assessed with application of the Eckardt scoring system.

Evaluation of the patient with an esophageal complaint suspected to be achalasia involves a thorough history and physical examination along with radiographic, endoscopic, and functional esophageal testing. A barium swallow may reveal the classic "bird's beak" appearance (Fig. 1). Endoscopy is recommended to rule out a mechanical obstruction such as malignancy, a benign stricture, or pseudoachalasia. In cases of long-standing disease, the esophagus may appear markedly dilated, and there may be retained food within the esophageal lumen. Functional esophageal testing in the form of high-resolution manometry (HRM) (Fig. 2) is the mainstay for the diagnosis of patients with achalasia. In type I achalasia, there is no esophageal contraction or esophageal pressurization with an integrated relaxation pressure (IRP, the mean of the 4 seconds of maximal deglutitive relaxation in the 10-second window beginning at upper esophageal sphincter [UES] relaxation on HRM) greater than 15 mm Hg. In type II achalasia, there is panesophageal pressurization and no peristaltic contraction. In type III achalasia, there are at least 20% premature (spastic) contractions. Depending on the HRM findings, achalasia and the subclassification of types can be further classified based on the Chicago Classification 3.0 (Fig. 3).

TREATMENT

There is no cure for achalasia. Available therapeutic interventions are aimed at relieving the functional obstruction at the LES. Intrasphincteric injection of botulinum toxin, pneumatic dilation of the LES, and myotomy via endoscopic and surgical means all achieve this goal with varying efficacy and duration of success. In cases of end-stage achalasia from long-standing disease or in the setting of previous myotomy, esophagectomy may be an option for medically fit patients.

Botulinum Toxin

In patients who have contraindications to general anesthesia and frail elderly patients, intrasphincteric injection of botulinum toxin may be a useful temporary measure. Injection is performed endoscopically

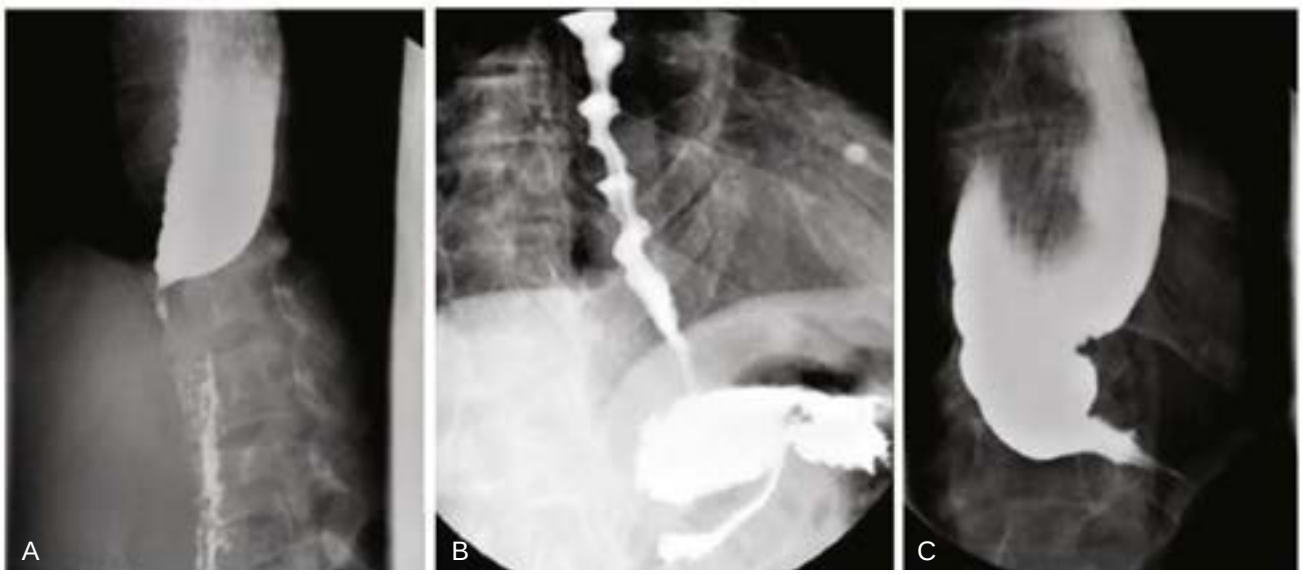


FIG. 1 Achalasia types shown on barium esophagography. **(A)** Classical barium esophagram showing tapering of the distal esophagus in (type I) achalasia, commonly referred to as a "bird's beak." **(B)** Spastic (type III) achalasia with a "corkscrew" type appearance. **(C)** Sigmoid-shaped esophagus from advanced achalasia. *(From Petrov RV, Fajardo RA, Bakhos CT, Abbas AE. Peroral endoscopic myotomy: techniques and outcomes.* Shanghai Chest. *2021;5:14).*

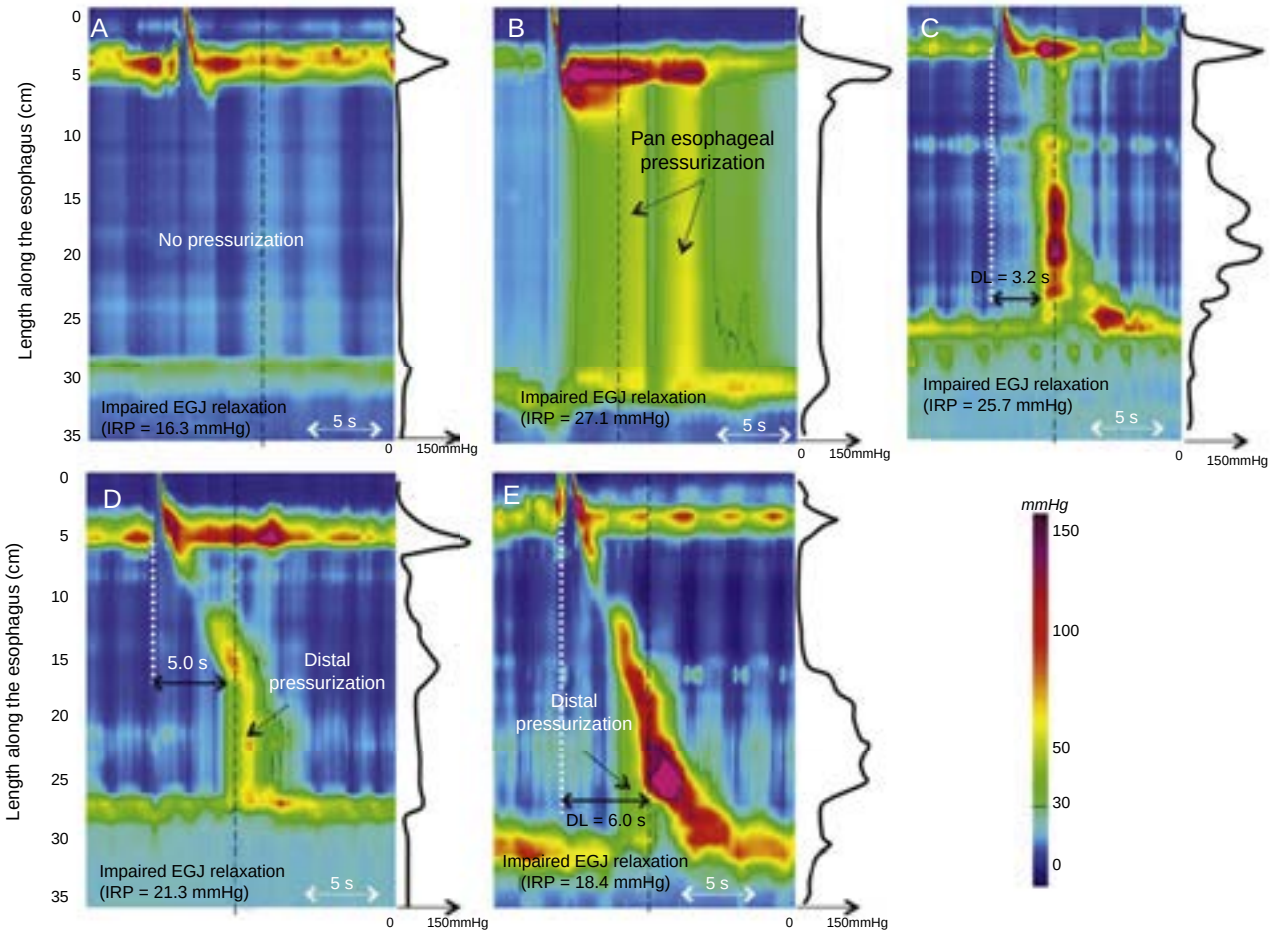


FIG. 2 High-resolution manometric images illustrating disorders associated with esophagogastric junction *(EGJ)* outflow obstruction. Impaired EGJ relaxation is evident by an integrated relaxation pressure (IRP, defined as the mean of the 4 seconds of maximal deglutitive relaxation in the 10-second window beginning at upper esophageal sphincter [UES] relaxation) >15 mm Hg. Instantaneous pressure along the *black dashed line* is represented by the *black line* on the *right* side of each panel. **(A)** Type I achalasia: characterized by no esophageal contraction or esophageal pressurization. **(B)** Type II achalasia: characterized by panesophageal pressurization and no peristaltic contraction. Note that pressurization corresponds to homogeneous pressure along the spatial pressure variation plot. **(C)** Type III achalasia: characterized by at least 20% premature contractions, defined as distal latency *(DL)* less than 4.5 seconds. DL is defined as the interval between UES relaxation and the contractile deflection point (CDP), which is a pressure topographic metric that demarcates peristalsis from ampullary emptying, localized within 3 cm of the proximal LES. Note the multiple peaks corresponding to contractions along the spatial pressure variation plot. EGJ outflow obstruction may represent achalasia **(D)** It might also be the consequence of a mechanical obstruction **(E),** such as a distal esophageal stenosis. *(From Kahrilas PJ, Bredenoord AJ, Gyawali CP, et al.; International High Resolution Manometry Working Group. The Chicago Classification of Esophageal Motility Disorders, v3.0.* Neurogastroenterol Motil. *2015;27[2]:160–174).*

and involves injecting the toxin into four quadrants of the LES. Typically, 80 to 100 units are injected (20–25 units/quadrant). Its mechanism of action involves irreversible inhibition of acetylcholine release from presynaptic terminals that eliminates the neurogenic component of the LES pressure. Therapeutic relief is short-lived, however, as new axonal growth will eventually occur, and the patient's symptoms will recur. Patients typically report an improvement in their symptoms for up to 1 year but often require repeat endoscopic injection. Repeat injection may be associated with local inflammatory reactions and fibrosis, which limit its repetition. Chest discomfort and rash are also known side effects of the therapy.

Pharmacologic therapies administered via the sublingual route before eating have also been employed in patients who are unfit for general anesthesia. These have included smooth muscle cell relaxants such as nitrates and calcium channel blockers that can lower the LES pressure. Side effects such as headaches limit the use of nitrates. Nifedipine administered via the sublingual route (30 mg/day) is also associated with headache, orthostasis, and dizziness and has limited efficacy. Sildenafil has also been trialed and has short-lived efficacy. Its use is limited by cost and potential side effects.

Pneumatic Dilation

Endoscopic dilation is the most effective nonsurgical option for achalasia. The principles of this therapy involve disruption of the circular muscle fibers of the LES as a result of dilation. Pneumatic dilators are more effective in achieving physical disruption of the muscle fibers in comparison with rigid dilators. These endoscopic procedures are performed under conscious sedation, and aspiration risk is not insignificant in this patient population because there may be retained food within the esophageal lumen. Implementation of a clear liquid diet for longer than 1 day may be advisable.

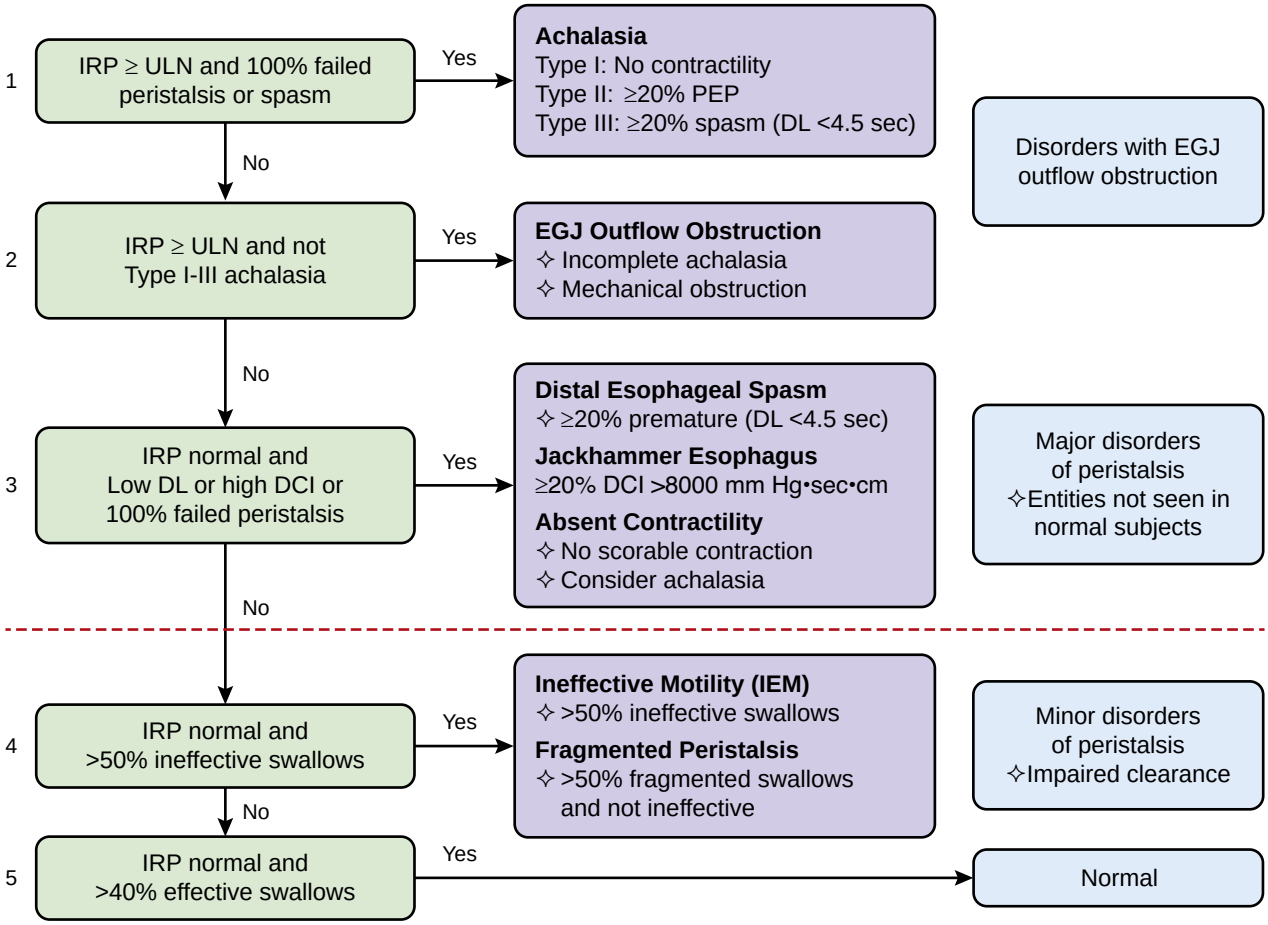


FIG. 3 The Chicago Classification version 3.0, a hierarchical analysis. The initial step involves evaluating the relaxation of the esophagogastric junction *(EGJ)* upon swallowing by using the integrated relaxation pressure (IRP, defined as the mean of the 4 seconds of maximal deglutitive relaxation in the 10-second window beginning at upper esophageal sphincter (UES) relaxation. If elevated (greater than upper limit of normal [ULN] of 15 mm Hg), patients should be classified as having achalasia or EGJ outflow obstruction, depending on the peristalsis. In the case of a normal IRP, peristalsis is classified based on its absence, distal latency (DL, defined as the interval between UES relaxation and the contractile deflection point, CDP, which is a pressure topographic metric that demarcates peristalsis from ampullary emptying, localized within 3 cm of the proximal lower esophageal sphincter, LES), distal contractile integral (DCI, defined as: amplitude × duration × length (mm Hg • s • cm) of the distal esophageal contraction exceeding 20 mmHg from the transition zone to the proximal margin of the LES) and fragmentation. If there are abnormalities, patients are classified as having a major or minor disorder of peristalsis. Major disorders are never observed in controls, in contrast with minor disorders. If a patient has a normal IRP and more than 50% of swallows are effective, esophageal motility is normal. *(From Pandolfino JE, Kahrilas PJ. Esophageal neuromuscular function and motility disorders. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th ed. Philadelphia: Elsevier; 2021:chap 44; Rohof WOA, Bredenoord AJ. Chicago Classification of Esophageal Motility Disorders: Lessons Learned.* Curr Gastroenterol Rep. *2017;19[8]:37.)*

Gastroscopy and fluoroscopy are used to guide inflation of the dilating balloon. Balloon sizes can range from 3.0 to 4.0 cm in 0.5 cm increments. A handheld manometer is used as the balloon is passed over a wire fluoroscopically. The "waist" of the balloon is created as a result of the LES and should essentially be carefully effaced during inflation. Long-lasting reduction in LES pressure typically involves dilation of the LES to 3 cm. A cautious approach should always be employed starting with the smallest balloon first. If the patient does not have symptomatic relief or there is an unsatisfactory result with dilation, it may be useful to repeat the dilation at a short interval (2–3 weeks).

Esophageal perforation is the most worrisome complication of pneumatic dilation and can occur at an incidence of 1%. Some practitioners perform a water-soluble followed by barium esophagram to follow each of their dilations routinely. Most perforations are apparent within the first hour after the procedure as fever, chest pain, and subcutaneous emphysema may be indicative of an esophageal leak. If the perforation is small, conservative measures including NPO, intravenous antibiotics and antifungals, and inpatient observation can be employed. If there is worsening fever, chest pain, or an uncontrolled leak, surgical therapy is recommended as early as possible (<6–8 hours). Computed tomography (CT) should also be employed, and a CT esophagram can be useful if available. Placement of a temporary esophageal stent for perforation after pneumatic dilation for achalasia is a more common intervention employed at institutions where the resources are available and should be employed if the esophageal leak is small.

The clinical efficacy of pneumatic dilation is variable and ranges from 30% to greater than 90%. This is believed to be a reflection in the variability in technique, practitioner-related variability in assessing outcomes, and variable approaches and timing for repeat dilation. Most patients will eventually require repeat dilation. Furthermore, future response to surgical myotomy is not influenced by the number of previous dilations.

Myotomy: Laparoscopic Heller Myotomy and Peroral Endoscopic Myotomy

Laparoscopic Heller Myotomy

In patients who can tolerate general anesthesia, laparoscopic Heller (or Heller's) myotomy (LHM) is effective and to date is the most durable surgical intervention for long-term control of achalasia. The procedure (myotomy) was first performed by the late German surgeon, Dr. Ernst Heller (Fig. 4). LHM is performed with the patient in the low-lying lithotomy position with bilateral arms tucked and padded. Before placing the patient in the lithotomy position, we carefully perform an esophagoscopy. Minimal insufflation is used, and the gastroscope is kept in the stomach after it is decompressed. The patient is then positioned. Precautions are taken to ensure that bony prominences on the upper and lower extremities are protected and cushioned in stirrups. A beanbag is used to create a bulky fold underneath the patient's gluteus and upper posterior thighs. This creates a "seat" and protects the patient's position from shifting during steep reverse Trendelenburg positioning. A test of steep reverse Trendelenburg positioning is always performed before prepping to ensure that the patient does not slip.

Ports are placed with the camera port 13 cm caudal to the base of the xiphoid in the midline. A pretzel liver retractor is placed in the right lower quadrant, curved around the left hepatic lobe, and then retracted to reveal the hiatus. The patient is then placed in the reverse Trendelenburg position, and the hiatus is better visualized. A 5-mm port is placed in the right mid-epigastric region, and a 12 mm port is placed in the left paramedian plane for the surgeon's working right hand. Lastly, a 5 mm assistant port is placed in the left lower quadrant.

The procedure is begun by identifying both the left and right crus and delineating the hiatal anatomy. The right crus is dissected from its medial portion and traced up anteriorly over the esophagus over toward the left crus. The esophagus is not circumferentially dissected. The gastric fat pad is then dissected off the lower esophagus exposing the anterior portion of the gastroesophageal junction (GEJ). The anterior vagus nerve and phrenoesophageal ligament are identified, and the contours of the fibers should be carefully noted. The cranial myotomy must extend across the GEJ in a manner that follows a straight line in the middle of the esophagus, and the caudal myotomy onto the stomach should remain as much as possible in an imaginary line that bisects the lesser and greater curvature.

A clear plane and potential trajectory for the myotomy should be kept in mind during the process (Fig. 5). We use two Maryland graspers to grab the esophageal muscle (starting with the outer, longitudinal layer) and apply equal pressure orthogonal to the long axis of the esophagus. Minimal cautery is used. This tedious teasing of fibers is continued until the mucosa is visualized. Oftentimes, strands of the circular muscle fibers remain, and these are individually peeled off and divided. Once the appropriate plane is established, the myotomy is extended 4 to 6 cm cranially into the mediastinum and 2 to 3 cm on to the stomach. At the end of the myotomy aspect of the procedure and before fundoplication, the mucosa is visualized endoscopically, and an insufflation test into the esophageal lumen is performed under saline.



Aus der Chirurgischen Klinik zu Leipzig (Direktor: Prof. Dr. E. Payr).

IV.

Extramuköse Cardiaplastik beim chronischen Cardiospasmus mit Dilatation des Oesophagus.

Von

Privatdocent Dr. E. Heller,
Oberarzt der Klinik.

(Hierzu 3 Abbildungen im Texte.)

Im ersten Heft des Archivs für klinische Chirurgie 1913 hat Heyrovsky eine subdiaphragmatische Oesophagusgastroanastomose beschrieben, die er bei zwei Fällen der sogenannten „idiopathischen Dilatation der Speiseröhre" mit Erfolg ausgeführt hat. Kurz nach dem Erscheinen dieser Mitteilung kam ein Patient mit chronischem Cardiospasmus und starker sackförmiger Dilatation des Oesophagus in die Behandlung der Leipziger chirurgischen Klinik, bei dem mir nach Lage des Falles chirurgische Hilfe zur Beseitigung des Leidens geboten erschien. Unter dem Eindruck der Heyrovskyschen Erfolge beabsichtigte ich den operativen Eingriff in der gleichen Weise vorzunehmen. Im Verlauf der Operation kam ich jedoch, bestimmt durch gewisse Schwierigkeiten der operativen Technik und später ausführende theoretische Ueberlegungen, zu einer vom ursprünglichen Plane abweichenden Durchführung der Operation, nämlich zur Ausführung einer extramukösen Cardiaplastik. Da der Erfolg, wie ich vorgreifend bemerken will, im funktionellen Sinne sehr befriedigend ausgefallen ist, und diese Aenderung des operativen Vorgehens meines Erachtens nicht unerhebliche praktische Vorteile gegenüber den für die Behandlung des Cardiospasmus mit Oesophagusdilatation vorgeschlagenen und ausgeführten operativen Maßnahmen besitzt, möchte ich mir erlauben, den Fall kurz mitzuteilen.

FIG. 4 Dr. Ernst Heller (1867 to 1964) and his publication from 1913 on extramucosal esophagomyotomy.

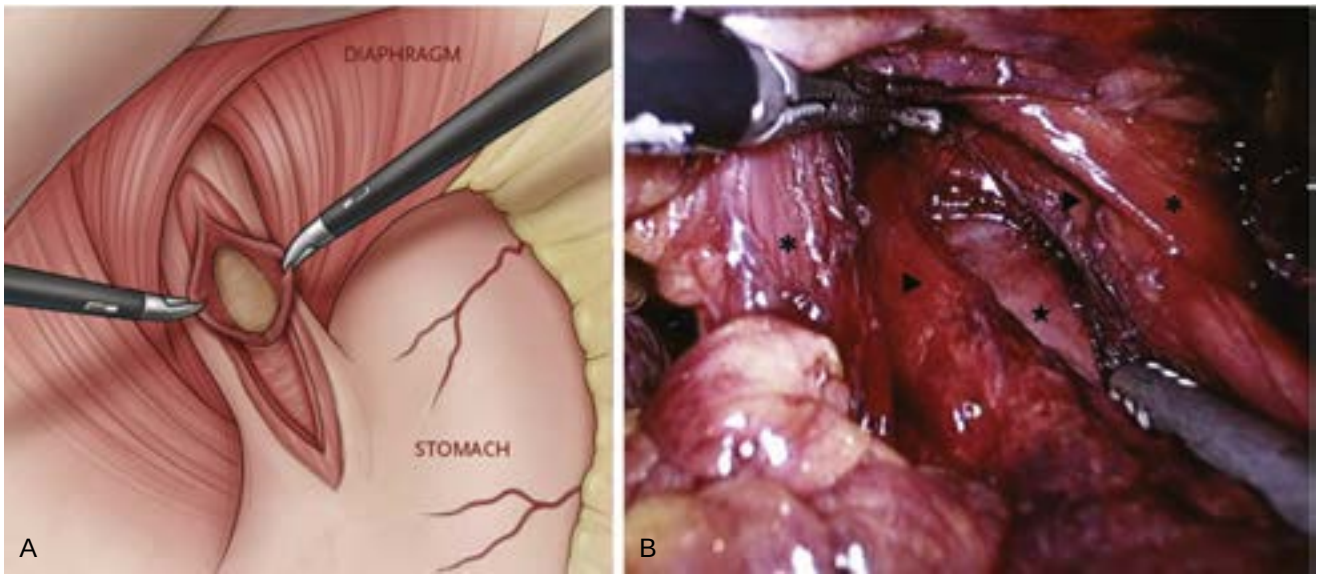


FIG. 5 Laparoscopic point of view during Heller myotomy. **(A)** Schematic showing left and right myotomy edges being elevated using the laparoscopic graspers with the mucosal layer in between. **(B)** Intraoperative photograph from a laparoscopic Heller myotomy showing the left and right crura *(asterisk)*, the left and right myotomy edges *(arrowheads)*, and the underlying exposed mucosa *(star)*. *(A, From Werner YB, Hakanson B, Martinek J, et al. Endoscopic or surgical myotomy in patients with idiopathic achalasia.* N Engl J Med. *2019;381[23]:2219–2229.)*

We invariably perform a Dor fundoplication and only take down some of the short gastric vessels if there is tension. Four intracorporeal sutures are used for the partial fundoplication. If the Dor fundoplication can be imaged as if it were a "door" covering the myotomized LES, the left myotomy edge is sutured to the inner aspect of the door, where the hinges would be. This is performed in two areas: one cranial and one caudal. The remaining tacking sutures to complete the Dor involve suturing the right myotomy edge to the free edge of the door, the side of which the doorknob is placed. 2-0 Ethibond (Ethicon) is used, and sutures are placed using the Endo Stitch suturing device (Medtronic, Minneapolis). The most cranial aspect of the fundoplication is also sutured to the right crus. A nasogastric tube is not routinely placed.

A barium swallow on postoperative day 1 is performed to evaluate for an esophageal leak. If negative, the patient is discharged on clear liquids for 3 days and full liquids for another 3 days, with soft food until the first postoperative visit at 2 weeks. The patient's diet is advanced as tolerated thereafter.

Peroral Endoscopic Myotomy

POEM is the newest surgical therapy to emerge in treating patients with achalasia. The procedure is performed in the operating room under general anesthesia with the patient supine. The procedure has four main components (Fig. 6). The mucosotomy is created approximately 10 to 15 cm proximal to the GEJ. The muscularis mucosa must be disrupted to expand the submucosal space with the injection of water. After mucosotomy, the submucosal fibers are dissected. To assist with separation and further creation of the tunnel, a methylene blue dye and water mixture is injected in this plane to delineate the underlying circular muscle fibers. The tunnel is created and must remain perpendicular to the circular muscle fibers of the esophagus. The tunnel takes a slight leftward turn at the GEJ and is extended a few centimeters past the GEJ. Commencement of the myotomy begins at the proximal extent of the tunnel posteriorly. A selective myotomy is performed proximally (circular muscle fibers only), and a full thickness (circular and longitudinal) myotomy is performed distally. The mucosa should be closely examined for inadvertent disruption in other areas remote from the mucosotomy. The mucosotomy is then closed using clips or an endoluminal suturing device.

The postoperative course after POEM is not dissimilar to that after LHM. A barium esophagram is obtained on postoperative day 1, and the patient may be discharged on clear liquids and proton pump inhibitor (PPI) therapy as long as there is no evidence of leak. Ambulatory pH testing and esophagogastroduodenoscopy should be performed between 3 and 6 months to evaluate for objective evidence of gastroesophageal reflux (GER).

Complications related to the procedure include inadvertent mucosal disruption, pneumothorax, pneumomediastinum, pneumoperitoneum, submucosal hematoma, and esophageal leak. Generally most complications are minor, and very few are severe.

Perioperative outcomes of patients who undergo LHM versus POEM are similar. The literature describing the long-term durability of POEM is scant and not yet precisely known. The longest follow-up report was recently published in 2021 by Campagna et al. and followed patients up to 55 months (4.5 years) after POEM. Clinical success (defined by an Eckardt score less than or equal to 3) was reported in 88/100 patients, with the remaining 12 noting a score greater than 3 at some point during the follow-up period. As there is no antireflux procedure that is performed alongside POEM, the risk of GER remains a significant postprocedural sequela that the patient must manage pharmacologically. In the above-mentioned study, approximately one-third of patients had evidence of GER on endoscopy. The durability of the LHM is well established in experienced hands and may be between 5 and 10 years.

As the data continue to accumulate, the approach to treat patients via endoscopic versus laparoscopic myotomy should be an individualized one. A patient-centric decision should be guided by the surgeon as to the best approach considering patient factors (e.g., BMI, previous operations, and overall preference) and institutional factors (e.g., clinician experience performing surgical vs. endoscopic myotomy vs. both and the institution's resources to manage complications). In July 2020, the Board of Governors from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommended (conditionally, low certainty of evidence) either POEM or LHM in the treatment of type I or type II achalasia in adults and children and POEM over LHM (based on expert opinion) in adults and children with type III achalasia (Fig. 7).

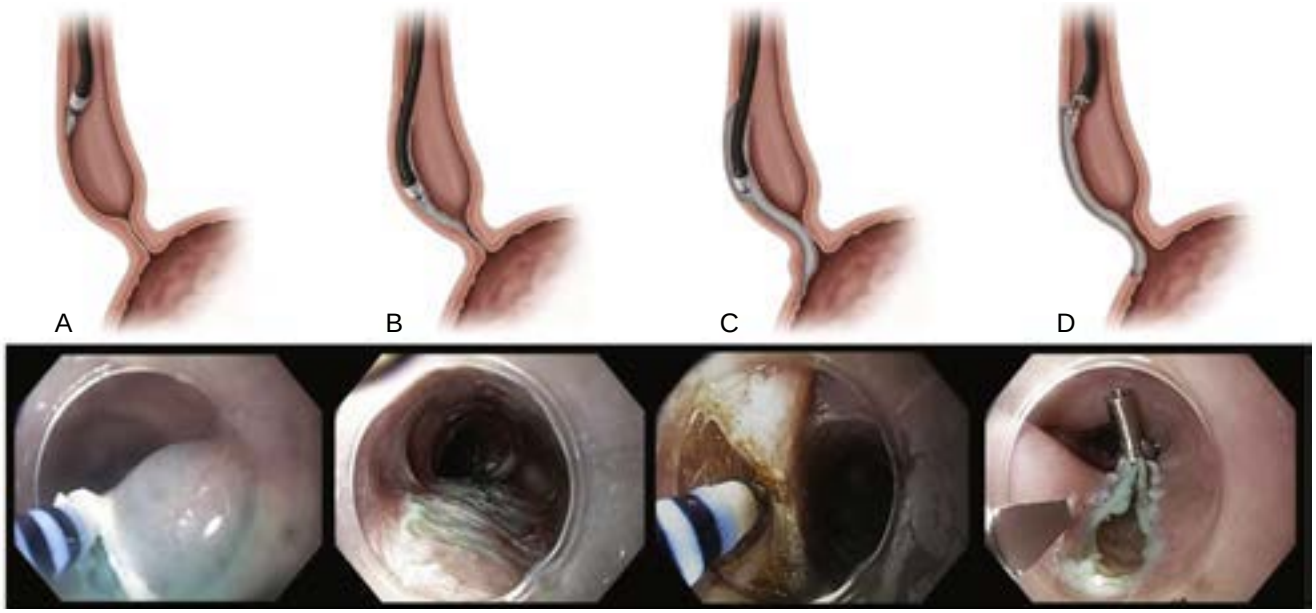


FIG. 6 Key elements of the peroral endoscopic myotomy procedure. **(A)** A mucosotomy is created with the corresponding endoscopic image beneath. **(B)** An endoscopic view of the completed submucosal tunnel after creation and completion. **(C)** Myotomy schematic and corresponding endoscopic image captured of the myotomy. **(D)** Closure of mucosotomy is performed with endoscopic placement of clips. *(From Petrov RV, Fajardo RA, Bakhos CT, Abbas AE. Peroral endoscopic myotomy: techniques and outcomes.* Shanghai Chest. *2021;5:14; corresponding endoscopic images provided courtesy Dr Henning Gerke, Clinical Professor from the University of Iowa Hospitals and Clinics.)*

TREATMENT FAILURE, ADVANCED DISEASE, AND FOLLOW-UP

Dysphagia in the postoperative course is likely an indication of treatment failure. The diagnostic workup should proceed with endoscopy, fluoroscopy with timed barium swallow, high-resolution impedance manometry, and, if available, functional lumen imaging probe (FLIP). Depending on the findings, pneumatic dilation versus repeat myotomy may be warranted. The patient should be evaluated for other factors that could be contributing to the esophageal complaints such as paraesophageal hernia or stricture. POEM may provide an avenue for patients who have had failed laparoscopic myotomy. POEM allows a dissection plane to be created endoscopically remote from a previously created dissection plane that was performed laparoscopically. In advanced cases in which the patient's disease process is refractory to multiple therapeutic interventions and there is severe esophageal dysfunction, esophagectomy may be warranted.

In patients with advanced disease, as evidenced by severe esophageal dysfunction and a dilated (sigmoid) esophagus, esophagectomy may be warranted if they are medically fit, especially in the setting of failed myotomy. Esophagectomy is both safe and effective. Both the transthoracic and transhiatal routes have been described with similar outcomes in experienced hands from tertiary referral centers. There are unique technical challenges that are important to consider when performing esophageal resection for end-stage achalasia. Prior myotomy may have created scarring between the esophageal submucosa and the aorta, and there may be large aortic esophageal arterial branches that must be carefully controlled during the dissection. Moreover, the dilated esophagus may be deviated into the right chest. We prefer a transhiatal approach for end-stage achalasia and start the procedure thoracoscopically to mobilize the esophagus under direct vision, control the large esophageal arterial branches, and ligate the azygous vein. Lastly, encircling the cervical esophagus may prove difficult in the neck.

There are no society-driven guidelines for surveillance endoscopy in patients with achalasia after myotomy. Chronic mucosal irritation from stasis esophagitis, long-standing GER, and Barrett's esophagus are risk factors for carcinoma. If surveillance is pursued, it is reasonable to perform surveillance upper endoscopy 15 years after the onset of symptoms.

Robotic Heller Myotomy with Dor Fundoplication

Robotic-assisted LHM with Dor fundoplication is well established, and the current literature shows nearly equal efficacy and outcomes in treating patients with achalasia. Surgeon experience with both the robotic or purely laparoscopic approach is probably the most important factor that determines a successful operation. The robotic platform offers improved visualization and may offer finer motor control with more comprehensive and robust instrument movement. Safe and careful patient positioning and port placement can be in similar positions to the laparoscopic approach or can also be placed in a horizontal line on either side of the umbilicus. The camera port is in the periumbilical region with two subsequent 8-mm ports on each side, each 8 cm lateral to the umbilical port and 8 cm away from each other. Retraction of the liver can be facilitated with a tip-up fenestrated grasper from the most lateral left-sided port. The robot is typically docked *after* the patient is placed in the steep reverse Trendelenburg position. The case proceeds in a similar fashion to the laparoscopic approach. Some surgeons use an endoscopically placed inflated balloon across the LES to better delineate the muscle fibers from the submucosal layers during dissection.

SUMMARY

Achalasia is a rare esophageal disease but represents the most common esophageal motility disorder. Based on the current status of evidence in the literature, a treatment algorithm is outlined in Figure 7. With the rapid and successful adoption of POEM in treating patients with achalasia and those who have failed laparoscopic (or robotic) myotomy, it is advisable that trainees and seasoned surgeons become more facile with advanced endoscopic interventions.

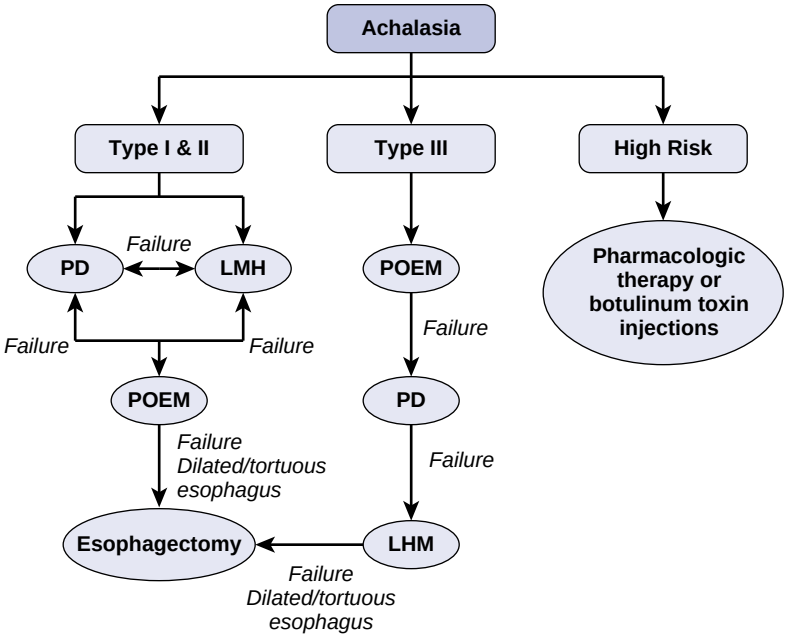


FIG. 7 Proposed treatment algorithm for achalasia. *LMH,* Laparoscopic Heller myotomy; *PD,* pneumatic dilation; *POEM,* peroral endoscopic myotomy. *(From the previous edition of this chapter by Eric Etchill, MD, and Stephen Yang, MD.)*

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Management of Disorders of Esophageal Motility

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Disorders of esophageal motility present a diagnostic and therapeutic challenge to gastroenterologists and surgeons. Achalasia, the most prevalent and best understood of these disorders, is addressed under "Management of Achalasia of the Esophagus" elsewhere in this textbook. Nonachalasia esophageal motility disorders are less prevalent, incompletely understood, and often difficult to treat. The optimal classification scheme for this group of disorders is a work in progress. Management strategies are also controversial, and there is no universally accepted standard of care. In this chapter, we attempt to guide the surgeon in a review of nonachalasia esophageal motility disorders and the application of their most current classification, with recommendations for management based on recent data.

PRESENTATION

Patients with disorders of esophageal motility may present with chest pain, dysphagia, regurgitation, heartburn, globus sensation, upper respiratory complaints, or some combination of these. Because

these symptoms are nonspecific and esophageal motility disorders are rare, workup for other life-threatening conditions is necessary. Cardiovascular and pulmonary causes usually have been ruled out already in the patient with chest pain before referral to the surgeon. A negative cardiac workup is reassurance enough for some patients who may be able to conservatively manage mild symptoms. Anxiety, depression, somatoform disorders, and other psychiatric diagnoses are more common in the population of patients with esophageal motility disorders; thus a psychiatric history is an important part of the evaluation. Gastroesophageal reflux disease (GERD) is another common cause of noncardiac chest pain. A trial of a proton pump inhibitor (PPI) is warranted, and further diagnostic testing should be carried out if troublesome symptoms persist. Concerning associated symptoms, such as dysphagia with weight loss, should heighten the suspicion for a mechanical or malignant process and prompt, expedient, and careful evaluation.

Diagnostic Testing

All patients evaluated for esophageal motility disorders must undergo a comprehensive diagnostic workup. This includes a contrast esophagram to help visualize anatomy, esophageal length, and the presence of a diaphragmatic hernia or esophageal diverticulum. A pH study with or without impedance is important to identify GERD, which may be the primary or contributing cause of symptoms. Endoscopic evaluation with biopsy is also mandatory to identify Barrett's esophagus, malignancy, peptic stricture or esophagitis related to acid exposure, eosinophilia, or infection. In the absence of mechanical obstruction or mucosal abnormalities, esophageal motility is evaluated next by manometry.

High-resolution manometry (HRM) with esophageal pressure topography (EPT) is the preferred method to evaluate for esophageal motility. HRM precisely defines esophageal contractile function, peristalsis, and bolus transit when impedance evaluation is included. Compared with conventional manometry, study acquisition is faster, more comfortable, and better tolerated by patients. For technicians and physicians, the topography contour plots increase diagnostic yield and provide an intuitive visual permutation of anatomic and physiologic characteristics.

Classification of Disease

Classifying esophageal motility disorders is an evolving process. Definitions of disease phenotype have changed over time, with improvements in diagnostic technology and better understanding of the clinical importance of various manometric patterns. In 2001, Richter systematically classified esophageal motility disorders using conventional manometric criteria. Using HRM, Kahrilas and colleagues redefined this scheme in 2008 with the first edition of the Chicago Classification of esophageal motility disorders. The Chicago Classification is currently in its fourth edition (CC v4.0), which is intended to simplify and clarify recognition of EPT patterns and physiologic metrics to better define clinically relevant phenotypes of esophageal dysmotility. CC v4.0 classifies the various manometric entities as *disorders of esophagogastric outflow obstruction* and *disorders of peristalsis* (Fig. 1). Manometric findings that do not meet criteria for these categories may be considered normal; however, when compared with CC v3.0, the most recent classification schema recognizes that manometry findings alone may be insufficient to provide a patient diagnosis or guide treatment. In particular, the

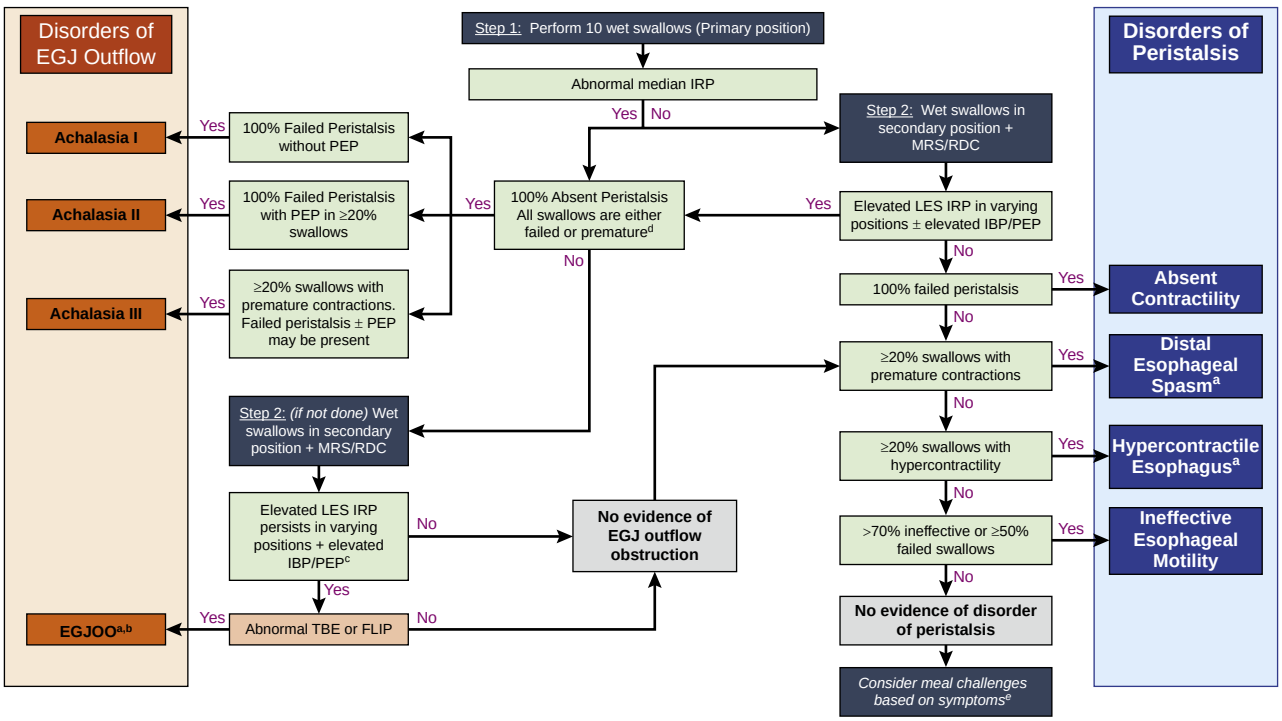


FIG. 1 Chicago Classification v4.0. *EGJ,* Esophagogastric junction; *EGJOO,* esophagogastric junction outflow obstruction; *IBP,* intrabolus pressure; *FLIP;* functional lumen imaging probe; *IRP,* integrated relaxation pressure; *LES,* lower esophageal sphincter; *MRS,* multiple rapid swallow; *PEP,* pan-esophageal pressurization; *RDC,* rapid drink challenge; *TBE,* timed barium esophagram. [a]Manometric patterns of unclear clinical relevance. [b]Patients with EGJOO may have features suggestive of achalasia or disorders of peristalsis. [c]RDC, solid test swallows, and/or pharmacologic provocation with amyl nitrite or cholecystokinin can be used to assess for obstruction. [d]Patients with previously defined absent contractility based on 10 swallows in the primary position may have achalasia if IRP is elevated in alternate position, with RDC, and/or with MRS. [e]A solid test meal can be added to rule out an obstructive pattern. *(From Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0.* Neurogastroenterol Motil. *2021;33:e14058.)*

clinical relevance of esophagogastric junction outflow obstruction (EGJOO), hypercontractile esophagus, and distal esophageal spasm (DES) require corroboration by additional diagnostic testing or presence of associated symptoms. This chapter reviews nonachalasia disorders of esophageal motility according to the hierarchic analysis of the most current version of the Chicago Classification.

Esophagogastric Outflow Obstruction

EGJOO may be the result of intrinsic or extrinsic pathology, which highlights the importance of the comprehensive esophageal workup. Hiatal hernia, peptic stricture, a stiff esophageal body resulting from scarring or radiation, prior surgical interventions, pseudoachalasia resulting from malignancy, or vascular obstruction from a diseased aortic arch are potential sources of mechanical outflow obstruction (Fig. 2A). Prominent vascular artifact on manometry or a history suggestive of malignancy should prompt adjunct evaluation with endoscopic ultrasonography (EUS) or computed tomography. In a retrospective study, findings on selective EUS altered clinical management in as many as 15% of concerning cases. When other mechanical causes of esophagogastric outflow obstruction and achalasia have been ruled out, idiopathic cases remain. This is identified by incomplete relaxation of the EGJ, currently defined by HRM as elevated integrated relaxation pressure and elevated intrabolus pressure in the setting of preserved peristalsis (Fig. 2B), differentiating EGJOO from achalasia.

EGJOO was first introduced as a distinct entity in CC v3.0, and since that time nearly 10% of patients undergoing HRM have been found to have morphology that fits this description. It is hypothesized that EGJOO may represent an incompletely expressed or precursor variant of achalasia, but this has not been verified in large numbers of patients. Furthermore, findings on HRM may be related to artifact, mechanical effects, viral etiology, or opiate use without clinical significance. A notable update to CC v4.0 recommends that in addition to manometric findings of EGJOO, the diagnosis should be supported by both the presence of symptoms such as dysphagia or noncardiac chest pain, and evidence of obstruction on either timed barium esophagram, or real-time impedance evidence of obstruction with the use of a functional lumen imaging probe (FLIP). As opiate medications have been demonstrated to be associated with type III achalasia and EGJOO, it is also recommended that patients be off of these medications before HRM testing. There is controversy over surgical treatment of EGJOO, and the definition of obstruction continues to evolve with subsequent versions of the Chicago Classification. Cases previously classified as hypertensive lower esophageal sphincter (HTLES) by older versions of the Chicago Classification would now likely meet criteria for EGJOO. Interestingly, patients diagnosed with HTLES were found to have paradoxically elevated esophageal acid exposure about 25% of the time, despite relative EGJ obstruction. Therefore, treatment of patients in this group should be tailored based on symptoms. PPIs should be considered if GERD is the major complaint. If dysphagia without abnormal esophageal acid exposure is identified, then medications directed to esophageal smooth muscle relaxation can be attempted. Endoscopic pneumatic dilation (PD) or botulinum toxin (Botox) injections are moderately effective options for relief of obstructive symptoms. Surgical therapy may be indicated in cases of severe or refractory symptoms. Esophageal myotomy, fundoplication, or a combination of the two may be tailored to the patient's symptoms and objective pathophysiology. Antireflux surgery without myotomy has been found to achieve good long-term results for patients with reflux and mild EGJOO caused by acid-induced spasm and inflammation, although preoperative dysphagia was found to predict a higher rate of failure. With dysphagia as the primary symptom, and either treated or normal esophageal acid exposure, laparoscopic Heller myotomy with partial fundoplication and peroral endoscopic myotomy (POEM) have been used successfully. In disorders such as EGJOO that do not affect the

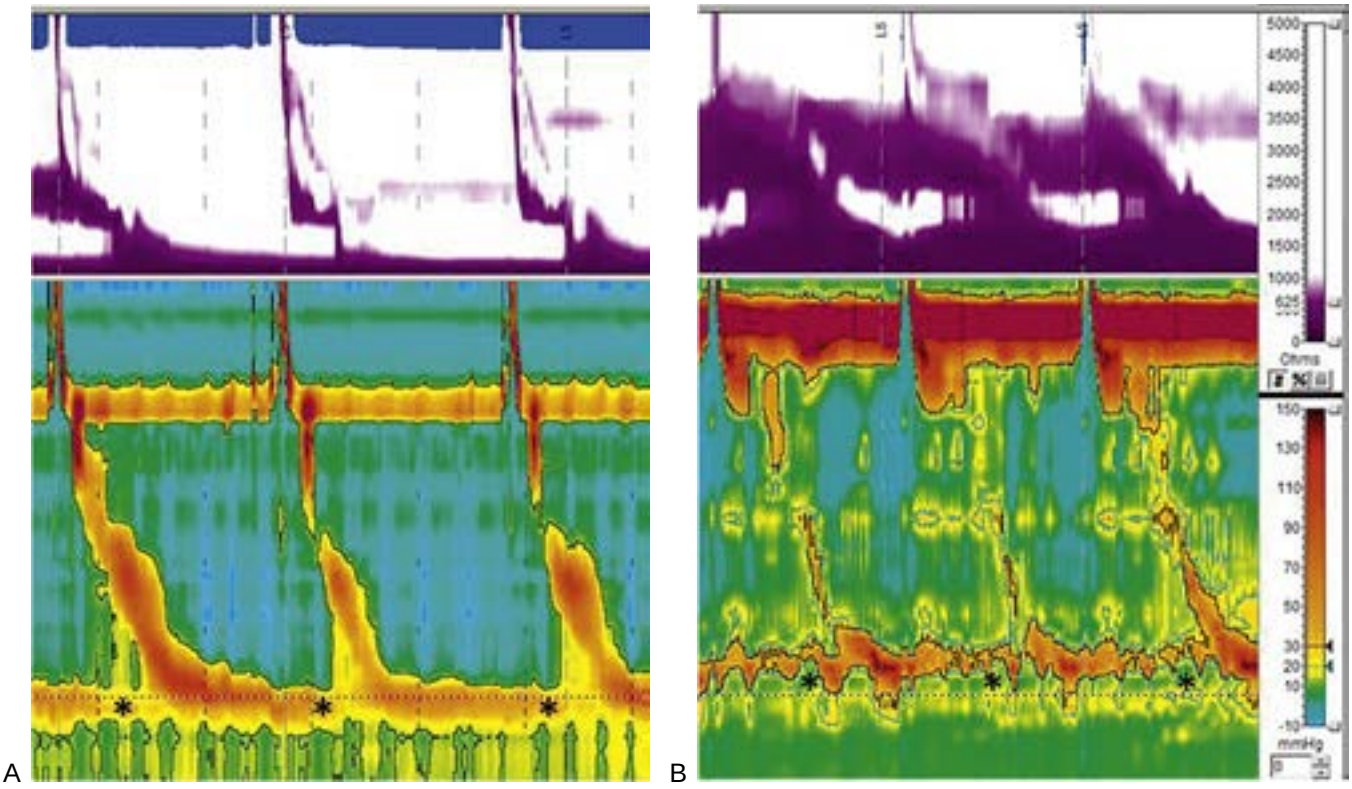


FIG. 2 Esophagogastric junction (EGJ) outflow obstruction. Note the high-pressure, nonrelaxing EGJ *(asterisks)*. **(A)** In this case caused by a hiatal hernia. **(B)** Idiopathic, in the setting of ineffective motility and incomplete bolus clearance. *(Courtesy The Oregon Clinic.)*

esophageal body, abdominal approaches for surgery are favored over thoracic approaches because adequate proximal dissection is possible without accessing the thoracic cavity. Abdominal fundoplication options also offer greater symptom relief and generally are considered less technically challenging.

Disorders of Peristalsis

This group of disorders was previously defined as major and minor esophageal motility disorders in older versions of the Chicago Classification. These disorders are considered when a disorder of esophagogastric outflow obstruction has been ruled out. This group of disorders includes manometric patterns of both hypercontractility and hypocontractility on HRM. Manometric findings may be present in the absence of clinical symptoms, and further supportive testing may be necessary before treatment.

Distal esophageal spasm (DES), also frequently referred to as *diffuse esophageal spasm,* is sometimes grouped with jackhammer esophagus or nutcracker esophagus and achalasia type III as hypercontractile or "spastic" motility disorders. The presence of clinical symptoms of chest pain, dysphagia, or regurgitation resulting from spastic contractions is required for the definition of DES as manometric findings of premature and spastic distal contractions may be seen in the absence of the disorder. The cause of DES is believed to be an impaired neurologic inhibitory pathway, allowing premature esophageal smooth muscle contractions. This disorder may overlap with or progress to achalasia. DES currently is defined by premature contractions in more than 20% of swallows with associated clinical symptoms including dysphagia and noncardiac chest pain. Premature contractions are indicated on HRM as a low distal latency, which is a truncated interval between initiation and deceleration of peristalsis (Fig. 3A). Barium esophagram classically shows a corkscrew pattern of simultaneous contractions, although this pattern is actually uncommon and not required for diagnosis (see Fig. 3B). Treatment options for DES vary. Patients initially may benefit from reassurance with dietary and behavioral modifications or pharmacologic therapy. Persistent cases may require endoscopic intervention with PD or Botox, or surgical myotomy of variable length, though these interventions are more successful in managing symptomatic dysphagia and less effective if the primary symptom is chest pain. Surgical approaches are discussed in more detail in the treatment section of the chapter.

Jackhammer esophagus was named to describe extreme hypercontractility and avoid confusion with DES. This cause of this disorder is believed to be excessive cholinergic drive, causing asynchronous contractions of circular and longitudinal muscle. *Jackhammer* is defined manometrically by at least two swallows with significant hypercontractile vigor as measured by a distal contractile integral (DCI) exceeding 8000 mm Hg • s • cm (Fig. 4A). The hypercontractile segment may involve the esophageal body or may be limited to the esophagogastric junction (EGJ), with EGJ relaxation pressure usually in the upper limit of normal.

Patients with jackhammer esophagus are consistently symptomatic with chest pain, dysphagia, or regurgitation. Nutcracker esophagus was first differentiated from jackhammer esophagus in the CC v3.0 as hypertensive peristalsis with DCI between 5000 to 8000 mm Hg • s • cm (Fig. 4B). Although some patients with DCI in this range are symptomatic, some symptom-free control patients also fall into this range. For this reason, the clinical relevance of nutcracker esophagus has been questioned. Further study of outcomes for these hypercontractile groups will be required with time. Treatment is aimed at controlling spasm and can include dietary and behavioral modifications, pharmacologic therapy, or endoscopic or surgical treatments, which are subsequently discussed.

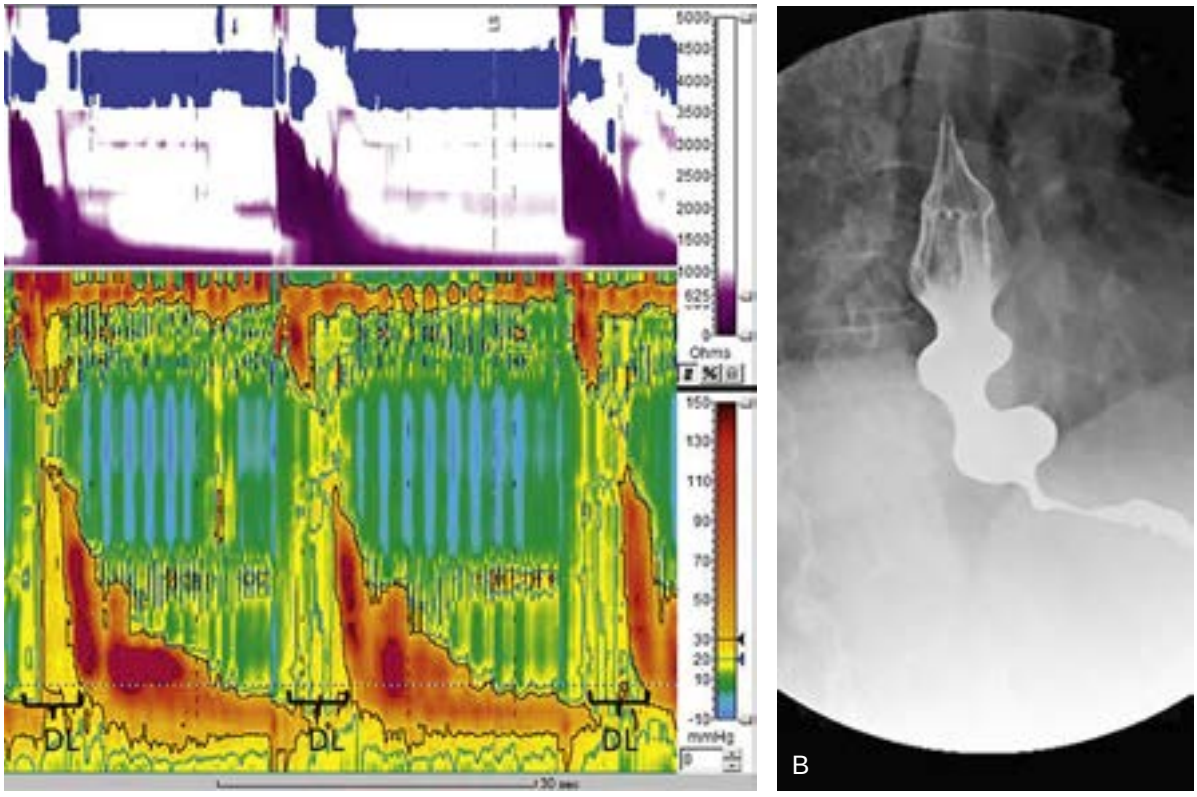


FIG. 3 Distal esophageal spasm. **(A)** Premature contractions with low distal latency (interval between initiation and deceleration of peristalsis). **(B)** Esophagogram with corkscrew pattern of simultaneous tertiary esophageal body contractions. *(Courtesy The Oregon Clinic.)*

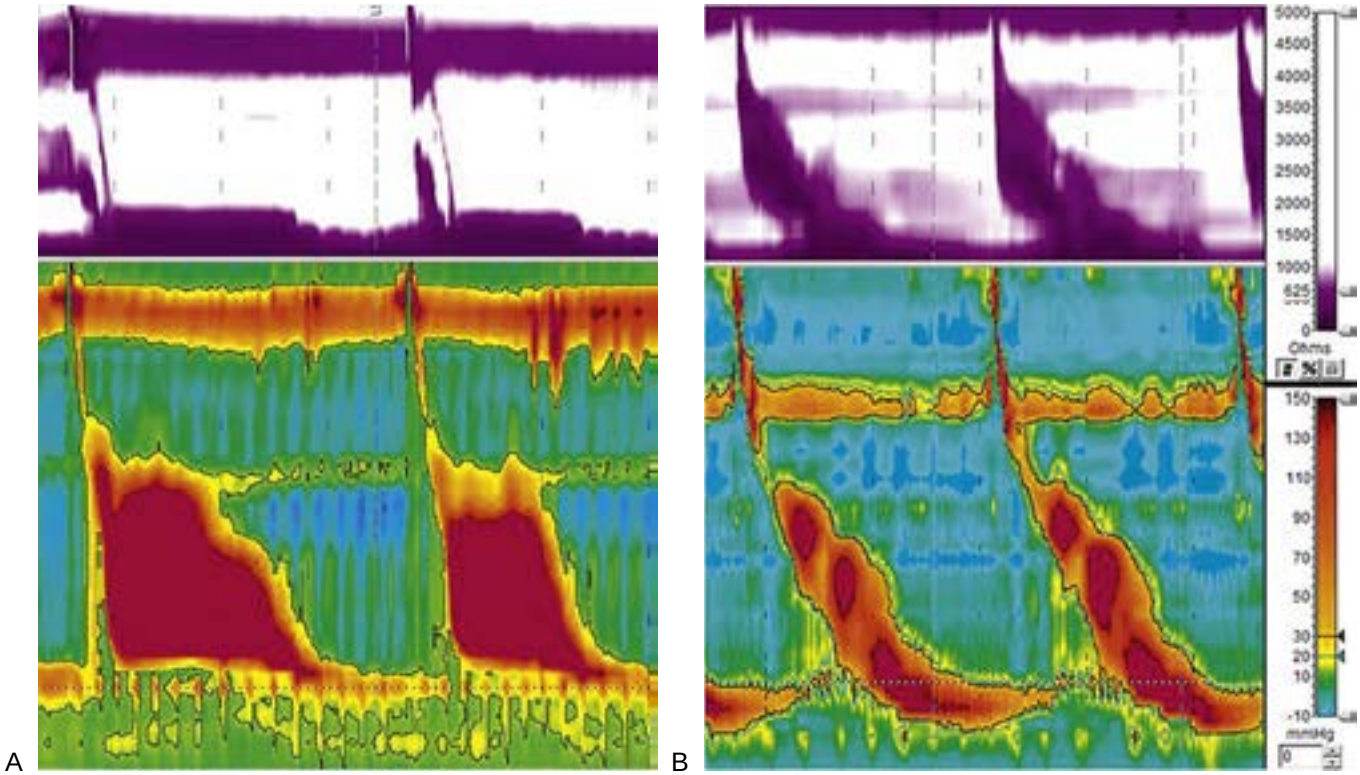


FIG. 4 Hypercontractile disorders. **(A)** Jackhammer esophagus. Extremely elevated contractile vigor (DCI in this case ranged from 12,000–50,000). **(B)** Nutcracker esophagus. Peristaltic, vigorous contractions with DCI 5000 to 8000. DCI, Distal contractile integral. *(Courtesy The Oregon Clinic.)*

The Chicago Classification additionally addresses clinical entities of absent contractility and ineffective esophageal motility. Absent contractility is defined as HRM with hypocontractility and failed peristalsis in 100% of swallows in the setting of an EGJ with normal relaxation pressure. Premature hypocontractile swallows with failed peristalsis are grouped here. In cases with borderline EGJ relaxation and evidence of esophageal pressurization, achalasia should be considered and the patient managed accordingly.

Systemic sclerosis (scleroderma) falls into the *absent contractility* category (Fig. 5). This figure demonstrates complete hypocontraction of esophageal smooth muscle, with preserved skeletal muscle contraction in the upper esophageal sphincter and diaphragm. Therapeutic options specific to diminished esophageal motility are limited, so treatment is directed primarily at the underlying systemic disorder as well as relief of symptoms. Unfortunately, no specific pharmacologic therapy improves contractility and function of esophageal smooth muscle. Prokinetic agents are fraught with side effects and are primarily avoided. GERD has been identified frequently in these patients and should be treated aggressively with PPIs. Antireflux surgery can be considered carefully for refractory GERD cases in this setting, but it should be approached with caution at the risk of exacerbating dysphagia. Because connective tissue disorders such as scleroderma also can affect gastric motility, one should be aware that GERD symptoms may be a result of overflow reflux and should not be treated by fundoplication alone. A small retrospective review of scleroderma patients treated with fundoplication or Roux-en-Y gastric bypass (RYGBP) revealed improvement in control of reflux and dysphagia in the RYGBP group compared with fundoplication. In very carefully selected cases, RYGBP may be considered for primary management of refractory GERD in scleroderma. Less-invasive endoscopic procedures such as suture plication or radiofrequency ablation may be more appealing for GERD in such fragile patients but are less effective at reducing reflux.

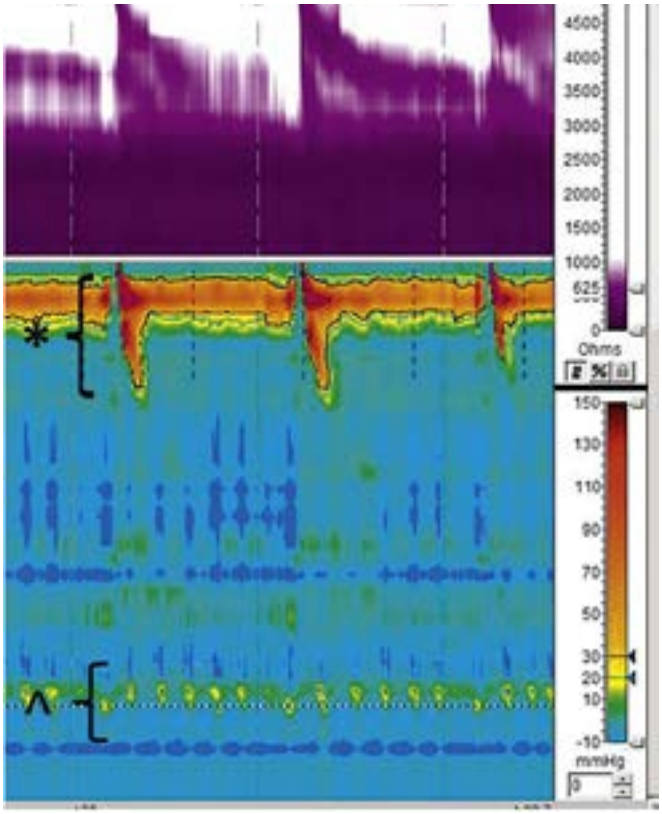


FIG. 5 Absent contractility. This is a case of scleroderma with complete hypomotility of esophageal smooth muscle; note preserved function of skeletal muscle of the upper esophageal sphincter *(asterisk)* and diaphragm *(circumflex)*. *(Courtesy The Oregon Clinic.)*

Ineffective esophageal motility (IEM) is a minor esophageal motility disorder defined by a significant number of weak or failed swallows. Presentation may include heartburn and regurgitation with or without dysphagia, and symptoms tend to be mild. GERD often plays a significant role in the underlying cause of IEM because many of these patients are found to have underlying abnormal esophageal acid exposure. IEM is redefined by HRM criteria in CC v4.0 as at least 50% failed peristalsis, or more than 70% ineffective swallows. Ineffective swallows are indicated by DCI less than 450 mm Hg • s • cm, failed peristalsis indicated by DCI less than 450 mm Hg • s • cm, or fragmented peristalsis (Fig. 6). Interestingly, symptom-free healthy patients may also exhibit a manometric pattern consistent with IEM. In the patient with IEM, the manometry technician may elect to perform additional provocative testing with multiple repetitive swallow (MRS) assessment. Deglutitive inhibition of the esophageal body and EGJ occurs during MRS, usually followed by augmented esophageal contraction vigor and improved bolus transit. Augmented contraction with MRS may be reassuring to the physician who is considering an antireflux procedure to treat underlying GERD while avoiding iatrogenic postoperative dysphagia. When MRS does not augment subsequent contraction, it is predictive of late dysphagia after fundoplication. Although evidence would indicate that there is a relatively low risk of postoperative dysphagia with Nissen fundoplication for patients with IEM, many surgeons choose to carefully tailor a partial fundoplication to avoid the risk of postoperative dysphagia. Clinical implications of MRS findings in this setting have yet to be defined clearly and require further study because these provocative maneuvers are used more frequently with HRM.

Therapeutic options are limited for IEM patients. Because many, if not most, IEM cases are related to chronic reflux disease, correction of GERD may result in correction of the motility disorder. Reassurance and antacid medications along with dietary and behavioral modifications may be helpful. As in other motility disorders, prokinetic drugs generally are not recommended. Low-dose antidepressants, especially tricyclic antidepressants or trazodone, may reduce functional chest discomfort, heartburn, and globus sensation but may not be effective for dysphagia.

Nonoperative Management

The main goals of any treatment for patients with esophageal motility disorders include reduction of chest pain and dysphagia. Treatment is focused on reducing spasm, GERD, and outflow obstruction to facilitate esophageal emptying. Reassurance alone can be beneficial. Reassurance not only helps relieve anxiety but also has been shown to reduce the severity of chest pain and the frequency of healthcare use.

Dietary and Behavioral Modifications

Dietary and behavioral modifications can be very helpful for avoiding chest pain or dysphagia. These modifications include sitting upright and allowing plenty of time for meals, taking small bites, chewing thoroughly, and taking sips of liquid between bites. Foods such as bread, meat, and rice are notorious for worsening dysphagia and should be ingested with caution or minimized. Extremely hot or cold foods can exacerbate esophageal spasm. Choosing soft or liquefied foods can be helpful during symptom flares.

Pharmacologic Therapy

Before pharmacologic therapy is initiated, it is important to carefully review the patient's home medications and minimize those that affect esophageal motility. DES in particular is associated with chronic opioid use and has been shown to improve with opioid cessation. A few classes of drugs have been used with some success in providing symptomatic relief of esophageal spasm. Smooth muscle–relaxing agents (nitrates or calcium channel blockers) taken 15 minutes before meals may provide some symptomatic relief in spastic or hypercontractile disorders, including DES, some cases of EGJOO,

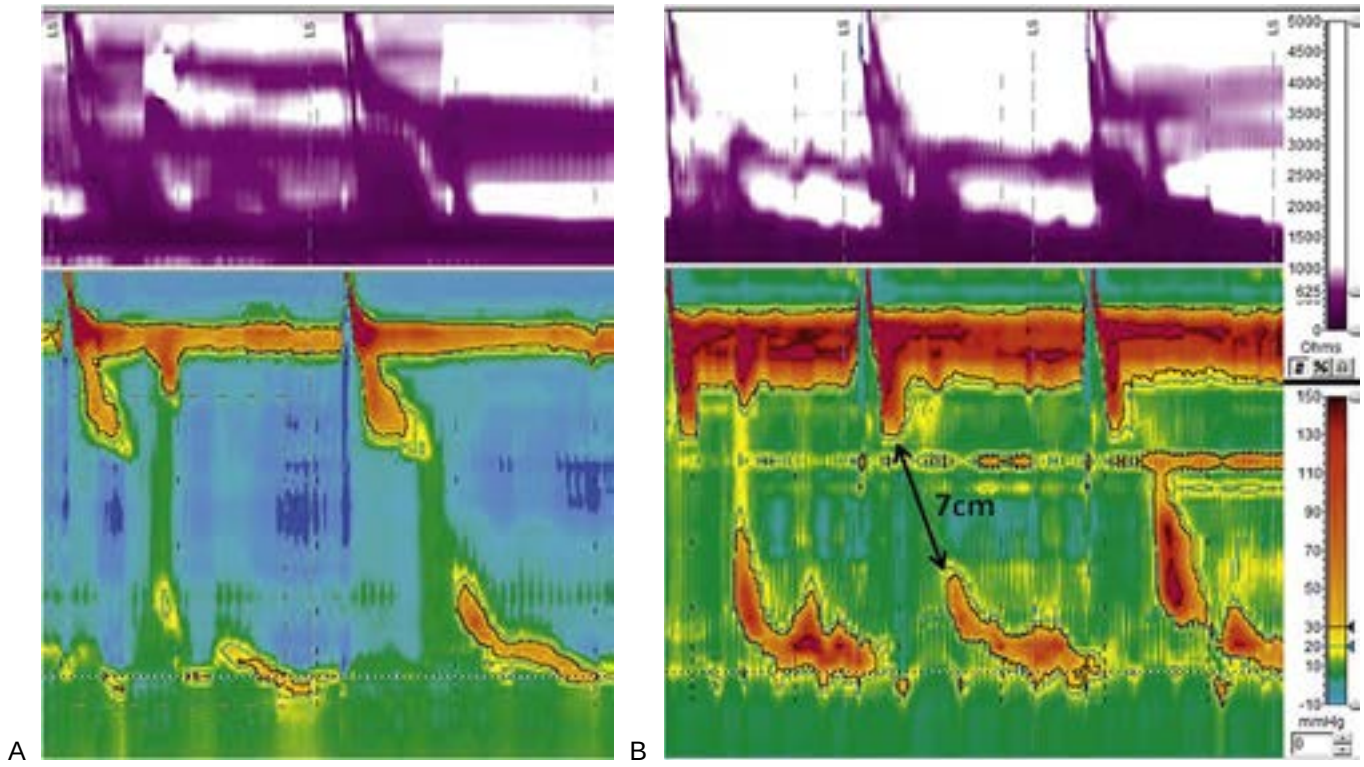


FIG. 6 Minor disorders of peristalsis. **(A)** Ineffective esophageal motility, weak peristalsis (DCI <450). **(B)** Fragmented peristalsis. Large breaks (>5 cm) with preserved contractile vigor (DCI >450). *DCI,* Distal contractile integral. *(Courtesy The Oregon Clinic.)*

and jackhammer esophagus. Phosphodiesterase-5 inhibitors such as sildenafil, which acts by blocking degradation of nitric oxide, also can be effective. These drugs may be tolerated poorly because of lightheadedness, headache, or other side effects, and tachyphylaxis has been noted. The cost of sildenafil may be prohibitive, and effects of daily long-term use of this agent in various populations of patients are unknown. Low-dose antidepressants, including tricyclic agents and trazodone, may provide pain modulation and anxiety relief for noncardiac chest pain. As previously discussed, GERD is frequently part of the clinical syndrome of esophageal dysmotility, although its role in pathogenesis is not understood completely. A trial of PPIs is warranted and may help reduce inflammation, pain, and spasm related to abnormal esophageal acid exposure.

Endoscopic Therapy

PD has been used to treat spastic esophageal motility disorders affecting the EGJ, including EGJOO, DES, and nutcracker esophagus, with variable success. In small studies, 26% to 70% of DES and nutcracker patients had a favorable response with PD, although there is concern that some of these cases may have been classified more accurately as achalasia. From the achalasia literature, there is a known risk of perforation with pneumatic dilation in the range of about 2% to 5% of cases performed by expert endoscopists. This rate of perforation is unacceptable to many endoscopists, who no longer use PD as first-line therapy.

Endoscopic injection of botulinum toxin (Botox) may be temporarily effective in relief of spasm in EGJOO, DES, or jackhammer disorders. The technique for administration of botulinum toxin has not been standardized; some report injection of the EGJ alone, and others include the esophageal body. Botox to the esophageal body may be helpful in cases such as DES or jackhammer, although it is uncertain exactly where and how much drug should be injected. Infection is an uncommon but serious risk of Botox injections. One death resulting from mediastinitis has been reported in a DES case treated with Botox, although other serious adverse events have been rare. Endoscopists may elect to use EUS to guide positioning and depth of injections into the thinner-walled esophageal body. In small studies of patients with EGJOO and DES, successful relief of symptoms with botulinum toxin injections was achieved in more than 50% of patients at 6 months, with further improvement from serial on-demand treatments thereafter. This was comparable to efficacy in achalasia. Fall-off of symptom relief is present in each of these disorders with time, which may require repeat treatments or escalation to surgical intervention. Prominent symptoms and spastic features may predict early recurrence of symptoms. Botulinum toxin before surgical myotomy has been noted to cause submucosal fibrosis and increase difficulty in identifying and maintaining the proper dissection plane. Prior Botox is not an absolute contraindication to surgery, however, and may be useful as a trial to determine if a patient may respond well to surgical myotomy. Long-term studies are not available evaluating the efficacy of repeated botulinum toxin injection for spasm.

Surgical Management

Surgical therapy is an option for nonachalasia esophageal motility disorders, but optimal timing and approach are controversial. Surgery generally has been reserved for medically refractory cases because outcomes are variable, somewhat unpredictable, and may be associated with surgical morbidity. As mentioned earlier, IEM patients with GERD, whether they also have dysphagia, tolerate antireflux surgery with a tailored fundoplication well, and treatment of the reflux often corrects the motility disorder as well. Classically, these patients have a partial fundoplication, most commonly a 270-degree posterior wrap (Fig. 7). Nissen fundoplication also has been shown to be well tolerated in select patients; a full wrap should be reserved for IEM patients with minimal symptoms of dysphagia before surgery and significant reflux disease. Endoluminal antireflux procedures such as Stretta (radiofrequency) and transoral incisionless fundoplication, which provide less-aggressive valve reconstructions, also may be good options for these patients.

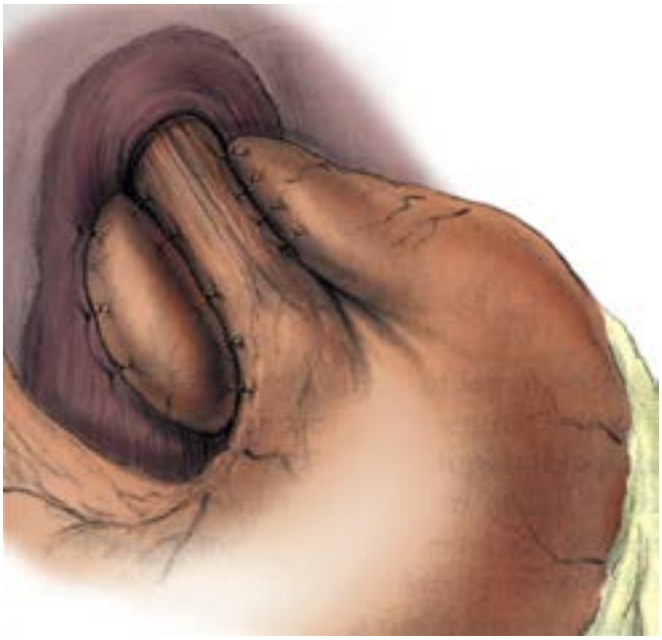


FIG. 7 Completed laparoscopic 270-degree posterior Toupet fundoplication.

Data on surgical outcomes for EGJOO, DES, and other hypercontractile disorders are limited to a few series, mostly small and nonrandomized over the past 50 years. As diagnostic modalities have improved and disease classifications have evolved, these data become even more difficult to interpret. In general, outcomes for surgery are better for relief of chest pain and dysphagia compared with medical or endoscopic therapies. In DES, which is the most frequently studied esophageal motility disorder aside from achalasia, favorable symptomatic outcomes are reported in about 70% of cases treated with surgical myotomy via an abdominal or thoracic approach at highly skilled centers. These outcomes are notably less successful than those for surgical myotomy for achalasia, so surgery often is reserved as a last resort for patients with nonachalasia motility disorders. Symptoms of chest pain are less reliably improved than dysphagia in these patients, and prior series have reported only 50% reduction in chest pain for patients with nutcracker esophagus. Therefore, many of these patients endure long courses of medical or endoscopic therapy because there is no clear definition of "medical failure."

Surgical techniques for esophageal myotomy are varied. Traditional open surgery largely has been replaced by minimally invasive techniques, and new endoscopic options are available. Length of the esophageal body myotomy, inclusion of the EGJ in the myotomy, and addition of a concomitant antireflux procedure are variable from surgeon to surgeon. Previous authors in this text have recommended a long thoracic myotomy for the treatment of DES or other esophageal body motility disorders and have described the technique in detail (Fig. 8). Thoracic access allows myotomy extension for the full length of the esophageal body, which is not possible with laparoscopic Heller myotomy. However, thoracic myotomy has the disadvantage of requiring single lung ventilation, chest tube placement, and typically a longer length of stay. The thoracic approach is complicated further if the surgeon desires a fundoplication or extended gastric myotomy.

POEM offers several advantages for esophageal myotomy and is preferred as a less invasive technique for patients with hypercontractile/spastic esophageal motility disorders. This natural orifice transluminal endoscopic surgery procedure is completely endoscopic

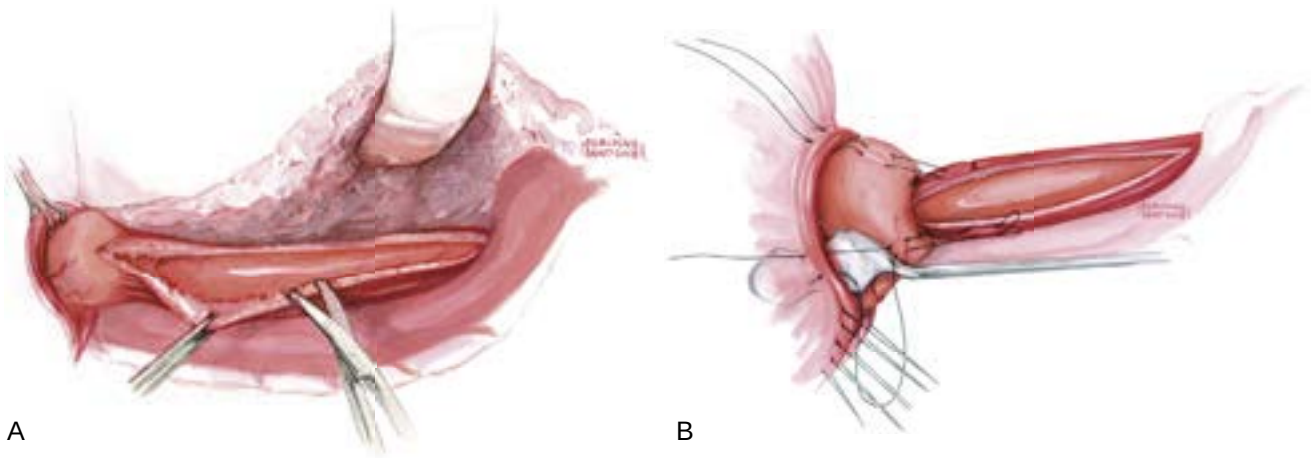


FIG. 8 (A) Thoracic myotomy and **(B)** Belsey fundoplication. Courtesy Corinne Sandone. *(From Cameron JL, Sandone C.* Atlas of Gastrointestinal Surgery, *vol 1. 2nd ed. Shelton, CT: People's Medical Publishing; 2007.)*

and incisionless. It provides the ability to tailor the length and location of the myotomy with ease because the entire affected esophageal body and EGJ are accessible. POEM allows the surgeon to produce a selective circular myotomy and avoids the risk of vagus nerve injury or disruption of the diaphragmatic crural component of the EGJ. Single lung ventilation, lateral or prone positioning, and chest tubes are not required. Moreover, postoperative pain is usually minimal.

POEM was first applied clinically for achalasia by Inoue in 2008, and since then more than 4000 cases have been performed worldwide with an excellent safety profile and good clinical results, mostly for patients with achalasia. Until recently, studies of POEM for nonachalasia esophageal motility disorders included only a few such cases and have not always been stratified by subtype. POEM is also used for spastic esophageal disorders such as DES, jackhammer esophagus, and EGJOO (including cases of nutcracker esophagus and HTLES as classified before CC v3.0) with favorable results. POEM has reported success rates of more than 80% for these disorders with relatively low morbidity at expert centers. In a meta-analysis by Khan et al. examining the clinical success of POEM in spastic esophageal disorders including type III spastic achalasia, DES, and nutcracker esophagus, 179 patients were pooled for analysis from 8 observational studies. Clinical success for all types of spastic esophageal disorders was 87%. Although these studies are small, they suggest comparable outcomes for extended POEM with low morbidity compared with traditional open or laparoscopic/thoracoscopic approaches for extended esophageal myotomy.

Given the subsequent weakening of peristalsis after esophageal body myotomy, it is recommended to extend the myotomy through the EGJ onto the stomach to prevent relative outflow obstruction and postoperative dysphagia, even in the setting of a normally relaxing EGJ. POEM myotomy length should be tailored based on HRM topography and endoscopic measurement of the high-pressure zone and has been extended proximally anywhere between 6 and 23 cm above the gastric cardia in such cases. POEM with variable length of myotomy was comparable to other surgical techniques for relief of dysphagia and chest pain and had less morbidity.

A disadvantage of POEM is the requisite learning curve, which is about 20 cases for experienced endoscopists as demonstrated by Kurian and colleagues. GERD is also a long-term risk of POEM, currently with a 20% to 46% risk based on cumulative data. This is in fact comparable to Heller myotomy with partial fundoplication, which has a postoperative rate of GERD between 21% and 42%, depending on the fundoplication technique. Postoperative GERD is asymptomatic in one-half of patients, so routine follow-up pH testing or endoscopy is prudent. Patients identified with GERD have been treated successfully with PPIs with avoidance of long-term sequelae of reflux thus far. POEM results in a low rate of clinically significant leak or stricture and has been shown to be safe and effective in revision after Heller myotomy, Botox, and PD. POEM does not preclude subsequent endoscopic, laparoscopic, or thoracoscopic procedures should they be required. Because of these benefits, extended myotomy by POEM should be the preferred approach for primary spastic motility disorders requiring intervention.

Peroral Endoscopic Myotomy Operative Technique

Previous chapters in this and other texts have described esophageal myotomy with or without fundoplication via abdominal and thoracic approaches, so these are not repeated in detail here.

POEM is performed in the operating room under general anesthesia. The procedure requires a high-definition endoscope for optimal visualization and CO_2 insufflation because it has a better safety profile than room air. The patient is placed in the supine position to allow access to the abdomen or chest. For a few days before the procedure, patients are given a Nystatin rinse prophylactically to clear any *Candida* esophagitis related to esophageal stasis and allowed only a liquid diet for 1 day to allow clearance of retained food. A preoperative antibiotic and a single preoperative dose of intravenous steroid are administered to prevent development of mucosal edema.

Upper endoscopy is performed to evaluate the anatomy, rule out *Candida* spp., and clear any fluid or food debris within the esophagus before proceeding. An endoscopic functional lumen imaging probe (EndoFLIP) is used to measure baseline esophageal diameter, pressure, cross-sectional area, distensibility, and compliance. An overtube is used for distal myotomy to stabilize the scope from overtorquing. No overtube is used for extended myotomy. The gastric wall is tattooed with indigo carmine 2 cm distal to the EGJ in the anterior position along the lesser curvature, marking the target for the distal extent of the myotomy. The location and extent of the myotomy and mucosotomy are calculated based on careful evaluation of the preoperative manometry and intraoperative evaluation of the high-pressure zone. An angled dissecting cap is attached to the high-definition endoscope to facilitate dissection and visualization. A mucosal lift is created with injectable saline with dilute indigo carmine in the anterior esophagus 2 to 4 cm proximal to the proximal extent of the planned myotomy (Fig. 9).

An endoscopic cautery knife is used to create a 1.5-cm longitudinal mucosal incision to expose the submucosa. Using the dissecting cap, the surgeon advances the endoscope through the mucosotomy and into the submucosal plane. Once inside, spray cautery and serial injections of lifting solution are used to create a submucosal tunnel, separating the mucosa from the circular muscle. Visible vessels are coagulated with the dissecting knife or grasped with hot biopsy

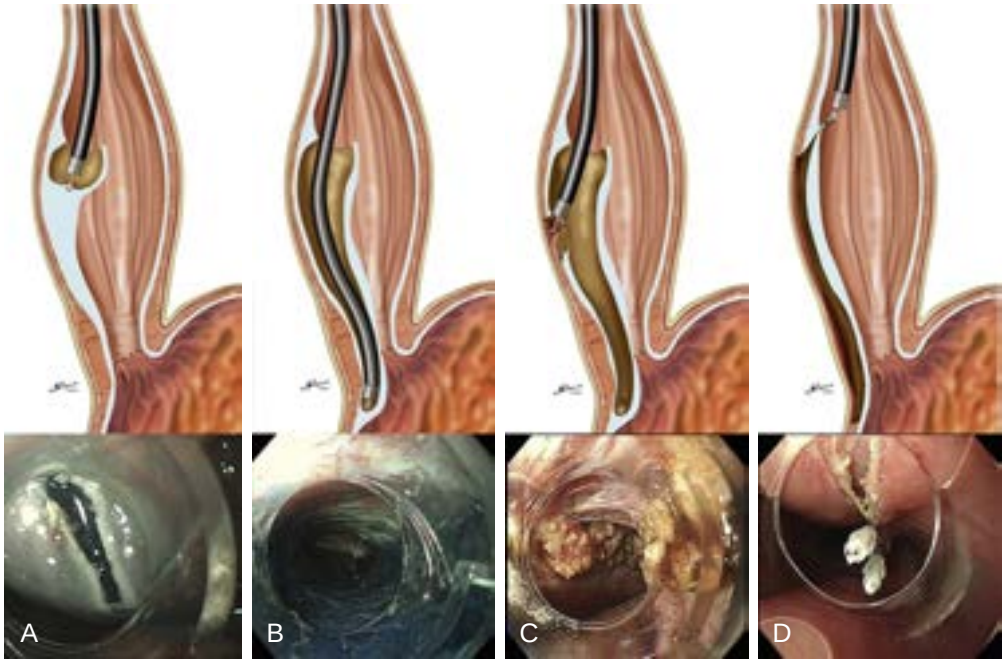


FIG. 9 Peroral endoscopic myotomy. **(A)** Entry into submucosal plane. **(B)** Creation of submucosal tunnel (mucosa is inferior, circular muscle is superior). **(C)** Myotomy of circular muscle. **(D)** Closure of mucosal entry site with clips. *(From Inoue H, Sato H, Ikeda H, et al. Per-oral endoscopic myotomy: a series of 500 patients.* J Am Coll Surg. *2015;221:256–264).*

forceps. The submucosal tunnel is extended distally across the GEJ and onto the gastric wall until the distal darker blue tattoo is reached.

Once satisfied with the extent of the tunnel, the endoscope is brought back, and the myotomy is created by selectively dividing the circular muscle layers. The thin longitudinal muscle layer is left intact whenever possible. Full-thickness breaches of the muscle are usually not critical as the mediastinal adventitial tissue is left intact. The myotomy is extended across the EGJ and onto the proximal gastric wall. During the procedure, exiting the tunnel to deflate insufflated gas from the stomach may be required to relieve gastric distension. Capnoperitoneum may develop in up to 30% of cases; it is often minor and self-limited but is evacuated easily with a Veress needle if abdominal overdistension or respiratory compromise develops.

After the myotomy is completed, the surgeon withdraws the endoscope, checking for hemostasis. Completion endoscopy identifies any inadvertent mucosal injuries, which are treated with endoscopic clips. The EndoFLIP catheter is replaced, and measurements are compared with those obtained before surgery to ensure adequacy of the myotomy before closure. Endoscopic clips then are used to close the proximal mucosotomy in a longitudinal fashion from distal to proximal.

Postoperative Care

The patient is kept NPO overnight, and a routine contrast esophagram is obtained on the first postoperative day. If no leaks or obstruction are identified, the patient is allowed clear liquids and crushed medications. The patient may be discharged on postoperative day 1 if liquids are tolerated and should maintain a puree-consistency diet for 1 week to avoid disruption of the mucosal closure clips. In most cases, postoperative pain is minimal and usually does not require narcotics.

Complications

Acute postoperative complications can include intratunnel bleeding, mucosal leak or dehiscence, or mediastinitis. No deaths have been reported. Bleeding may require transfusion and repeat endoscopy to achieve hemostasis. Mucosal leaks or dehiscence may seal with conservative management but often require repeat endoscopy and repair with additional clips or suturing. Mediastinitis is treated with antibiotics and may require percutaneous or surgical drainage. Postprocedure adverse events in the meta-analysis reported by Khan et al. for all types of spastic esophageal disorders were 14%. Most of the adverse events (74%) were managed conservatively. Five patients required prolonged hospitalization and/or an intervention for pneumothorax, pulmonary embolism, capnoperitoneum, or bleeding.

CONCLUSION

There is work to be done in the realm of nonachalasia esophageal motility disorders as HRM diagnostics and treatment options evolve. To achieve the best possible outcome, therapeutic options should be considered carefully and individually tailored. Patients should be advised on expectations because treatment outcomes are somewhat unpredictable and may be disappointing in some cases. POEM is a promising, minimally invasive treatment option for hypercontractile and spastic disorders and perhaps will be considered as an early surgical intervention rather than salvage therapy, given its relative success and safety profile. For hypomotility disorders associated with GERD, partial fundoplications remain the gold standard, although Nissen fundoplication also has been shown to be well tolerated in many cases of at least partially preserved peristalsis. There also may be a role for newer endoscopic antireflux procedures, although there are insufficient data at this time to define their application for these relatively rare disorders.

ACKNOWLEDGMENT

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Management of Esophageal Cancer

Fatima G. Wilder, MD, and Stephen C. Yang, MD

EPIDEMIOLOGY

Esophageal cancer is the eighth deadliest cancer in the world as reported by the World Health Organization in 2020. The two predominant histologic types are adenocarcinoma (most common in the United States) and squamous cell carcinoma (most common worldwide). Notable risk factors include gastroesophageal reflux, smoking, alcohol consumption, nutritional deficiencies, environmental carcinogens, long-standing achalasia, and caustic injury.

CLINICAL PRESENTATION

Commonly reported symptoms at the time of presentation include regurgitation, odynophagia, weight loss, and hematemesis. Dysphagia is the most common presenting symptom in patients with esophageal cancer. In the early phases of obstruction, patients typically compensate for their symptoms by adjusting their diet and consuming semisolid and liquid nutrition as tolerated. Dysphagia does not typically present until the tumor occludes two-thirds of the lumen. A notable component of the patient's past medical history is often a long-standing history of gastroesophageal reflux disease with or without a hiatal hernia. Due to the fact that symptoms often present late, patients are typically at an advanced stage at the time of diagnosis. However, those with a history of reflux disease may be diagnosed earlier on surveillance endoscopy.

DIAGNOSIS/STAGING

Diagnosis and staging should be carried out in an expeditious manner to avoid delay in therapy, potentially compromising outcome. The eighth edition of the American Joint Committee on Cancer (AJCC) staging of epithelial cancers of the esophagus and esophagogastric junction (EGJ) presents separate classifications for clinical (cTNM), pathologic (pTNM), and postneoadjuvant (ypTNM) stage groups, and differs slightly between adenocarcinoma and squamous cell histologies (Fig. 1).

Barium swallow should be the first study in the diagnostic workup of esophageal cancer, as it will provide critical information regarding the source of obstruction. However, esophagogastroduodenoscopy (EGD) remains the gold standard for evaluation and tissue diagnosis when there is a concern for malignancy. It allows for identification of anatomical location of the mass, tumor characteristics, relation to surrounding structures, and tumor grade. Evidence of Barrett's esophagus should be characterized according to the Prague criteria.

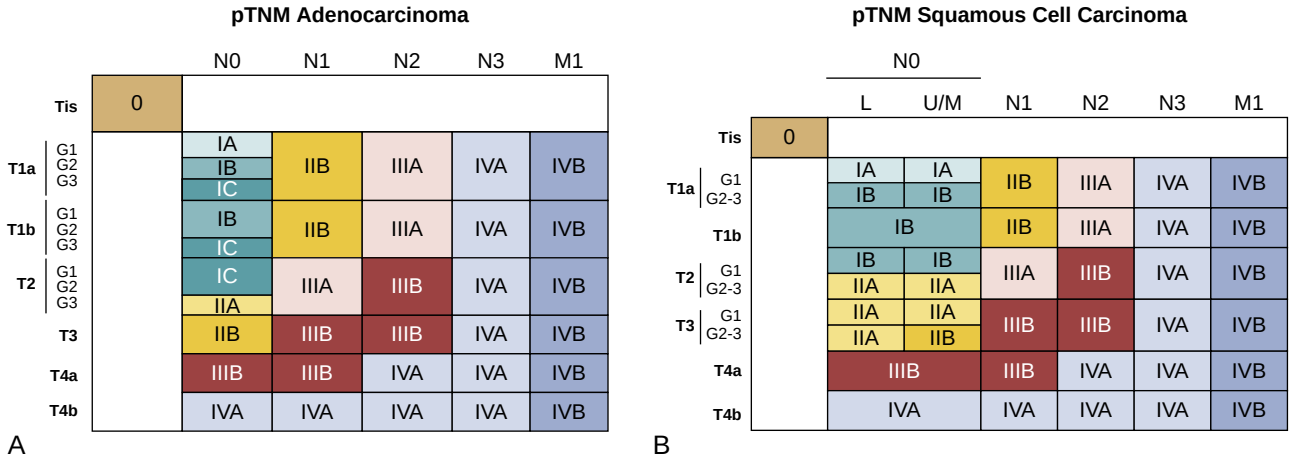


FIG. 1 Staging of esophageal cancer, American Joint Committee on Cancer Manual, eighth edition. Pathologic stage groups (pTNM) for **(A)** adenocarcinoma and **(B)** squamous cell carcinoma. *(From Rice TW, Ishwaron H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer. J Thoracic Oncol. 2017;12[1]:36–42.)*

TABLE 1 Siewert Classification

Siewert Type	Description
I	Adenocarcinoma of the lower esophagus with the epicenter located within 1 to 5 cm above the anatomic GEJ
II	True carcinoma of the cardia with the tumor epicenter within 1 cm above and 2 cm below the EGJ
III [Considered gastric cancer; utilize gastric cancer algorithm for management guidelines]	Subcardial carcinoma with the tumor epicenter between 2 and 5 cm below the EGJ, which infiltrates the EGJ and lower esophagus from below

All suspicious lesions should be biopsied simultaneously. Based on the Seattle protocol, six to eight four-quadrant biopsies of the mass utilizing standard size endoscopy forceps should be obtained along every centimeter of gross disease.

If available at the time of EGD, endoscopic ultrasound (EUS) is important as an early staging modality and to determine the Siewert classification (Table 1), as location will determine optimal treatment pathways. EUS will also assess tumor invasion (T stage), presence of suspicious lymph nodes (N stage), and, at times, presence of regional metastases (M stage). The addition of fine-needle aspiration (FNA) aids in the accuracy of diagnosis.

Endoscopic mucosal resection (EMR) can be considered therapeutic especially in patients with early-stage disease (T1a or T1b). This typically correlates with small, nodular lesions ≤2 cm. Focal nodules should be completely excised and sent for pathology. Tumor samples should be assessed for depth of invasion, degree of differentiation, and presence of vascular and/or lymphatic invasion. Presence of poor differentiation, deep submucosal invasion, and/or lymphovascular invasion (LVI) are associated with greater risk of lymph node involvement.

Additional workup including computed tomography (CT) of the chest, abdomen, and pelvis with oral and IV contrast is indicated to evaluate for metastatic disease, assess the locoregional extent of the disease, and evaluate for issues of unresectability. CT is poorly sensitive for early-stage disease, type of Siewert location, and limited in its ability to distinguish T3 from T4 lesions. However, esophageal thickening of more than 5 mm clearly is considered abnormal. Whole body ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT is done to assess for metastatic disease. In patients with tumor that is at or above the carina, with no evidence of M1 disease, bronchoscopy should be performed.

Symptom management in the preoperative settings includes esophageal dilation for those with obstructive symptoms. Tumor ablation with Nd:YAG laser, photodynamic therapy (PDT), and cryoablation can be utilized for long-term ablation. Expandable metal or plastic stents can also be utilized to relieve obstructive disease but should not be placed if radiation therapy is offered for local control.

STAGE-BASED TREATMENT STRATEGIES/ ALGORITHMS

There are subtle differences in the treatment of esophageal cancer based on stage depending on the histology; these are briefly listed in Table 2.

T1 tumors involving the mucosa and superficial submucosa may be addressed with EMR or endoscopic submucosal dissection; deeper submucosal lesions may be treated with esophagectomy. Data regarding treatment of squamous cell carcinoma with EMR are limited.

Optimal management of T2N0M0 disease is somewhat controversial. Due to unreliable clinical staging modalities, a significant percentage of patients are under- and overstaged. Although historical evidence supports induction therapy for this group, there are a growing number of studies that suggest induction therapy is not beneficial in those with node-negative disease. Current NCCN guidelines suggest that, for patients who are medically fit, there are a variety of treatment possibilities including definitive chemoradiation and esophagectomy with or without induction or adjuvant therapy.

Treatment selections also take into consideration low- versus high-risk lesions. cT1b-cT2, N0 low-risk lesions that are <3 cm in size and well-differentiated should be resected with esophagectomy (including for noncervical squamous cell cancer). Generally, higher risk lesions (LVI, ≥3 cm, poorly differentiated), cT1b-cT2N+, or cT3-cT4aN+ should undergo preoperative chemoradiation (for noncervical squamous cell) or definitive chemoradiation (for cervical squamous cell). In patients with adenocarcinoma, preoperative

TABLE 2 Treatment Strategies for Adenocarcinoma and Squamous Cell Carcinoma in Medically Fit Patients

Tumor Classification	Adenocarcinoma	Squamous Cell
pTis	ER ± ablation Esophagectomy	ER and/or ablation Esophagectomy
pT1a	ER ± ablation Esophagectomy	ER and/or ablation Esophagectomy
Superficial pT1b	ER ± ablation Esophagectomy	Esophagectomy
cT1bN0-cT2N0 (low-risk lesions: <3 cm, well differentiated)	Esophagectomy	Esophagectomy (noncervical esophagus)
cT2N0 (high-risk lesions: LVI, ≥3 cm, poorly differentiated) cT1b-cT2N+ or cT3-cT4a, any N	Induction chemoradiation therapy Definitive chemoradiation therapy (for those who decline surgery) Induction chemotherapy	Induction chemoradiation therapy (noncervical esophagus) Definitive chemoradiation (for cervical esophagus)
cT4b	Definitive chemoradiation therapy or chemotherapy alone	Definitive chemoradiation therapy or chemotherapy alone

ER, Endoscopic resection; *LVI,* lymphovascular invasion; *Tis,* tumor in situ.
Adapted from National Comprehensive Cancer Network treatment guidelines, August 3, 2021.

chemoradiation is preferred. Definitive chemoradiation should be reserved for patients who decline surgery, have poor performance status, and those with bulky, multistation nodal involvement.

Approximately 32% of patients with esophageal cancer are found to have regional disease at the time of diagnosis. Survival is found to only be in the 10% to 30% range. Management of patients with T3-4aN0, T1-4aN1M0 is highly variable. NCCN guidelines suggest a variety of combinations of esophagectomy and chemoradiation as opposed to definitive chemoradiation. Recent studies suggest that induction chemoradiation followed by surgery is the optimal treatment for patients with T3-4a tumors or nodal disease. Additionally, a recently published randomized trial demonstrated a survival benefit to induction chemoradiation after surgery compared with surgery alone for esophageal or EGJ cancer.

OPERATIVE APPROACHES TO ESOPHAGEAL CANCER

Surgical Resection

Before any operative planning, patients should be assessed for their ability to undergo general anesthesia and major surgery. One must take into account a patient's age and performance status in making this decision. Although no defined number of lymph nodes has been definitively established, NCCN guidelines suggest that patients who have not received induction chemoradiation should have at least 15 lymph nodes resected and assessed for adequate staging. Cervical or cervicothoracic esophageal carcinomas located less than 5 cm from the cricopharyngeus should be treated with definitive chemoradiation. Consideration should be given to placement of a feeding tube (jejunostomy tube preferred) before induction therapy if the patient is near totally obstructed and cannot tolerate any oral liquids.

Approaches to resection of esophageal cancer include (open versus minimally invasive) Ivor Lewis, McKeown, transhiatal, or left transthoracic/thoracoabdominal approach with the anastomosis in the chest or neck. Selection of the operative approach depends on tumor location and surgeon expertise. Options for a conduit are the stomach (preferred), colon, or jejunum. NCCN guidelines recommend definitive chemoradiotherapy for patients with cervical esophageal squamous cell carcinoma. Minimally invasive techniques include laparoscopy, thoracoscopy, and robotic approaches; there are hybrid approaches that combine open/minimally invasive, but available data show no superiority for any specific technique.

Ivor Lewis Esophagectomy

Ivor Lewis esophagectomy is the most commonly performed method of esophageal resection worldwide in patients with esophageal cancer. Although open resection is still utilized by some, minimally invasive esophagectomy (MIE) has rapidly become the more common approach. Data have suggested decreased morbidity and faster recovery times with this approach when compared with open resection. Ivor Lewis esophagectomy is ideal for intraabdominal and intrathoracic exposure in patients with cancer in the mid- and distal esophagus. With either the open or minimally invasive approach, resection begins with the patient in the supine position. In MIE, the patient is placed in a split-leg position with moderate reverse Trendelenburg. Intraperitoneal access is obtained by standard upper midline laparotomy for open resection. In the MIE approach, five intraabdominal ports and an atraumatic liver retractor for the left hepatic lobe are positioned to expose the hiatus. The intraperitoneal space should be carefully inspected to rule out any metastatic disease. Once this is confirmed, dissection is started at the gastrohepatic ligament, exposing the right crus. Care is taken to preserve a large accessory or replaced left hepatic artery. A complete D2 lymph node dissection is performed starting at the celiac trunk and following the hepatic and left gastric artery, the superior margin of the portal vein, and the peripancreatic tissue. The left gastric vascular pedicle is divided with a stapling device or suture ligation. A thorough node dissection is particularly important for adenocarcinoma of the cardia, which has higher propensity to metastasize to these lymph nodes. Equally important is an en bloc dissection of the distal mediastinum, which is easily done from the laparoscopic approach. The gastrocolic ligament is then divided just distal to the gastroepiploic arcade taking care not to injure the perigastric vascular structures, which might compromise the blood flow to the newly formed gastric conduit (Fig. 2). In situations where there is difficulty with identification of the right gastroepiploic artery, fluorescence imaging and Doppler at this stage can facilitate identification and determine the adequacy of perfusion at the distal conduit.

The dissection is carried out medially to the level of the duodenum and then extended to the fundus by dividing the short gastric vessels and the lateral phrenoesophageal ligament. The stomach is then lifted anteriorly, and the retroperitoneal attachments are divided. Pyloroplasty or botulinum toxin injection of the pylorus is performed at this stage to aid the emptying of the conduit. Transhiatal dissection of the esophagus is then performed dividing the phrenoesophageal ligament and dissecting the paracardial and lower paraesophageal nodes and dividing the peritoneum from the crurae bilaterally. A Penrose drain is used to encircle the distal esophagus for retraction during both the abdominal and thoracic phase. A 3 to 5 cm-wide gastric conduit is then created by dividing the stomach with multiple findings of a linear stapler, starting at the level of the incisura on the medial side all the way proximal to the fundus leaving the last 5 cm of stomach undivided to allow retrieval during the thoracic phase (Figs. 3 and 4). The staple line can be reinforced either with a running or interrupted Lembert suture. As a final step, a feeding jejunostomy tube is inserted in the small bowel.

After the abdominal portion is complete and the incisions are closed, the patient is re-positioned in the left lateral decubitus position. While this is the traditional approach, there are centers that complete the thoracic portion with the patient in the prone position. Anesthesia is asked to collapse the right lung either by use of a double lumen endotracheal tube or capnothorax with minimally invasive ports. A posterolateral thoracotomy incision is made in the fifth intercostal space and access is gained to the thorax. In the MIE approach, four trocars are placed in the thoracic wall in a diamond pattern. The pulmonary ligament is divided to the level of the inferior pulmonary vein. A retractor (fan retractor if MIE) is placed to improve visualization of the posterior mediastinal pleura at the level of the azygos vein. The azygos vein is divided with a vascular stapler to allow exposure of the entire esophagus (Fig. 5).

The Penrose drain left around the esophagus is retrieved and used to retract the esophagus and facilitate dissection. The esophagus is dissected out of the mediastinum, being extremely careful using energy devices in the subcarinal and paratracheal areas to avoid injury to the airway. Proximal dissection should be carried out to provide a margin of 5 cm from the tumor's edge. The esophagus is then divided and the proximal margin is sent for frozen section to assess for the presence of Barrett's esophagus and tumor.

With the esophagus mobilized from the mediastinum, lymph node dissection is performed in the paratracheal, subcarinal, and inferior pulmonary ligament regions. Some surgeons also prophylactically ligate the thoracic duct by passing sutures at the T9 and/or T10 level in the prevertebral tissues.

The gastric conduit is then gently pulled up into the chest up to the level of the staple line that was previously created, making sure no twists are present. A transoral circular end-to-end anastomotic (EEA) stapler is then inserted through the patient's mouth into the esophageal stump. The nasogastric tube connected to the anvil is passed through a small opening next to the staple line and removed through one of the trocars. At this point, fluorescence imaging can be used again to determine appropriate perfusion of the conduit. This can be trimmed to a point of maximal perfusion, making sure that excessive tension is avoided. The EEA stapler is introduced

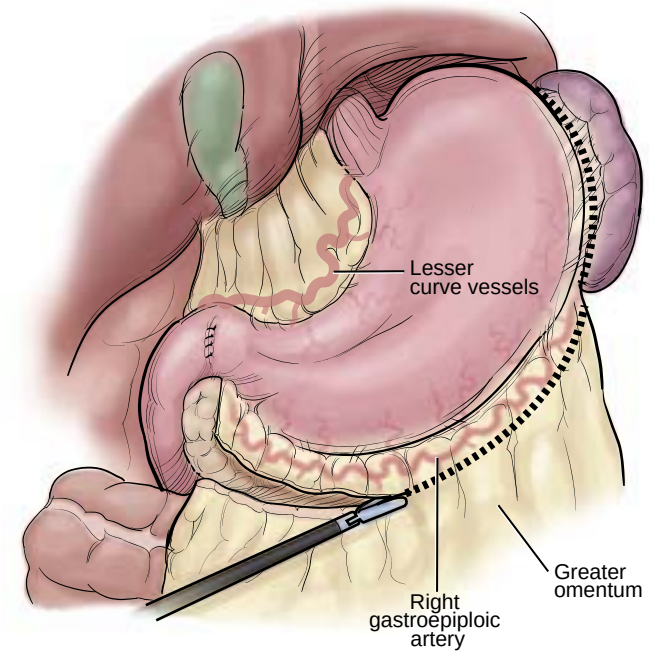


FIG. 2 Division of gastrocolic ligament with preservation of the right gastroepiploic vessels during the abdominal portion of the esophagectomy. *(From Khatri V.* Atlas of Advanced Operative Surgery. *Philadelphia: Elsevier; 2012.)*

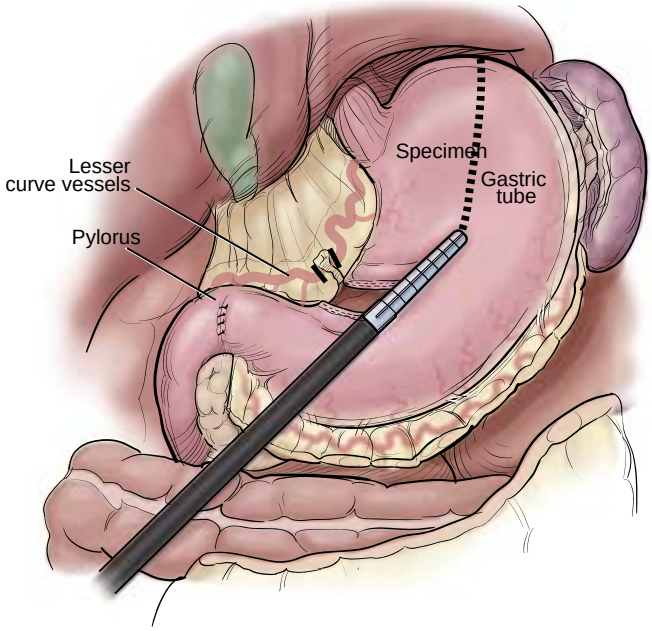


FIG. 3 Creation of the conduit. *(From Khatri V.* Atlas of Advanced Operative Surgery. *Philadelphia: Elsevier; 2012.)*

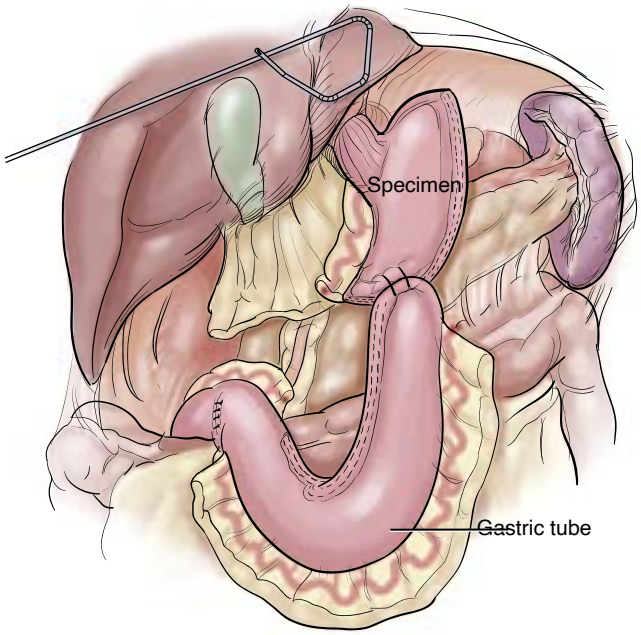


FIG. 4 Creation of the conduit. *(From Khatri V.* Atlas of Advanced Operative Surgery. *Philadelphia: Elsevier; 2012.)*

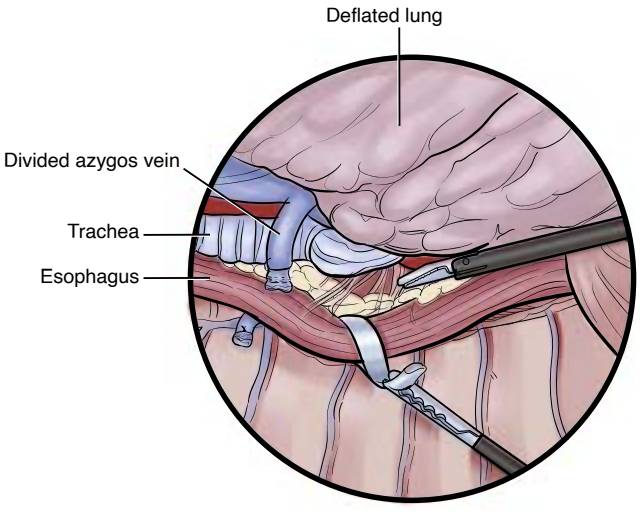


FIG. 5 Thoracic mediastinal exposure after division of the azygos vein. *(From Khatri V.* Atlas of Advanced Operative Surgery. *Philadelphia: Elsevier; 2012.)*

through an opening made in the proximal gastric conduit. The conduit is pulled over the stapler to allow the piston to come out next to the greater curvature of the stomach in the area chosen for the anastomosis (Fig. 6). The anvil and the stapler are engaged, and the stapler is fired to complete the anastomosis. Using a linear stapler, the specimen is trimmed from the conduit (Fig. 7). The specimen is then extracted with the help of a wound protector and the gastric margin is checked. If excess perigastric fat is available from the conduit, this is placed around the anastomosis to decrease the chance of an anastomotic leak.

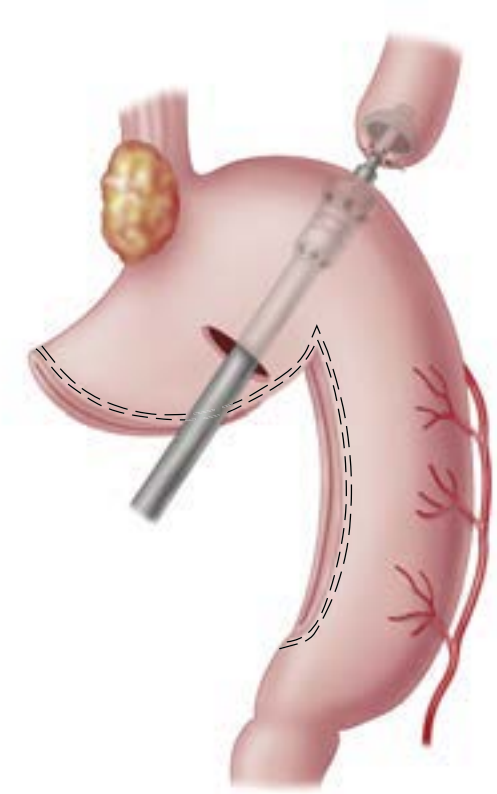


FIG. 6 Insertion of the EEA stapler and creation of the anastomosis. *(From Zwischenberger JB.* Atlas of Thoracic Surgical Techniques. *Philadelphia: Elsevier; 2010.)*

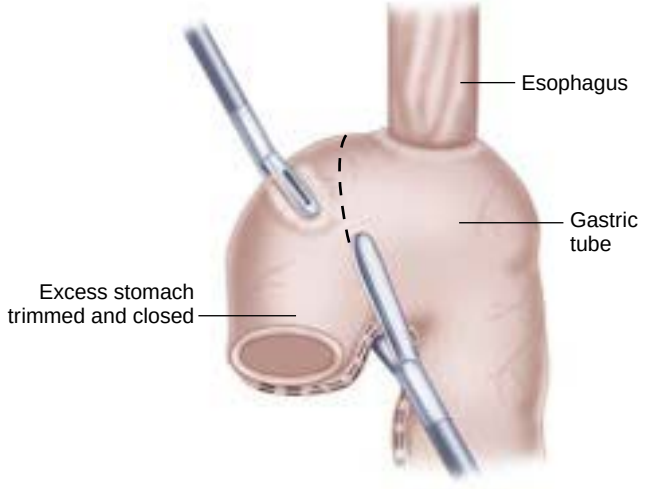


FIG. 7 Trimming of the excess conduit at the esophago-gastric anastomosis. *(From Zwischenberger JB.* Atlas of Thoracic Surgical Techniques. *Philadelphia: Elsevier; 2010.)*

McKeown

The McKeown (three-field) esophagectomy is utilized for patients with a proximal thoracic tumor located near the airways, with extensive Barrett's esophagus, or if there is a concern for attaining an adequate proximal margin that is tumor free. A McKeown esophagectomy has a cervical anastomosis that may represent a better option for proximal esophageal disease. The steps of the operation are the same as for an Ivor Lewis esophagectomy except that the thoracic portion is performed first. After the abdominal portion is complete, through an oblique incision anterior to the sternocleidomastoid muscle, the thoracic inlet is then dissected and the specimen is extracted through this incision. A single-layer esophagogastric anastomosis is constructed using interrupted 3-0 silk sutures. Alternatively, if there is enough overlap of the esophagus and gastric conduit, the posterior row can be made with a GIA 30 stapler, and the remaining closed with interrupted sutures in two layers, as originally described by Orringer.

Transhiatal

A transhiatal esophagectomy should be the procedure of choice for lower esophageal early-stage disease. With this approach, a right thoracotomy is avoided. The transhiatal approach includes an initial abdominal approach, similar to the Ivor Lewis esophagectomy, with preparation of the gastric conduit. Following this, the patient remains in the supine position and a cervical anastomosis is created, after the blunt transhiatal dissection. Transhiatal MIE uses laparoscopic abdominal dissection and preparation of the gastric conduit followed by a cervical anastomosis in the left neck as previously described. Mediastinal dissection of periesophageal lymph nodes, including those in the subcarinal station, can be accessed through the hiatus, using the lighting and magnification afforded by the laparoscope. The esophageal specimen is removed through the neck. The transhiatal operation is the least invasive esophagectomy, requires less operative time, and has excellent functional outcomes. The chest need not be violated for early-stage disease, unless there is concern for an inadequate gastric conduit length to perform a safe cervical anastomosis. Although long-term survival differences have not been demonstrated, many experts believe this operation has a lower oncologic yield, although this has not been analyzed for the minimally invasive approach where en bloc dissection of the distal mediastinum is possible.

COMPLICATIONS

Some of the most common postesophagectomy complications can be related to respiratory events, chyle leak, anastomotic/conduit complications, and atrial fibrillation.

Atrial fibrillation is a common complication after esophageal resection. It is reportedly more common in older patients and those who have undergone neoadjuvant therapy. The occurrence of atrial fibrillation should prompt a workup for possible anastomotic leak. Standard atrial fibrillation management includes electrolyte correction, medical management with antiarrhythmics, and defibrillation if needed.

Respiratory complications are additionally a common event after esophagectomy. Aspiration and subsequent pneumonia increases a patient's risk for worse outcome, including an increased mortality risk. Aspiration precautions should be strictly followed in the postoperative period.

Chyle leak is another well-documented complication. Low-volume chyle leaks can be managed by making the patient nil per os (NPO), initiating parenteral nutrition and conservative management until chest tube output declines. If output remains high despite these changes, one can consider invasive management, either with thoracic duct embolization by interventional radiology or by surgical ligation.

Anastomotic complications include anastomotic leak and stricture. In the setting of anastomotic leak, management depends on the approach to the primary surgery. If the patient has undergone Ivor

Lewis esophagectomy, an anastomotic leak can be handled by placement of a metallic or plastic stent (if small and contained), or reoperation. In the setting of a cervical anastomosis with a McKeown or transhiatal esophagectomy, an anastomotic leak is more easily managed with a bedside neck washout and negative pressure therapy, if needed. Patients should be treated with antibiotics if systemic signs of illness appear and repeat assessment of the leak should be completed at an interval time.

Recurrent laryngeal nerve injury has been reported more commonly in patients with cervical anastomoses and three-field lymph node dissections. There is an increased risk of pulmonary complications in the postoperative period in patients with recurrent laryngeal nerve injury. Swallow evaluation should be carried out and, if necessary, vocal cord medialization can be performed.

CONCLUSION

The management of esophageal cancer continues to evolve. Minimally invasive interventions such as ablation, EMR, and ESD are increasingly common as improved screening tools have led to earlier diagnosis. With these less invasive techniques, up to 90% cure rates have been seen. Detailed preoperative workup and staging remains paramount to appropriate management. Minimally invasive surgical approaches are quickly becoming the gold standard for surgical treatment in most centers, as the data are trending toward better functional outcomes and quality of life compared with totally open procedures.

Perhaps one of the most impactful recent advances that has been instituted as standard of care is the addition of nivolumab as adjuvant therapy for patients with resected esophageal (or gastroesophageal junction) cancers with residual pathologic disease if they had received induction chemoradiation therapy. In the recently completed CheckMate-577 trial, nivolumab given postoperatively doubled the median disease-free survival versus placebo (22 vs. 11 months, respectively), translating to a 31% reduction in the risk of disease recurrence. Better understanding of the patient-specific risk factors for treatment failures as well as patient-specific tumor profiling and treatments has ushered in an era of minimally invasive and precision therapeutics that holds a promise of improved outcomes for this highly lethal disease.

Suggested Readings

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Multimodality Therapy in Esophageal Cancer

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OVERVIEW

In patients with locally advanced esophageal adenocarcinoma and esophageal squamous cell carcinoma, optimal treatment involves multimodal therapy. This rapidly evolving field includes surgery, chemotherapy, radiotherapy, and more recently immunotherapy. The goal of this multimodal approach is to increase R0 resection rates, decrease local and systemic recurrence, and improve disease-specific and overall survival. With current treatment regimens, 5-year survival has increased to nearly 50% in patients with resectable disease; however, risk of recurrence remains high in individuals without a complete pathologic response to neoadjuvant therapy. In this chapter, we review the current status of multimodal therapy in treatment of locally advanced esophageal cancer, with special focus on the emerging role of immunotherapy in resectable disease and new approaches to oligometastatic disease. This chapter is intended to provide an overview of the key studies driving current practice rather than serve as an exhaustive review of all multimodal combinations currently in trials for esophageal cancer.

DEFINITIONS OF MULTIMODAL THERAPY AND INDICATIONS IN ESOPHAGEAL CANCER

Multimodal therapy refers to the use of surgery in combination with chemotherapy, radiotherapy, and immunotherapy in the oncologic treatment of malignant disease. Surgery involves esophagectomy with reconstruction, which can be performed using open, minimally invasive, or robotic-assisted techniques. The procedural conduct of esophagectomy is discussed in detail in the chapter entitled "Management of Esophageal Cancer" and therefore will not be reviewed here. Oncologic treatment occurring before surgery is termed *neoadjuvant therapy,* while treatment occurring after surgery is termed *adjuvant therapy*. Both neoadjuvant and adjuvant therapy may include chemotherapy alone or chemotherapy combined with radiotherapy (i.e., chemoradiotherapy). Similarly, immunotherapy may be delivered in the neoadjuvant or adjuvant setting, alone or in combination with chemotherapy or chemoradiotherapy. In some publications, the term *induction therapy* is used interchangeably with *neoadjuvant therapy;* however, *induction* specifically refers to the delivery of chemotherapy before radiation therapy, in contrast with concurrent chemoradiotherapy. In this chapter, we will refer to all treatment before surgical resection simply as *neoadjuvant therapy.*

The success of multimodal therapy regimens is determined through quantified improvements in overall survival and disease-specific survival. Surrogate markers of successful response include increased R0 resection rate, decreased time to recurrence, and increased likelihood of obtaining a complete pathologic response, meaning the absence of residual disease identified in the resection specimen following neoadjuvant treatment. These surrogates are highly correlated with improved survival and are often reported after a shorter follow-up time, allowing for clinical practice to be influenced by interim trial results while awaiting results of the primary survival endpoints.

The two main histologic subtypes of esophageal cancer are esophageal adenocarcinoma and esophageal squamous cell carcinoma. Together they represent 19,000 new cases per year in the United States alone and are associated with 15,000 deaths annually. Worldwide, squamous cell carcinoma is the more common subtype, with high prevalence in Asia and Africa. Esophageal squamous cell carcinoma has well-defined and strongly associated risk factors, including use of tobacco, alcohol, and betel quid and ingestion of very hot

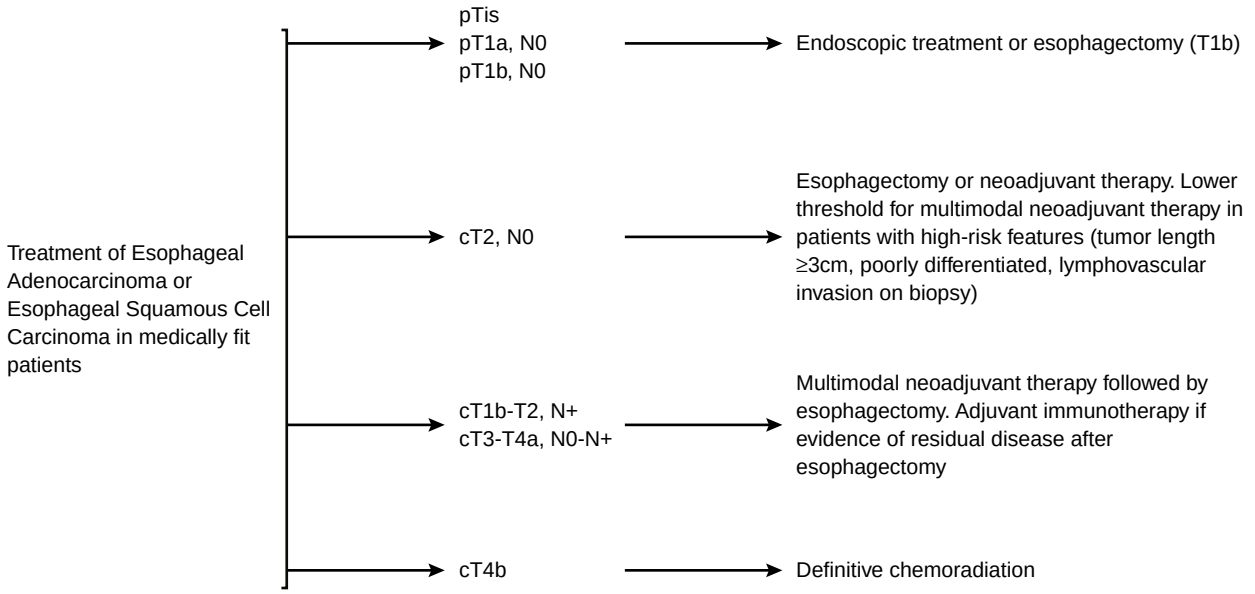


FIG. 1 Treatment algorithm for adenocarcinoma and squamous cell carcinoma in medically fit patients. *(Data from National Comprehensive Cancer Network.)*

temperature liquids, as well as some genetic predisposition. In contrast, adenocarcinoma is the dominant histology in Western Europe and the United States, with risk factors including gastroesophageal reflux disease, Barrett's esophagus, and obesity, without clearly defined genetic predisposition. Both types of esophageal cancer are significantly more common in men than in women.

In both histologic subtypes, multimodal therapy in the neoadjuvant setting has demonstrated survival benefits and is now standard-of-care for patients with locally advanced disease (Fig. 1). This includes patients with at least clinical T3 disease or clinical N1 disease. Neoadjuvant multimodal treatment for patients with clinical T2N0 esophageal cancer is controversial and nuanced. Up to 50% of patients with clinical T2 disease will have occult nodal disease not identified on staging computed tomography–positron emission tomography. These patients with occult nodal disease stand to benefit from neoadjuvant treatment, while those without nodal disease may not. Factors supporting the upstaging of T2N0 disease and use of neoadjuvant therapy in this setting include tumor length ≥3cm, poorly differentiated histology, and evidence of lymphovascular invasion on biopsy. Consideration for neoadjuvant multimodal therapy in patients with T2N0 disease should be discussed in a multidisciplinary tumor board within the context of the patient's unique risk factors and tolerance for multimodal therapy before surgery.

Traditional Multimodal Treatment

Esophageal Adenocarcinoma and Gastroesophageal Junction Adenocarcinoma

Current multimodal treatment of esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma involves concurrent perioperative chemotherapy and radiotherapy. The benefit of perioperative chemotherapy as a single modality was definitively demonstrated through the randomized controlled MAGIC trial in 2006 (Table 1). A regimen of three preoperative cycles of epirubicin, cisplatin, and fluorouracil (5-FU) (ECF) followed by three postoperative cycles of the same was compared with surgery alone in patients with resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus, and demonstrated substantial improvements in both R0 resection rate and 5-year survival (36% vs. 29%) with neoadjuvant chemotherapy. Ychou et al. reported similar results in 2011 comparing a regimen of three cycles each of preoperative and postoperative cisplatin with 5-FU with surgery alone. More recently, the FLOT4 trial demonstrated the superiority of four preoperative and postoperative cycles of docetaxel, oxaliplatin, leucovorin, and 5-FU (FLOT) compared with ECF dosed according to the MAGIC protocol, with an increase in median survival from 35 months to 50 months with FLOT4. The major downside to these regimens has been the number of patients (almost 50% in some series) who are unable to complete the postoperative chemotherapy because of operative complications, patient deconditioning, or intolerance. Given this limitation, there has been a push toward total neoadjuvant treatment, with active studies using FLOT4 and FOLFOX (folinic acid, 5-FU, oxaliplatin) regimens in the preoperative setting. The use of chemotherapy alone in the neoadjuvant setting tends to be more common in European and Asian centers, while North American centers tend to favor delivery of chemotherapy with concurrent radiation, with or without an initial induction phase of chemotherapy in a total neoadjuvant approach, before surgical resection for locally advanced disease. The use of concurrent chemoradiation in the neoadjuvant setting for gastroesophageal adenocarcinoma dates to the 1990s, when Bass et al. performed a randomized controlled trial comparing surgery alone against a treatment regimen of two cycles of neoadjuvant 5-FU and cisplatin along with external beam radiation on days 1 to 5, 8 to 12, and 15 to 19. Patients with adenocarcinoma who received this regimen demonstrated an increase in overall survival to 76 months compared with 23 months for patients treated with surgery alone. Tepper et al. replicated these results using a similar regimen of neoadjuvant cisplatin, 5-FU, and radiotherapy, demonstrating a 5-year survival of 39% in the multimodal treatment arm versus 16% in the surgical monotherapy arm ($P = 0.002$). Unfortunately, this study was closed early because of poor patient accrual.

In a direct comparison of neoadjuvant chemoradiotherapy to neoadjuvant chemotherapy alone, Stahl et al. demonstrated significantly higher rates of pathologic complete response and negative lymph nodes at time of resection in patients who received two cycles of cisplatin, 5-FU, and folinic acid in conjunction with 30 Gray of radiation as compared with patients who received 2.5 cycles of neoadjuvant chemotherapy alone. However, this study was also closed early because of poor patient accrual, and no significant survival benefit was demonstrated. Using a similar regimen, Burmeister et al.

TABLE 1 Summary of Landmark Randomized Controlled Trials Using Traditional Multimodal Treatment of Esophageal Adenocarcinoma/Gastroesophageal Junctional Adenocarcinoma and Squamous Cell Carcinoma

Study	Publication Year	N	Histology	Control Regimen	Experimental Regimen	Overall Survival (Control vs. Experimental)
Ancona et al.[1]	2001	94	ESCC	Surgery alone	2–3 preoperative cycles of cisplatin and 5-FU	5 year: 22% vs. 34%
MRC Oesophageal Cancer Working Party[2]	2002	802	ESCC	Surgery alone	2 preoperative cycles of cisplatin and 5-FU	Median: 13.3 months vs. 16.8 months
Cunningham et al. (MAGIC)[3]	2006	503	EAC	Surgery alone	3 preoperative and 3 postoperative cycles of epirubicin, cisplatin, and 5-FU	5 year: 29% vs. 36%
Lv et al.[4]	2010	238	ESCC	Surgery alone	2 preoperative cycles of paclitaxel and cisplatin with concurrent radiotherapy OR 2 postoperative cycles of paclitaxel and cisplatin with concurrent radiotherapy	5 year: 33.8% (control) vs. 43.5% (preoperative) vs. 42.3% (postoperative)
Boonstra et al.[5]	2011	169	ESCC	Surgery alone	2–4 preoperative cycles of cisplatin and etoposide	5 year: 17% vs. 26%
Ychou et al.[6]	2011	224	EAC	Surgery alone	3 preoperative and 3 postoperative cycles of cisplatin and 5-FU	5 year: 24% vs. 38%
Alderson et al. (0E05)[7]	2017	897	EAC	2 preoperative cycles of cisplatin and 5-FU	4 preoperative cycles of epirubicin, cisplatin, and capecitabine	Median: 23.4 months vs. 26.1 months
Yang et al. (NEOCRTEC5010)[8]	2018	451	ESCC	Surgery alone	2 preoperative cycles of vinorelbine and cisplatin with concurrent radiotherapy	Median: 66.5 months vs. 100.1 months
Al-Batran (FLOT4)[9]	2016, 2019	716	EAC	3 preoperative and 3 postoperative cycles of ECF/ECX	4 preoperative and 4 postoperative cycles of FLOT	5 year: 36% vs. 45%
van Hagen (CROSS)[10,11]	2012, 2015, 2021	368	EAC/ESSC	Surgery alone	5 preoperative cycles of carboplatin, paclitaxel, and concurrent radiotherapy	5 year: 33% vs. 47%

5-FU, Fluorouracil; *EAC,* esophageal adenocarcinoma; *ECF,* epirubicin/cisplatin/Fluorouracil; *ECX,* epirubicin/cisplatin/capecitabine; *ESCC,* esophageal squamous cell carcinoma; *FLOT,* docetaxel/oxaliplatin/leucovorin/fluorouracil; *MRC,* Medical Research Council.

[1]Ancona E, Ruol A, Santi S, et al. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma. *Cancer.* 2001;91:2165–2174.

[2]Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet.* 2002;359(9319):1727–1733.

[3]Cunningham D, Allum WH, Stenning SP, et al.; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355(1):11–20.

[4]Lv J, Cao XF, Zhu B, Ji L, Tao L, Wang DD. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. *World J Gastroenterol.* 2010;16(13):1649–1654.

[5]Boonstra JJ, Kok TC, Wijnhoven BP, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. *BMC Cancer.* 2011;11:181.

[6]Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29(13):1715–1721.

[7]Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2017;18(9):1249–1260.

[8]Yang H, Liu H, Chen Y, et al.; AME Thoracic Surgery Collaborative Group. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. *J Clin Oncol.* 2018;36(27):2796–2803.

[9]Al-Batran SE, Homann N, Pauligk C, et al.; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948–1957.

[10]van Hagen P, Hulshof MC, van Lanschot JJ, et al.; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–2084.

[11]Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. 2015. Neoadjuvant Chemoradiotherapy plus Surgery versus Surgery Alone for Oesophageal or Junctional Cancer (CROSS): Long-Term Results of a Randomised Controlled Trial. Lancet Oncol. 16(9):1090–1098.

[12]Eyck BM, van Lanschot JJB, Hulshof MCCM, et al.; CROSS Study Group. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. *J Clin Oncol.* 2021;39(18):1995–2004.

showed an improvement in histopathologic response in patients who received neoadjuvant chemoradiotherapy over patients who received neoadjuvant chemotherapy alone.

More recently, the CROSS trial demonstrated significantly improved overall and progression-free survival with neoadjuvant chemoradiotherapy as compared with surgery alone using a regimen of six cycles of carboplatin and paclitaxel in combination with 41.4 Gray of radiation given in 23 fractions. This survival benefit was seen in both adenocarcinoma and squamous cell carcinoma, but it was more pronounced in the latter group, which also demonstrated a higher rate of pathologic complete response following neoadjuvant therapy. In long-term follow-up of the CROSS trial, 5-year and 10-year survival have been 47% and 38%, respectively. Given the durable success of this neoadjuvant chemoradiotherapy regimen, it has become standard-of-care at many centers. Ongoing trials of additional regimens, including neoadjuvant FOLFOX, neoadjuvant FLOT, induction chemotherapy before the CROSS regimen, use of Herceptin for Her2-positive tumors, and proton beam therapy rather than traditional radiation, are currently underway.

Esophageal Squamous Cell Carcinoma

Treatment of esophageal squamous cell carcinoma with chemotherapy and chemoradiotherapy in conjunction with surgical resection has been studied for the past several decades. In 2001, a randomized controlled trial published by Ancona et al. failed to demonstrate an overall survival benefit with neoadjuvant chemotherapy using two to three cycles of cisplatin and 5-FU, but did report a significant survival advantage in subgroup analysis among patients whose tumors responded to preoperative chemotherapy. The overall survival benefit for preoperative chemotherapy in squamous cell carcinoma was subsequently demonstrated in two separate randomized controlled trials conducted by the medical research council on esophageal cancer working party and Boonstra et al. using regimens of cisplatin and 5-FU and cisplatin and etoposide, respectively.

Over the past decade, several randomized controlled trials have demonstrated a survival benefit to preoperative chemoradiotherapy compared with surgery alone. These studies include the CROSS trial, the NEOCRTEC5010, and a separate analysis by Lv et al. In the NEOCRTEC5010 trial, 2 cycles of neoadjuvant vinorelbine and cisplatin delivered concurrently with 40 Gray of radiation in 20 fractions was compared with surgery alone. In contrast, Lv et al. randomized patients to either neoadjuvant or adjuvant delivery of two cycles of cisplatin/paclitaxel concurrently with 40 Gray of radiation in 20 fractions. Meanwhile, the CROSS trial, as described earlier, demonstrated the greatest relative benefit for the subgroup of patients with squamous cell carcinoma, with median survival of 81.6 months in the neoadjuvant group versus 21.1 months in the surgery alone group. Despite the differences in neoadjuvant regimens used, all three studies demonstrated a significant benefit to neoadjuvant chemoradiation in both overall and disease-free survival in patients with locally advanced squamous cell carcinoma (Table 1).

There have been few published studies directly comparing neoadjuvant chemoradiotherapy to neoadjuvant chemotherapy, though this is an ongoing area of study. Early results from Wang et al. directly comparing a regimen of cisplatin and paclitaxel with or without 40 Gray of concurrent radiation have shown an improvement in complete pathologic response among those receiving chemoradiotherapy, although it remains to be seen whether this will translate into an overall or disease-specific survival benefit.

Immunotherapy in Neoadjuvant and Adjuvant Settings

Immunotherapy is an increasingly important tool in medical oncology that utilizes the body's natural defense mechanisms to fight cancer cells. Common targets of immunotherapy agents include the programmed cell death protein (PD-1) and the associated programmed cell death ligand 1 (PD-L1). PD-1 is a cell surface receptor expressed on activated immune cells, including T cells, B cells, and myeloid cells, while PD-L1 is expressed on the surface of some cancer cells to trigger immune evasion. When PD-1 is bound to PD-L1, an immune checkpoint is activated, preventing the T cells from targeting cancer cells for death. Novel immunotherapeutic medications include monoclonal antibodies that bind either PD-1 on the surface of T cells (nivolumab, pembrolizumab, and toripalimab) or PD-L1 on the surface of tumor cells (atezolizumab, avelumab, and durvalumab) to block this immune checkpoint and thus reactivate the T-cell–mediated antitumor immune response. This targeted approach can lead to more effective tumor targeting and cytotoxic response with less systemic side effects than traditional chemotherapeutic agents.

Although better tolerated than traditional chemotherapy, immunotherapy-related toxicities can occur. Most commonly this involves an autoimmune response that can affect the gastrointestinal tract, skin, endocrine glands, and liver. More serious, but less common, adverse immune responses can include myocarditis, pneumonitis, and disorders of the central nervous system. These events may require cessation of immunotherapy and treatment with glucocorticoids.

The benefits of immunotherapy regimens utilizing checkpoint inhibitors have been demonstrated in several cancers, including malignant melanoma and non–small cell lung cancer. The efficacy of these agents as first-line therapy in esophageal adenocarcinoma has been shown in advanced unresectable disease and in recurrent or metastatic disease.

Recently, the CheckMate 577 trial demonstrated the efficacy of immunotherapy in multimodal treatment through use of adjuvant nivolumab in patients with locally advanced esophageal adenocarcinoma and esophageal squamous cell carcinoma. Patients treated with total neoadjuvant chemoradiotherapy with residual pathologic disease after resection were randomized to treatment with nivolumab versus placebo. Patients in the treatment arm demonstrated a significant improvement in median disease-free survival compared with placebo (22.4 months vs. 11.0 months). The success of this trial has led to additional studies exploring the potential benefits of immunotherapy in the neoadjuvant setting (Table 2). As the results of these trials are reported, the multimodal treatment of esophageal cancer, both adenocarcinoma and squamous cell carcinoma, may change rapidly in the next several years.

Multimodal Therapy for Recurrent and Oligometastatic Disease: A New Frontier for Surgery?

Despite improvements in the treatment of resectable locally advanced esophageal cancer, patients who present with recurrent or oligometastatic disease continue to have an extremely poor prognosis. In patients with distant organ metastasis, 5-year survival is less than 5%, even in the setting of aggressive chemotherapy regimens. In an effort to improve these outcomes, several groups have evaluated the potential benefit of multimodal therapy in patients with recurrent and/or oligometastatic disease. For these patients, there is potential benefit to definitive local therapy (e.g., resection or radiation) to the oligometastatic site in conjunction with systemic therapy.

Data supporting the local treatment of oligometastatic disease have been reported by Li et al. In their retrospective analysis of 576 patients with oligometastatic disease, radiotherapy or chemoembolization to the metastatic site were independent factors associated with improved progression-free and overall survival. Similarly, Port et al. demonstrated prolonged survival in patients who underwent surgical resection followed by adjuvant chemoradiation for recurrent nodal disease or oligometastatic solid organ metastasis as compared with definitive chemoradiation alone. These results have been replicated in several other publications demonstrating improved survival in patients treated with chemoradiotherapy or surgical resection for recurrent oligometastatic disease in individuals who had previously undergone esophagectomy. Moreover, the site of oligometastatic

TABLE 2 Summary of Completed and Active Trials Utilizing Adjuvant and Neoadjuvant Immunotherapy Regimens

Study	Histology	Inclusion Criteria	Control Regimen	Experimental Regimen	Primary Outcome*	Status
CheckMate 577[1]	EAC/ESSC	Neoadjuvant chemotherapy with incomplete pathologic response in esophagectomy specimen	Placebo	Adjuvant nivolumab	Disease-free survival (11.0 vs. 22.4 months; $P < 0.001$)	Completed
FRONTiER[2]	ESSC	Locally advanced disease	NA	Neoadjuvant chemotherapy plus nivolumab	Dose-limiting toxicity	Active trial
HCHTOG1909[3]	ESSC	Locally advanced disease	Neoadjuvant Chemotherapy	Neoadjuvant chemotherapy plus toripalimab	Event-free survival	Active trial
Hong et al.[4]	ESSC	Locally advanced disease	NA	Neoadjuvant chemoradiotherapy plus neoadjuvant pembrolizumab followed by adjuvant pembrolizumab	Complete pathologic response (46.1%)	Completed
PROCEED[5]	EAC/ESSC	Locally advanced disease	NA	Neoadjuvant chemoradiotherapy plus neoadjuvant pembrolizumab followed by adjuvant pembrolizumab	Complete pathologic response	Active trial

EAC, Esophageal adenocarcinoma; *ESCC,* esophageal squamous cell carcinoma; *NA,* not applicable
*Control versus experimental.
[1]Kelly RJ, Jaffer A, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384(13):1191–1203.
[2]Yamamoto S, Kato K, Daiko H, et al. Feasibility study of nivolumab as neoadjuvant chemotherapy for locally esophageal carcinoma: FRONTiER (JCOG1804E). *Future Oncol.* 2020;16(19):1351–1357.
[3]Zheng Y, Liu XB, Sun HB, et al.; written on Henan Cancer Hospital Thoracic Oncology Group (HCHTOG). A phase III study on neoadjuvant chemotherapy versus neoadjuvant toripalimab plus chemotherapy for locally advanced esophageal squamous cell carcinoma: Henan Cancer Hospital Thoracic Oncology Group 1909 (HCHTOG1909). *Ann Transl Med.* 2021;9(1):73.
[4]Hong MH, Kim H, Park SY, et al. 2019. A Phase II trial of preoperative chemoradiotherapy and pembrolizumab for locally advanced esophageal squamous cell carcinoma (ESCC)." *J Clin Oncol.* 2019;37(15_suppl):4027–4027.
[5]Pembrolizumab, Radiotherapy, and Chemotherapy in Neoadjuvant Treatment of Malignant Esophago-Gastric Diseases (PROCEED)." 2017. Clinicaltrials.gov. February 27, 2017. https://clinicaltrials.gov/ct2/show/NCT03064490.

disease plays a role, with improved survival associated with lung metastasis as compared with brain or liver metastasis.

Although promising, all of these studies are limited by retrospective study design and/or a lack of randomization. For patients who present with limited metastatic gastroesophageal junction adenocarcinoma, a survival benefit to neoadjuvant therapy followed by surgical resection of the primary tumor and all metastatic sites has been shown in the FLOT3 trial. Although there is much still unknown, these studies indicate a potential benefit to aggressive systemic and local treatment of limited metastatic and recurrent disease.

Additional Considerations to Multimodal Therapy

The success of a multimodal approach for the treatment of locally advanced esophageal cancers, both adenocarcinoma and squamous cell carcinoma, is dependent on the patient's ability to tolerate the effects of chemotherapy and radiotherapy and to recover from major surgery. Although minimally invasive approaches can decrease surgical morbidity, aggressive neoadjuvant protocols can also increase the complexity of surgery, and many surgeons may feel more comfortable with open surgical approaches in this setting. Frailty, sarcopenia, and malnutrition limit the ability of patients to complete multimodal treatment and increase the risk for postoperative complications and postdischarge institutionalization. This is exacerbated by symptomatic dysphagia, which often accompanies locally advanced esophageal cancers.

To improve the likelihood of successful completion of multimodal therapy, several adjunctive measures have been utilized. First, there has been a shift toward total neoadjuvant therapy. By giving all chemoradiotherapy during the preoperative period, delays in treatment that may occur as a result of postoperative complications or deconditioning are eliminated. Moreover, total neoadjuvant treatment increases the likelihood of obtaining a complete pathologic response and can give a better indication of expected prognosis at the time of surgery. A summary of current neoadjuvant and total neoadjuvant treatment regimens is included in Table 3.

To improve patient fitness for major surgery, the concept of prehabilitation has gained traction. Prehabilitation has shown early

TABLE 3 Summary of Current Neoadjuvant and Total Neoadjuvant Treatment Regimens

Neoadjuvant with Adjuvant				
Regimen	**Tumor Type**	**Preoperative Cycles of Chemotherapy**	**Postoperative Cycles of Chemotherapy**	**Chemoradiation**
Cisplatin, 5-FU	EAC/ESCC	3 cycles of Cisplatin and 5-FU	3 cycles of Cisplatin and 5-FU[1]	None
FLOT4	EAC	4 Cycles of Docetaxel, Oxaliplatin, Leucovorin, 5-FU	4 Cycles of Docetaxel, Oxaliplatin, Leucovorin, 5-FU[2]	None
Total Neoadjuvant				
Regimen	**Tumor Type**	**Induction Chemotherapy**	**Chemoradiation**	**Trial Status**
FOLFOX Plus Radiotherapy	EAC	8 Cycles of Folinic Acid, 5-FU Oxaliplatin	50.4 Gray with Concurrent Carboplatin/ Paclitaxel[3]	Ongoing
FLOT4 Plus Radiotherapy	EAC	8 Cycles of Docetaxel, Oxaliplatin, Leucovorin, 5-FU	50.4 Gray with Concurrent Carboplatin/ Paclitaxel[4]	Ongoing
CROSS	EAC/ESCC	None	41.4 Gray with Concurrent Carboplatin/ Paclitaxel (5 cycles)[5]	Published

EAC, Esophageal adenocarcinoma; *ESCC,* esophageal squamous cell carcinoma; *5-FU,* fluorouracil

[1]Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29(13):1715–1721.

[2]Al-Batran SE, Homann N, Pauligk C, et al.; FLOT4-AIO Investigators. 2019. chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948–1957.

[3]Roeland E, Kanter K, Jennifer Yon-Li Wo J, et al. 2020. Preliminary analysis of total neoadjuvant therapy for patients with locally advanced gastric (G) and gastroesophageal (GE) adenocarcinoma. *J Clin Oncol.* 2020;38:(4_suppl):393–393.

[4]Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. 2015. Neoadjuvant Chemoradiotherapy plus Surgery versus Surgery Alone for Oesophageal or Junctional Cancer (CROSS): Long-Term Results of a Randomised Controlled Trial. *Lancet Oncol.* 16(9):1090–1098.

[5]Eyck BM, van Lanschot JJB, Hulshof MCCM, et al.; CROSS Study Group. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial. *J Clin Oncol.* 2021;39(18):1995–2004.

promise in patients with esophageal cancer and other malignancies that require major operations and prolonged multimodal treatment in either the neoadjuvant or adjuvant setting. Often, these multimodal treatments are described as a *marathon,* with the idea that pretreatment "training" may improve outcomes and reduce associated morbidity and mortality. Prehabilitation regimens include aerobic exercise, strength-based exercise, and inspiratory muscle training. Unfortunately, well-designed studies evaluating the effectiveness of these interventions are limited at present. The strongest evidence for use of preoperative training regimens has been reported by Minella et al. In a randomized controlled trial of patients undergoing multimodal treatment for esophageal cancer, they demonstrated a significant improvement in functional capacity both before and after surgery in the treatment group that underwent preoperative home-based aerobic and strength training as compared with a control group without prehabilitation. Although prehabilitation seems instinctively beneficial, additional trials are needed to optimize training programs and resource allocation.

An additional challenge in the multimodal treatment of esophageal cancer is the associated difficulty in maintaining adequate nutrition. Because the stomach is most often used as the conduit for reconstruction after esophagectomy, gastric feeding tubes are generally avoided in the preoperative setting. Patients who need additional preoperative or postoperative nutritional supplementation often undergo jejunal feeding tube placement, either before neoadjuvant therapy, during neoadjuvant treatment, or at the time of esophagectomy. Less desirable alternatives include total parenteral nutrition (TPN) or nasoenteral feeding tubes. The optimal feeding strategy for patients undergoing esophagectomy for esophageal cancer has been explored in multiple studies. In several randomized controlled trials, jejunostomy tube feeding demonstrated superiority both to TPN and long-term nasoenteric tube feeding. Studies comparing enteral feeding without a jejunostomy tube to jejunostomy tube feeding have had more mixed results, and the optimal strategy remains unclear. Although jejunal feeding tube placement certainly benefits a subset of the population, they are also associated with an up to 30% complication rate. Determining which patients may benefit from a jejunal feeding tube and the optimal timing of placement is an area of active investigation. For now, the decision regarding placement of a jejunal feeding tube remains dependent on specific patient, operative, and institutional factors.

CONCLUSIONS

The past two decades have brought major advances in the treatment of locally advanced esophageal cancer, including both adenocarcinoma and squamous cell carcinoma. Multimodal therapy involving neoadjuvant chemotherapy or chemoradiotherapy has become standard-of-care for locally advanced disease and has led to major improvements in the prognosis of patients with this disease. Outcomes have dramatically improved, and patients and clinicians can expect a 5-year survival approaching 50% with current regimens. The role of surgery and localized radiation or radiofrequency ablation in patients with recurrent disease or oligometastatic disease is an area of active investigation, and there is evidence that multimodal therapy can benefit well-selected patients within this high-risk patient subgroup that was previously considered unresectable.

In the next 5 to 10 years, the field is expected to undergo a second revolution with the addition of immunotherapy to current treatment regimens in both the adjuvant and neoadjuvant settings. This will come along with continued refinement and direct comparison of current in-trial neoadjuvant chemotherapy and chemoradiotherapy regimens.

Finally, as the arsenal of the surgical oncologist has grown, there is even greater need for patient optimization before surgery, as patients must now endure major surgery involving esophageal resection and reconstruction after completing often-grueling neoadjuvant regimens, with the potential for additional adjuvant treatments after recovery from surgery. To reap the maximal benefit from these ongoing advances in multimodal therapy, concomitant work will be needed to combat frailty and malnutrition and to maintain patient quality of life along with enhanced survival.

Suggested Readings

Al-Batran SE, Homann N, Pauligk C, et al.; FLOT4-AIO Investigators. 2019. chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948–1957.

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Use of Esophageal Stents

Matthew D. Grunwald, MD, Anthony N. Kalloo, MD, and Dmitriy O. Khodorskiy, MD

First described by French surgeon Leroy D'Etiolles in 1845, esophageal stenting (ES) was, at its inception, reserved mainly for the palliation of severe dysphagia in advanced esophageal cancer (EC). Over the years, the use of esophageal stent has steadily increased with an expansion of its indications to include benign disease. Improvement in stent design, endoscopic techniques, and complication rates have made it an attractive therapeutic option for patients with either mechanical or functional dysphagia, perforations, leaks, or fistulas. ES generally has one of two main goals: (1) to maintain luminal patency and relieve severe dysphagia in the setting of benign or malignant strictures and (2) to stave off potentially fatal luminal contamination of the mediastinum. For patients with debilitating disease, ES offers the prospect of improved oral intake, symptomatic relief of dysphagia or aspiration, and the avoidance of morbid surgical interventions.

This chapter reviews the evolution of ES, currently available stents, most current indications for ES, stent placement techniques, and complications.

STENTS THROUGH THE AGES

D'Etiolles' stents, which were made of decalcified ivory, were unfortunately unsuccessful. Over the next 4 decades, several attempts by the likes of Sir Morrell Mackenzie in England yielded similarly disappointing results. The first successful esophageal stent was designed by Sir Charters Symonds in 1885. Symonds' stent, which was blindly inserted, featured an esophageal tube affixed to a boxwood funnel by a silver wire and was secured to the ear by a silk thread passing through the mouth or nose. Over the next decades, as interest in plastic polymers grew, stent design evolved. The first stents widely used in the esophagus were constructed from silicon rubber. These early stents were inserted with the assistance of a rigid esophagoscope but had a high rate of stent misplacement and migration. In the late 1950s, Celestin successfully palliated a malignant esophageal stricture using a plastic stent inserted via an open gastrostomy. The next few years would see an evolution in stent placement technique as endoscopic tools evolved. In the 1970s, Atkinson introduced an endoscopically inserted plastic prosthesis. Unfortunately, a significant drawback of the Atkinson stent was its small internal diameter, which proved rate limiting when patients resumed a regular diet. High complication rates plagued many of these early plastic endoprostheses. Because of their rigidity and fixed internal as well as external diameters, most stents required endoscopic dilation, which invariably led to perforations. Additionally, their inability to conform intimately to the strictural morphology caused frequent stent migrations requiring intervention. In 1983, the modern era of esophageal stent innovation was ushered in when Frimberger published the first description of the endoscopic placement of a self-expanding metal stent (SEMS) for a patient with a malignant esophageal stricture. In the 1990s, SEMS grew in popularity, in part fueled by the results of a series of trials conducted by Knyrim et al., which demonstrated that SEMS had higher patency rates, successful placement rates, and a better safety profile than available rigid plastic endoprostheses. Over the next few years, stent design and materials would continue to evolve. The modern esophageal stent is self-expanding and made of either plastic, Nitinol (a metal alloy), or biodegradable material. It may also come fully or partially covered. Table 1 reviews currently available stents and their characteristics.

STENT SELECTION

Selecting the appropriate stent for a given lesion—a critical step in preprocedural planning and a significant determinant of outcome—requires an understanding of the mechanical and physical properties of the various stents models (Fig. 1).

The majority of SEMS are made of Nitinol, a nickel-titanium alloy, that has superelasticity and shape memory. This property allows a metal's shape to be easily modulated by small temperature variations, but there is also a spontaneous return to the original shape when the temperature is outside of the transformative range. These unique characteristics are exploited in SEMS as they expand at body temperature to fit the morphology of a given lesion. Nitinol is also resistant to corrosion and hypoallergenic. Although biologically inert, it triggers a mild inflammatory response with resulting fibrosis that is useful in reducing stent migration. Unfortunately, this same property can be a major drawback of uncovered SEMS (uc-SEMS), fostering stent stenosis by allowing fibrotic tissue ingrowth through the openings in the mesh material. To counter this phenomenon, fully covered and partially covered stents were developed. These stents feature proximal and distal ends that remain bare and uncovered to provide additional luminal anchorage. Covered stents are believed to have less tumor ingrowth but can potentially be more

TABLE 1 Selected Overview of Currently Available Esophageal Stents and Relevant Characteristics for Clinical Practice

Product	Manufacturer	Placement	Material	Diameter Stent Body (mm)	Length (cm)	Cover
Alimaxx-ES	Merit Medical	OTW	Nitinol	12/14/16/18/22	7/10/12	FC
EndoMAXX	Merit Medical	OTW	Nitinol	19/23	7/10/12/15	FC
Choostent	M.I. Tech	OTW	Nitinol	18/20/22/24	6/17	FC
Evolution	Cook	OTW	Nitinol	18/20	8/10/12	FC/PC
HILZO	BCM	TTS/OTW	Nitinol	20/22	10/12/15	FC/PC
Hanarostent	M.I. Tech	TTS/OTW	Nitinol	18/20/22/24	6/8/10/12/15	FC/PC
Niti-S: single-layered	Taewoong Medical	TTS/OTW	Nitinol	16/18/20/22/24/28	6/8/10/12/14/15	FC/PC
Niti-S: double-layered	Taewoong Medical	OTW	Nitinol	16/18/20/22/24/28	6/8/10/12/14/15	FC + UC
SX-ELLA-HV	Ella-CS	OTW	Nitinol	18/20	8.5/11/13.5/15	FC
SX-ELLA-BD	Ella-CS	OTW	Biodegradable	18/20/23/25	6/8/10/13.5	UC
Flexella Plus	Ella-CS	OTW	Nitinol	18/20	8.5/11/13.5/15	FC
Ultraflex	Boston Scientific	OTW	Nitinol	18/23	10/12/15	PC
Wallflex	Boston Scientific	OTW	Nitinol	18/23	10/12/15	FC/PC
Agile	Boston Scientific	TTS	Nitinol	14/18	6.2/10.2/11.9/14.8/	FC/PC
Polyflex	Boston Scientific		Polyester/silicone			FC

FC, Fully covered; *OTW*, over-the-wire; *PC*, partially covered; *TTS*, through-the-scope; *UC*, uncovered. Modified from Vermeulen BD, Siersema PD. Esophageal stenting in clinical practice: an overview. *Curr Treat Options Gastroenterol*. 2018;16:260–273.

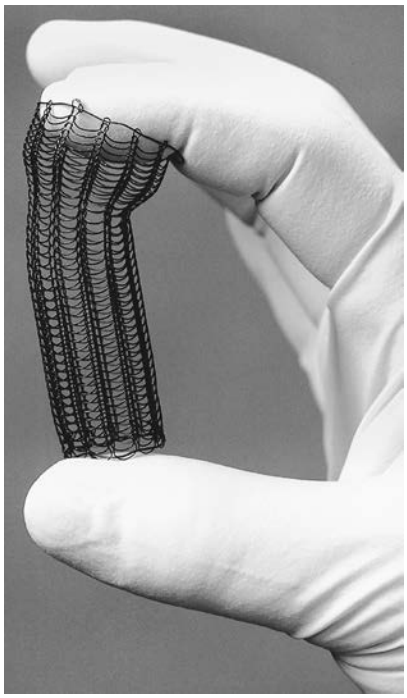


FIG. 1 Self-expanding metal stent.

susceptible to stent migration, especially in high-risk areas such as at the distal esophagus.

Self-expandable plastic stents (SEPS) are double-layered, featuring polyester mesh on their external surface with an embedded silicon layer forming a smooth inner surface. To prevent migration, flared distal and proximal ends facilitate luminal anchorage. Considering that their internal diameter tends to decrease under tension, SEPS are easily retrieved endoscopically, making them ideal for short-term stenting.

Introduced in the mid-2000s, biodegradable stents (BDS) are mainly used in the setting of benign strictures, as they negate the need for retrieval. These are made of plaited polydioxanone, a monofilament that undergoes hydrolytic degradation over 8 to 12 weeks. These maintain their mechanical strength for 4 to 6 weeks.

PATIENT SELECTION

Careful clinical evaluation and characterization of the lesion of interest are necessary to optimize clinical outcome in patients receiving ES. Baseline assessment of dysphagia, nutritional status, and quality of life (QOL) will provide a reference point from which the efficacy of the intervention can be measured. The Dysphagia Scoring Scale by Ogilvie et al. (Table 2) is a simple and effective tool to assess dysphagia in patients with strictures. Combining radiographic modalities such as esophagram, positron emission tomography, computed tomography (CT), and endoscopy can provide invaluable information about the lesion's location, size, morphology, and relationship to adjacent extrinsic structures and thus inform stent selection.

INDICATIONS

The Food and Drug Administration (FDA) has approved ES for the preservation of luminal patency in the setting of intrinsic or extrinsic malignant strictures, and the occlusion of concurrent esophageal fistula. In practice, however, the list of lesions amenable to ES has increased, owing to better stent design, improved safety profile, and sophisticated endoscopic techniques. In the United States and other developed nations, stenting for malignant esophageal strictures has decreased because of improved outcomes with single-dose brachytherapy. Conversely, ES for the management of various benign conditions, such as refractory benign esophageal strictures (RBES),

TABLE 2 Dysphagia Scoring Scale

Class	Dysphagia Scoring Scale
0	Able to consume normal diet
1	Dysphagia with certain solid foods
2	Able to swallow semisolid foods
3	Able to swallow liquids only
4	Unable to swallow saliva (complete dysphagia)

Data from Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative intubation of oesophagogastric neoplasms at fiberoptic endoscopy. *Gut*. 1982;23:1060–1067.

esophageal perforations, variceal bleeding, postsurgical anastomotic leaks, and achalasia has increased by more than 50% in the past decade.

Malignant Esophageal Disease

Malignant Esophageal Strictures

Malignant esophageal dysphagia results from luminal narrowing either by intramural growth of primary esophageal tumors or extrinsic compression from mediastinal and airway tract neoplasms. Primary EC remains one of the most lethal cancers of the alimentary tract. Because of its insidious course, clinically apparent disease is typically synonymous with advanced stage. In these patients, relief of dysphagia and resumption of oral intake provides an invaluable improvement in QOL and, in some cases, survival prospects. Since its inception, ES has been regarded as the first-line therapy for the palliation of malignant dysphagia. SEMS provides prompt relief and the opportunity to optimize patients' nutritional status. Interest in regionally targeted radiation modalities such as brachytherapy has transformed the clinical approach to malignant dysphagia. A randomized controlled trial (RCT) comparing SEMS to single-dose brachytherapy demonstrated that, although stenting resulted in earlier relief of dysphagia, brachytherapy provided longer-lasting relief, higher QOL scores, and significantly less morbidity as evidenced by a rate of major complication of 13% compared with 25% for SEMS. Despite these findings, the initial enthusiasm for brachytherapy is fading due to the frequently noted need to insert rescue stents. Brachytherapy may be considered for carefully selected patients with mild to moderate dysphagia who have a longer life expectancy. ES thus remains the first line of intervention for patients with moderate to severe dysphagia who are not candidates for other modalities or patients with recurrent dysphagia after brachytherapy. Fully covered SEMS (fc-SEMS) are the stents of choice for the management of malignant strictures. Recent studies have demonstrated a lower rate of tumor ingrowth compared with uc-SEMS and a lesser risk of stent migration when compared with SEPS. Although there is no difference in outcomes between fc-SEMS and partially covered SEMS (pc-SEMS), the latter is often subject to tumor ingrowth at its uncovered distal and proximal ends, thus making for challenging endoscopic retrieval.

Malignant Esophageal Fistulas

Malignant esophageal fistulas result primarily from esophageal tumor infiltration into surrounding structures, such as the trachea, mediastinum, pleura, and proximal abdominal cavity, and less commonly from extrinsic infiltration of respiratory tract tumors or chemoradiation-induced tumor necrosis. Regardless of the mechanism, temporary suspension of oral intake, drainage of involved spaces, and endoscopic insertion of a fc-SEMS are frequently recommended. The Amplatzer atrial septal defect (ASD) occluder has also been used off-label for closure of trachea-esophageal fistulas in limited studies. Currently, successful fistula closure rates are more than 70%, and recent evidence suggests a modest survival advantage once closure is achieved. The early appeal of concurrent stenting of the tracheobronchial tract (Fig. 2), or "dual stenting," has been largely overshadowed by a higher risk of highly lethal intermural and vascular erosions due to synergistic pressure necrosis. Despite the scarcity of data available regarding the most appropriate stent for malignant fistulas, fc-SEMS are the modality of choice by consensus.

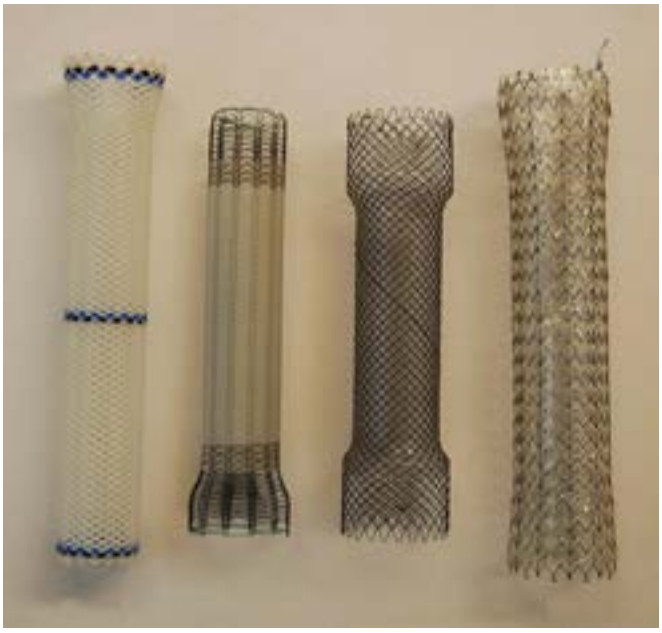


FIG. 2 Left to right, Self-expandable plastic stent, partially covered self-expanding metal stent (pc-SEMS), double-layer fully covered SEMS (fc-SEMS).

Gastroesophageal Junction Tumors

Palliation of gastroesophageal junction (GEJ) strictures by endoscopic means is technically challenging, owing to intrinsic anatomic peculiarities. Unlike the upper and middle esophagus, the GEJ features an acute angle and varying luminal diameters, which may interfere with satisfactory stent fixation. ES at this location is frequently associated with an increased risk of acid reflux, distal migration, and ineffective palliation. The higher rate of complications is often compounded by the overall poorer survival ascribed to GEJ tumors and has long been a basis for the argument against stenting of these lesions. In clinical practice, pc-SEMS are considered the stent of choice for GEJ strictures, as their bare ends allow for better anchorage. The introduction of modified fc-SEMS featuring progressive step flaring of the distal end (conforms better to the gastric opening) and one-way reflux valves at the distal end theoretically favors improved treatment of GEJ lesions. A recent RCT by Persson et al. comparing modified fc-SEMS with pc-SEMS in 95 patients with malignant GEJ strictures showed no difference in stent migrations, although there was a trend toward better relief of dysphagia with fc-SEMS.

Bridge to Surgery

Preoperative ES in patients with locally advanced EC undergoing neoadjuvant therapy may allow for nutritional optimization before surgical resection. Although several small studies have demonstrated improved oral intake, weight stabilization, and QOL when SEMS, SEPS, or BDS were used as a bridge-to-surgery in a neoadjuvant setting, a retrospective study by Mariette et al. reported worse oncologic outcomes with SEMS. A lower rate of complete resection

(71.0% vs. 85.5%; $P = 0.041$), shorter disease-free interval (6.5 vs. 9.0 months; $P = 0.040$), and worse 3-year overall survival (25% vs. 44%; $P = 0.023$) were noted in the preoperative SEMS group. One possible explanation resides in the fact that SEMS-induced mural inflammation may distort the tissue planes and interfere with the completeness of resection. There is currently no evidence regarding oncologic outcomes with preoperative stenting during neoadjuvant therapy for SEPS and BDS. Of note, although stent migration rates in this setting are upward to 50%, they may represent a favorable response to neoadjuvant therapy.

Benign Esophageal Disease

Benign Refractory Esophageal Strictures

The mainstay in the treatment of benign esophageal stricture is periodic endoscopic balloon dilation. However, for a subset of patients, dysphagia will persist despite repeated dilation, thus requiring more aggressive interventions. RBES are most commonly encountered after caustic injuries, radiation to the chest or mediastinum, postsurgically after esophagodigestive anastomoses, or after endoscopic interventions such as per-oral endoscopic myotomy (POEM) and endoscopic mucosal resection. Although no study has, to date, evaluated the impact of dilation time on outcomes, proponents of temporary stenting for RBES purport that continued radial pressure on the esophageal lumen may result in sustained luminal patency. The challenge in selecting a stenting modality for RBES resides in the transient nature of the intervention. The ideal stent needs to be easily retrievable and yet resistant to migration. To this end, fc-SEMS are the most commonly used. Although initially showing great efficacy, Polyflex, the only FDA-approved SEPS for RBES, was discontinued in the United States owing to a disappointing safety profile. Its insertion resulted in migration rates up to 50% and a rate of severe stent-related complication nearing 25%. There are currently no RCTs evaluating outcomes for various stent designs in the management of RBES. A recent meta-analysis by Thomas et al. examined the performance of fc-SEMS in 199 patients with RBES. The efficacy of fc-SEMS for palliation was 46.2% with a migration rate of 26.4% and a successful retrieval rate of 87%. BDS has shown similar efficacy to fc-SEMS and has the added advantage of not requiring retrieval. However, BDS has a higher rate of stent-related complications such a retrosternal pain and bleeding. In brief, ES with either fc-SEMS or BDS is an intervention of last resort in benign esophageal strictures, reserved for carefully selected patients with RBES.

Benign Perforations, Anastomotic Leaks, and Fistulas

Benign esophageal perforations (BEP) can be classified as spontaneous, such as in Boerhaave's syndrome, iatrogenic, or traumatic. As for fistulas, contamination of surrounding mediastinal or pleural spaces by esophageal luminal contents can have dire consequences, triggering highly lethal inflammation and infection. Early determination of the etiology and severity of the leakage is crucial, as these considerations will guide therapeutic management and determine outcomes. A contained perforation or anastomotic leak in an otherwise clinically stable patient may be successfully treated with conservative measures. In these patients, nil per os, intravenous hydration, nasogastric drainage, and broad-spectrum antibiotics are the mainstays of therapy. In patients with noncontained leaks, ES may allay the potential morbidity of surgical intervention and is now increasingly used (Figs. 3 and 4). As with traditional surgical approaches, the goal of therapy in using stents in these patients remains complete drainage of the contaminated spaces, successful sealing of the leak, diversion of oral secretions, and prevention of widespread infection. In a recent meta-analysis comparing SEMS to surgical intervention in patients with esophageal leakage, Persson et al. reported a higher success rate (88% vs. 83%) and a lower mortality rate (7.5% vs. 17%) when SEMS were used. We recommend the use of covered stents—either fc-SEMS or pc-SEMS—for the management of hemodynamically stable patients with BEP. Concurrent drainage of the involved space, broad systemic antibiotic therapy, intravenous fluid administration, and temporary diversion of oral secretions are often employed to optimize clinical outcomes.



FIG. 3 Acquired tracheoesophageal fistula. *(Courtesy Dr. Richard K. Freeman, MD.)*

Achalasia

The role of ES in the treatment of achalasia is evolving. Over the last 3 decades, the introduction of temporary stenting using retrievable SEMS has renewed interest in this modality. In 2010, a long-term follow-up of a prospective comparison of pneumatic dilation and SEMS of various diameters in 120 patients with achalasia showed a higher clinical remission rate at 13 years (83.3% vs. 0) when 30-mm SEMS were used compared with pneumatic dilation. Although surgical and endoscopic interventions such as Heller myotomy and POEM are the mainstays of definitive therapy for achalasia, temporary retrievable stenting with SEMS may be an option for patients who are not surgical candidates (Fig. 5).

Refractory Esophageal Variceal Bleeding

Fully covered SEMS may be used for refractory esophageal variceal bleeding. There are specially designed SEMS with a wide diameter (at least 25 mm) for this indication. There are multiple small studies that have been published with encouraging results. In a recent meta-analysis, technical success was achieved in 97% of cases and bleeding was controlled in 96%. However, one small trial comparing SEMS to balloon tamponade showed no difference in survival. All studies performed for this indication have reported adverse events that include stent migration and ulceration.

PROCEDURE

Meticulous planning is necessary when considering ES. Although both conscious sedation and general anesthesia are comparable, the latter would best serve a patient at high risk for aspiration. Preprocedural endoscopic evaluation of the lesion should be comprehensive. The luminal diameter, location, and size of the lesion of interest must be carefully assessed and documented. Evaluating the friability of the luminal tissue is equally important, as it could portend a greater risk than usual of bleeding, pressure necrosis, or mural erosion after the procedure. Endoscopic predilation of the lesion is no longer routinely performed but could be considered for the small subset of patients in whom the severity of the stenosis might



FIG. 4 **(A)** Upper gastrointestinal (GI) series with water-soluble oral contrast medium demonstrating extraluminal extravasation of contrast medium from the left side of the esophagus approximately 2 cm below the level of the carina, consistent with esophageal perforation. **(B)** Repeat upper GI series with water-soluble oral contrast medium in the same patient as in **(A)** demonstrates a distal esophageal stent in good position. There is no evidence of contrast medium extravasation to suggest a persistent leak.

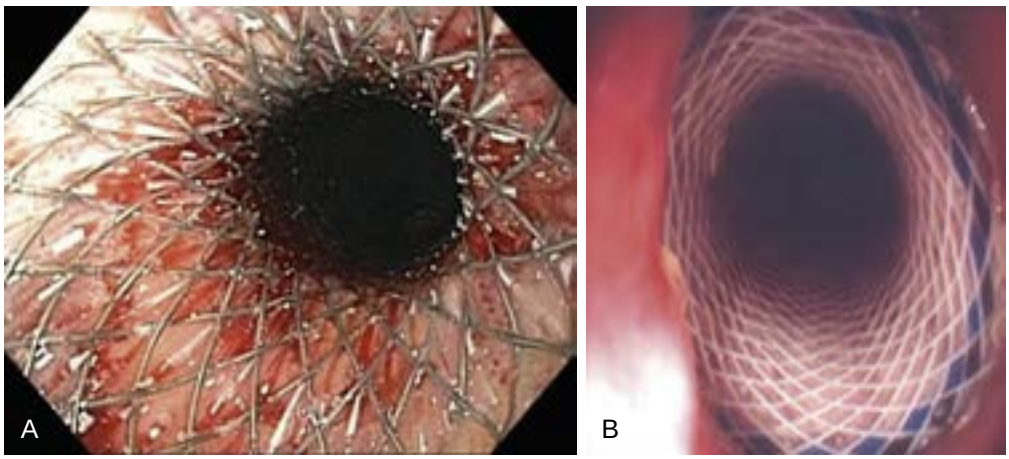


FIG. 5 Endoscopic view of deployed and expanded self-expanding metal stent **(A)** and self-expandable plastic stent **(B).**

prevent stent insertion. Particular attention should be paid to stent size. The internal diameter of the stent should be slightly larger than the lesion of interest, thus allowing for adequate radial force to be applied. An inadequately small stent diameter may increase the risk of migration, whereas an oversized stent may lead to perforation and excessive pressure necrosis. The length of a stent should be at least 4 cm longer than that of the lesion, overlapping it both proximally and distally by at least 2 cm. However, the location of an esophageal obstruction may necessitate modification to the general technique for stent deployment. Most notably, stent placement in the proximal esophagus is known to be challenging. In patients with esophageal strictures near the upper esophageal sphincter (UES), the placement is adjusted so that the proximal margin of the stent is below the UES (i.e., the proximal stent margin may be <2 cm). Stent placement in the distal esophagus or across the GEJ may also be challenging. In these instances, it is important to avoid an excessively long stent so that the distal margin of the stent does not result in contact with the contralateral gastric wall and lead to ulceration or perforation.

ES can be achieved using either fluoroscopic guidance, endoscopic guidance, or both. One technique is the Seldinger technique, in which a guidewire is endoscopically advanced into the esophagus 2 to 3 cm past the distal end of the lesion, the endoscope is removed,

and the stent delivery system is advanced over the guidewire. The endoscope is then reinserted, and the stent positioned and deployed under direct visualization. Caution should be used to ensure that the stent is not fully deployed until satisfactory positioning has been achieved. Using fluoroscopy, the guidewire is inserted using a catheter. Once a satisfactory position has been secured, a small amount of water-soluble contrast medium is injected through the catheter to delineate the stricture. Radiopaque markers are then used to delineate the location and length of the stricture on the patient's skin. Next, after the catheter is removed, the delivery system is advanced over the guidewire, and the stent is deployed under continuous fluoroscopic monitoring.

The development and increased availability of through-the-scope (TTS) SEMS has allowed for this technique to be performed by advancing the stent catheter under direct visualization through the accessory channel of a therapeutic double channel upper endoscope.

After deployment, the stent expands against the stricture and the mucosa at the margins of the stricture. This anchors the stent in place and helps prevent stent migration. Repeat endoscopy or an upper gastrointestinal series 24 to 36 hours postdeployment is often performed before resumption of oral intake. The stent is expected to completely expand within 48 to 72 hours. When oral intake is resumed, patients are discharged with written diet instructions based on results of stent placement and the expected gradual expansion of the stent. Patients are typically advised to consume liquids only for 24 to 48 hours and then to advance to a soft solid diet as tolerated, as well as to adhere to long-term avoidance of fibrous foods such as raw vegetables and large pieces of meat.

COMPLICATIONS

Close to 30% of patients undergoing an esophageal stent placement experience complications (Table 3). These events are often classified as early or late (Table 4). Events of mild to moderate severity such as retrosternal pain or reflux symptoms typically resolve within 1 or 2 weeks postprocedure. Persistence of retrosternal pain beyond 2 weeks may indicate the need for endoscopic removal of the stent. Recent studies have shown improvement of reflux symptoms with the use of stents equipped with a distal reflux valve, especially in patients with GEJ lesions. Other measures to prevent acid reflux and aspiration of gastric contents include maintaining an upright (or semi-upright) position at all times and a daily proton pump inhibitor.

Stent occlusion secondary to tumor in-growth is most commonly seen with uncovered or partially covered stents but can now be successfully managed with a stent-in-stent technique (Fig. 6). This chapter focuses on the major complications of stent migration and vascular and aerodigestive erosions.

TABLE 3 Overview of Adverse Events Related to Esophageal Stent Placement for Different Indications

Complications	Malignant Dysphagia (n = 1017)	Benign Dysphagia (n = 232)	Esophageal Leakage (n = 599)
SERIOUS ADVERSE EVENT (%)			
Major bleeding	8.0	3.0	1.3
Aspiration pneumonia	5.0	1.3	0.7
Perforation	2.0	1.3	1.0
ADVERSE EVENTS (%)			
Retrosternal pain	30.0	4.3	0.5
Reflux symptoms	7.0	2.6	0.5
Recurrent dysphagia	31.0	29.0	20.0
Stent migration	11.0	24.5	16.5
Tissue ingrowth/overgrowth	14.0	2.2	2.7
Food obstruction	7.0	2.2	1.1

Modified from Vermeulen BD, Siersema PD. Esophageal stenting in clinical practice: an overview. *Curr Treat Options Gastroenterol*. 2018;16:260–273.

TABLE 4 Common Early and Late Complications After Esophageal Stent Placement

Early Complications (<2 weeks), 10%–20%	Late Complications (>2 weeks), 15%–37%
Retrosternal pain	Migration
Minor hemorrhage	Stent fracture
Aspiration	Obstruction/tumor ingrowth
Gastroesophageal reflux disease	Erosion
Migration	Airway erosion/compression
Occlusion	Vascular erosion
Airway erosion/compression	
Vascular erosion	

Modified from Vermeulen BD, Siersema PD. Esophageal stenting in clinical practice: an overview. *Curr Treat Options Gastroenterol*. 2018;16:260–273.

Tissue Erosion

Stent erosion into neighboring mediastinal structures such as the big vessels and airway is rare but highly lethal when it occurs. Tissue necrosis resulting from high radial pressure exerted on the esophageal wall is often compounded by poor tissue perfusion and impaired wound healing secondary to malnutrition or radiation exposure. Some studies have shown that a history of radiation to the chest or mediastinum increases the risk of tissue erosion from ES. Similarly, dual stenting of the esophagus and trachea is also associated with an increased risk of tissue erosion.

Vascular Erosion

Vascular erosion is rare but highly lethal. Although aortoesophageal fistula is perhaps the most common, vascular erosion involving the retroesophageal subclavian and common carotid arteries have been reported. One must always have a high degree of suspicion as to its possibility. For example, an abrupt sentinel hematemesis associated with retrosternal chest pain in a patient with a history of esophageal stent placement should prompt immediate evaluation and intervention before a potential catastrophic exsanguination. Emergent management of an aortoesophageal fistula involves prompt control of the potentially fatal hemorrhage, followed by timely vascular repair (Fig. 7). Concurrent activation of the massive transfusion protocol and airway protection may be necessary. In such an emergent setting, endoscopic balloons can often be used to control the bleed, and some surgeons have even successfully used Sengstaken-Blakemore tubes for this purpose. Temporary intravascular occlusion and emergent surgery are also options. Once control is obtained, it can be followed with endovascular repair of the aortic defect. After the patient is stabilized, attention can then be turned to the esophageal defect. After removal of the offending stent, a small defect may be primarily repaired with muscle interposition. An esophagectomy may be necessary for larger defects. Alternatively, in moribund patients, a conservative approach involving diversion of esophageal contents and palliative care may be more appropriate.

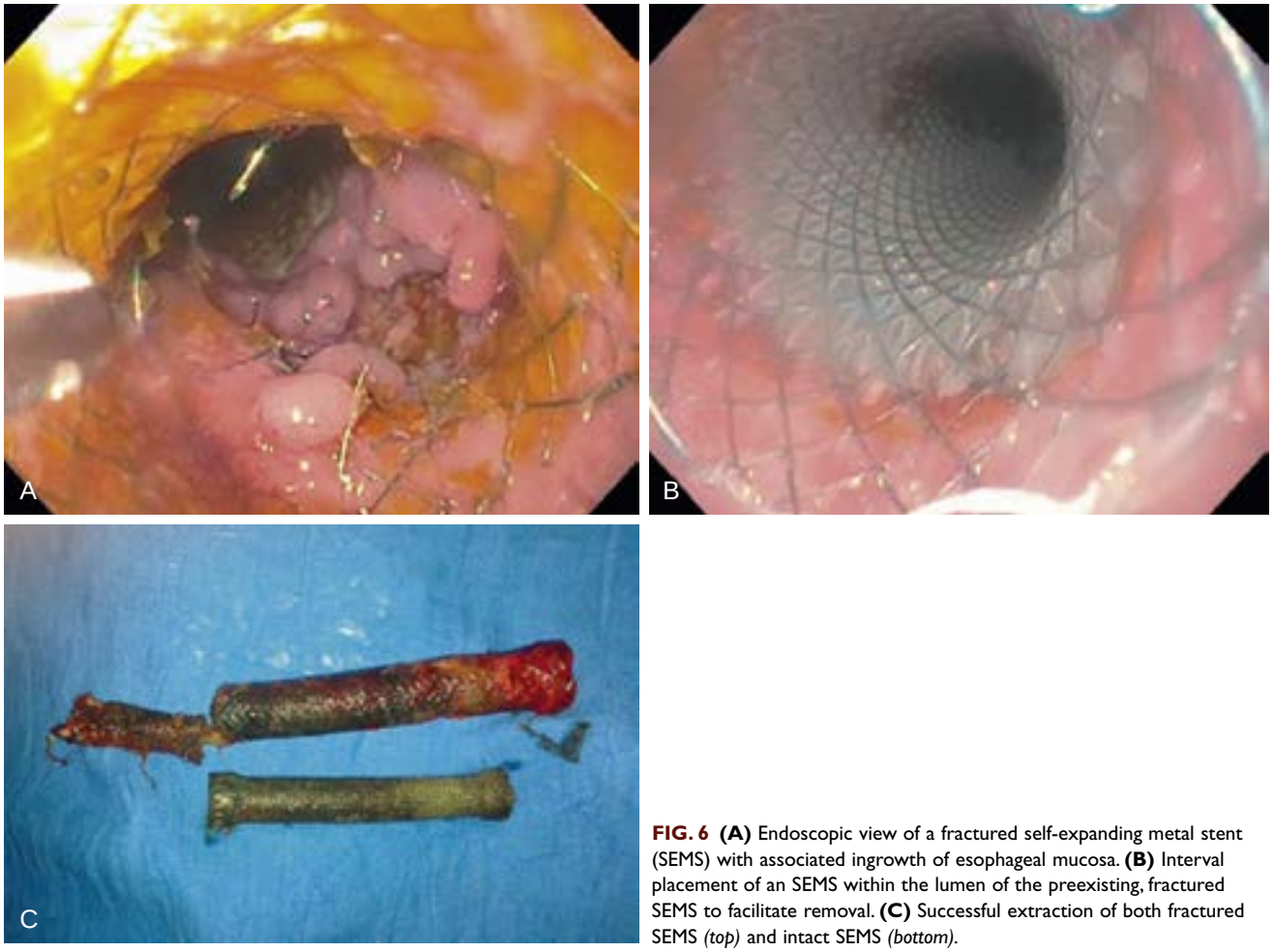


FIG. 6 **(A)** Endoscopic view of a fractured self-expanding metal stent (SEMS) with associated ingrowth of esophageal mucosa. **(B)** Interval placement of an SEMS within the lumen of the preexisting, fractured SEMS to facilitate removal. **(C)** Successful extraction of both fractured SEMS *(top)* and intact SEMS *(bottom)*.



FIG. 7 Thoracic endovascular aortic repair of aortic defect after an aortoesophageal fistula. **(A)** Circled area shows contrast medium leaking from the aortic defect. **(B)** Arch aortogram showing the endovascular stent graft. *(From Liang H, Chen C, Liu W, Yu F. Definitive treatment for aortoesophageal fistula by endovascular stent graft.* Indian J Surg. *2016;78:151–154.)*

Aerodigestive Erosion

Tracheoesophageal erosions have been reported in 4% to 8% of patients after ES (see Fig. 4). Unlike the dramatic presentation seen with vascular erosion, patients often present with nonspecific symptoms such as dyspnea and frequent pulmonary infections. Although a chest CT scan may help identify the lesion of interest, bronchoscopic and endoscopic evaluations are often necessary to characterize the extent and size of the defect. The management of tracheoesophageal fistulas depends on the patient's hemodynamic status and on the underlying pathology that led to esophageal stricture. In a patient who presents in extremis, securing the airway must be the priority. One should maintain spontaneous ventilation if possible, but the patient should be promptly intubated if there is an inability to ventilate. A variety of intubation methods can be used if ventilation is difficult including contralateral mainstem intubation, use of a double

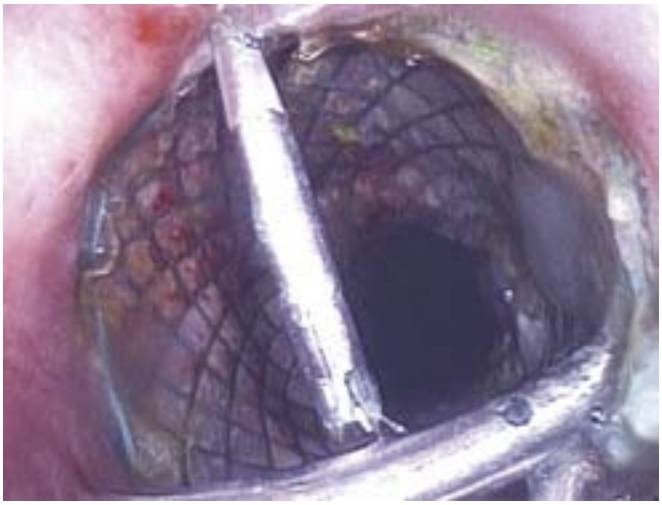


FIG. 8 Endoscopic view of an esophageal clip that stabilizes the proximal aspect of an esophageal stent.

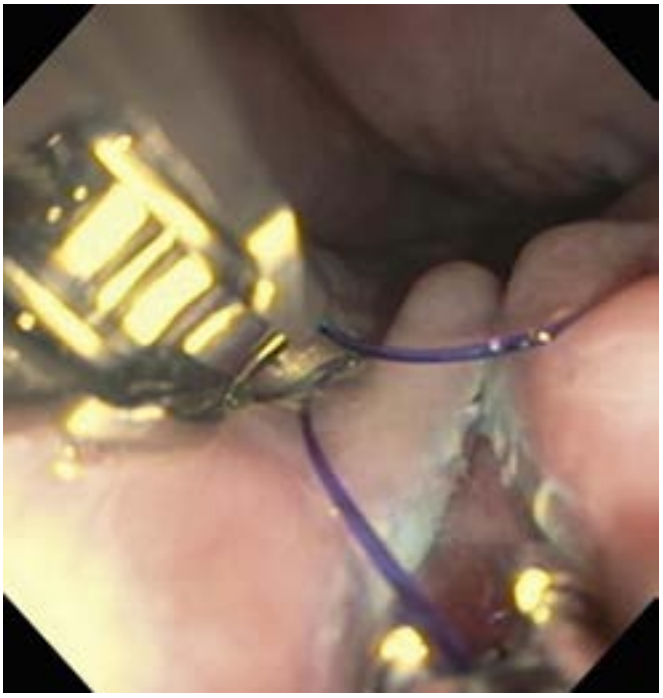


FIG. 9 Endoscopic view of the Apollo Overstitch device used for suture fixation of the proximal aspect of an esophageal stent to the esophageal mucosa.



FIG. 10 Comparison of the Apollo Overstitch device appearance at the distal end of the dual channel endoscope *(left)* and the Apollo Overstitch Sx device appearance at the distal end of the single channel endoscope *(right)*.

lumen tube, employing a bronchial blocker, or sedating the patient to ventilate. In some cases, tracheal stenting and esophageal diversion may be needed, and definitive management may be delayed. Stable patients with good functional status and with good esophageal tissue integrity can undergo either a primary repair with muscle interposition or an esophagectomy. Otherwise, tracheal stenting, esophageal diversion, and palliative care should be considered.

Stent Migration

Stent migration is perhaps the most common complication of esophageal stricture, occurring in 11% to 33% of cases. Over the past 2 decades, various interventions aimed at reducing the frequency of migrations, such as anchoring the stent to the esophageal wall, have been introduced. Endoclips are used to secure the proximal stent end to the esophageal wall, but a high migration rate persists (Fig. 8). Endoscopic suturing using Apollo OverStitch and Apollo OverStitch Sx devices (Figs. 9 and 10) has also shown some benefit in small studies; however, high-quality evidence is not available. More recently, a specialized over-the-scope clip (OTSC) has become available for stent fixation with promising results. Small studies indicate reduced migration rates that, however, still exceed 15%. Additionally, off-label use of lumen-apposing metal stent (LAMS) has been studied for management of short-segment benign gastrointestinal strictures. Their unique dumbbell-shaped design helps to fix the stent in place (Fig. 11). LAMS is an alternative to traditional options; however, data are limited and future studies are needed to measure their efficacy. The best treatment of migration is probably prevention. A study

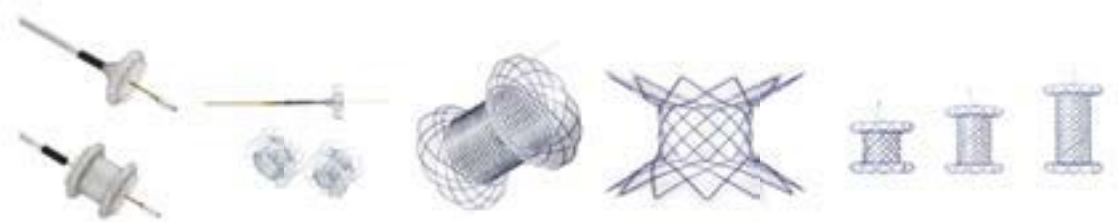
	Axios (Boston Scientific, Natick, MA, United States)	**Spaxus (Taewoong Medical, Gimposi, South Korea)**	**Nagi (Taewoong Medical, Gimposi, South Korea)**	**Aixstent (Leufen Medical, Berlin, Germany)**	**Hanarostent Plumber (M.I Tech, Pyeongtaek-si, South Korea)**
Stents					
Availability in United States	Yes	No	No	No	No
Flange diameter (mm)	21, 24, 29	23, 25, 31	20, 25, 31	25	22 to 28
Length (mm)	10	20	10, 20, 30	30	10, 30
Lumen diameter (mm)	10, 15, 20	8, 10, 16	10, 12, 14, 16	10, 15	10, 12, 14, 16
Delivery catheter (Fr)	10.8	10	9, 10	10	10.5
Material	Silicone-covered Nitinol-braided stent	Silicone-covered Nitinol-stent	Silicone-covered Nitinol-stent	Silicone-covered Nitinol-stent	Silicone-covered Nitinol-stent
Deployment through-the-scope	Yes	Yes	Yes	Yes	Yes
Delivery in single step	Yes	No	No	No	No

FIG. 11 List of currently available LAMS with representative images. *From Sharma P, McCarty TR, Chhoda A, et al. Alternative uses of lumen apposing metal stents.* World J Gastroenterol. *2020;26(21):2715–2728.*

TABLE 5 Rates of Complication Based on Stent Indwelling Time in the Management of Esophageal Leaks and Perforations

	Anastomotic Leak			Perforation		
	<2 Weeks	>2 Weeks	*P* Value	<4 Weeks	>4 Weeks	*P* Value
Number	29	16		96	21	
Migration	4 (14%)	7 (44%)	0.04	9 (9%)	9 (43%)	0.0007
Dysphagia	5 (17%)	8 (50%)	0.04	4 (4%)	6 (29%)	0.0022
Hemorrhage	0	1 (6%)	0.4	0	2 (10%)	0.03
Stent fracture	3 (10%)	6 (38%)	0.05	5 (5%)	7 (33%)	0.001
Airway compromise	1 (3%)	2 (13%)	0.3	3 (3%)	2 (10%)	0.2

Data from Freeman RK, Ascioti AJ, Dake M, Mahidhara RS. An assessment of the optimal time for removal of esophageal stents used in the treatment of an esophageal anastomotic leak or perforation. *Ann Thorac Surg*. 2015;100:422–428.

by Freeman et al. evaluating the impact of stent indwelling time in 162 patients treated with ES showed a significant reduction in stent-related complications in patients who had a shorter indwelling time (Table 5). In patients with anastomotic leaks, a 30% ($P = 0.04$) reduction in stent migration rates was noted with a stent duration of fewer than 14 days. Patients with acute perforation experienced a 34% reduction in stent migration when the indwelling time was fewer than 28 days.

CONCLUSION

ES remains a mainstay in the palliation of advanced malignant strictures. Although its indications have greatly expanded to include various benign esophageal diseases, complications associated with this procedure mandate thorough preprocedural evaluation of the patients as well as an individualized therapeutic approach.

SUGGESTED READINGS

Anderson M, Sippey M. Endoscopic stent placement: indications and success rates. *Annals of Laparoscopic and Endoscopic Surgery*. 2019;4:55.

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Knyrim K, Wagner HJ, Bethge N, Keymling M, Vakil N. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. *N Engl J Med*. 1993;329:1302–1307.

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Vermeulen BD, Siersema PD. Esophageal stenting in clinical practice: an overview. *Curr Treat Options Gastroenterol*. 2018;16:260–273.

MANAGEMENT OF ESOPHAGEAL PERFORATION

Juan A. Muñoz-Largacha, MD, and James M. Donahue, MD

INTRODUCTION

Despite advances in diagnostic imaging and early recognition, esophageal perforation continues to be a life-threatening condition with high morbidity and mortality rates. Reported mortality ranges between 10% and 25% when diagnosis and treatment are initiated within 24 hours and can be as high as 40% to 60% when diagnosis and treatment are delayed. Other patient-related factors such as comorbidities, functional condition, presence of sepsis and multiorgan failure, and location and cause of perforation can also influence mortality in this group of patients.

Iatrogenic injuries resulting from endoscopic procedures (diagnostic, biopsy, dilation, sclerotherapy, laser therapy, photodynamic therapy, stent placement, transesophageal echocardiogram, esophageal ultrasound) are the most common cause of esophageal perforation, accounting for 60% to 70% of cases. Spontaneous rupture, or *Boerhaave's esophagus,* is the second most common cause of esophageal perforation (15%–30%). Other, less frequent causes include trauma (penetrating or blunt), foreign body or caustic ingestion, cervical, nonesophageal surgery (thyroidectomy, mediastinoscopy, spine surgery), and malignancy of the esophagus, lung, or other mediastinal structures. Esophageal perforation has also been described in association with infectious processes in immunocompromised patients (candida, herpes, syphilis, and tuberculosis), in the setting of severe gastroesophageal reflux, and following Mallory-Weiss tears (Table 1).

DIAGNOSIS

A prompt diagnosis of esophageal perforation is crucial to improve outcomes and survival, and a high level of suspicion should be

TABLE 1 Causes of Esophageal Perforation

Iatrogenic	Endoscopic procedures (diagnostic, biopsy, dilation, stent placement) Transesophageal echocardiography Esophageal ultrasonography
Spontaneous	Barogenic-Boerhaave syndrome
Traumatic	Blunt Penetrating Surgical intervention: cervical intervention or mediastinal surgery (i.e., thyroidectomy)
Ingestion	Caustic Foreign body
Neoplastic	Primary esophageal malignancy Mediastinal malignancy with esophageal involvement and erosion
Infectious	Candida, herpes, syphilis, tuberculosis

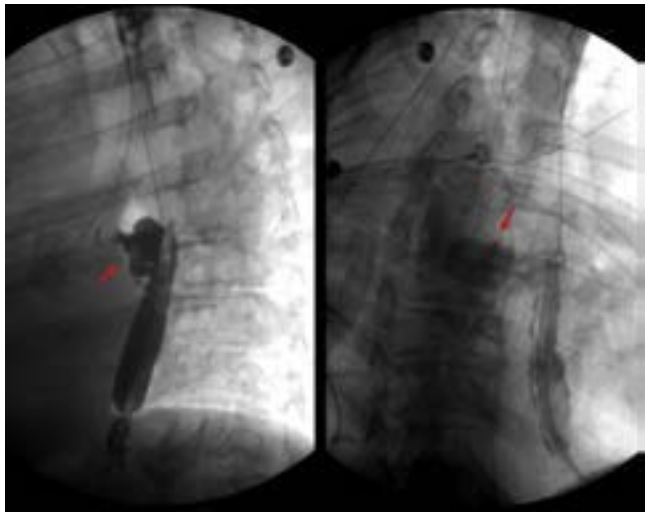


FIG. 1 Esophagram with water-soluble contrast. Evidence of esophageal perforation and contrast extravasation in the right posterolateral aspect of the mid-esophagus (red arrows).

maintained to achieve this goal. A detailed history and physical examination are of utmost importance and will help determine the most likely cause of perforation. Commonly, patients will report recent esophageal instrumentation or forceful vomiting. Initial complaints often involve a vague description of pain localized to the neck, chest, shoulder, or epigastrium. As the process progresses, patients may experience dyspnea, dysphagia, or odynophagia. On physical examination, patients may remain hemodynamically stable or present with signs of septic shock or mediastinitis such as tachycardia or hypotension. Laboratory values generally reveal a leukocytosis. Commonly, a chest x-ray is performed as part of the initial assessment of these patients, which may reveal presence of pneumomediastinum, pleural effusion, pneumothorax, subcutaneous emphysema, or an abnormal cardiomediastinal contour. When esophageal perforation is on the differential diagnosis, further imaging studies such as contrast esophagram and computed tomography (CT) are performed for better evaluation of the extent of the injury, location, and degree of mediastinal and pleural contamination.

Esophagram

An esophagram is a noninvasive diagnostic tool that can help determine the presence and location of a perforation. Either water-soluble contrast (Gastrografin) or diluted barium can be used. Gastrografin is generally preferred over barium because of the lower risk of mediastinitis. However, the sensitivity of Gastrografin has been reported between 60% and 70%, so negative results do not completely exclude perforation, especially in the cervical esophagus, because of the rapid transit of the contrast. In addition, barium has been shown to have better resolution for differentiating between contained and noncontained perforations. In practice, a Gastrografin esophagram is often obtained first, and if inconclusive, repeat images with diluted barium can be obtained as necessary for improved sensitivity and specificity. If Gastrografin demonstrates free perforation into the pleural space or abdominal cavity, the procedure is terminated. Figure 1 shows evidence of esophageal perforation on a Gastrografin esophagram.

Computed Tomography

CT is readily available and provides important supportive information related to an esophageal perforation, such as differentiating between a contained versus noncontained perforation. A contained perforation is characterized by no or minimal extravasation of contrast at the site of perforation without evidence of pleural or peritoneal contamination, or by contrast drainage back into the esophagus. In addition, CT allows for evaluation of the location of injury as well as the severity of mediastinal, pleural, or peritoneal contamination if present. Figure 2 shows evidence of esophageal perforation on chest CT.

Computed Tomography Esophagography

CT esophagography is a more recently available option with the potential to improve workflow and expedite the diagnosis of esophageal perforations by reducing the need for two radiologic examinations. Multiple reports over the past decade have shown its utility for the evaluation of postoperative leaks after esophagectomy; however, its use in the setting of acute esophageal perforations must be clarified. This technique is generally readily available, is less cumbersome for the patient, and does not require a fluoroscopy suite, an additional technician, and a supervising radiologist. One of the main limitations of a fluoroscopic esophagram is that critically ill patients may not be able to swallow the contrast or stand and change positions, which are requisite parts of the examination. In CT esophagography, noncontrast images are obtained first. For patients who cannot swallow, this allows for repositioning of a nasogastric tube (NGT) into the proximal esophagus to allow for contrast administration. These precontrast images are also useful to identify any radiopaque structures (i.e., staples, calcifications) that could be confounded with the contrast in subsequent images. Then, oral contrast is either ingested or administered via the NGT, and supine images are obtained. The reported sensitivity and specificity of this technique are comparable to those for fluoroscopic esophagography, with an equal, if not superior, accuracy for the diagnosis of acute esophageal perforations. In practice, a fluoroscopic esophagram is often obtained following a negative CT esophagram before enteral nutrition is implemented.

Endoscopy

Endoscopy is another helpful diagnostic and potentially therapeutic tool for management of esophageal perforations. Its use should be considered in patients with high suspicion for perforation who could not undergo a swallow examination or underwent a nondiagnostic study. It allows for direct visualization and careful inspection of mucosal integrity and viability as well as characterization of the

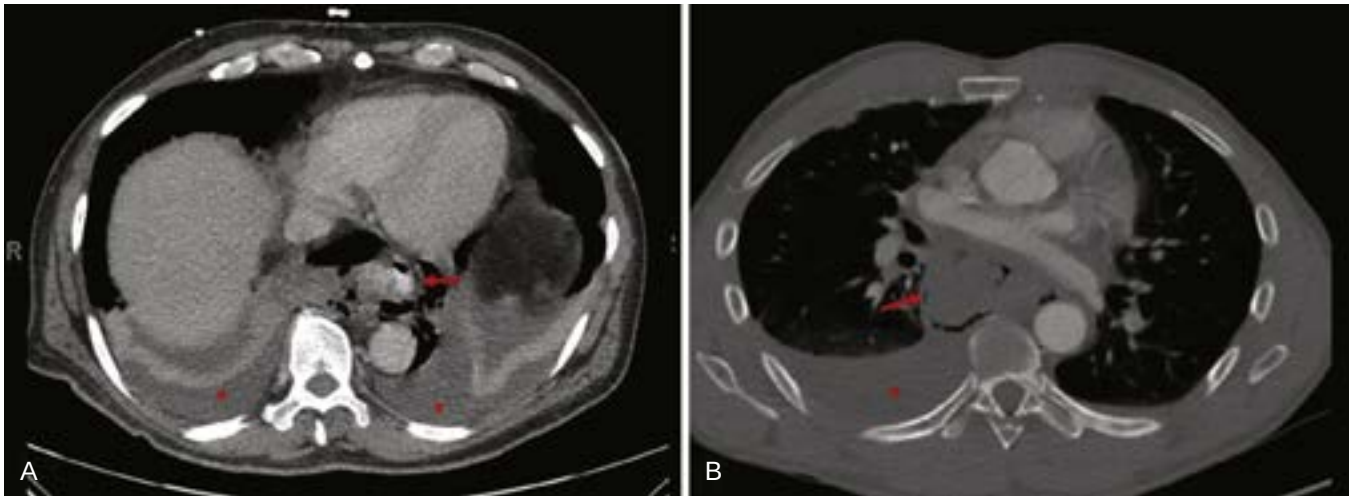


FIG. 2 Chest CT with contrast. **(A)** Patient with spontaneous distal esophageal perforation with pneumomediastinum and periesophageal fluid with contrast extravasation *(red arrow)* and bilateral small pleural effusions *(asterisks)*. **(B)** Large periesophageal fluid collection *(red arrow)* with associated pneumomediastinum and small right pleural effusion *(asterisk)*.

anatomic location of the injury and identification of other pathologic changes or underlying diseases of the esophagus such as strictures or neoplasms. Careful inspection with minimal air insufflation should be performed because this could potentially increase the size of the perforation or cause a tension pneumothorax through a free perforation into the pleural space. As discussed later, endoscopy can also be used for therapeutic purposes, as a stent may be placed in the same setting as the diagnostic procedure.

Assessing Severity of Illness and Prognosis

Several illness severity scoring systems, such as the APACHE system, have been applied to patients with esophageal perforation with various degrees of accuracy. The Pittsburgh Severity Score (PSS) is a scoring system specially devised for esophageal perforation patients that was first described by Abbas et al. in 2009. The authors attempted to identify clinical factors that could predict survival and potentially identify those patients amenable to nonoperative management. The score includes 10 clinical variables that were considered by the authors to be potentially important indicators of injury severity and patient outcomes, which are assigned a value from 1 to 3 (Table 2). In their report, all survivors had PSS ≤3.3, and all patients who died had a PSS ≥6.5. Lower PSS scores were also associated with successful nonoperative management, shorter length of stay, and decreased morbidity. Similar findings have been found in other, independent cohorts. The PSS is a useful tool in terms of estimating prognosis for patients with esophageal perforation, but its validation with the use of prospective studies and potential improvement with more rigorous analysis of clinical data are still needed to definitively guide management.

TABLE 2 Pittsburgh Severity Score

Variables	Points Assigned
• Age >75 years • Tachycardia (>100 bpm) • Leukocytosis (>10.000 WBC/mL) • Pleural effusion on imaging*	1
• Fever (>38.5°C) • Noncontained perforation† • Respiratory distress (>O_2 requirements, RR >30, need for mechanical ventilation) • Time to diagnosis >24 hours	2
• Hypotension • Malignancy	3

*Chest x-ray, esophagram, or chest CT.
†Esophagram or chest CT.
bpm, Beats per minute; *RR,* respiratory rate; *WBC,* white blood cells.

MANAGEMENT

The management of patients with confirmed esophageal perforation after appropriate diagnostic workup can be determined by clinical and imaging characteristics. In a select group of patients with contained perforations, a nonoperative approach may be appropriate. For patients with free perforations, operative management with open primary repair of the perforation has been the traditionally preferred approach, particularly when the repair can be undertaken within 24 hours of the perforation. Recent evidence has shown that a less invasive approach consisting of endoscopic stenting and thoracoscopic mediastinal and pleural drainage produces encouraging results. In the most dire situations, esophageal resection and exclusion may be necessary. Regardless of the therapeutic approach chosen, initial management of patients with esophageal perforation should include close monitoring in a surgical critical care unit. Patients should be maintained *nil per os* (NPO), appropriately resuscitated with intravenous fluid, and started on broad-spectrum antibiotics to include fungal coverage. Adequate intravenous analgesia and a proton pump inhibitor (PPI) should be started, and early total parenteral nutritional support can be considered if a prolonged course is expected.

Nonoperative Management

Criteria for nonoperative management were initially described by Cameron et al. in 1979 and further modified by Altorjay. These included early diagnosis, contained perforations or perforations draining back into the esophagus, no significant mediastinal contamination, absence of sepsis or multiorgan failure, and perforation not associated with malignancy or obstruction of the esophagus. If

hemodynamically stable without signs of sepsis or multiorgan failure, the patient is admitted to the surgical critical care unit for 48 to 72 hours of observation. Patients should be maintained NPO with the head of the bed elevated, started on 72 hours of broad-spectrum antibiotics and a PPI, and, dependent on premorbid nutritional status, considered for parenteral nutritional support. Repeat imaging is obtained in 72 to 96 hours. If this demonstrates no evidence of free perforation, a liquid diet may be initiated. It is important to remember that these patients require close observation to ensure that they continue to meet nonoperative criteria. Should the patient's clinical condition deteriorate as evidenced by the development of fever, leukocytosis, tachypnea, tachycardia, or mental status changes, repeat imaging and possible endoscopy are indicated.

Endoscopic Stenting with Thoracoscopic Mediastinal and Pleural Drainage

For patients with evidence of free contrast extravasation into the mediastinum, endoscopic covered stent placement or endoluminal clipping to attempt to seal the perforation can be performed as an alternative to open surgical repair. It is vital to remember that this approach does not address the associated mediastinal and possible pleural contamination. For this reason, early video-assisted thoracoscopic surgery (VATS), performed either immediately after stent placement or within 1 to 2 days following the procedure, is generally required for debridement and drainage of the mediastinum and pleural cavity. At the conclusion of the VATS procedure, depending on the degree of contamination, at least one chest tube is left in the pleural space, and another (often a Blake drain) is left adjacent to the esophagus. Typically, a contrast esophagram is performed 48 hours after stent placement to determine if sealing of the esophageal perforation has occurred. If there is no evidence of extravasation, a clear liquid diet can be started and advanced to full liquids. It is advisable to leave the tube in place adjacent to the esophagus while the liquid diet is being initiated to monitor the character of the output as well as the patient's clinical condition. On the other hand, if the esophagram shows extravasation of contrast around the stent into the mediastinum or the drainage character changes after liquids are begun, the patient should be returned to NPO status and will require placement of a jejunostomy tube.

In their study, Ben-David et al. showed encouraging results in 76 patients with esophageal perforation (majority iatrogenic or spontaneous) managed with endoscopically placed metallic covered stents in addition to laparoscopic or VATS drainage and enteral feeding access placement. All patients were treated within 24 hours of initial presentation, and perforation occlusion was confirmed within 48 hours after stent placement in 68 patients (89.5%). Additionally, no need for an open esophageal procedure was required, avoiding the morbidity of a more invasive operation. However, stent placement was not without complications, with an almost 40% migration rate requiring additional intervention within the first week of placement.

The ideal time for esophageal stent removal remains controversial and may depend on the size of the perforation. Some studies have shown adequate healing within 10 days for small perforations, while this process may take up to 8 weeks for larger defects. Ben-David et al. showed a mean length of 36 days from initial placement to final stent removal. In practice, waiting between 4 and 6 weeks, depending on the size of the perforation, is reasonable. Imaging confirmation of perforation healing with an esophagram should be obtained following stent removal before a liquid diet is initiated. If the perforation has not healed at the time of stent removal, the stent can be replaced for another 4 to 6 weeks.

Endoscopic Techniques

The use of endoluminal stents for the management of esophageal perforations is not a new concept, and in fact the most used self-expanding metal stents (SEMS) have been available since the 1990s. Technology improvement with better deployment mechanisms have also increased their use. The development of covered stents with different polymers has increased the technical and clinical success of the management of esophageal perforations and, at the same time, has decreased the rate of stent-related complications. Esophagogastroduodenoscopy (EGD) is performed to localize the defect, determine the extent of the perforation, and identify anatomic landmarks and other esophageal abnormalities. Under direct vision and with the concomitant use of fluoroscopy, a careful assessment of the landing zones and the desired diameter and length of the stent is conducted. Once this assessment is completed, the landmarks for the proximal and distal extent of the stent are marked with radio-opaque markers under fluoroscopy. A guidewire is then introduced under fluoroscopy. Figure 3 shows an endoscopic view of a perforation and subsequent stent placement. Ideally, the stent deployment will successfully cover the perforation on the first attempt, however the stent can be endoscopically repositioned to achieve complete coverage of perforation if needed. If there is evidence of incomplete radial deployment, a balloon dilation may be performed to attain complete contact between the stent and esophageal mucosa. An NGT can be placed under direct vision for gastric decompression in the acute setting. An anteroposterior and lateral chest x-ray should be obtained after stent placement to have a baseline for its location and facilitate further assessment of adequate positioning. As noted, a contrast esophagram should be obtained 48 hours after stent placement before liquids are begun. Figure 4 shows a SEMS in adequate position without evidence of contrast extravasation.

Stent complications include migration, bleeding, erosion, and tissue overgrowth, among others. Migration is the most common complication reported in about 8% to 40% of cases, with less migration rates reported with the use of metallic stents compared with plastic stents. Some studies have reported endoscopic suturing or clipping to secure the stent and prevent migration with favorable results.

Endoscopic suturing or clip placement may also be used to attempt to primarily repair small, early perforations. Previous reports demonstrate higher rates of closure, with an average defect size of 8 mm and higher failure rates when the lesion is greater than 13 mm. EGD is performed, and the esophageal defect is identified to confirm healthy mucosal edges for adequate clip placement. Through-the-scope clips can be used for defects less than 1 cm, and an over-the-scope clip system can be used for larger lesions. Suction can be used to help approximate the lesion edges and aid with better clip deployment. Even though acceptable results have been reported in the literature, this technique is not commonly used given that patients usually present with a more advanced disease process requiring more aggressive interventions.

Open Repair

Currently, little data exist to guide surgeons as to whether to proceed with an open repair or choose stent placement with pleural/mediastinal drainage. Elderly patients and those with multiple medical comorbidities are likely better served with the endoscopic/thoracoscopic approach. Although the likelihood of success of an open repair diminishes over 24 hours from the perforation event, several reports describe successful repairs being performed for perforations beyond the 24-hour mark. Following initial resuscitation efforts, patients who remain hemodynamically labile may still undergo successful repair, although a less invasive approach has obvious advantages in these patients. Ultimately, the decision is left to surgeon judgment and experience of the surgeon and his or her team with each approach. If open repair is chosen, it is critical to identify the location of the perforation to guide the surgical approach. This may require performance of endoscopy in the operating room before incision. Whenever feasible, two-layer closure should be performed and reinforced with a pedicled buttress. In cases of delayed perforation, single-layer closure may be all that is possible.

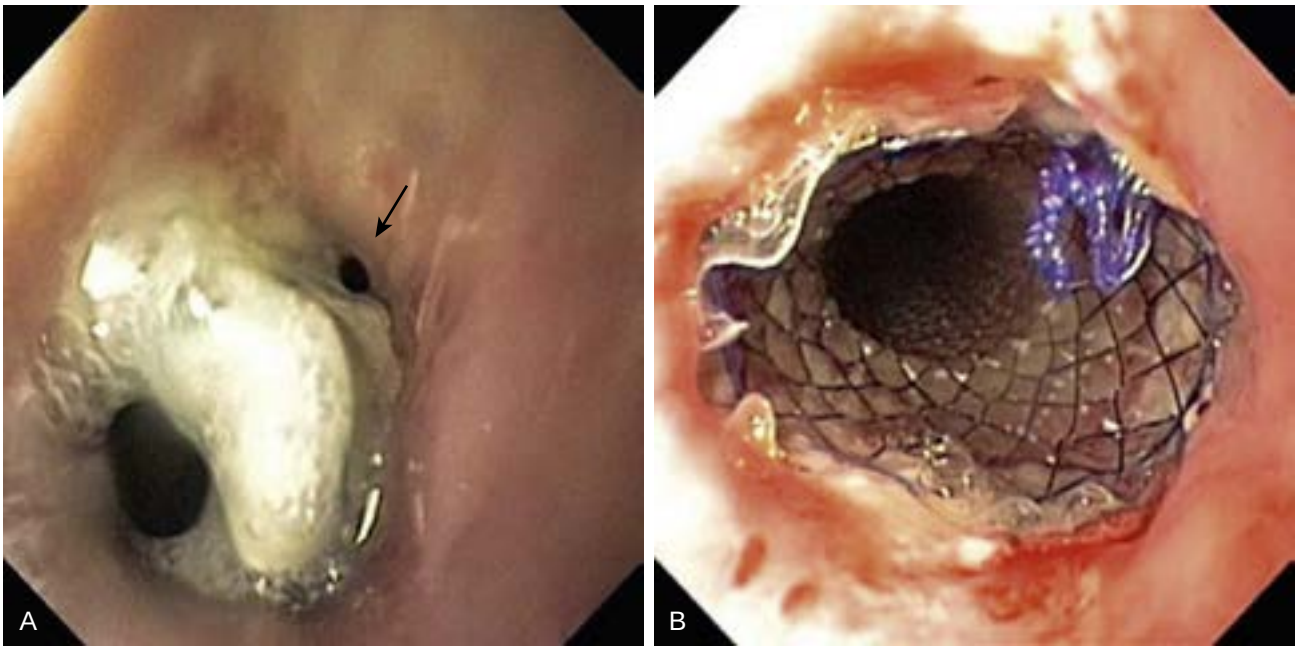


FIG. 3 Endoscopic treatment of esophageal perforation. (**A**) Endoscopic view of a perforation in the middle third of the esophagus *(arrow)*. (**B**) Endoscopic view of the stent in place. *(From Chirica M, Champault A, Dray X, et al. Esophageal perforations. J Visc Surg. 2010;147[3]:e117–e128.)*

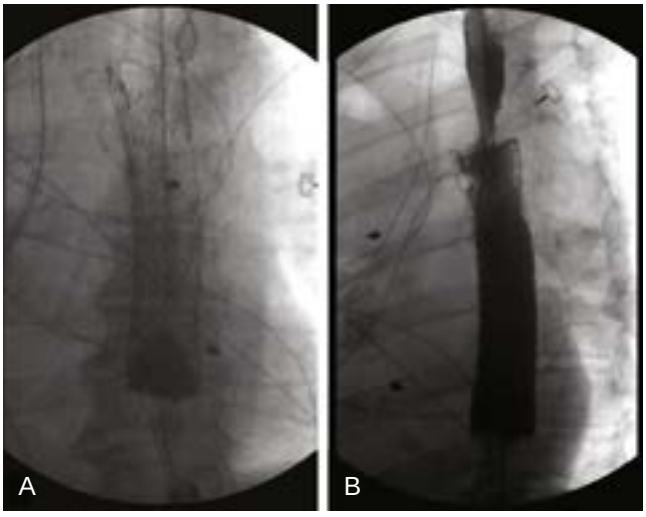


FIG. 4 Esophagram. (**A**) Esophageal stent in adequate position covering a prior perforation. (**B**) Stent in place without evidence of contrast extravasation.

Thoracic Perforations

Perforations of the upper and middle thirds of the esophagus are best approached through a right posterolateral thoracotomy via the fourth or fifth intercostal space. The intercostal muscle (ICM) within the interspace is harvested at this time using electrocautery to ultimately buttress the repair. The cautery tip is positioned near parallel with the surface of the superior rib to avoid injury to the neurovascular bundle. The ICM is freed from the rib to the level of the lumbar-dorsal fascia. Care must be taken to identify this landmark because further dissection risks injury to the intercostal vessels. The ICM flap is transected anteriorly after ligating or clipping the anterior aspect of the muscle to prevent bleeding. Next, the pleura is opened in the area of the perforation, and the esophagus is dissected enough to obtain clear visualization of the perforation. The edges of the perforation should be debrided to determine the full extent of the injury. Of note, the mucosal injury may extend a greater distance than the visualized muscular injury. The esophageal mucosa is closed with running or interrupted absorbable suture (4-0 Vicryl or PDS), and the muscularis is closed with interrupted 3-0 silk sutures. The pleural side of the ICM flap is then placed in contact with the repair and secured to the muscle layer of the esophagus with multiple interrupted silk sutures. Pleural and mediastinal drainage tubes are placed at the conclusion of the operation.

Perforations of the lower third of the esophagus should be approached through a left posterolateral thoracotomy in the seventh or eighth intercostal space. Although an ICM flap is generally used as a buttress, a diaphragmatic flap is also an option. A posteriorly based full-thickness diaphragmatic flap of adequate length and width can be mobilized to reach the area of primary repair. The flap is secured to the esophageal muscle with interrupted silk sutures to cover the repair. The diaphragm then is closed primarily with nonabsorbable suture. Advantages of diaphragmatic flap use include its, thickness, ease, and extent of mobility.

Cervical Perforations

The preferred method of exposure for cervical esophageal perforation is a left-sided neck incision along the anterior border of the sternocleidomastoid muscle (SCM). It may be necessary to ligate the middle thyroid vein for improved exposure. The trachea and thyroid gland are retracted medially for exposure of the esophagus (Fig. 5). The retroesophageal space is entered bluntly along the prevertebral fascia, with care taken to preserve the recurrent laryngeal nerve. Blunt dissection should be continued down to the posterior mediastinum to drain all fluid collections. If the perforation is identified, the defect is repaired primarily as described earlier. A strap muscle can be used to buttress the repair. If the defect is not clearly identified, closed drainage of the area is performed.

Abdominal Perforations

Patients with abdominal esophageal perforation and uncontained leak should be taken to the operating room for primary repair.

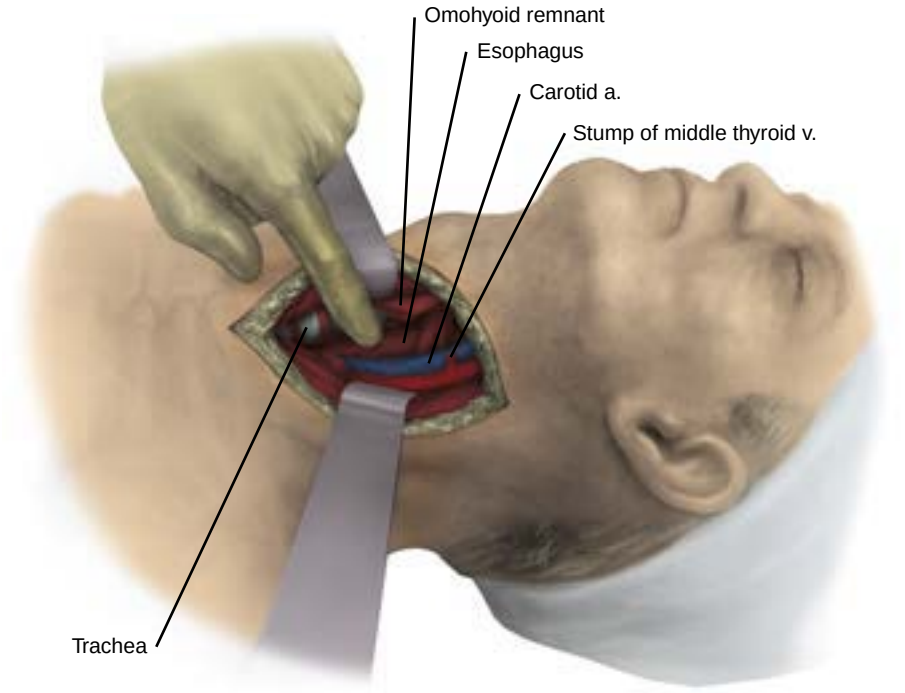


FIG. 5 Cervical esophagus exposure. Incision is made over the anterior border of the sternocleidomastoid muscle. If necessary, the middle thyroid vein and inferior thyroid artery can be ligated. Medial retraction of the trachea and thyroid gland is performed to help expose the esophagus. *(From Cooke DT, Lau CL. Primary repair of esophageal perforation.* Op Tech Thor Cardiovasc Surg. *2008;13[2]:126–137.)*

Perforations of the abdominal esophagus can be approached via an upper midline incision. Once debrided, the perforation should be closed primarily and buttressed with omentum or, more commonly, a fundoplication.

Nutritional Management Following Repair

Traditionally, following transthoracic repair, patients were immediately repositioned for a laparotomy and underwent placement of a gastrostomy tube for gastric decompression and a jejunostomy tube for nutritional access. This has become less commonly performed over time. If patients are requiring inotropic support following the repair, spending extra time in the operating room to place these tubes is not warranted. Furthermore, if the repair is successful, oral nutrition may be able to be started within 1 week, obviating the need for the feeding tube. To promptly begin nutritional support, as an alternative to a surgical feeding tube, a Dobhoff tube may be placed at the time of the repair under direct vision before the repair has been completed. The tube can then be advanced to a post-pyloric position postoperatively to allow early initiation of enteral feeding. An NGT could also be placed at this same time to allow for gastric decompression if the surgeon feels this is necessary. Early initiation of total parenteral nutrition is another option. Regardless of the initial nutritional strategy, an esophagram is obtained approximately 5 to 7 days after surgery depending on the patient's condition. If no leak is identified, liquids may be started and slowly advanced to a soft diet. If there is a persistent leak, this may be managed with subsequent stent placement, which may seal the leak. If the leak persists following stent placement, the patient will require jejunostomy tube placement as several weeks or more will likely be required for healing of the perforation. Although it can be difficult to maintain patience, ultimate healing is still very likely to occur following adequate mediastinal debridement, appropriate antibiotic therapy, and good nutritional support.

Resection with Diversion

Although every attempt should be made to preserve the patient's esophagus, there are rare instances in which this is not possible. These include long (generally >6 cm) perforations that are not amenable to stenting, a large segment of devitalized esophagus, which generally is seen with long delays in diagnosis, or perforated cancers that cannot be stented because of the size of the perforation or tumor. In stable patients, when large defects are encountered, options like stenting followed by operative coverage of the defect with biodegradable mesh and a muscle flap, such as the serratus anterior or latissimus dorsi, can be considered. Although the healing process will take months, an intact, functional esophagus is still possible. Previous reports have described use of a T-tube to create a controlled esophageal fistula for management of very large defects. This is often cumbersome to care for postoperatively and has generally been abandoned. When repair is deemed not to be possible, esophageal exclusion is recommended over resection and immediate reconstruction. The risk of anastomotic failure in patients who are hemodynamically unstable and/or have significant mediastinal contamination is very high.

Once the decision has been made to perform an esophageal exclusion procedure, the esophagus should be mobilized as much as possible in the chest. The esophagus is dived as far distally as possible near the gastroesophageal junction with a 45-mm stapler. After the chest is closed, the patient is then turned to the supine position. A left-sided neck incision is made along the anterior border of the SCM, as described for cervical esophageal perforations. The esophagus should be dissected circumferentially with care taken to avoid injury to the recurrent laryngeal and vagus nerves. Once mobilized from the prevertebral fascia and posterior mediastinum, the esophagus is elevated into the wound. It is vital to preserve as much viable esophagus as possible to aid in future reconstruction. After the esophagus has been transected, it is tunneled subcutaneously onto the left chest, and an end esophagostomy is created. A jejunostomy tube is then placed. If the surgeon wishes to place a gastrostomy tube for gastric decompression, care must be taken not to compromise the use of the stomach as a conduit for later reconstruction.

Special Situations

Malignancy

When esophageal perforation involves a malignancy, consideration must be given to the treatment of both problems. If drainage is adequate, placement of an esophageal stent to control contamination is favored, reserving resection and anastomosis for a later time. If the

patient is found to have massive contamination with hemodynamic instability not amenable to stent placement, resection, cervical esophagostomy, tube placement, and gastrostomy should be considered as described earlier.

Achalasia

Patients with a known diagnosis of achalasia with perforation require special consideration. These patients may experience esophageal perforation during pneumatic dilation, at the time of myotomy, or with other previously mentioned mechanisms. Because of the elevated intraluminal pressure proximal to the esophageal sphincter, healing of the repair often is precluded. Following repair of the perforation, these patients require myotomy for adequate healing. The myotomy should be performed on the opposite side of the esophagus from the perforation.

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Benign Gastric Ulcer

Daniel T. Dempsey, MD, MBA

Benign gastric ulcer is a discrete macroscopic wound in the luminal surface of the stomach, extending into the submucosa or muscularis propria and rarely to the serosa of the organ. It is generally believed to start as a mucosal defect that remains unrepaired and deepens because of an imbalance between gastric mucosal defenses and aggressive luminal forces, primarily acid and pepsin. The early natural history of benign gastric ulcer is poorly understood, but most patients presenting to a surgeon with this problem are believed to have had the ulcer for weeks or months or even years. However, gastric ulcers related to drugs (nonsteroidal antiinflammatory drugs [NSAIDs] or cocaine) or stress may form and create clinical problems more rapidly. Most gastric ulcers are caused by (or strongly associated with) *Helicobacter pylori* infection, NSAID use (including aspirin), smoking, or physiologic or psychological stress. There are undoubtedly other factors that play a role in ulcer formation and healing, such as abnormalities in locoregional gastric blood flow, gastroduodenal motility, or duodenogastric reflux.

It is likely that microscopic defects occur commonly in the surface epithelial layer of the gastric mucosa. These are repaired by a process of rapid restitution, restoring an intact layer of surface epithelial cells (SECs). Numerous mucosal defenses are necessary for this local healing process to occur, lest luminal acid and pepsin enter the lamina propria, causing further tissue damage. The mucus secreted by the SECs forms a physiologic bandage over the denuded mucosa, while healthy SECs move in from the periphery to reconstitute an intact epithelial layer. Mucosal blood flow is augmented during this process. Prostaglandins are important mediators. The causes of gastric ulcer described above interfere with these mucosal defenses. NSAIDs and aspirin block prostaglandin production. Smoking decreases mucosal blood flow. Helicobacter causes chronic mucosal inflammation, priming the lamina propria with inflammatory cells and mediators, which interfere with local defenses. These inflammatory cells are probably upregulated when the mucosal layer breaks, exposing them to acid and pepsin. Helicobacter infection also interferes with acid and gastrin secretion. Severe physiologic or psychologic stress can interfere with mucosal blood flow, gastric motility, and acid secretion.

TYPES OF BENIGN GASTRIC ULCER

Johnson initially defined three types of gastric ulcer (Fig. 1). Type 1 ulcers are the most common benign gastric ulcer. They typically occur at or near the angularis incisura on the lesser curvature of the stomach where the parietal cell containing body transitions to the gastric antrum (locus minoris resistentiae). Type 1 gastric ulcers are not associated with gastric acid hypersecretion, and thus vagotomy has not traditionally been part of the surgical treatment. Type 2 ulcers usually occur in the distal stomach and are associated with duodenal ulcer disease, either active or chronic. Type 3 ulcers occur in the prepyloric region. Pathophysiologically, type 2 and 3 gastric ulcers are believed to resemble duodenal ulcers, and thus truncal vagotomy to ameliorate acid hypersecretion has been part of the surgical treatment. Recently two additional types of gastric ulcer have been described, resulting in a "modified Johnson classification" (Table 1). Type 4 gastric ulcer occurs high on the lesser curvature near the gastroesophageal (GE) junction. Excision of type 4 ulcers may get close to the esophagus, requiring Roux reconstruction (Csendes operation). Type 5 gastric ulcers are believed to be drug induced and typically occur toward the greater curvature, making them amenable to simple wedge resection. Neither type 4 nor 5 gastric ulcers are believed to be associated with acid hypersecretion, so vagotomy is probably unnecessary.

SURGICAL OPTIONS FOR GASTRIC ULCER

When operating on a patient with gastric ulcer, the choice of operation depends on a variety of technical and clinical factors, which will be discussed further below. Fundamentally, operations for gastric ulcer fall into two categories: those that excise the ulcer and those that do not (Table 2). If the ulcer is not excised, it must be biopsied to rule out cancer. Formal gastric resection with anastomosis is avoided in unstable patients. Before embarking on resection, it is prudent to assess during surgery whether the ulcer involves the pancreas, portal triad, or celiac artery or branches. For low-risk patients with distal gastric ulcers, distal gastrectomy with (type 2 and 3 ulcers) or without (type 1 ulcers) truncal vagotomy is the treatment of choice. Reconstruction consists of Billroth 1 gastroduodenostomy or Billroth 2 gastrojejunostomy (Fig. 2). The latter may be preferred when there is concomitant duodenal ulcer disease (type 2 gastric ulcer). With both types of reconstruction, we prefer to do the anastomosis to the greater curvature side of the gastric remnant. Roux reconstruction is much preferred with small gastric remnants when the gastrojejunostomy is close to the GE junction, but it should be avoided with large gastric remnants. For low-risk patients with high gastric ulcers (type 4), distal subtotal gastrectomy and in-continuity excision of the high lesser curvature ulcer can be considered, with reconstruction via Roux-en-Y esophagogastrojejunostomy (Csendes procedure) if resection encroaches on the gastric cardia (Fig. 3). For type 4 ulcers that are more distally located (or type 1 ulcers that are unusually proximal), a more limited distal gastric resection and lesser curvature extension can be performed, with reconstruction by gastrojejunostomy (Billroth 2 or Roux) (Pauchet procedure). Simple wedge resection is a good option for type 5 gastric ulcers, but it is difficult to perform for prepyloric ulcers (type 2 and 3), juxtacardial

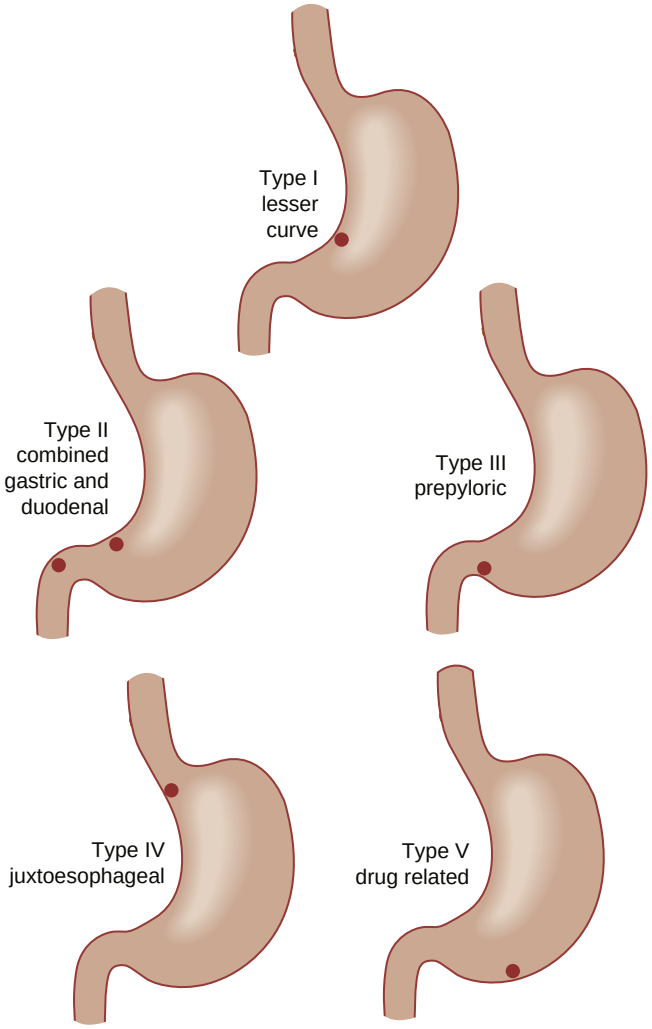


FIG. 1 Types of gastric ulcer. *(From Matthews JB, Silen W. Operations for peptic ulcer disease and early operative complications. In: Sleisenger MH, Fordtran JS, eds. Gastrointestinal disease. Philadelphia: Saunders; 1993.)*

TABLE 1 Modified Johnson Classification

Type	Location	Acid Hypersecretion
I	Lesser curvature, incisura	No
II	Body of stomach, incisura, and duodenal ulcer (active or healed)	Yes
III	Prepyloric	Yes
IV	High on lesser curve, near gastroesophageal junction	No
V	Anywhere (medication induced)	No

ulcers (type 4), and ulcers on the lesser curvature. For type 2 and 3 gastric ulcers that are left in situ, truncal vagotomy and gastrojejunostomy (with ulcer biopsy) may be a reasonable alternative to distal gastric resection. Similarly, for type 4 gastric ulcers, distal gastrectomy without ulcer excision (but with ulcer biopsy) can be considered (Kelling-Madlener operation).

TABLE 2 Choice of Operation for Gastric Ulcer by Type*

Gastric Ulcer Type	Option 1 (Resect Ulcer)	Option 2 (Biopsy Ulcer)
1	Distal gastrectomy	Vagotomy and drainage (with or without wedge excision)
2	Distal gastrectomy and vagotomy	Vagotomy and drainage
3	Distal gastrectomy and vagotomy	Vagotomy and drainage
4	Csendes or Pauchet procedure	Kelling-Madlener procedure, or vagotomy and drainage
5	Wedge resection	Patch/oversew

*Simple patch or oversew with biopsy is a reasonable option for all types of gastric ulcer in unstable patients.

INDICATIONS FOR OPERATION

Most patients with benign gastric ulcer never see a surgeon. They present to primary care or gastrointestinal (GI) practices or emergency departments, with complaints of upper abdominal pain, nausea, vomiting, or iron deficiency anemia. These complaints are evaluated with upper endoscopy with or without upper GI radiology. If a gastric ulcer is diagnosed, it is aggressively biopsied to rule out gastric cancer. If biopsy and cytology specimens are benign, the patient is treated with acid suppression, and the causative factors discussed above (*H. pylori,* NSAIDs, smoking) are eliminated if possible. Then the upper endoscopy is repeated in 2 to 3 months to document ulcer healing and to perform repeat biopsy. With this approach, the likelihood of misdiagnosing a gastric adenocarcinoma or lymphoma as a benign gastric ulcer is 1%.

If helicobacter is eradicated, NSAID and aspirin use is stopped, and smoking is eliminated, almost all gastric ulcers will heal with a 2- to 3-month course of proton pump inhibitor therapy, and recurrence or nonhealing is unusual. But, if helicobacter infection, NSAID or aspirin use, or smoking persists, recurrent gastric ulcer is the rule after the cessation of acid suppression. It is doubtful that definitive operation can completely nullify this fact, although recurrence of peptic ulceration (gastric or marginal ulcer or both) may be delayed after operation. For optimal results after operation for gastric ulcer, it is very important to strive for and document after surgery the absence of helicobacter infection, NSAID use, and smoking. Vagotomy or long-term acid suppressive medication may prevent recurrent peptic ulcer in some patients, and clearly patients having operation for gastric ulcer who require long-term NSAIDs or aspirin should receive long-term acid-suppressive medication. Selective COX-2 inhibitors should be considered in patients with ulcers requiring NSAIDs because these may have a lower risk of peptic ulceration.

PERFORATED GASTRIC ULCER

The most common indication for operation in benign gastric ulcer is perforation. Patients with gastric ulcer perforation present with acute abdominal pain and tenderness, usually with signs of peritoneal irritation (i.e., rebound tenderness and referred rebound tenderness). Because of the severity and acuteness of the symptoms, these patients most commonly present to the emergency department

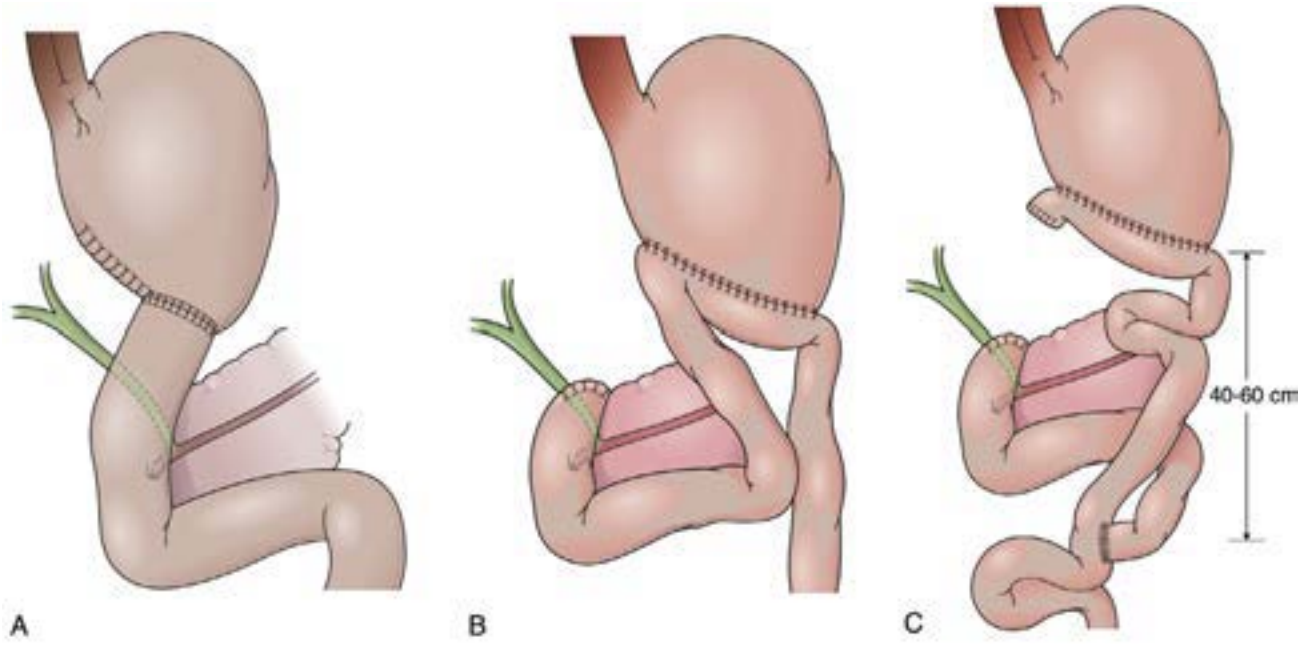


FIG. 2 Three types of reconstruction after distal gastrectomy. **(A)** Billroth I: A gastroduodenostomy is performed toward the greater curvature. **(B)** Billroth II: A gastrojejunostomy is created to reestablish the alimentary transit. Several variations may be observed in this type of reconstruction. **(C)** Roux-en-Y: To prevent biliopancreatic reflux into the stomach, a 50-cm to 60-cm Roux limb is anastomosed to the stomach with the biliopancreatic limb brought in 50 to 60 cm distal to the gastrojejunostomy. *(Modified from Ginsburg GG, Kochman ML, Norton ID, Gostout CJ.* Clinical gastrointestinal endoscopy. *2nd ed. Philadelphia: Elsevier, 2011.)*

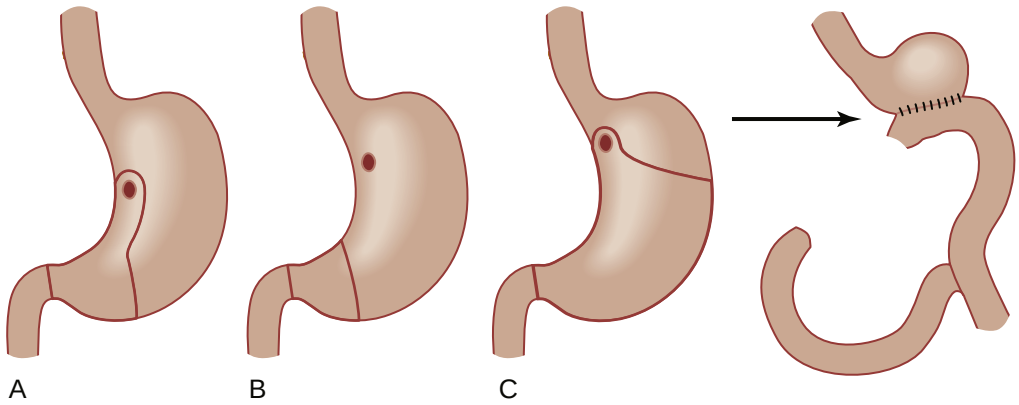


FIG. 3 Operations for a type 4 gastric ulcer. **(A)** Pauchet procedure. **(B)** Kelling-Madlener procedure. **(C)** Csendes procedure **(esophagogastrojejunostomy).** *(Modified from Seymour NE. Operations for peptic ulcer and their complications. In: Feldman M, Scharschmidt BF, Sleisenger MH, eds.* Gastrointestinal disease. *Philadelphia: Saunders; 1998.)*

where computed tomography (CT) scanning reveals free intraperitoneal air, usually with free fluid as well. If water-soluble oral contrast has been administered, the scan often reveals extravasation from the stomach. Gastric wall thickening is difficult to evaluate on CT if the stomach is collapsed. Simple upright chest radiography usually shows free air under the diaphragm, but this classic radiologic finding may be absent in 20% of patients with perforated gastric ulcer.

Intravascular volume depletion is the rule, so fluid resuscitation begins with 1 to 2 L of isotonic fluid. Induction of general anesthesia in the patient with severe hypovolemia may result in cardiovascular collapse and cardiac arrest. Intravenous antibiotics (cefazolin and fluconazole) are administered. Careful insertion of a nasogastric (NG) tube before surgery for gastric decompression is prudent, especially if water-soluble oral contrast has recently been administered or if imaging shows gastric distention. Operation is planned to occur usually within 2 hours of presentation. Rarely, nonoperative treatment is indicated if the patient is clinically stable, without signs and symptoms of sepsis, and with good radiologic evidence that the perforation has sealed.

Operation may be done open or laparoscopically. Copious irrigation of the soiled peritoneal cavity is performed with 5 to 10 L of warm saline. The entire anterior surface of the stomach is inspected. If no perforation is seen, the lesser sac is entered through the gastrocolic omentum and irrigated and the posterior stomach inspected. If still no perforation is found, it may be along the greater or lesser curvatures. If the patient is hemodynamically unstable or a poor operative risk, the perforated gastric ulcer should be biopsied and closed, either with a Graham (omental) patch or with a wedge resection of

TABLE 3 Choice of Operation for Gastric Ulcer by Indication

Indication	Option 1	Option 2	Option 3
Perforation	Patch or wedge excision	Patch or wedge excision with vagotomy and drainage	Distal gastrectomy*
Bleeding	Oversew or wedge excision	Oversew with vagotomy and drainage	Distal gastrectomy*
Obstruction	Vagotomy and distal gastrectomy	Vagotomy and gastrojejunostomy	
Nonhealing/Intractability	Distal gastrectomy (with vagotomy for type 2 and 3)	Wedge excision with vagotomy and drainage	

*Consider addition of vagotomy for type 2 and 3 gastric ulcer.

TABLE 4 Rockall Score to Assess Rebleeding and Mortality Risk in Upper Gastrointestinal Bleeding

Variable	0 Points	1 Point	2 Points	3 Points
Age (yr)	<60	61–79	>80	
Shock	None	P >100; BP >100 systemic	BP <100 systemic	
Comorbidity	None		CHF, ASCVD, COPD	Renal or liver failure; metastatic cancer
Diagnosis	Mallory-Weiss	All other	GI cancer	
Bleeding stigmata	None		Visible vessel, active bleeding	

ASCVD, Atherosclerotic cardiovascular disease; *BP,* blood pressure; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *GI,* gastrointestinal; *P,* pulse.

the ulcer (Table 3). The latter is appropriate for perforations that occur along the greater curvature, or on the anterior or posterior surface of the proximal stomach. In the low-risk patient who is hemodynamically stable, definitive operation can be considered, either distal gastrectomy, including the ulcer in the specimen (vagotomy should be considered for type 2 and type 3 ulcers), or vagotomy and drainage with ulcer biopsy and closure for inconveniently located ulcers (high juxtacardiac ulcers, peripyloric ulcers with scarred duodenum or inflammatory mass). Giant (>2 cm) perforated gastric ulcers may be too big to securely patch with omentum and thus may require resection. If resection is deemed hazardous, it may be possible to achieve closure by anastomosing the perforation to a Roux limb (mucosa to mucosa). Before closure of the abdomen, the NG tube is positioned appropriately in the stomach and secured to the nose. We test the repair with both air insufflation and methylene blue via the NG tube. If postoperative reinsertion of the prematurely pulled NG is deemed a risk to the ulcer repair or suture line, it should be sutured or "bridled" to the nose before leaving the operating room. After surgery antibiotics are continued until the patient is fever free with a normal white blood cell count. Once GI function has returned, gastrografin swallow is performed before the initiation of a liquid diet. Leakage at the repair site is managed without surgery, if adequately drained and the patient is doing well. Otherwise, early reoperation is necessary, the primary goal of which is to achieve adequate drainage of the leak, and enteral access for proximal decompression (e.g., gastrostomy) and feeding distally (e.g., jejunostomy).

BLEEDING GASTRIC ULCER

Although still a common reason for hospitalization, bleeding gastric ulcer is increasingly less common as an indication for operation. This is likely due to the increasing effectiveness of medical and endoscopic treatment for bleeding gastric ulcer. The most common cause of GI bleeding in hospitalized patients is peptic ulcer, and annually in the United States a few thousand patients die of peptic ulcer bleeding. About half of these patients succumb to bleeding gastric ulcer. Essentially all the deaths from bleeding ulcer occur in patients with risk factors for persistent or recurrent bleeding. Thus, it is important to identify this high-risk group, which represents about one-quarter of patients admitted to the hospital with bleeding peptic ulcer. Risk assessment tools have been developed for this, such as the Rockall score (Table 4). None of these tools can predict with 100% accuracy who does and does not have a life-threatening ulcer bleed, but they are useful as guides. Patients with a Rockall score of 0 to 1 are very unlikely to have a life-threatening GI hemorrhage, whereas patients with a score from 9 to 11 may very well succumb to the bleed. In general, patients at high risk present with hematemesis, hypotension, or the requirement for multiple units of blood transfusion. These patients require early surgical consultation. Urgent upper endoscopy often shows high-risk endoscopic features, such as active bleeding or visible vessel in the ulcer base. Such patients should have endoscopic hemotherapy consisting of cautery, injection of epinephrine, and application of clips. Intravenous acid suppression and fluid resuscitation are important. Rebleeding can usually be managed with repeat endoscopic therapy, but angiography with possible embolization should also be considered. In the occasional patient in whom these modalities fail, operation should be considered. In general, candidates for operation for bleeding gastric ulcer have been transfused more than a few units of blood, have recurrent or refractory hemorrhagic shock, or have ulcer erosion into a large artery such as the left gastric or splenic artery. The operative mortality rate is around 25%.

Biopsy and oversewing of the bleeding ulcer is the appropriate operation for high risk or hemodynamically unstable patients. Wedge resection should be considered for bleeding ulcers on the greater curvature or free wall of the proximal stomach. Formal resection should be reserved for good risk and hemodynamically stable patients. Rebleeding is more common when the ulcer is not resected, but ultimate hospital mortality is similarly high in patients who are initially managed with oversewing and those initially managed with

resection. Postoperative bleeding might respond to angiographic embolization.

OBSTRUCTING GASTRIC ULCER

The most common cause of gastric outlet obstruction in the adult patient is cancer (pancreatic, duodenal, or gastric). So, when considering operation for obstructing distal gastric ulcer, the surgeon must ask whether the patient might have malignant obstruction. Whereas upper endoscopy, biopsy, contrast radiography, endoscopic ultrasound, CT, or magnetic resonance imaging may all be reassuring that the obstruction is benign, misdiagnosis, although rare, remains a real possibility. The classic operation for obstructing gastric ulcer is vagotomy and distal gastrectomy, but vagotomy and gastrojejunostomy may be an acceptable alternative. The latter procedure has a lower operative mortality risk, and, in the event of severe dumping, the gastrojejunostomy is potentially reversible if gastric outlet patency can be maintained. However, distal gastrectomy confirms the absence of cancer. Vagotomy should be performed because obstructing gastric ulcers are likely to be Johnson type 2 or 3 lesions.

NONHEALING GASTRIC ULCER (INTRACTABILITY)

Operation for nonhealing gastric ulcer should be unusual today because our understanding of ulcer pathophysiology is more complete than ever. Acid suppression, eradication of helicobacter, elimination of NSAIDs, and smoking cessation should heal the ulcer. So why would the gastric ulcer persist? Could it be cancer? Is the patient noncompliant? Is there unrecognized gastric stasis or enterogastric reflux? Are there important factors in ulcer pathogenesis that we have not discovered yet? These are all important questions for the surgeon to consider before operating on a patient for nonhealing gastric ulcer. Furthermore, it must be recognized that patient noncompliance and unknown pathophysiologic factors may predispose to ulcer recurrence or poor functional results after gastrectomy for nonhealing ulcer. This may be particularly problematic in thin patients who are easy to operate on but who have insufficient nutritional reserves in the event of a poor functional outcome.

In the event that operation for nonhealing ulcer is necessary, the ulcer should be excised either with distal gastrectomy or wedge resection. This both excludes cancer and resects the vulnerable part of the stomach. If distal gastrectomy, the classic operation, is performed, then vagotomy should be added for type 2 and 3 gastric ulcers. If the ulcer is wedged out, then vagotomy and drainage should be added.

MARGINAL AND RECURRENT ULCER

Ulcers that occur at or near the gastroenterostomy are termed *marginal ulcers*. They may occur on either side of the anastomosis. When on the distal side, they are generally believed to be due to acid/peptic injury to small bowel mucosa, which is ill equipped to defend itself against unbuffered gastric juice. This occurs more commonly in Roux gastrojejunostomy because the anastomosis is devoid of the buffering effects of duodenal contents, which help protect a Billroth 2 anastomosis. When on the proximal side of the anastomosis, the ulcer is generally thought to be due to ischemia, stasis, foreign body (suture), bile reflux, or the circumstances that led to the gastric ulcer in the first place (recurrent ulcer). Marginal ulcer complicates Roux-en-Y gastric bypass in about 8% of patients, and presently this is the most common cause of marginal ulcer, which may also complicate gastrojejunostomy for cancer or ulcer.

The medical treatment of marginal ulcer is identical to gastric ulcer: acid suppression, eradication of helicobacter, elimination of NSAIDs, and smoking cessation. Indications for operation are also identical to those for gastric ulcer: perforation, bleeding, obstruction, and intractability. The realization that reoperation for recurrent or marginal ulcer puts the patient at increased risk (and closer to total gastrectomy) underscores the importance of patient education and good management after the first ulcer operation, which includes minimizing the risk factors for ulcer recurrence. In addition to elimination of helicobacter, NSAIDs, and smoking, we consider every patient who has had an operation for gastric ulcer a candidate for lifelong acid suppression, unless the patient has had a vagotomy.

Perforated marginal ulcer may be treated with simple patch closure, which is certainly appropriate in high-risk and unstable patients. It may also be the preferred treatment in patients with Roux-en-Y gastric bypass because resection may necessitate esophagojejunostomy. In stable low-risk patients with perforated gastrojejunostomy after distal gastric resection, resection of the anastomotic region (segmental jejunal resection with additional gastrectomy) is preferred. The addition of truncal vagotomy may be considered. If the remaining gastric remnant is 30% or less, reconstruction should be Roux gastrojejunostomy to avoid bile reflux esophagitis. If the remaining remnant is larger than 30%, reconstruction should be via Billroth 1 or 2 technique to minimize recurrence of marginal ulceration. If the original operation was a simple loop gastrojejunostomy, consideration may be given to reversal (if the gastric outlet is patent) or distal gastrectomy with Billroth 1 or 2 reconstruction.

Bleeding marginal ulcer can usually be managed without surgery with the help of endoscopic hemostatic techniques or angiographic embolization, unless the ulcer has eroded into a named visceral vessel such as the splenic, left gastric, or middle colic artery. Those patients requiring emergency operation may have torrential bleeding and often present with a less impressive "herald bleed." Whereas gastroenterotomy and transluminal oversewing of the bleeding vessel may prove adequate, resection of the anastomotic region may be expeditious and safer. Postoperative angiographic embolization might complement the operation. Marginal ulcers associated with obstruction or intractability should be treated with elective resection of the anastomosis, followed by Roux or Billroth reconstruction, depending on how close the anastomosis is to the GE junction.

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Management of Duodenal Ulcers

Daniel T. Dempsey, MD

INTRODUCTION

Duodenal ulcer is an acute or chronic localized wound of the duodenal mucosa caused by acid/peptic injury. Superficial ulcers involve the submucosa; deeper ulcers involve the muscularis propria or the serosa and may penetrate posteriorly or perforate anteriorly. Common predisposing factors are *Helicobacter pylori* infection, use of nonsteroidal antiinflammatory drugs (NSAIDs) or aspirin, smoking, and stress. Less common causative factors include gastrinoma (Zollinger-Ellison syndrome), radiation, Crohn's disease, cocaine, and gastroduodenal dysmotility. The most common symptoms of duodenal ulcer are abdominal pain, nausea, vomiting, and anemia.

The reasons for hospitalization resulting from duodenal ulcer are (in decreasing order) upper gastrointestinal (GI) bleeding, perforation, obstruction, and intractability. Peptic ulcer is the most common cause of clinically significant upper GI bleeding requiring hospitalization, but nowadays very few of these patients require operation. Currently the most common indication for operation in duodenal ulcer patients is perforation. Surgery for bleeding and obstruction is less common, and surgery for medically intractable duodenal ulcer is very uncommon. The operative (90-day) mortality rate for emergency peptic ulcer surgery is about 30%. After surgery for duodenal ulcer, recurrent ulcer can be minimized if all of the following conditions are met: eradication of *H. pylori* infection, diligent and permanent avoidance of NSAIDs and aspirin, and long-lasting abstention from smoking. If compliance with these management principles cannot be followed, eventual ulcer recurrence is likely. Testing for *H. pylori* infection should be performed in all patients with active peptic ulcer disease or a history of peptic ulcer disease unless previous cure of *H. pylori* infection has been documented. Testing should also be strongly considered if long-term aspirin or NSAIDs are required. All patients who test positive should be treated. Testing for *H. pylori* infection should be performed in all patients with peptic ulcer, mucosa-associated lymphoid tissue (MALT), early gastric cancer, and those on long-term aspirin or NSAID regimens (Box 1). With the appropriate 10- to 14-day multidrug regimen (which takes into account local antibiotic resistance and recent antibiotic usage) and patient compliance, *H. pylori* eradication will be confirmed in about 85% of patients who undergo a urea breath test, fecal antigen test, or endoscopic biopsy (*H. pylori* serology should not be used to test for cure of *H. pylori* infection). Consultation with a gastroenterologist or infectious diseases specialist with an interest and expertise in *H. pylori* treatment and cure should be considered.

If medically indicated, daily aspirin for cardiovascular prophylaxis may be taken safely, provided a daily proton pump inhibitor (PPI) is also taken. It is not unreasonable to consider long-term PPI treatment (e.g., omeprazole 20 mg before breakfast) for all patients who have required hospitalization for duodenal ulcer unless a vagotomy has been performed, particularly in patients for whom the above conditions cannot be assured. It is unclear whether definitive duodenal ulcer surgery (e.g., vagotomy and drainage; vagotomy and antrectomy [V/A]) is as effective in preventing ulcer recurrence as it was in the past. The acid suppressive effect of vagotomy may be no more profound than a properly taken PPI, but admittedly the former does not depend on patient compliance. Clearly, the concept that a more complex surgery is better should be used carefully and sparingly today in ulcer surgery, particularly during emergency surgery, which now is far more common than elective surgery. Gastrectomy for duodenal ulcer should be avoided in thin or chronically malnourished patients.

MEDICAL MANAGEMENT OF DUODENAL ULCER

Most patients with duodenal ulcer are treated medically as outpatients and never seen by a surgeon. Typically, the diagnosis is made with esophagogastroduodenoscopy (EGD). Biopsy of duodenal ulcer is unnecessary, but gastric biopsies should be taken to rule out *H. pylori* infection. Medical management includes acid suppression with a PPI, diagnosis and treatment of *H. pylori* infection (present in up to 90% of duodenal ulcer patients), elimination of NSAIDs, smoking cessation, and (in the appropriate clinical setting) evaluation for gastrinoma. Unless the patient has required hospitalization for an ulcer complication, long-term PPIs are not indicated. The obvious exceptions are duodenal ulcer patients who require long-term NSAIDs, aspirin, or anticoagulants, all of whom require PPI ulcer prophylaxis.

Perforated Duodenal Ulcer

Duodenal ulcer perforation (Fig. 1), the most common indication for surgery, presents as an acute abdomen. The patient usually can pinpoint the onset of severe abdominal pain. There may or may not be a history suggestive of chronic duodenal ulcer. The longer surgery is delayed from the onset of perforation, the higher the mortality risk. On examination, the patient is very uncomfortable and loath to move. Tachycardia may be the only early vital sign abnormality. Fever and tachypnea then ensue, and hypotension is a late finding. The abdomen is rigid, and there is obvious peritonitis. Leukocytosis is common. Anemia suggests the possibility of a second, usually posterior, bleeding ulcer ("kissing ulcers"), which can be evaluated intraoperatively with direct inspection or EGD. An upright chest x-ray usually shows pneumoperitoneum (absent in 10% to 15% of cases). Computed tomography (CT) nearly always reveals extraluminal air in the upper abdomen, often with free peritoneal fluid. The mortality risk of perforated duodenal ulcer in the modern era is high, up to 30% in some series. Although this may be caused in part by the frailty of the patient population affected, there is no doubt that delayed treatment increases mortality risk. Prompt fluid

BOX 1 *Helicobacter pylori* Tests

Tests for *H. pylori* (All Positive Patients Should Be Treated)

- Fecal antigen test
- Urea breath test
- Esophagogastroduodenoscopy and biopsy
- Rapid urease test
- Histology
- Culture
- Molecular real-time polymerase chain reaction (RT-PCR)

Some Common *Helicobacter* Treatment Regimens (10–14 Days)

- Clarithromycin triple therapy (PPI, clarithromycin, amoxicillin, or metronidazole)
- Bismuth quadruple therapy (PPI, bismuth, tetracycline, nitroimidazole)
- Sequential therapy (PPI and amoxicillin for 5–7 days, and then a PPI, clarithromycin, and nitroimidazole for 5–7 days)
- Hybrid therapy (a PPI and amoxicillin for 7 days, and then a PPI, amoxicillin, clarithromycin, and nitroimidazole for 7 days)

PPI, Proton pump inhibitor.

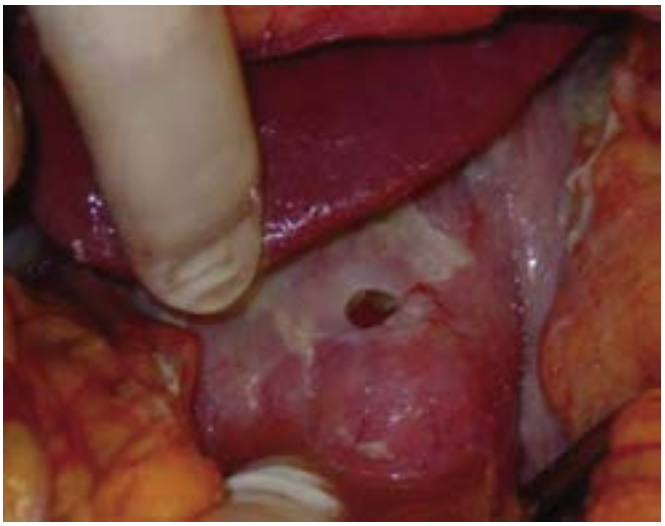


FIG. 1 Perforated duodenal ulcer.

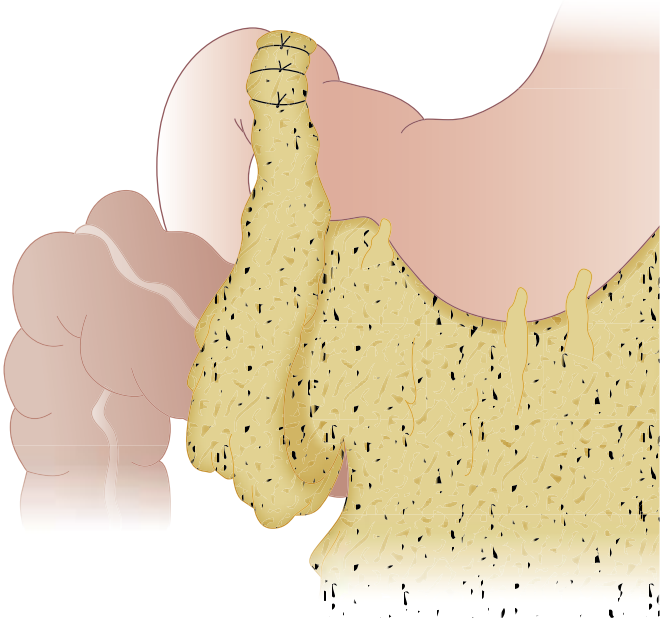


FIG. 2 Graham patch of perforated duodenal ulcer. *(From Townsend C. Sabiston Textbook of Surgery, 21st ed. Philadelphia: Elsevier, 2021.)*

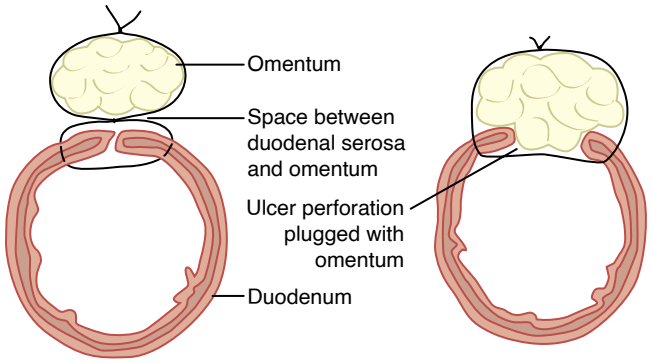


FIG. 3 This technique creates better apposition between the omentum and the duodenum. *(From Yeo CJ. Shackleford's Surgery of the Alimentary Tract. 8th ed. Philadelphia: Elsevier, 2019.)*

resuscitation and intravenous (IV) antibiotics are important, but so is prompt surgery. Medical optimization, although necessary, should not be an excuse for prolonged delay in surgical treatment. In addition to routine empiric broad-spectrum perioperative antibiotics, selective antifungal treatment may be considered in frail, immunosuppressed, or hospitalized patients. Routine use of antifungal agents is not indicated. Rarely, a stable patient without peritonitis and with a radiologically documented sealed perforation may be cautiously managed nonoperatively. Laparotomy or laparoscopy with peritoneal washout (5 to 10 L) and omental patch closure of the perforation is the treatment of choice for most patients with a perforated duodenal ulcer. Peritoneal fluid should be sent for culture and sensitivity (including fungal studies). Routine ulcer biopsy is not necessary but should be performed if there is any suspicion of malignancy. At least one closed-suction peritoneal drain is placed. Leakage at the repair site is not uncommon.

Omental Patching

Omental patching (Graham patching), a technique attributed to Dr. Roscoe Graham, is the most common method of perforated duodenal ulcer repair (Fig. 2). Typically, the hole in the duodenum is small (<1 cm) and is not repaired primarily before application of a well-vascularized tension-free piece of omentum. The duodenal tissue immediately adjacent to the perforation is friable, and attempts at primary closure often result in the sutures pulling through, enlarging the hole considerably. Primary closure may also further narrow an already scarred gastric outlet. The omental patch is held in place by interrupted seromuscular Lembert sutures placed into healthy duodenum on either side of the perforation. We usually place two or three interrupted bridging sutures, lay the patch on, and then tie the sutures gently but snugly over the omental patch. This technique creates better apposition between the duodenum and the omentum than the technique of using the suture "tails" from a primary closure to secure the omentum (Fig. 3). If necessary, additional sutures may be placed circumferentially between the healthy duodenum and the omental patch. Once the patch is secure, the adequacy of the seal can be tested by submerging the site under irrigation fluid while injecting air and/or methylene blue into the nasogastric (NG) tube (which remains in place postoperatively), and a closed-suction peritoneal drain is placed.

Special Considerations for Large Ulcer Perforations

Large ulcer perforations (>2 cm) merit special considerations. They are difficult to securely close with the Graham patch technique described earlier, but primary repair of a large perforated chronic duodenal ulcer is more prone to break down than primary repair of a similar-size acute duodenal laceration. And in the high-risk patient, an expeditious surgery is important. After peritoneal irrigation, the perforation is closed if possible with sutures or stapling, and the closure is buttressed with omentum or a falciform ligament. If it can be done safely, a Kocher maneuver facilitates primary closure. Multiple drains are placed. If the large perforation cannot be closed primarily, it can be plugged with omentum or falciform, which is pulled into the perforation using double-armed sutures placed first in the plug and then "inside out" into the duodenum surrounding the perforation (Fig. 4). Alternatively a loop of jejunum can be used as a serosal patch. Treatment of large perforations by direct intubation with or without an omental buttress is prone to ongoing leakage, but it can be used as a last resort or bailout procedure (Fig. 5). Multiple peritoneal drains are placed. In unstable patients, a damage control approach might be considered.

The fact that large perforated duodenal ulcers are hard to fix is indicated by the wide variety of (sometimes anecdotal) repair techniques. One useful ancillary procedure that has been evaluated with a retrospective controlled study is the *triple-tube technique*, which

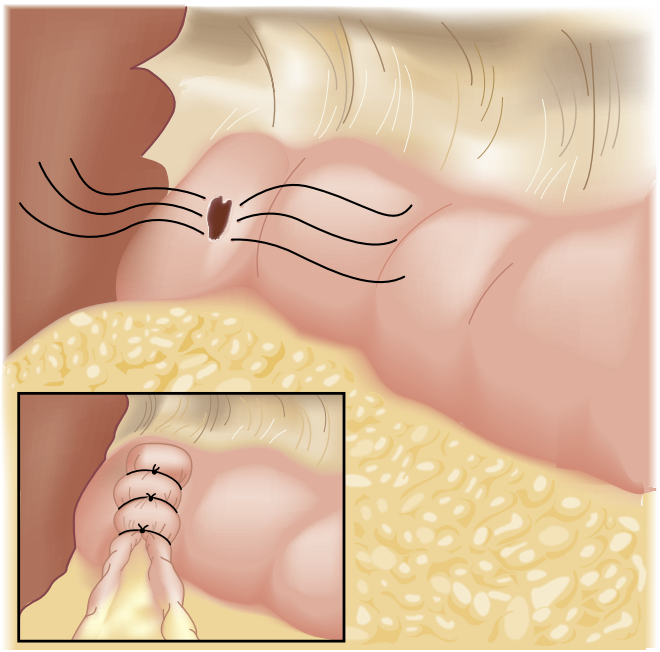


FIG. 4 Technique to "pull" an omental patch into a large perforated duodenal ulcer. *(From Townsend C. Sabiston Textbook of Surgery. 21st ed. Philadelphia: Elsevier, 2021).*

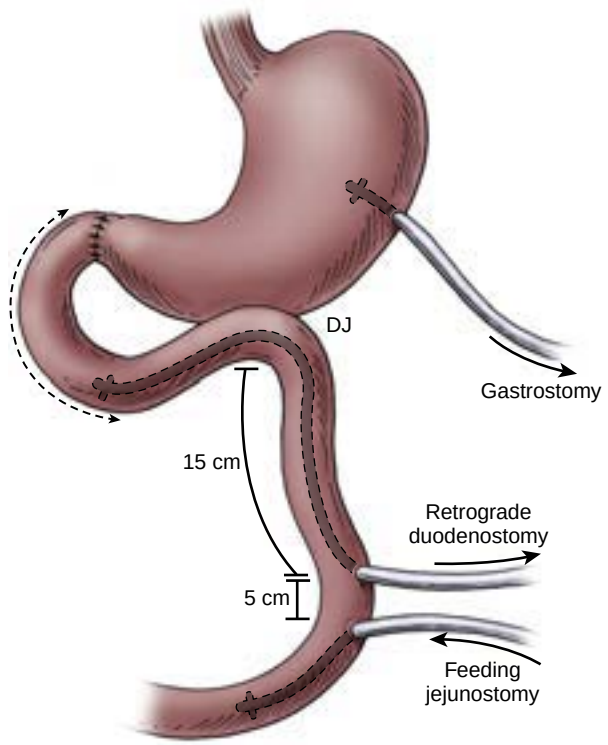


FIG. 5 Triple tube technique for high-risk perforated duodenal ulcer.

should be considered in high-risk perforations, whether repaired as described earlier or with one of the more complex surgeries described later. This involves placement of a gastrostomy, antegrade feeding jejunostomy, and a retrograde jejunostomy tube that is passed into the duodenum for decompression. This technique is safe and quick, and we have never regretted using it in the setting of high-risk duodenal perforation. We much prefer this to lateral duodenostomy or transpyloric intubation. For the most tenuous duodenal closures, we consider pyloric exclusion (pyloric closure with heavy absorbable suture and dependent loop gastrojejunostomy). One other option for repair of a large chronic duodenal perforation in a stable low-risk patient is a Roux-en Y duodenojejunostomy in which a tension-free two-layer anastomosis is created between the debrided duodenal opening and a Roux limb.

Definitive Ulcer Surgery

Definitive ulcer surgery can be considered in stable patients of low to medium risk (ASA 1 or 2) requiring emergency surgery for a perforated duodenal ulcer if there is a clinical history of duodenal ulcer, or if the perforation is large (>2 cm). Definitive surgery should not be performed if peritonitis is severe or well established (exudative). All of these contingencies (low-risk patient with a positive history or large perforation and without serious peritonitis) mean that the majority of patients with a perforated duodenal ulcer are *not* candidates for definitive ulcer surgery. Parietal cell vagotomy as a definitive ulcer surgery in this setting is largely of historical interest. Currently the two options for definitive surgery are (1) truncal vagotomy and gastrojejunostomy ([V/GJ] with or without temporary pyloric closure) after repair of perforation as described earlier; or (2) truncal V/A if the perforated duodenum can safely be resected with the antrum and a secure duodenal stump fashioned. If the ampulla is deemed to be at risk, a biliary Fogarty catheter can be advanced from above via the cystic duct or common bile duct. Resection should not be contemplated if a tenuous duodenal stump is likely or if injury to the ampulla or bile duct is an obvious possibility.

Minimally Invasive Surgery

Minimally invasive surgery for perforated duodenal ulcer is now commonplace, and some studies suggest that the laparoscopic approach is superior to open operation. Laparoscopy confirms the diagnosis, including the size and location of the perforation and the severity of peritonitis. Thorough irrigation of the peritoneal cavity can readily be accomplished laparoscopically. Laparoscopic omental patch closure of the perforation is usually straightforward for the typical small perforation. Even when conversion to open surgery is necessary, the laparotomy incision is smaller and optimally placed after laparoscopic evaluation. In the unlikely event that a definitive surgery is indicated, it can be performed either open or laparoscopically. Even a modest size perforation can be repaired laparoscopically, and vagotomy is straightforward for the minimally invasive surgeon with some foregut experience. A dependent loop gastrojejunostomy completes the ulcer surgery. Two types of vagotomy may be considered: (1) the more traditional bilateral truncal vagotomy or (2) a modified Taylor procedure. The latter consists of posterior truncal vagotomy and division of the segmental vagal branches to the anterior stomach with preservation of the anterior innervation to the antropyloric region. This technique may facilitate gastric emptying.

Postoperative Management

Postoperative management for many perforated ulcer patients starts in the ICU with continued optimization of critical organ function, fluid management, and treatment of sepsis. The decision to remove the NG tube and initiate oral liquids is made on clinical grounds. Postoperative contrast study (fluoroscopy or CT) is usually performed to rule out ongoing leak and to demonstrate gastric emptying. Antibiotics are discontinued on postoperative day 5 unless there is obvious ongoing infection. Peritoneal drains are removed 24 hours after the initiation of oral liquids if drainage is benign and the patient is doing well. Reoperation is sometimes required for persistent leakage from the perforation site or from abdominal wound dehiscence. Percutaneous drainage can be performed for localized infected fluid collections, but multiple fluid collections or extensive peritoneal fluid in the setting of sepsis may be a manifestation of uncontrolled

leakage and is best treated with reoperation and washout. Some sort of abdominal reintervention is necessary in about 25% of patients after repair of a perforated duodenal ulcer. We think emergency surgery for duodenal ulcer is an indication for chronic PPI therapy and empiric treatment of *H. pylori* infection. Patients are strongly advised to avoid NSAIDs, aspirin, and smoking. Low-dose aspirin is permissible provided chronic PPI treatment is continued.

BLEEDING DUODENAL ULCER

The most common reason for hospitalization and death in the duodenal ulcer patient is bleeding. However, bleeding has become an infrequent indication for surgery in duodenal ulcer largely because of the effectiveness of medical and endoscopic treatment. There also has been an increased appreciation of the risks associated with surgery for bleeding duodenal ulcer, including rebleeding, postoperative complications, and a postoperative in-hospital mortality rate as high as 40%. Endoscopic hemostatic therapy with cautery, topical agents, epinephrine injection, and/or clips has clearly decreased the need for surgery; selective angiography with embolization probably has too.

Risk Stratification

Three-fourths of patients with bleeding duodenal ulcer (Fig. 6) will stop bleeding with only IV fluid and IV PPIs. These are administered to all patients admitted to the hospital with upper GI bleeding. The other 25% will continue to bleed or rebleed, and essentially all deaths related to bleeding duodenal ulcer occur in this group. Therefore it is important to identify patients in this group. Not surprising, these are the patients with the bigger bleeds. They are more likely to have hematemesis, hypotension, a multiunit transfusion requirement, and/or endoscopic stigmata (visible vessel and/or active bleeding). Two commonly used prognostic systems for risk-stratifying patients with upper GI bleeding are the Glasgow-Blatchford score (GBS) and the Rockall score (Box 2). The former is designed to identify low-risk patients who do not require hospitalization (GBS 0–1) versus high-risk patients who require treatment (usually endoscopic) to stop the bleeding (GBS ≥6 indicates a 50% likelihood of requiring treatment). The Rockall score predicts mortality risk. High-risk bleeding duodenal ulcer patients should be seen in consultation by an endoscopist and surgeon, and they should be watched carefully in the hospital, perhaps initially in the ICU. Endoscopic findings and the treatment plan should be understood by the surgeon if the surgeon is not the endoscopist. Deep posterior bleeding ulcers in the proximal duodenum are particularly worrisome because they may involve the gastroduodenal artery, which can cause exsanguinating hemorrhage. Hemostasis usually can be achieved with PPI infusion and endoscopic treatment. Rebleeding should prompt repeat endoscopic treatment and consideration of arteriography and possible angioembolization. Surgery should be considered for persistent or recurrent bleeding in patients with hemodynamic instability or a transfusion requirement in excess of 6 units of red blood cells, but recognizing (for example) that predicted postoperative mortality in an older adult patient with a bleeding duodenal ulcer, hypotension, chronic obstructive pulmonary disease (COPD), and a visible vessel on EGD is 40% by the Rockall score.



FIG. 6 Bleeding duodenal ulcer. *(Courtesy Dr. Gregory Ginsberg.)*

BOX 2 Risk Stratification for Upper Gastrointestinal Bleeding

Glasgow-Blatchford Score*

• Elevated BUN	2–6 points
• Low Hgb	1–6 points
• Low BP	1–3 points
• Elevated HR	1 point
• Melena	1 point
• Syncope	2 points
• Liver disease	2 points
• Heart failure	2 points

Rockall Score**

• Age	0–2 points
• Shock	0–2 points
• Comorbidity	0–3 points
• EGD stigmata	0–2 points
• EGD diagnosis	0–2 points

*0 points = outpatient management.; 6+ points = 50% need endoscopic hemostatic Rx

**0–1 points = 0% mortality; 5 points = 10% mortality; 8+ points = 40% mortality

BP, Blood pressure; *BUN,* blood urea nitrogen; *Hgb,* hemoglobin; *HR,* heart rate.

Surgery for Bleeding Duodenal Ulcer

There are three surgical options for bleeding duodenal ulcer: (1) oversewing alone, (2) oversewing with vagotomy and drainage, and (3) V/A. Clinical trials from a previous era suggest that the ultimate result (i.e., survival) is similar with either of the two latter surgical options, but reoperation for rebleeding is less common after V/A. However, resection for bleeding duodenal ulcer is rarely done nowadays because most surgical patients are at high risk. Furthermore, fashioning a secure duodenal stump can be difficult because the bleeding ulcer either must be resected, or, if not resected, it must be oversewn. Review of National Surgical Quality Improvement Program data suggests that vagotomy and drainage for a bleeding peptic ulcer may result in a significantly lower 30-day postoperative mortality rate (12%) than vagotomy and resection (23%) or oversewing alone (27%).

Oversewing of a Bleeding Duodenal Ulcer

Oversewing of a bleeding duodenal ulcer starts with exposure of the lesion, usually through a longitudinal duodenotomy or pyloroduodenotomy. The Kocher maneuver is done first because this not only decreases tension on the closure, but facilitates manual control of a bleeding gastroduodenal artery with the left hand of the surgeon standing on the patient's left side (long fingers behind the head of the pancreas, thumb in front). Deep posterior ulcers usually require placement of two or three heavy suture ligatures placed in figure-of-8 or over-and-over fashion in the ulcer bed. The U-stitch has been well described. Surgeons with advanced hepato-pancreato-biliary experience might be tempted to ligate the gastroduodenal artery extralumenally above and below the duodenum, but this is usually hazardous and inadvisable, and it misses the pancreatic branch for which the U-stitch was conceived. Once hemostasis is achieved, the ulcer bed should be abraded with the sucker tip to ensure that rebleeding does not occur. The anterior incision can then be closed either longitudinally, or transversely as a pyloroplasty.

Definitive Ulcer Surgery

Definitive ulcer surgery may be appropriate for some patients with a history of ulcer chronicity or for those with a large (>2 cm) deep posterior ulcer, but this is clearly contraindicated in ASA 4 and 5 patients and should be done quite selectively in ASA 3 patients. If the patient is stable and exposure straightforward, truncal vagotomy and drainage (pyloroplasty or gastrojejunostomy) is the preferred definitive surgery. In the setting of bleeding ulcer, parietal cell vagotomy, probably comparable to PPI therapy, is not indicated, and gastric resection is quite likely to be problematic, as discussed earlier.

Postoperative Management

Postoperative management is similar to that after repair of a perforated duodenal ulcer. High-dose PPIs in the early postoperative period may decrease rebleeding risk. There is no evidence that transfusion triggers must be increased after surgery for a bleeding ulcer. Early rebleeding should be evaluated with upper endoscopy and arteriography (CT angiography or standard arteriography). Long-term smoking cessation is imperative. If NSAIDs are medically necessary, a selective COX-2 inhibitor should be considered, and long-term PPI therapy is necessary. Similarly, long-term PPIs are definitely prescribed if chronic aspirin or anticoagulants are necessary, and this treatment may not be unreasonable for all patients admitted for duodenal ulcer complications unless definitive surgery has been performed.

GASTRIC OUTLET OBSTRUCTION

Chronic gastric outlet obstruction secondary to chronic inflammation and scarring is now the second most common indication for duodenal ulcer surgery in some hospitals. Patient history and endoscopic findings can usually differentiate between an acute potentially reversible obstruction and chronic obstruction. Patients usually experience nausea, nonbilious vomiting, epigastric distension, and weight loss. A succussion splash may be present on abdominal auscultation, and in the setting of high-grade obstruction and dehydration, hypokalemic hypochloremic metabolic alkalosis is often present. The differential diagnosis obviously includes cancer because most patients with these symptoms have malignant gastric outlet obstruction (pancreatic, duodenal, or gastric cancer). Evaluation includes EGD and biopsy, upper gastrointestinal fluoroscopy with oral barium, and CT. Endoscopic dilation and medical ulcer treatment may delay surgery for 1 to 2 years in one-half of patients with benign gastric outlet obstruction from duodenal ulcer, but most patients requiring hospitalization or dilation will ultimately undergo surgery.

Surgery for Obstructing Duodenal Ulcer

Vagotomy and Antrectomy

V/A is the gold standard surgery for obstructing duodenal ulcer, but V/GJ is a good alternative in some patients. The advantage of V/A is lower recurrence rate and reassurance that the cause of the obstruction is benign. The disadvantage is higher operative mortality risk (2%). The advantage of V/GJ is a lower operative mortality and the potential for reversal of the GJ in the unlikely event that dumping becomes intolerable. Another advantage is that V/GJ is readily accomplished laparoscopically. A disadvantage of V/GJ is that obstructing cancer may be missed, and marginal ulcer may occur. The remote possibility of pyloric channel or proximal duodenal cancer must be considered in the operative planning for obstructing ulcer because optimal surgical treatment may involve pancreaticoduodenectomy.

V/A can be done through an upper midline or transverse incision. A mechanical retractor is helpful. Exploration of the gastroduodenal area for any evidence of malignancy is done. Truncal vagotomy is accomplished first. The peritoneum over the abdominal esophagus is incised, and the gastrohepatic ligament is opened above the hepatic vagal branches. Pulling down on these branches makes the anterior vagal trunk stand out, and it is clipped and severed easily; a short segment is sent to pathology. The phrenoesophageal ligament then is opened along the right crus, and the retroesophageal space is entered where the posterior vagus is reliably located, clipped, severed, and sent for biopsy. Unless it appears that duodenal stump closure would be difficult, we then proceed with antrectomy. The lesser curvature neurovascular bundle is divided at the angularis incisura, and the right gastroepiploic arcade is divided on the greater curvature at a point directly opposite. This is where the stomach is transected with a green handheld GIA or a purple or black laparoscopic GIA cartridge. The chronically obstructed stomach may be unusually thick walled, and it is important that adequately large staples be used lest the gastric closure dehisce. The gastrocolic ligament attached to the antrum (i.e., the specimen) is taken usually outside the gastroepiploic arcade, progressing distally to the right gastroepiploic pedicle, which is ligated and divided. The right gastric is also ligated and divided. The pylorus and duodenal bulb are carefully separated from the pancreas, and then the postpyloric duodenum is transected with a GIA or TA stapler. The outlet obstruction should be resected. If the obstruction is prepyloric, it is important that the surgeon ensure that the distal staple line is in fact distal to the pylorus to avoid retained antrum. Rarely, resection of the obstruction is difficult or hazardous because it is in the second portion of the duodenum. The surgeon should try hard to rule out cancer if the site of outlet obstruction is left behind, and intraoperative consultation with an hepato-pancreato-biliary colleague may be helpful.

Antecolic isoperistaltic Billroth II gastrojejunostomy is performed on the greater curvature side of the gastric remnant, with the afferent loop on the greater curvature side and the efferent limb on the lesser curvature side. We avoid Roux-en Y reconstruction with a large gastric remnant because of the possibility of marginal ulceration and/or delayed gastric emptying. We usually do not oversew the duodenal staple line but after allowing some time to ensure complete hemostasis and no bile staining on the stump, just before abdominal closure we irrigate the staple line and cover it with well-vascularized omentum held in place by two or three strategically placed sutures. A closed-suction right upper quadrant drain is placed, although admittedly routine peritoneal drainage after gastrectomy is not supported by clinical evidence.

V/GJ can be performed with an open or minimally invasive technique. After evaluation of the stomach and proximal duodenum, vagotomy is performed. Either a bilateral truncal or posterior truncal with anterior highly selective technique is acceptable. Loop gastrojejunostomy is then constructed to the dependent greater gastric

curvature. We divide the little branches from the gastroepiploic to the stomach for a length of 6 to 8 cm, creating a target for the hand-sewn or stapled antecolic isoperistaltic gastrojejunostomy. Patients with obstructing chronic duodenal ulcer disease who are treated with V/GJ should be followed closely for 2 years to ensure that an obstructing cancer was not missed. If the patient is not doing well clinically, reevaluation and open exploration should be considered with conversion of the loop GJ to distal gastrectomy, which should include the area of obstruction.

INTRACTABLE DUODENAL ULCER

The endoscopically documented persistence of a benign symptomatic duodenal ulcer despite adequate medical treatment should be a very unusual indication for surgery nowadays. The 50+-year-old literature describing the salutary effect of ulcer surgery for intractability is largely irrelevant to this situation nowadays. Assuming gastrinoma and cancer have been ruled out, a duodenal ulcer will heal if *H. pylori* infection has been cleared (best documented with a urea breath test, fecal antigen test, or endoscopic biopsy), the patient diligently takes PPIs as prescribed, diligently avoids NSAIDs and aspirin, and does not smoke. Surgery should not be considered for intractability unless the surgeon is certain that all of these conditions have been fulfilled. Though it may take a while, ulcer recurrence is almost inevitable after definitive ulcer surgery for intractability in patients who cannot give up NSAIDs or smoking. It is also important to keep in mind that *if* the patient has persistent peptic ulceration despite all the aforementioned conditions being fulfilled, perhaps the patient has some other unusual poorly understood factors predisposing to duodenal ulcer (e.g., stress or dysmotility). This may contribute to the high incidence of debilitating postoperative symptoms in patients undergoing vagotomy and drainage or V/A for intractable duodenal ulcer in the modern era.

MANAGEMENT OF THE DIFFICULT DUODENAL STUMP

The routine closure of the proximal duodenum during Billroth II distal gastrectomy is accomplished most easily with a GIA- or TA-type stapler (blue cartridge). A two-layer suture closure is also straightforward in routine cases, but excessive suturing and imbrication should be avoided because it may predispose to stump leakage. Occasionally ulcer location or size or the extensiveness of the inflammation and/or scar may render secure duodenal closure difficult. In this situation, difficult duodenal stump closure is best avoided by not performing a distal gastrectomy because operative mortality skyrockets with postoperative duodenal leakage. However, a difficult duodenal stump is occasionally unavoidable. If the ulcer has destroyed the posterior duodenal wall, the anterior edge of the open duodenum can be sewn to the proximal or distal "lip" of the ulcer on the pancreas with interrupted suture. Secure hemostasis in the ulcer bed must be accomplished. The integrity of the closure is tested by placing the tip of the NG tube at the ligament of Treitz (through the gastrojejunostomy) and distending the duodenum with air. Additional sutures may be necessary to render the duodenal closure air tight. Then healthy omentum is sewn over the closure, and multiple closed-suction drains are placed. Duodenal decompression should be performed, ideally with a retrograde tube via the proximal jejunum; other options include lateral duodenostomy or NG decompression by threading the NG tube through the gastrojejunostomy into the afferent limb and duodenum. The latter option requires suturing or bridling the NG to the nose, and it soon becomes uncomfortable unless it can be converted to a percutaneous transgastric arrangement. As discussed earlier, placement of a large tube into the end of the duodenal stump inevitably leaks around the tube and should only be performed if no other primary duodenal closure options are available. Postoperative duodenal stump leakage is usually managed nonoperatively unless the patient develops diffuse peritonitis or worsening sepsis. At reoperation, wide drainage and source control are paramount. Suture closure of a leaking stump is destined for failure. Generally an appropriately sized tube is brought through the abdominal wall and placed into the leak, and the duodenum is gently snugged up around this tube, which is buttressed with omentum or falciform or peritoneum/skeletal muscle. Multiple closed-suction drains are placed. If a chronic fistula persists, a definitive repair can be attempted much later with Roux-en-Y duodenojejunostomy or resection.

CONCLUSION

Duodenal ulcer is no longer considered a surgical disease. The effectiveness of modern medical management means that only a very small percentage of patients with this diagnosis will ever see a surgeon. However, general and acute care surgeons still have an important role in the management of hospitalized patients with duodenal ulcer. About 25% of this group have a perforated duodenal ulcer, and essentially all require emergency surgery. Prompt resuscitation and surgery in this group will save lives because even a delay of a few hours substantially increases mortality risk. The appropriate surgery for most of these patients is patch of the ulcer with peritoneal irrigation and drainage. About 75% of hospitalized duodenal ulcer patients experience bleeding, and only a small number require surgery, but the right surgery at the right time can rescue these patients. For the highest-risk patients (ASA 4 and ASA 5), probably the best surgery is secure oversewing of the bleeding ulcer and high-dose acid suppression. For patients with lower operative risk (ASA 1–3), probably the best surgery is secure oversewing of the ulcer, truncal vagotomy, and drainage. Duodenal ulcer patients requiring surgery for perforation or bleeding are a small, high-risk subgroup of hospitalized patients that largely accounts for the high postoperative mortality rate (up to 30%). Finally, most patients with ulcer-related chronic gastric outlet obstruction will be seen in the surgical clinic instead of the hospital, and the majority will eventually come to surgery. V/A remains the surgery of choice in this group. Other important but less common issues related to ulcer surgery are also discussed.

SUGGESTED READINGS

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Management of Zollinger-Ellison Syndrome

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Zollinger-Ellison syndrome (ZES) is a constellation of symptoms comprising severe peptic ulcer disease, chronic diarrhea, and gastroesophageal reflux disease (GERD). It is caused by gastrin-secreting tumors of the pancreas or duodenum that result in increased stimulation of the acid-secreting parietal cells of the stomach. Patients with ZES have two problems that must be addressed: control of the acid hypersecretion that causes refractory peptic disease (and its complications) and control of the gastrinoma, which is malignant in the majority of cases. The terms *gastrinoma* and *ZES* are often used synonymously. However, *gastrinoma* refers to the neuroendocrine tumor (NET) that secretes gastrin, and ZES refers to the clinical manifestations of the disease. Many tumors, including some non-NET neoplasms, synthesize gastrin, but in most it is not fully processed to biologically active gastrin. Consequently these tumors do not cause ZES as they do not secrete sufficient amounts of fully processed gastrin. Therefore, they are not referred to as *gastrinomas* by most clinicians and in the classification of pancreatic NETs (pNETs). The syndrome was first described in 1955 by Zollinger and Ellison, who reported two patients with severe ulcer diathesis associated with jejunal ulcerations who ultimately required total gastrectomy after undergoing several failed ulcer operations. In both of the initial patients, non–beta islet cell tumors were identified in the pancreas. Zollinger and Ellison postulated that these tumors were potentially secreting a hormone that caused acid secretion with resultant peptic ulcer disease. The paper was presented at the American Surgical Association in 1955, and in discussion, Dr. Lester Dragstedt, the father of vagotomy, opined that these tumor cells may be similar to the antral cells that produce gastrin. Interestingly, six additional cases were disclosed by discussants of the paper. The syndrome's name was subsequently suggested by Dr. Ben Eiseman in 1956. In 1960, researchers using a tumor extract bioassay at the University of Liverpool discovered that tumors from ZES patients contained large amounts of a gastrin-like substance. Before the 1970s, ZES diagnosis required incisive clinical review and a high index of suspicion as there was an absence of blood or imaging tests to confirm the diagnosis.

In 1966, a radioimmunoassay (RIA) for gastrin was described by James D. McGuigan and now serves as the linchpin of diagnosis. Before the development of gastrin RIA, patients usually underwent multiple gastric operations before diagnosis. Recommended treatment at that time became total gastrectomy as it reduced the mortality of the syndrome, which was generally related to ulcer diathesis complications, such as perforation or bleeding. Later advances in pharmacologic control of acid secretion with histamine-2 (H_2) antagonists and proton pump inhibitors (PPIs) have essentially eliminated the need for total gastrectomy. Presently, it is recognized that ZES is caused by gastrin secretion from neuroendocrine tumors that arise from the pancreas, duodenum, or rarely ectopic sites. These tumors are called *gastrinomas.*

In 20% to 25% of cases, ZES is associated with multiple endocrine neoplasia type 1 (MEN-1), an autosomal dominant disorder, whereas nearly 50% of patients with MEN-1 will have gastrinomas. An average of 8 years is reported from the start of symptoms to diagnosis secondary to the widespread use of PPIs. Current surgical treatment is predicated upon gastrinoma resection. It also relies on long-term pharmacologic suppression of acid secretion for control of the peptic ulcer disease and management of the hyperparathyroidism and other endocrine disorders associated with MEN-1.

CLINICAL PRESENTATION

Behind insulinoma, gastrinoma is the second most common functional neuroendocrine tumor, with an annual incidence of 1 to 3 cases per 1 million people. Gastrinoma is the underlying cause of peptic ulcer disease in only 0.1% to 1% of patients and is one of the rarest of all causes of ulcer disease.

ZES is usually diagnosed in the fifth decade of life, and it is diagnosed between 20 and 60 years of age in 90% of patients. It is more common in men. ZES most commonly occurs as a noninherited disease; however, it is associated with MEN-1 in 20% to 25% of cases. Gastrinoma is the most common functional neuroendocrine tumor in MEN-1, occurring in 50% of patients with the syndrome. Hence, MEN-1 must be excluded in the workup of patients with suspected gastrinoma, and patients with MEN-1 should also be screened for gastrinoma. Patients with MEN-1 have their disease onset almost a decade earlier; the average age of onset of ZES is 33.2 years for patients with MEN-1 compared with 43.5 years for sporadic gastrinoma patients. Gastrinoma is also seen in association with von Hippel-Lindau syndrome and von Recklinghausen's disease.

Gastric acid secretion is usually controlled by negative feedback mechanisms from the release of somatostatin by gastric D cells. This normally maintains gastric acid homeostasis and pH. Because of the unopposed gastrin release by the gastrinoma, severe peptic ulcer disease results from the excess gastric acid secretion via the trophic effect of gastrin on parietal cells. Significantly, ZES is not the initial diagnosis in 97% of affected patients. Presenting symptoms for this disease have altered little despite successful pharmacologic treatment of gastric hypersecretion and the pervasive use of these drugs for symptoms of dyspepsia and other digestive ailments. The clinical presentation of gastrinoma is often not specific. There is often overlap of the symptoms associated with this illness and other more common gastrointestinal conditions that result in a high frequency of misdiagnosis and diagnostic delays. In most series, abdominal pain and diarrhea were the most common symptoms, reported in more than 70%, followed by heartburn (44%), nausea (33%), vomiting (25%), and weight loss (17%).

Despite an increased awareness of ZES, multiple experts have remarked that the diagnosis is more difficult today given the nearly ubiquitous use of PPIs. Diagnosis can normally be confirmed by measurement of fasting serum gastrin levels when the patient is off of PPIs, however the average time from symptom onset to diagnosis remains between 6 and 8 years. Another reason for the delay in diagnosis is that many patients with ulcer disease are symptomatically improved by H2 antagonists or PPIs without excluding the possibility of ZES. This treatment controls the acid secretion and related symptoms but may delay diagnosis if gastrinoma is not initially considered in the differential diagnosis.

CLINICAL PATHOLOGIC CORRELATION

In nearly 70% of patients, gastrinomas are found in the pancreas or duodenum within the region known as the *gastrinoma triangle.* This devised triangle is bounded by the cystic duct, the second and third portion of the duodenum, and the neck and body of the pancreas. Rarely, gastrinomas may occur in ectopic locations, including the stomach, bile duct, periportal lymph nodes, lungs, heart, and ovaries. Most gastrinomas (50%–70%) are located in the duodenum rather than the pancreas. They are most common in the first portion of the duodenum with a diminishing incidence as one progresses distally. Duodenal gastrinomas may be very small and hence difficult to identify preoperatively and intraoperatively. Both pancreatic and duodenal gastrinomas occur in MEN-1 patients, however these patients are more likely to have multiple tumors in the pancreas or duodenum. Initially, it was thought that, similar to insulinomas,

almost all sporadic gastrinomas occurred in the pancreas. However, it is now established that most (60%–95%) occur in the duodenum; in a recent series, they were 3- to 9-fold more frequent than pancreatic gastrinomas. Duodenal and pancreatic gastrinomas differ in their biologic behavior. Although both are associated with frequent lymph node metastases (30%–70%), pancreatic tumors have a much higher rate of liver metastases, which is the primary determinant of long-term survival. Hence, patients with pancreatic gastrinomas have a poorer prognosis. Sporadic gastrinomas are malignant in 60% to 90% of cases; approximately 13% to 53% (mean 34%) of patients have liver metastases at presentation, with most being diffuse liver involvement.

Gastrinomas are generally well differentiated and slow growing. They have a low proliferative rate with a Ki-67 of 1% to 2%. The tumors are usually more indolent and slower growing than other gastrointestinal malignancies. Duodenal gastrinomas have a greater incidence of lymph node metastases than pancreatic gastrinomas, 70% versus 40%, respectively. Liver metastases occur in approximately 25% of patients and are more common with pancreatic primary tumors (50% vs. 10%), particularly those occurring to the left of the superior mesenteric vessels. Unlike lymph node metastases, liver metastases herald a poor prognosis, with the extent of liver involvement an important predictor of survival. In patients with diffuse liver metastases, the 10-year survival is 10% to 15% compared with 95% in the absence of liver metastasis. The prognosis is also more favorable in patients with single-lobe liver metastasis, with a 10-year survival of nearly 60%. Regardless of location, primary tumor size is predictive of distant metastasis (Table 1).

TABLE 1 Primary Tumor Size and Frequency of Distant Metastases

Tumor Class	Diameter Range (cm)	Patients (No.)	Distant Metastases (%)
T0 (no tumor)	0	18	0
T1	0.4–1.0	21	10
T2	1.2–2.0	22	14
T3	2.2–2.6	16	12
T4	3.0–8.5	29	59

Modified from Ellison EC, Johnson JA. The Zollinger-Ellison syndrome: a comprehensive review of historical, scientific, and clinical considerations. *Curr Probl Surg.* 2009;46:13-106.

DIAGNOSIS

Although rare, a patient should be referred for prompt ZES workup in the presence of refractory peptic ulcer disease, long-standing diarrhea, ulcer disease in the absence of *Helicobacter pylori* infection, or failure to improve after treatment for established *H. pylori* and acid suppression therapy. In addition, the presence of hypercalcemia or nephrolithiasis should raise suspicion of possible MEN-1, and such patients should be screened for gastrinoma and MEN-1. The algorithm for the diagnosis of gastrinoma is shown in Figure 1. The diagnostic steps include measurement of gastric acid, baseline fasting gastrin levels, and secretin-stimulated serum gastrin levels as well as cross-sectional imaging.

Fasting serum gastrin is the appropriate initial diagnostic test, but it is insufficient alone to prove the diagnosis. Several medical conditions may cause hypergastrinemia, including pernicious anemia and atrophic gastritis, which are the two most common causes of hypergastrinemia. In affected patients, it is common for the fasting gastrin level to exceed 1000 pg/mL. Therefore, a fasting serum gastrin level greater than 1000 pg/mL is not diagnostic for ZES unless it occurs in association with increased gastric acid secretion (gastric pH <2). Other conditions that may cause fasting hypergastrinemia associated with increased acid hypersecretion include *H. pylori* infection, peptic ulcer associated gastric outlet obstruction, antral G-cell hyperplasia, retained antrum, renal failure, and short bowel syndrome. However, it is pharmacologic acid suppression that often confounds diagnosis, as such agents may cause achlorhydria. This can produce hypergastrinemia as a consequence of the absence of acid suppression of gastrin secretion from the G cells in the gastric antrum. It is important to emphasize that determination of gastric pH and verification of acid production is mandatory to confirm the diagnosis of ZES. A patient who is not being treated with PPIs is unlikely to have ZES in the absence of gastric acid. Basal acid output tests have 98% sensitivity if levels greater than 15 mEq per hour are seen in an unoperated patient or greater than 5 mEq per hour for those who had a previous resection.

Serum gastrin is measured by RIA. The patient should discontinue pharmacologic acid suppression with PPI for a minimum of 72 hours (ideally, 7 days) before testing. H2 receptor antagonists may be taken during this time to control acid secretion and symptoms. In ZES, a normal fasting gastrin is very rare, occurring in less than 3% of patients. This makes serum gastrin measurement an excellent screening test for ZES, with a sensitivity that approaches 99%. Patients with suspected ZES who have fasting hypergastrinemia and gastric pH measurement revealing the presence of gastric acid should undergo confirmation with provocative stimulation of gastrin with

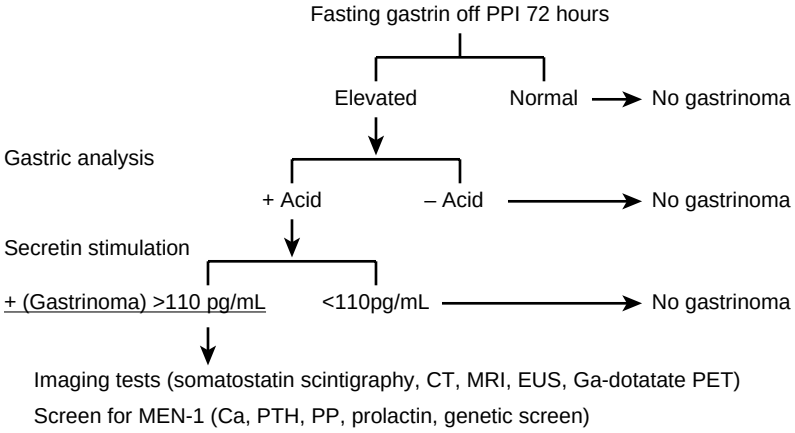


FIG. 1 Diagnostic algorithm for Zollinger-Ellison syndrome. *Ca,* Calcium; *CT,* computed tomography; *EUS,* endoscopic ultrasound; *MEN-1,* multiple endocrine neoplasia type 1; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography; *PPI,* proton pump inhibitor; *PTH,* parathyroid hormone.

secretin. Following an overnight fast, patients are given an intravenous bolus injection of secretin of 0.4 μg/kg of body weight. Blood samples are collected for determination of gastrin levels at 0, 2, 5, 10, 20, and 30 minutes following secretin administration. It is not necessary to discontinue PPIs or H2 antagonists for this test. Side effects of intravenous secretin administration are minimal and include nausea and flushing. The accepted threshold for a positive secretin test is an increase in gastrin of 110 pg/mL over baseline. This threshold has been found to be accurate in nearly 100% of patients. Rarely, false-negative or false-positive tests occur. The false-positive rate is 0% in patients without achlorhydria when an increase over baseline of more than 110 pg/mL is used. Once the biochemical diagnosis of gastrinoma is confirmed, the patients should be screened for MEN-1 with measurement of ionized calcium, parathyroid hormone, prolactin, and pancreatic polypeptide. MEN-1 is strongly suspected if patients have primary hyperparathyroidism, and parathyroidectomy is recommended initially.

TUMOR LOCALIZATION

Imaging is obligatory to localize the tumor before surgical intervention. Initial localization should be attempted with computed tomography (CT) of the abdomen and pelvis, with fine cuts through the pancreas (pancreas protocol CT). Magnetic resonance imaging (MRI) may also be used and may be more sensitive for detecting metastatic disease. Neuroendocrine tumors are hypervascular and demonstrate a greater degree of enhancement than the normal pancreas during the arterial and capillary phases of the contrast bolus. This is useful in identification and differentiation of pancreatic neuroendocrine tumors (PNETs) from pancreatic adenocarcinoma. Dual-phase MRI of the abdomen, with delayed images, may be useful to delineate the primary tumor or metastases to the liver. Somatostatin receptor scintigraphy (SRS) can also be helpful in the preoperative localization of gastrinoma. SRS is sometimes called an *OctreoScan* and employs indium-labeled octreotide with a strong affinity for type 2 somatostatin receptors, which are expressed on gastrinoma cells. SRS has been reported to be significantly better than all of the conventional imaging methods in the identification of gastrinomas subsequently found at surgery, but SRS will not detect 20% of gastrinomas. 68Ga-Dotatate positron emission tomography (PET) CT is replacing SRS for localization of neuroendocrine tumors, including those causing ZES (Fig. 2). 68Ga-Dotatate PET/CT is more accurate for staging and superior to OctreoScan in the detection of overall number of lesions in the body, bones, and viscera. 68Ga-Dotatate PET/CT also allows for calculation of standardized uptake value, has less whole-body radiation, and is quicker than OctreoScan. In contrast with fluorodeoxyglucose (FDG) PET/CT, 68Ga-Dotatate PET demonstrates a high uptake because neuroendocrine tumors express extensive somatostatin 2 receptors. Standard 18F-fluorodeoxyglucose PET/CT is not recommended for evaluation because the slow metabolic activity of gastrinomas renders them typically indemonstrable. The National Comprehensive Cancer Network guideline has added 68Ga-Dotatate PET/CT as an appropriate test in the diagnosis and management of neuroendocrine tumors. Endoscopic ultrasound (EUS) is an invasive alternative to be considered if cross-sectional imaging and 68Ga-Dotatate PET have not identified the location of a gastrinoma. In addition, a biopsy can be accomplished at the time of EUS. The sensitivity of EUS to localize small PNETs approaches 97% compared with CT (85%) or MRI (70%).

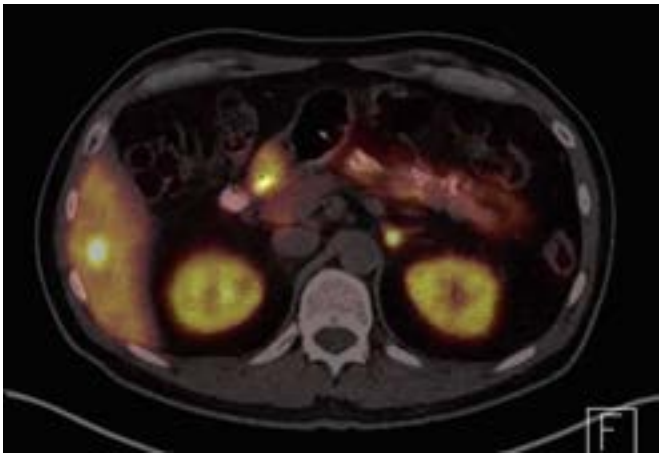


FIG. 2 ^{68}Ga-Dotatate positron emission tomography showing duodenal gastrinoma and liver metastasis.

Although rarely used currently, a selective secretin stimulation test may be performed with direct secretin injection into the hepatic, splenic, gastroduodenal, and superior mesenteric artery with sampling from the right hepatic vein for measurement of serum for gastrin. Secretin is selectively administered intraarterially with sampling at 0, 20, 40, and 60 seconds. A "step-up" in hepatic vein gastrin will indicate the dominant blood supply of the tumor and therefore its likely location. Small case series report sensitivities ranging from 77% to 100% for the combination of selective angiography and selective stimulation. This technique is an option for patients in whom conventional imaging fails to localize a tumor.

For cost-effectiveness, consider the following sequence in imaging: Cross-sectional imaging with CT or MRI followed by 68Ga-Dotatate PET. If these studies are negative, then EUS should be considered. If that is negative, consider selective secretin testing.

SURGICAL MANAGEMENT OF GASTRINOMA

The surgeon should consider whether an operation is indicated only after a diagnosis of gastrinoma is confirmed. It is recommended that in sporadic ZES surgical resection should be carried out if a complete tumor resection can be performed and there are no comorbidities limiting life expectancy or increasing surgical risks to unacceptable levels. The surgical approach to the sporadic gastrinoma, whenever possible, is recommended for several reasons. Imaging modalities have markedly improved in sensitivity, making it possible to better localize the primary tumor and stage the disease, decreasing unsuccessful surgery. More recent surgical studies have demonstrated increased disease-free rates approaching 40% to 63% of patients operated upon without Whipple resections and higher in patients with Whipple resections, although the latter finding may represent a selection bias. Importantly, two studies have provided evidence that surgical resection in sporadic ZES leads to a decreased rate of the development of liver metastases. Finally, the surgical approach to locate duodenal gastrinomas has been evaluated and demonstrates that certain specific techniques are needed to find the tumor (duodenotomy, mobilization of duodenum, intraoperative transillumination of duodenum in some cases).

The importance of routine lymphadenectomy in sporadic ZES has recently been studied in a number of studies. Although controversial, it is now recommended by some authors. One larger study showed that in 41 patients who underwent potentially curative surgery, systematic lymphadenectomy with excision of more than 10 lymph nodes resulted in a higher rate of biochemical cure after surgery than no or selective lymphadenectomy (13 of 13 vs. 18 of 28 patients; $P = 0.017$). There was also a trend toward prolonged disease-specific survival and a reduced risk of death. The presence of primary lymph node gastrinomas is controversial, even though several studies have reported long-term (up to 20 years) disease-free survival after resection if only a gastrinoma-containing lymph node was resected. Therefore, routine lymphadenectomy may increase the

disease-free survival rate. The number of positive lymph nodes or the lymph node ratio may also have important prognostic significance in gastrinomas and other pNETs. Other reported negative prognostic factors for disease-specific survival include tumor size larger than 25 mm, Ki-67 index more than 5%, preoperative gastrin level greater than 3000 pg/mL, and liver metastases. Sex, age, type of surgery, and presence of lymph node metastases had no influence on disease-free or disease-specific survival.

In sporadic gastrinoma patients, exploration is warranted in the presence of confirmatory imaging studies. Sporadic gastrinoma patients with negative imaging merit exploration as tumors in the duodenum, pancreas, or lymph node primaries may be very small and undetectable by imaging. One study demonstrated that in patients with sporadic ZES with negative preoperative imaging studies, an experienced surgeon will find a gastrinoma in 98% of the patients, with 50% of patients made disease free. This is not different from the results in patients with positive preoperative imaging. Interestingly, survival in patients who have negative imaging studies or no tumors identified at operation is very high, approaching 90% 20-year disease-free survival without later-stage progression.

In the MEN-1 patient, surgical treatment of the associated parathyroid hyperplasia is fundamental. This requires a 3½ gland parathyroidectomy or a total parathyroidectomy, followed by autotransplantation of parathyroid tissue. Control of hyperparathyroidism with normalization of serum calcium will reduce baseline gastrin levels and may reduce the medication requirements to control gastric acid secretion. Although reports of simultaneous parathyroidectomy and abdominal exploration exist, most surgeons prefer to perform parathyroidectomy as the first procedure and exploration for gastrinoma subsequently.

The role of resection of gastrinoma in MEN-1 patients is still evolving. Although some advocate pancreaticoduodenectomy or total pancreatectomy for gastrinoma with MEN-1, most experts do not. Guidelines from the National Institutes of Health, the European Neuroendocrine Tumor Society, and the North American Neuroendocrine Tumor Society do not recommend such aggressive resections. Reasons include that these patients may survive up to 30 years without aggressive resection and the metabolic sequelae, including diabetes and pancreatic insufficiency, may worsen the quality of life for these patients. One algorithm is that the decision to resect the gastrinoma in a patient with MEN-1 is determined by imaging. Image-negative patients are carefully observed and do not undergo exploration given the low cure rates with surgery. Image-positive patients without distant metastases undergo exploration for local surgical resection as resection has been shown to improve survival independent of a biochemical cure.

SURGERY FOR ZOLLINGER-ELLISON SYNDROME

As Ellison emphasizes, the primary goal of surgery in ZES is tumor control. First, removal of the primary tumor or tumors is accomplished to reduce the possibility of metastatic disease at a later date. Second, removal of all tumors can potentially correct the hypergastrinemia that causes ZES and reduce the need for long-term PPI use. Size is clearly related to the presence of distant metastases, and pancreatic gastrinomas are more likely to metastasize to the liver, even when they are small (<2 cm). Norton and colleagues showed that ZES patients who have surgical resection have improved long-term survival and are less likely to develop metastases. Currently, the preferred approaches, if possible, are enucleation, local resection for pancreatic head lesions, or distal pancreatectomy when necessary for distal pancreatic lesions. Whipple resections are generally reserved for large pancreatic head or duodenal lesions that are unamenable to enucleation. One of the main problems with rendering patients disease free is that lymph node metastases are found in 30% to 70% of cases and therefore are often missed without more extensive surgery, such as a Whipple resection. Some studies support an increased disease-free rate with Whipple resection. Because of possible long-term complications, coupled with the excellent prognosis of patients who are not cured but with minimal residual disease, more aggressive general use of Whipple resections is currently not recommended. Ellison showed a long-term survival advantage in both sporadic and MEN-1 patients having an R0 or R1 resection compared with those having an R2 resection. R0 is defined as complete surgical excision with normal postoperative serum gastrin levels, R1 is defined as residual microscopic disease or complete tumor excision and persistent hypergastrinemia, and R2 is defined as gross residual disease with persistent hypergastrinemia.

SURGICAL EXPLORATION AND RESECTION TECHNIQUES

Preoperatively, the serum gastrin levels, secretin test, and imaging should be reviewed and confirmed. The surgeon should consider the special equipment that may be necessary including intraoperative ultrasound and an endoscope. The morning of surgery, the patient should receive an intravenous administration of a PPI. General endotracheal anesthesia is preferred. A nasogastric tube is inserted. The anesthesiologist should monitor the nasogastric tube output as large volumes of gastric secretion may occur. Laparotomy is performed through a midline or bilateral subcostal incision. Although reports of laparoscopic and robotic exploration exist, an open approach still provides the surgeon with the best exposure and tactile feedback to help identify very small tumors, especially in the duodenum. Our exception for minimally invasive surgery is for clearly localized PNETs that appear amenable to enucleation on preoperative cross-sectional imaging or EUS. Concomitant gastroduodenal procedures are only performed if there are specific complications of ZES that may require surgical treatment, such as gastric outlet obstruction or bleeding ulcer.

Upon opening the abdomen, palpation of the intraabdominal organs, including "running" the small intestine, is necessary to exclude secondary tumors or ectopic tumors. Masses in the liver may be further examined by ultrasound, and an excision or needle biopsy should be performed depending on the size and location. Given the extensive preoperative imaging in gastrinoma, the surgeon will rarely be surprised by unsuspected metastatic disease, observed in only 2% of patients. Therefore, diagnostic laparoscopy is rarely indicated before laparotomy. Exposure requires a wide Kocher maneuver to facilitate bimanual palpation of the head of the pancreas and possible use of intraoperative ultrasound. Division of the gastrocolic omentum is then performed to widely open the lesser sac for exposure of the body and tail of the pancreas.

Pancreatic evaluation is performed by bimanual palpation of the head of the pancreas after a thorough Kocher maneuver, taking note of any masses for later excision. Bimanual palpation of the body and tail of the pancreas is facilitated by incising the peritoneum overlying the inferior edge of the body and tail of the pancreas. Intraoperative ultrasound may be used to assess the head, uncinate process, body, and tail of the pancreas, noting any hypoechoic masses for later excision. Palpation of the hepatoduodenal ligament and removal of any enlarged lymph nodes is then performed. These are sent for standard histology unless no primary gastrinoma is identified in the typical locations, in which case they are sent for frozen section as they may represent the rare ectopic lymph node primary tumor.

Local excision of tumors smaller than 2 cm in diameter may be performed in the head of the pancreas and uncinate process if the pancreatic duct is not involved as determined by intraoperative ultrasound. These tumors are hypervascular, and use of bipolar coagulation aids in the dissection. We have also found the ultrasound coagulating device (harmonic scalpel) to be very useful. As mentioned, larger tumors may require a pancreaticoduodenectomy.

In the body and tail of the pancreas, the tumors usually are adjacent to the pancreatic duct and, as such, distal pancreatectomy and splenectomy are preferred to avoid injury to the pancreatic duct. Because the majority of gastrinomas are malignant, splenectomy is currently recommended, as is distal pancreatectomy to remove lymph nodes in the splenic hilum.

The next step is examination of the duodenum and removal of duodenal nodules. This requires a longitudinal duodenotomy and internal palpation of the duodenum. Most gastrinomas are in the first portion of the duodenum. Use of external palpation or ultrasound only identifies 20% to 30% of these tumors. Intraoperative endoscopy and transillumination of the duodenum may also be helpful in some cases for identification. Suspected duodenal gastrinomas may be locally excised and do not require duodenal resection. The tumors are submucosal, and closure of the mucosal defect created by the excision is recommended. For lesions on the anterior or lateral wall of the duodenum, full-thickness excision is possible. The duodenum is closed longitudinally or transversely with a single layer closure based on the surgeon's preference. A closed suction drain is placed near any sites in the pancreas in which a tumor was locally excised or the transected pancreas if a pancreatectomy was performed.

If a laparoscopic approach is performed, we place the patient in the lithotomy position and use the standard five-port technique for minimally invasive foregut or pancreatic procedures. For proximal lesions, the lesser sac is entered and a Kocher maneuver is performed as noted earlier for open procedures. Enucleatable lesions may be removed using an ultrasonic dissector or a hook electrocautery device. I place a traction suture through the lesion to facilitate dissection. Formal resections may be performed using well-described techniques. Liberal use of intraoperative endoscopy and ultrasound are recommended.

Postoperative Management

The nasogastric tube is removed at the discretion of the attending surgeon. PPI treatment is continued by intravenous administration and then switched to an oral form when the patient is taking liquids orally. Hypergastrinemia induces parietal cell hyperplasia that may take 3 months to resolve; as such, PPI treatment should be continued for 3 months in a patient with normal postoperative fasting gastrin. A fasting gastrin level is drawn on day 3 and repeated at the first postoperative visit. In a patient with established ZES, postoperative false-positive elevations of gastrin caused by continued PPI therapy are rarely seen. If postoperative fasting gastrin levels are elevated, then PPI therapy should be continued and repeat imaging completed at 6 months after surgery. If there is positive imaging, reexploration should be considered.

Results of Treatment

Biochemical cure of sporadic gastrinoma is reported in 30% to 50% of patients with recurrence documented in almost one-third of patients. The usual time to recurrence is 5 to 10 years. Regardless of achieving biochemical cure, complete resection of all gross tumor is associated with improved survival. The 10-year disease-specific survival in patients having R0/R1 resection of sporadic gastrinoma is 85% compared with 40% for patients having R2 resection and 25% for those having no resection. Pancreatic gastrinoma survival favorably compares well with other PNETs (Table 2). In large experiences of MEN-1 patients operated for curative intent, cure was achieved in only 6% of patients. The 10-year survival with gastrinoma in MEN-1 with R0/R1 resection was 90% compared with only 45% for patients having an R2 resection or no resection. Because R2 resections do not increase survival, MEN -1 patients with extensive metastatic disease or locoregional spread that proscribes complete resection benefit little from surgical resection, and these patients are typically not offered surgery.

TABLE 2 Median Survival of Pancreatic Gastrinoma Compared with Other Pancreatic Neuroendocrine Tumors

Tumor Type	Median Survival (Yr)
Insulinoma	12.7
Gastrinoma	10.2
VIPoma	7.7
Mixed tumors	3.4

Modified from Keutgen XM, Nilubol N, Kebebew E. Malignant-functioning neuroendocrine tumors of the pancreas: a survival analysis. *Surgery*. 2016;159:1382-1389.

Recurrent Gastrinoma

Norton et al. reported 223 patients who had an initial operation for ZES in a prospective database. They reported that 52 patients (23%) underwent reoperation a mean of 6 years for recurrent ZES with gastrinoma on imaging after the initial surgery. Of the 53 reoperated patients, 12 had ZES with MEN-1. After reoperation, 18 of 52 patients were initially free from disease (35%); after a mean follow-up of 8 years, 13 of 52 remained disease free (25%). During follow-up, 9 of 52 (17%) of the reoperated patients died, of whom 7 died of disease (13%). The overall survival from initial surgery was 84% at 20 years and 68% at 30 years. These findings suggest that ZES patients should have systematic imaging after excisional surgery, and if gastrinoma recurs or is persistent, they should be given the option for reoperation. Patients with persistent or recurrent gastrinoma with negative imaging are unlikely to benefit from reexploration. Data concerning reoperation for recurrent image-positive gastrinoma in MEN-1 are less clear; most experts are unlikely to recommend reoperation in this scenario.

Management of Metastatic or Locally Advanced Disease

Similar to other advanced NETs, the role of surgical resection in patients with ZES with advanced metastatic disease or even with extensive invasive localized disease is not well defined. Unfortunately, most patients presenting with hepatic metastases with gastrinomas have metastases in both hepatic lobes, with only 5% to 15% having localized hepatic metastases. If imaging studies support the resectability of the metastases, then surgical resection is generally recommended if patients are operative candidates without other medical conditions precluding surgery. Similarly, if most or all disease is thought surgically resectable, surgery is generally recommended. Patients with gastrinomas may present with local invasion and/or vessel encasement or possible involvement, which has led them to not being considered surgical candidates. One recent study demonstrated that 17% of all gastrinomas fall into the category demonstrating possible major vascular involvement; in fact, 42 patients had a pNET that could be resected, with only 9 patients requiring vascular reconstruction; 30% showed long-term disease-free status, and after resection, the patients had a 10-year survival of 60%. This result led the investigators to conclude that surgical resection of pNETs with vascular abutment/invasion is indicated and generally successful without requiring vascular reconstruction and should not be a contraindication to surgery.

TABLE 3 Treatment Options for Metastatic Disease

Liver Resection	Metastases Resection	Effective if Unilobar
Liver transplant	Liver replacement	30% 5-year survival
Targeted liver therapy (TACE, RFA)	Direct liver metastasis damage	For nonsurgical candidates, paucity of published data
Chemotherapy (doxorubicin, streptozocin, 5-Fluorouracil)	Historical treatment	Limited efficacy, limiting toxicity
Everolimus	mTOR inhibitor	Considered second-line therapy after somatostatin analogues or liver-directed therapy
Sunitinib, sorafenib	Tyrosine kinase inhibitors	Limited response, clinical trials ongoing
Somatostatin analogues	Activate somatostatin	First-line therapy, acid reduction largely replaced by PPI, 50% short-term response in tumor growth effects
Lutetium 177, peptide receptor radionuclide therapy	Targeted radiolabeled somatostatin analogue	Partial response in 70%

PPI, Proton pump inhibitor; *RFA*, radiofrequency ablation; *TACE*, trans-arterial chemoembolization.

Patients with malignant gastrinoma often present with liver metastases. In these situations, it is essential for the surgeon to work collaboratively with a multidisciplinary team. The extent of disease burden in the liver often dictates the quality and length of survival. Surgical excision of both the primary tumor and liver metastases has been reported in the literature; however, its use should be considered cautiously. Some authors suggest that select patients may see a survival benefit if a complete or near-complete (90% or more) resection of hepatic metastases can be achieved. Orthotopic liver transplantation has been considered an exploratory option for patients who are unamenable to limited hepatic resection. The 5-year disease-free survival rate was similar (approximately 30%) to that of hepatic resection in the two largest series. Considering the risks and resources involved, transplantation was considered to be an investigational method in the treatment of ZES. Prospective clinical trials are needed to determine the true benefits of orthotopic liver transplantation.

Those with advanced disease need to have multidisciplinary input for more nonsurgical options including chemotherapy with everolimus, sunitinib, and somatostatin analogs, chemoembolization, radioembolization, and radiofrequency ablation. A variety of options for the treatment of metastatic disease is shown in Table 3. The decision to proceed with treatment depends on the rate of disease progression and the patient's symptoms. Because gastrinoma is a rare condition, clinical trials should be considered to define the best treatments in the future.

SUMMARY

ZES is a syndrome caused by gastrinoma. Two-thirds of cases are located within the gastrinoma triangle and associated with symptoms of peptic ulcer disease and diarrhea. The diagnosis of ZES is established by measuring fasting levels of serum gastrin, gastric pH, and secretin provocative gastrin stimulation. ZES is frequently associated with MEN-1; therefore this must be excluded in all patients. Treatment of ZES consists of medical control of symptoms with PPIs and evaluation for potentially curative surgery. Preferred preoperative imaging studies include cross-section MRI or CT and 68Ga-Dotatate PET/CT scans. EUS may be performed to further evaluate primary tumors if other testing is negative. All patients with resectable sporadic gastrinoma should undergo surgical exploration. The goal of surgery is tumor control. Intraoperative tumor localization requires methodical exposure of the pancreas and duodenotomy for possible duodenal gastrinoma. In patients with MEN-1, surgical resection should be pursued only if there is a tumor localized on imaging in the absence of metastatic disease. Patients with sporadic ZES and negative imaging should also undergo surgery. In patients who have synchronous or metachronous liver metastases, surgery should be performed if all visible tumor can be removed safely. Patients with recurrent ZES should be restaged and operation considered if localized tumor is identified. Patients with liver metastases benefit from multidisciplinary care and not infrequently will have survival prolonged by surgical resection.

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Management of Mallory-Weiss Syndrome

Michael G. House, MD

Mallory-Weiss syndrome was first described by G. Kenneth Mallory and Soma Weiss in 1929, with an initial description of 15 patients who developed violent vomiting leading to massive hematemesis. Mortality resulted in four patients, and autopsy revealed vertical gastric mucosal lacerations at the gastroesophageal junction (GEJ). Mallory-Weiss tears (MWTs) of the GEJ are most commonly due to forceful retching and vomiting, but other precipitating factors have been described including injury during rigid and flexible endoscopy, blunt abdominal trauma, prolonged coughing, persistent hiccups, and tonic-clonic seizures. Large case series of flexible esophagogastroduodenoscopy (EGD) indicated for new onset acute upper gastrointestinal bleeding (UGIB) have reported MWT as the source of bleeding in up to 10% of patients.

PATHOPHYSIOLOGY AND RISK FACTORS FOR MWT

Forceful vomiting causes a sudden increase in the resting pressure gradient between the abdominal and thoracic cavities. The pyloric channel tightens while the lower esophageal sphincter, gastric cardia, and diaphragmatic hiatus relax. Simultaneously, the abdominal wall, diaphragm, and stomach contract to propel gastric contents retrograde. This action leads to retrograde prolapse of the proximal stomach mucosa into the esophageal lumen and results in tearing of the gastric and occasionally esophageal mucosa. Alternatively, the sudden increase in intragastric pressure and relaxation of gastric cardia leads to sudden dilation of gastric cardia and distal esophagus that causes tension-related linear lacerations of the GEJ mucosa. For patients without paraesophageal hernia, MWTs tend to be located at the GEJ, most commonly along the lesser curvature (Fig. 1). Regardless of size, an existing paraesophageal hernia may be associated with MWTs involving the gastric cardia alone. Isolated esophageal mucosal tears are unusual for Mallory-Weiss syndrome. Multiple small case series have observed a paraesophageal hernia in 20% to 30% of patients with MWT.

MWTs account for about 7% to 10% of all cases of acute UGIB. Approximately one-half of patients with MWT-associated bleeding have either a recent or active history of alcohol use, whereas alcohol use is present in only 20% of patients with bleeding peptic ulcers. Patients with underlying liver disease or cirrhosis tend to have more severe MWT-associated bleeding. The prevalence of MWT in patients with hepatic cirrhosis is similar to the prevalence of MWT in the general population. Bleeding from MWT is less likely to result in hemorrhagic shock; 1.4% risk compared with 6.7% for peptic ulcer bleeding. Also, patients with MWT bleeding carry higher American Society of Anesthesiologists risk scores compared with patients with bleeding peptic ulcers. Distinct differences exist between the characteristics of patients bleeding from MWT and patients bleeding from peptic ulcers.

DIAGNOSIS

A typical patient with bleeding from MWT presents with an acute history of forceful nonbloody emesis followed by hematemesis. Less than 10% of patients with MWT report a history of recent melena, and abdominal pain is uncommon. Recent alcohol consumption is variable but may be the causative factor for otherwise unexplained emesis. Definitive diagnosis of MWT is established with direct visualization by flexible endoscopy. Flexible endoscopy has become the standard diagnostic tool for evaluating UGIB. Esophagogastroscopy with retroflexed views of the GEJ permits visualization of MWTs at the cardia mucosa; however, 75% of tears will have no active bleeding at the time of endoscopy. Most MWTs are 0.5 to 2.5 cm in length, but some can measure up to 5 cm. Complete evaluation of the esophagus, stomach, and duodenum is necessary to evaluate for other concomitant sources of UGIB. Bleeding from esophageal or gastric varices, gastritis, duodenitis, or peptic ulcers is often present in patients with MWT.

Other less common diagnostic tests for UGIB include tagged red blood cell scan, direct angiography, and multidetector computed tomography (CT) angiography. For patients actively bleeding from MWT, direct angiography of the left gastric or inferior phrenic artery may show a linear contrast collection at the GEJ. CT angiography has largely replaced direct angiography and is a sensitive modality for diagnosing any source for gastrointestinal bleeding.

TREATMENTS FOR MWT: ENDOSCOPY, ANGIOGRAPHY, AND SURGERY

All patients with UGIB need to be evaluated emergently for hemodynamic instability before considering diagnostic studies or interventions. The treatment outline is summarized in Figure 2. Like any critical care situation, shock protocols should be implemented for patients with active UGIB. Assessment of airway, respiratory, and circulatory status is part of the primary survey. Initial laboratory studies should include blood typing and adequate blood supply cross-matching for the potential of a massive transfusion requirement. Other immediate lab testing should include a complete blood count for hemoglobin level and platelet count, coagulation parameters, and comprehensive metabolic panel with hepatic function. Patients with thrombocytopenia or receiving antiplatelet therapy may require platelet transfusion. Coagulopathy due to liver disease or anticoagulation therapy should be corrected promptly with proper agents.

Large bore (e.g., 14- or 16-gauge catheter) peripheral venous access should be obtained immediately in patients with active UGIB. If peripheral venous access cannot be established for a patient in hemorrhagic shock, a central venous catheter (e.g., 8.5 French) should be placed for resuscitation with blood products. Organ perfusion status should be monitored invasively in a critical care unit.

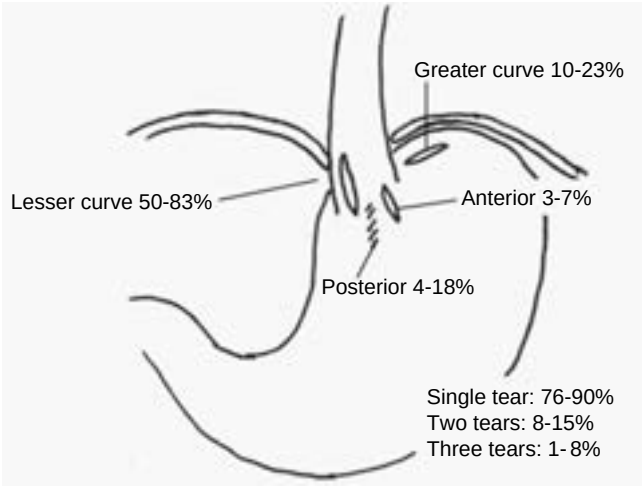


FIG. 1 Distribution of tear(s) in Mallory-Weiss syndrome.

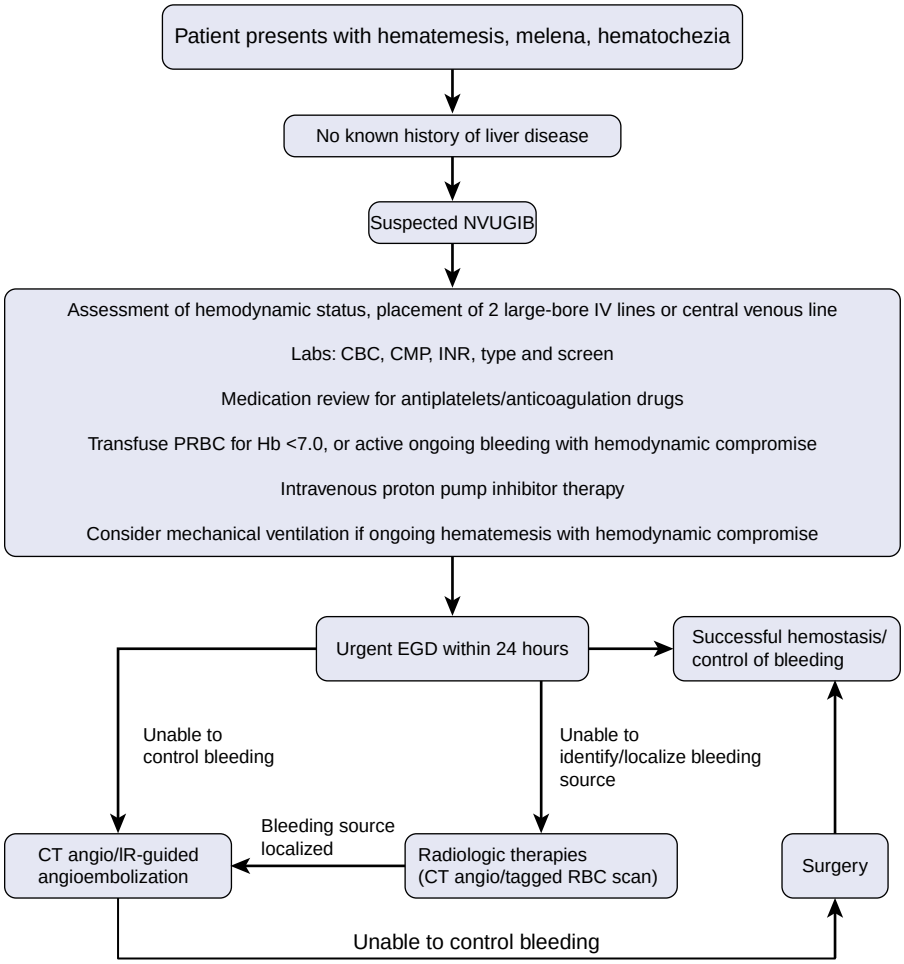


FIG. 2 Initial evaluation and management of nonvariceal gastrointestinal bleeding. *CBC*, Complete blood count; *CMP*, comprehensive metabolic panel; *CT*, computed tomography; *EGD*, esophagogastroduodenoscopy; *Hb*, hemoglobin; *INR*, international normalized ratio; *IR*, interventional radiology; *IV*, intravenous; *NVUGIB*, nonvariceal upper gastrointestinal bleeding; *PRBC*, packed red blood cells. *(Modified from Samuel R, Bilal M, Tayyem O, Guturu P. Evaluation and management of nonvariceal upper gastrointestinal bleeding. Dis Mon. 2018;64:333–343.)*

Antinausea medication should be started for patients with nausea and vomiting, and a dual or triple lumen 18 French nasogastric tube should be placed to decompress the stomach. Gastric lavage through the nasogastric tube will confirm UGIB and helps clear blood from the stomach before upper endoscopy. Gastric acid suppression with high-dose proton pump inhibitors decreases the need for endoscopic intervention and transfusion for patients with any source of UGIB and facilitates early healing of mucosal disruptions of the stomach.

Endoscopic Treatment

Endoscopic treatment is successful in 99% of patients with MWT-associated bleeding and in 95% of patients with low-risk bleeding from peptic ulcer disease. Gastroscopy with retroflex visualization of the GEJ is essential for the diagnosis and treatment of MWT. At the time of endoscopy, 50% to 70% of MWTs will have no bleeding. These tears can be treated with antiacid therapy alone for 2 weeks and do not require repeat endoscopy for proof of healing. Modalities for treating active bleeding during endoscopy include hemoclip, ligation banding, thermal coagulation, and injection of sclerosing or vasoconstricting agents. Each modality has its own advantages, but no comparative outcomes data exist to support one treatment over another. Injection of 15 to 30 mL of dilute epinephrine (1:10,000) causes local vasoconstriction to stop bleeding. Sclerosing agents, such as cyanoacrylate, can be injected into the bleeding site to cause vascular thrombosis; however, incidents of sclerosing agents causing extensive tissue necrosis leading to perforation have been reported. Hemoclip placement in addition to epinephrine or sclerosant injection decreases the risk for rebleeding even further. Thermal coagulation with monopolar or bipolar electrical energy or argon plasma coagulation (APC) is highly effective in stopping bleeding from MWT. Endoscopic techniques that use an over-the-scope clip application are also remarkably effective to address MWT bleeding. This device allows clip placement in a tangential rather than head-on approach. Topical hemostatic agents that concentrate coagulants at the site of mucosal tear or ulceration are typically not necessary for MWT. Endoscopic suturing devices have been described for controlling sources of bleeding at the GEJ but are rarely needed for MWT.

Angiography

Transcatheter arterial embolization or infusion of vasopressin is a treatment option for patients who are poor surgical candidates and who have failed endoscopic treatment to control bleeding from MWT. Targeted vasopressin infusion has been replaced by angioembolization because of a higher risk of recurrent bleeding with the former. Selective angioembolization involves direct injection of microspheres, small coils, or glue into the bleeding damaged vessel. Even during hemodynamic instability, angiography will demonstrate active vessel extravasation in less than half of patients with MWT due to generalized vasoconstriction from hypovolemia or temporary thrombus formation. Provocative angiography with injection of vasodilators or anticoagulants such as heparin can induce bleeding and reveal the

culprit bleeding vessel. Bleeding from an MWT usually involves either the left gastric artery or inferior phrenic artery. Empiric embolization of these arteries based on endoscopic localization may be necessary if angiography is unable to identify active extravasation. Compared with surgical treatment, angioembolization has a higher rebleeding rate. However, even nonselective angioembolization may be indicated for patients who are otherwise poor operative candidates.

Surgical Treatment

Endoscopic therapy is successful in 99% of UGIB caused by MWT. Unlike endoscopy, few advancements have been applied to the surgical treatment of MWT. As a result of the introduction of advanced endoscopy, less than 1% of patients with MWT will require surgical intervention. Patients who fail initial endoscopic therapy should undergo a second procedure with an experienced endoscopist before proceeding to surgery. Before operation, the bleeding site location must be identified by endoscopy. A high anterior longitudinal gastrotomy allows visualization of the mucosal tear at the GEJ. The MWT is oversewn within the gastric lumen using absorbable sutures. If the lesion cannot be visualized because of massive hemorrhage, direct tamponade with a sponge stick will stop active bleeding and allow time for resuscitation. The surgeon should look for other lesions after repair of MWT because most cases of MWT requiring operation will harbor other lesions. The anterior gastrotomy should be closed in two layers. Placing a large transoral bougie at the time of the gastric closure will prevent narrowing at the GEJ leading to gastric inlet obstruction. A coexisting paraesophageal hernia should not create challenges if proper caudal traction in placed on the stomach during the gastrotomy, MWT oversewing, and gastric closure. Laparoscopic-assisted oversewing of MWT with endoscopic guidance has been described through an anterior gastrotomy. However, almost all cases of MWT requiring operation are complicated by brisk bleeding that impairs visualization with endoscopy and laparoscopy.

SUMMARY

MWT is a linear laceration of the mucosa at the GEJ that is most associated with repeated retching or violent emesis. Acute UGIB caused by MWT is self-limited in 80% to 90% of cases. Initial management of patients with upper gastrointestinal bleeding associated with hemodynamic instability requires rapid resuscitation, often with blood products. Urgent endoscopy should be the first intervention for diagnosis and definitive treatment. Less than 1% of patients with bleeding from MWT will require surgical treatment.

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Management of Gastric Adenocarcinoma

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INTRODUCTION

Gastric cancer represents the 14th highest cancer incidence and 13th highest cause of cancer death in the United States. Worldwide, however, the prevalence is even more pronounced serving as the 5th most common cancer and third leading cause of cancer death with highest rates of disease in East Asia and Central and South America. Gastric cancer disproportionately affects men representing 60% of new cases, with higher associated mortality in African Americans, Asian Americans, and Hispanics as compared with Caucasians. It is more frequently seen in older individuals with peak incidence in the seventh decade of life. Late-stage diagnoses and limited effective therapeutic options are two prominent causes for its associated mortality risks. Due to its rampant prevalence, Japan (and in limited fashion Korea) has initiated gastric cancer screening protocols allowing earlier disease detection with associated improvements in mortality.

RISK FACTORS

Although most commonly observed as a sporadic disease with multifactorial etiology, there are multiple established risk factors for gastric cancer. Risk factors include both environmental and genetic factors, many of which end in a similar common thread of chronic inflammation leading to dysplasia. Environmental risk factors include long-term infection with *Helicobacter pylori (H. pylori)*, atrophic gastritis, gastroesophageal reflux disease, pernicious anemia, tobacco use, high-salt foods, and smoked meats with high levels of nitrates. Low intake of fruits and vegetables is also associated with increased risk of gastric cancer. Nitrogen compounds found in tobacco smoke or generated after nitrate ingestion can be damaging to the stomach mucosa. Ascorbic acid contained in fresh fruits and vegetables can bind to and remove the carcinogenic inflammatory nitrogen compounds and oxygen free radicals mitigating some of this risk. The overall mortality rate and incidence of gastric cancer have been slowly declining, perhaps related to decreased rates of smoking, changes in diet, and improved refrigeration.

In addition to extrinsic environmental factors, emerging evidence support a growing impact of genetic risk factors including overexpression of COX2, cyclin D2, p53 mutations, or microsatellite instability (MSI). Furthermore, a subset of "familial gastric cancers" is associated with inherited genetic syndromes including hereditary diffuse gastric cancer, hereditary nonpolyposis colorectal

cancer, Li-Fraumeni syndrome, and polyp-associated gastric cancer syndromes.

PATHOLOGY

More proximal gastric cancer has been seen in the past few decades. The proximal lesser curvature, cardia, and esophagogastric junction represent the most common sites of gastric cancer in the United States. Adenocarcinomas comprise most primary gastric malignancies at 95% with the remaining made up of lymphoma (4%) and gastrointestinal stromal tumor (<1%). This chapter will focus on adenocarcinoma.

The Borrmann classification of gastric cancer in 1926 was developed based on the gross appearance of endoscopic findings: *Type I* for polypoid; *Type II* for a fungating lesion; *Type III* for presence of ulceration; and *Type IV* for diffusely infiltrating growths classically termed linitis plastica. The Lauren classification proposed in 1965 is the most useful and widely used classification system dividing adenocarcinoma into two broad histologic subtypes: intestinal and diffuse. The intestinal type has increasing incidence with age and is often associated with extrinsic environmental risk factors or precancerous conditions such as atrophy and metaplasia. The diffuse type of gastric cancer presents as tiny clusters of small, uniform, signet ring cells and is more likely to be poorly differentiated with high rates of early metastasis via submucosal lymphatic spread and transmural extension.

DIAGNOSIS AND STAGING

Symptoms related to gastric cancer are typically vague and nonspecific, often leading to delayed disease diagnosis due to the assumption of dyspepsia, peptic ulcer disease, or gastritis. Most frequently these symptoms include early satiety and weight loss with more advanced lesions associated with obstruction and dysphagia depending on the location of the tumor. Bleeding may occur with 40% of patients having some form of anemia at the time of diagnosis. Physical examination is often limited to identification of distant metastatic nodal disease including the Sister Mary Joseph, or periumbilical, node. Of historical note, Sister Mary Joseph was surgical assistant to Dr. William Mayo. When preparing patients for surgery, she observed that the presence of a palpable periumbilical mass was predictive of patients with advanced intraabdominal disease on laparotomy (Fig. 1). Other eponymous signs of distant metastatic disease of interest include Virchow's node (supraclavicular adenopathy), Krukenberg tumor (drop metastases to the ovary), or Blumer's shelf (peritoneal metastases palpated in the pouch of Douglas on rectal examination).

The American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) have jointly developed the TNM staging system utilized in the Western Hemisphere. This includes the depth of tumor invasion (T), number of involved lymph nodes (N), and presence or absence of metastatic disease (M). Baseline clinical staging guides the development of appropriate initial treatment. The stage of disease at the time of diagnosis is of utmost importance for outcome measures with approximately 50% of people presenting with advanced disease; of those with locoregional disease, 70% to 80% have regional lymph node involvement. Multiple modalities have improved the ability to obtain accurate initial clinical staging including endoscopy, endoscopic ultrasound (EUS), computed tomography scan (CT), positron emitted tomography (PET), magnetic resonance imaging (MRI), and diagnostic laparoscopy with peritoneal washings.

Endoscopy is the primary tool for the diagnosis of gastric adenocarcinoma. While Japan and Korea have implemented initial broad screening strategies with upper endoscopy and barium radiography, upper endoscopic screening is not done in the United States apart from selective screening for patients with specific risk factors including the presence of gastric polyps, pernicious anemia, or genetic disorders. The usual indications for diagnostic endoscopy are anemia with or without weight loss or dysphagia. Biopsy of suspicious lesions provides tissue for a confirmatory pathologic diagnosis. The NCCN currently recommends multiple biopsy specimens from different areas of the lesion. Endoscopy also localizes the disease for surgical planning with special attention to the relation of proximal tumors to the gastroesophageal junction (GEJ). The Siewert-Stein classification proposed in 1996 describes the relationship of a proximal gastric tumor to anatomic landmarks:

Type I: distal esophagus 1 to 5 cm above the GEJ
Type II: cardia up to 1 cm above and 2 cm below GEJ
Type III: subcardial 2 to 5 cm below GEJ

Siewert type III lesions are considered gastric cancers and thus should be treated as described by this chapter, ensuring adequate esophageal resection to obtain negative margins. For a small number of select patients with gastric adenocarcinoma, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) can be performed for small lesions <2 cm with the potential to be definitive treatment for Tis or T1a tumors limited to the mucosa.

CT imaging of the chest, abdomen, and pelvis with oral and IV contrast is routinely used in preoperative staging. CT readily detects most primary tumors and any gross adenopathy, and particularly looks for metastatic disease in the liver or elsewhere. Ascites on CT is a bad prognostic sign usually indicating peritoneal carcinomatosis. PET can be utilized as an adjunct to CT either to identify occult metastatic disease with a negative CT or to further evaluate suspicious lesions identified by CT. PET may also have a role when evaluating the response to neoadjuvant therapy. When metastatic disease is detected, biopsy may be recommended when confirmatory diagnosis is required.

EUS is frequently performed as a vital component of initial staging workup for gastric adenocarcinoma. This provides the most accurate evaluation of the depth of tumor invasion and assessment of perigastric lymph node involvement. Fine-needle aspiration (FNA) should be implemented in the case of identification of suspicious lymph nodes identified on EUS. EUS is particularly useful for smaller tumors with no gross adenopathy on CT; those patients may be candidates for upfront surgery instead of neoadjuvant therapy.

Laparoscopic staging can detect occult metastases and is routinely implemented due to the relatively low sensitivity of CT and PET/CT. In a study conducted over a period of 10 years, 657 patients with potentially resectable gastric adenocarcinoma underwent laparoscopic staging with metastatic disease detected in 31% of patients. The NCCN thus recommends staging laparoscopy for *all patients with T2 or greater gastric cancer and no prior evidence of metastatic disease on imaging*. Cytologic assessment of peritoneal fluid offers additional improvement in laparoscopic staging through identification of occult carcinomatosis, a poor prognostic factor associated with a lower disease-free survival following resection. Positive peritoneal cytology in the absence of visible peritoneal implants offers a challenging paradigm. Clearing of cytology-positive disease by induction chemotherapy is associated with improved disease-specific survival; however, cures remain uncommon. The role of repeat staging laparoscopy following neoadjuvant treatment for advanced disease remains a question with no definitive answer; however, occult metastatic disease may still be detected following induction even with a negative staging laparoscopy.

As noted, the point of staging workup is to determine the best course of therapy. Generally, patients with early T1 tumors with no evident adenopathy (N0) and no distal disease (M0) are offered upfront surgery, whereas patients with T2 or T3 depth of invasion or with any evident adenopathy are counseled for neoadjuvant chemotherapy followed by surgery. Patients with significant bleeding or obstruction are usually treated by surgery first with adjuvant chemotherapy following. Often, however, patients present with advanced metastatic disease and resection for cure is not an option. This includes those with distant



FIG. 1 **(A)** Sister Mary Joseph (birth name Julia Dempsey) was a nurse and administrator at the St. Mary's Hospital in Rochester, MN. In addition to her role as William Mayo's surgical assistant, she was the head nurse and superintendent of the hospital for almost 50 years. **(B)** Sister Mary Joseph's nodule in a patient with stage IV gastric adenocarcinoma. **(C)** CT scan of patient above demonstrating subcutaneous umbilical mass. *(Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)*

metastasis, including N3 (root of mesentery nodal involvement) and N4 (paraaortic nodal involvement) disease or encasement of major vascular structures (excluding the splenic vessels). For the small subset of patients with low burden peritoneal disease or occult peritoneal disease found on washings in the absence of visible lesions, we offer hyperthermic intraperitoneal chemotherapy (HIPEC) in addition to gastrectomy after neoadjuvant therapy.

Increasingly, molecular profiling is used to both understand the biologic behavior of the tumor and identify targets for biologic immune therapy. Human epidermal growth factor receptor 2 (HER2) gene expression has been implicated in the development of gastric adenocarcinoma with reported rates of overexpression in 9% to 23% of patients with gastric cancer. While the prognostic significance of HER2 status in patients with gastric adenocarcinoma remain debated, HER2 testing is now recommended by the NCCN for all patients with metastatic disease at the time of diagnosis. The expression of programmed cell death ligand-1 (PD-L1) represents another pathologic feature that may influence treatment decisions in gastric cancer. The PD-L1 pathway inhibits the differentiation and proliferation of T cells, and its inhibition through immunotherapy is an area of ongoing research. MSI is caused by mutations in DNA mismatch repair and is found in ~10% of gastric cancers. This is a subgroup associated with older age, female sex, lower number of lymph node metastases, and a distal stomach location. The presence of MSI is thought to be predictive of superior survival outcomes compared with patients with microsatellite stable (MSS) gastric tumors. Interestingly, unlike MSS counterparts, MSI tumors do not show benefit of chemotherapy added to surgery; in fact, in some studies, it results in worse survival. Thus, chemotherapy is typically not recommended for this subset of patients. Emerging data report strong immunogenicity and increased expression of checkpoint ligands like PD-L1 in MSI subtype, and these patients may be more suitable for immunotherapeutic treatment approaches.

SURGERY

Surgery remains the standard of care for patients with potentially resectable locoregional disease who are medically able to tolerate major surgery. The goal of surgery is for complete extirpation of disease with wide margins and an adequate regional lymphadenectomy. The stomach has a rich supply of lymphatics with each nodal station described by the location relative to the stomach. The number of metastatic lymph nodes does correlate with survival, and the extent of lymphadenectomy remains an area of ongoing debate. A D1 nodal dissection comprises a gastrectomy and resection of both the greater and lesser omenta including the perigastric lymph nodes along the lesser and greater curvature, suprapyloric nodes along the right gastric artery, and infrapyloric nodes: stations 1 to 7. A D2 nodal dissection includes D1 as well as those along the named vessels of the celiac axis: left gastric, common hepatic, celiac, splenic artery, and splenic hilum: stations 1 to 12. A D3 includes additional clearance of periaortic nodes: stations 1 to 16. While early randomized controlled trials showed no survival benefit for D2 lymphadenectomy, later trials including follow-up from The Dutch Gastric Cancer Trial noted improved disease-specific survival for D2 dissection over D1. D3 dissections have not shown to offer survival benefit but do increase morbidity and thus are not recommended or routinely employed. NCCN guidelines recommend a D2 dissection without splenectomy. Of note, in many Western populations, surgeons often will forgo complete dissection of the splenic artery and hilum and employ "cherry-picking" of any evident station 10 or 11 nodes, thus complete removal of 1 to 9 and 12 has been termed "D1 over" by some and is a common substitute for D2 lymphadenectomy.

Open surgery utilizing an upper midline abdominal incision is a common approach in the United States, but minimally invasive techniques, both laparoscopic and robotic, are being increasingly used. In experienced hands, the short-term outcomes are comparable to the open approach. Prospective trials are ongoing to address any potential differences in durable oncologic outcomes between an open and minimally invasive approach; initial observational retrospective data suggest relative equivalency.

The technique of total versus partial gastrectomy is determined based on the location of the tumor. Cancers of the distal stomach including the body and antrum can be approached via a distal or subtotal gastrectomy with the proximal stomach transection point depending on the proximal extent of tumor, typically with a 4- to 5-cm gross margin. The distal transection is across the first portion

of the duodenum just distal to the pylorus. For practical purposes, the surgeon can mobilize the first portion of the duodenum until the gastroduodenal artery is completely exposed and then divide the duodenum to the right of this vessel after having first divided the right gastroepiploic artery. For all gastrectomies, dissection and high ligation of the left gastric artery with associated station 7 lymph nodes is best accomplished by elevating the stomach and putting this vessel on stretch, facilitated by partially using the resected gastroepiploic vessels as a partial handle (Fig. 2). Reconstruction following distal or subtotal gastrectomy is most commonly performed with a Roux-en-Y. A Billroth II gastrojejunostomy, which can lead to more alkaline reflux gastritis, is usually only done for patients with stage IV disease. Assessment of margins by frozen section is recommended routinely before reconstruction is performed. For any distal gastrectomy, a positive margin mandates further resection. With a total gastrectomy, a positive margin is not desirable, but a multiinstitutional series suggests that further resection of esophagus in the event of a microscopic frozen section positive margin may afford little survival advantage, even though it satisfies the oncologic desire of the surgeon. A total gastrectomy is employed for most midbody and proximal tumors. When performing a total gastrectomy, the authors favor the formation of an intestinal pouch to serve as an increased reservoir (Fig. 3). This is believed to lead to improved functioning in the short and long term, allowing many patients improved ability to eat.

Proximal Gastrectomy

Although uncommonly utilized in the United States, a proximal gastrectomy can be performed in appropriately selected patients with smaller gastric tumors near the GEJ (Fig. 4). Oncologic outcomes are believed to be equivalent, although the total lymph node harvest may be less with proximal gastrectomy. Earlier retrospective studies reported higher rates of anastomotic stenosis and reflux esophagitis following proximal gastrectomy; however, these operations usually resect the majority of the stomach whereas a contemporary proximal gastrectomy does not. Further, a larger remnant pouch may offer improved postoperative nutrition. Japanese studies have demonstrated better functional results with proximal gastrectomy than total gastrectomy with Roux-en-Y reconstruction if more than 50% of the stomach remains. If oncologic resection mandates removal of greater than 50% of stomach tissue, then proximal gastrectomy no longer offers benefit over the total gastrectomy counterpart secondary to bile reflux. Proximal gastrectomy may also be appropriate for patients with less physiologic reserve to tolerate a more aggressive total gastrectomy. Exposure for both dissection and reconstruction is facilitated by dividing the diaphragm by electrocautery in the midline after ligating the crossing phrenic vein. The crura are distracted laterally with stay sutures, and a self-retaining retractor is placed in the opened diaphragmatic hiatus. This allows mobilization of the distal mediastinal esophagus. A primary esophagogastrostomy is performed in an end-to-side manner over a nasogastric (NG) tube, which is left overnight (Fig. 5). The anastomosis comes to lie in the low mediastinum after reapproximation of the diaphragm (Fig. 6).

A pylorus-preserving gastrectomy has been offered in Korea and Japan for patients with early gastric cancer (T1N0M0) located in the middle-third of the stomach at least 4.0 cm away from the pylorus. Ongoing studies are attempting to find the ideal balance between optimizing postoperative quality of life while still achieving a complete, appropriate oncologic resection and lymphadenectomy.

Surgery can still be considered in carefully selected patients with advanced disease. Locally advanced gastric adenocarcinoma with extension into nearby organs requires a multivisceral en bloc resection of involved structures. While multivisceral resection increases morbidity and perioperative mortality compared with total gastrectomy alone, the achievement of an R0 resection in these patients leads to clinically and statistically significant survival benefit compared with palliative resection or chemotherapy alone. This is particularly in reference to distal pancreatectomy splenectomy or pancreaticoduodenectomy in the case of adherence or direct pancreatic invasion. Highly selected individuals with limited peritoneal disease equating to a peritoneal cancer index score of ≤7 may benefit from cytoreductive surgery (CRS) and HIPEC in addition to systemic chemotherapy and gastrectomy. Use of preoperative diagnostic or staging laparoscopy as described earlier is imperative to identify this subgroup of patients who may see benefit from the aggressive CRS and HIPEC approach. A complete cytoreduction and HIPEC with mitomycin C, in addition to complete gastrectomy and lymphadenectomy, have been associated with encouraging overall survival. A phase II trial of cytoreduction, gastrectomy, and HIPEC for 20 patients with gastric cancer and metastatic peritoneal disease resulted in an encouraging median overall survival of 2.1 years from the time of diagnosis. Guidelines will evolve as clinical trials for individuals with low volume peritoneal carcinomatosis continue and mature. These complex patients should be referred to experienced centers with established multidisciplinary gastric cancer teams to ensure optimal outcomes.

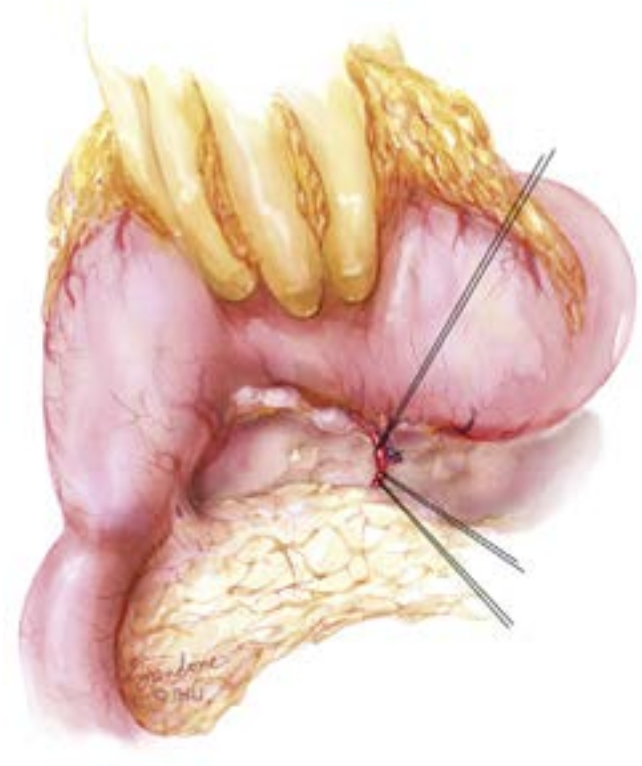


FIG. 2 Illustration of identification, dissection, and high ligation of left gastric artery at its takeoff from the celiac trunk just cephalad to the pancreas.

POSTOPERATIVE RECOVERY

Distal gastrectomy is associated with a low leak rate of 1% to 2%, and thus the authors' practice is to pull the NG tube in the operating room and initiate a clear liquid diet the night of surgery or the following day. This is advanced to a regular diet on enhanced recovery after surgery (ERAS) pathway with typical discharge on postoperative day 3 to 5.

Total gastrectomy requires a longer stay and slower transition in diet. Typically with an esophageal anastomosis that carries a much higher risk of leak, a fluoroscopic swallow study is obtained on postoperative day 3 followed by progression from liquids to soft foods. Total gastrectomy patients may be discharged on either soft or

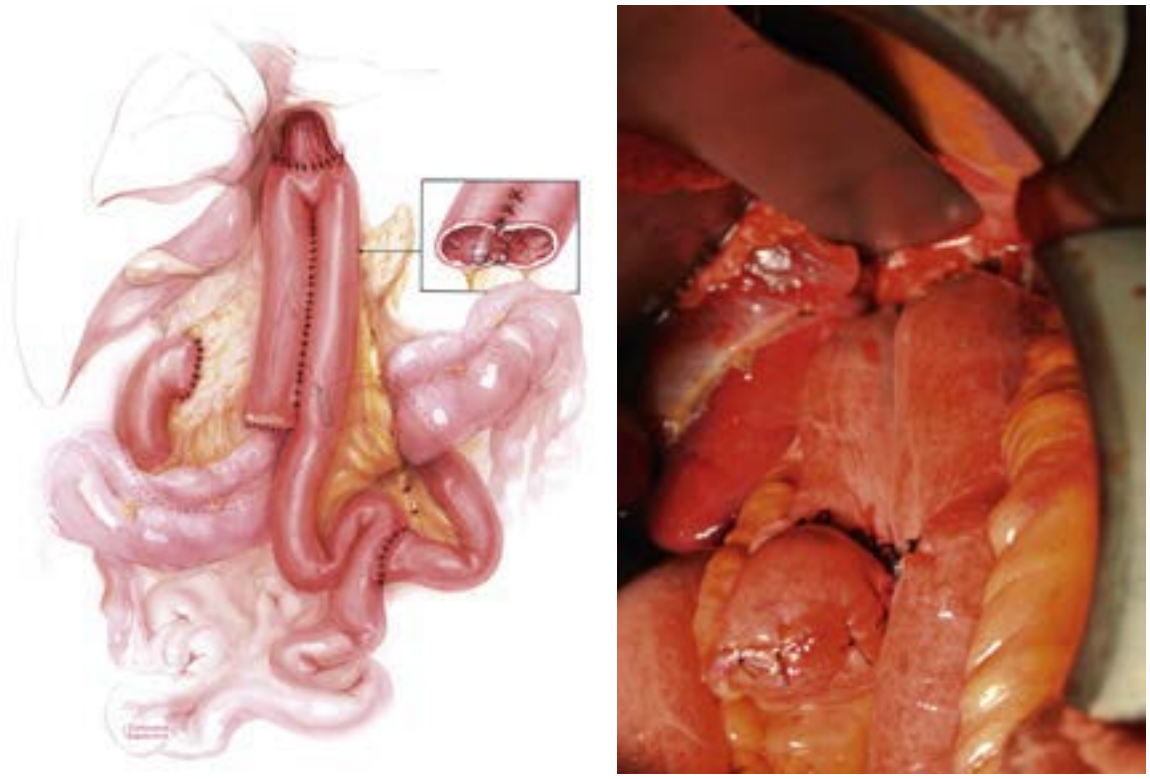


FIG. 3 Reconstruction and formation of jejunal pouch following total gastrectomy. *(From Cameron JL, Sandone C.* Atlas of Gastrointestinal Surgery, *Vol II, 2nd ed. Shelton, CT: People's Medical Publishing; 2014.)*

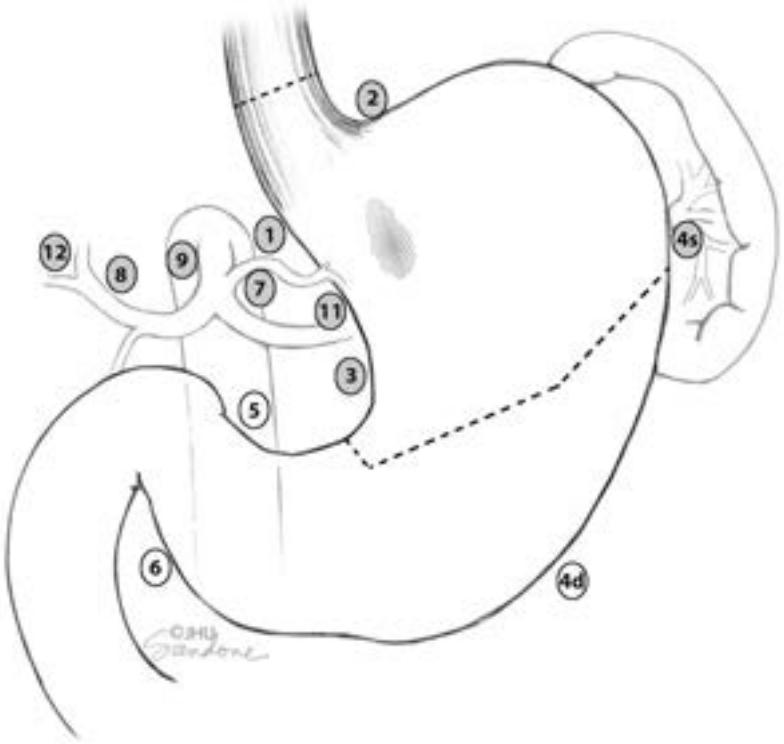


FIG. 4 Proximal gastrectomy for select smaller tumors near the gastroesophageal junction. The dashed lines show the transection of the esophagus proximally and the oblique transection of the stomach 4 to 5 cm distally. At least 50% of the stomach should be preserved in which case the functional results are better than with total gastrectomy. The shaded lymph nodes (1-4s,6-10,12) are included with the resection, while the suprapyloric and infrapyloric nodes that are extremely rarely involved by proximal tumors are left behind.

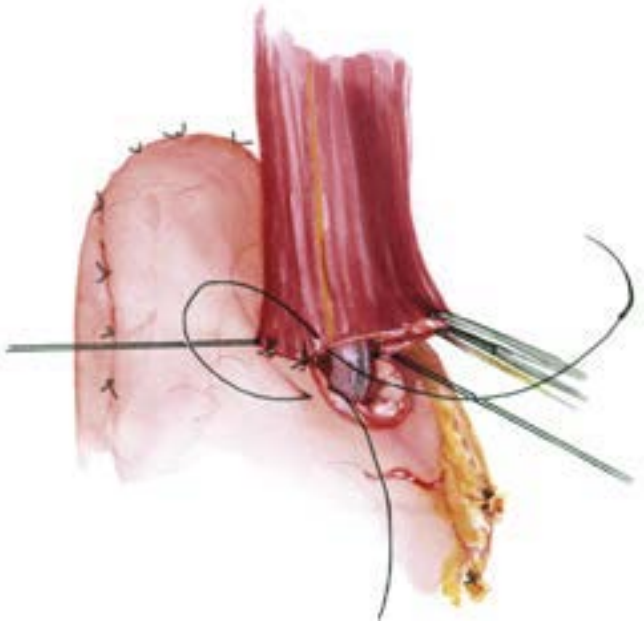


FIG. 5 A primary esophagogastrostomy performed as reconstruction after proximal gastrectomy. In this case, a two-layered handsewn anastomosis is employed with an outer layer of interrupted 3-0 silk and an inner layer of interrupted 3-0 Vicryl. A nasogastric tube is passed across the anastomosis after completing the posterior inner layer.



FIG. 6 The esophagogastrostomy comes to lie at or above the diaphragm in the low mediastinum after proximal gastrectomy. The diaphragm has been divided after ligating the crossing phrenic vein to facilitate exposure. It will be reapproximated with interrupted 0-PDS.

regular diet. All gastrectomy patients are seen by a dietician on the nutrition team. The authors do not routinely utilize a jejunal tube for feeding with only select use in older patients with significant preoperative weight loss, malnutrition, or frailty.

SYSTEMIC THERAPY

Gastric adenocarcinoma is a biologically aggressive cancer with high recurrence and mortality, thus multimodal systemic therapy is utilized to maximize survival for surgical candidates. Multiple clinical trials and meta-analyses support survival advantage of systemic chemotherapy in combination with complete oncologic resection for patients with greater than T2N0 disease. First-line regimens include 5-fluorouracil (5FU), leucovorin, oxaliplatin, and docetaxel (FLOT); capecitabine and oxaliplatin (CAPOX); 5FU, leucovorin, and oxaliplatin (FOLFOX); and epirubicin, cisplatin, and 5FU (ECF). The CLASSIC trial was a phase III, randomized controlled trial in Asia that enrolled 1035 patients with stage II-IIIB gastric cancer who underwent gastrectomy with D2 lymphadenectomy. They were assigned to receive adjuvant capecitabine and oxaliplatin or surgery alone. The trial was stopped early due to a clear survival advantage of the chemotherapy plus surgery group with a 3-year disease-free survival of 74% compared with 59% in the surgery only group.

Despite the clear data supported advantage of adjuvant chemotherapy, there is a high rate of failure to complete adjuvant treatment secondary to multiple issues including surgical complications and patient performance status, thus there has been a recent focus on neoadjuvant rather than postoperative adjuvant therapy. The MAGIC trial enrolled 503 patients with stage II or higher gastroesophageal cancer to either surgery alone or perioperative chemotherapy with a 3-week cycle of ECF preoperatively and three additional cycles postoperatively. The systemic therapy plus surgery group had better pathologic results with lower T stage in the final specimen and a higher proportion of limited nodal disease (N0 or N1) compared with surgery alone. Local recurrence, distant metastases, and 5-year overall survival were all improved in the chemotherapy plus surgery group compared with surgery only.

A phase II trial treated 49 patients with locally advanced gastric cancer with cisplatin, docetaxel, and capecitabine, finding an overall R0 resection rate of 63%, much higher than historical rates of as low as 30%. At a median follow-up of 51 months, median progression-free survival was not reached with predicted 5-year overall survival of 54% for patients in this study without peritoneal disease but classified as locally advanced due to adjacent organ involvement. A separate Japanese phase II study of 55 patients with locoregionally advanced disease studied neoadjuvant irinotecan and cisplatin followed by gastrectomy and D3 lymphadenectomy. R0 resection rate was 65% with a 3-year survival rate of 27%.

The FLOT4-AIO phase III trial compared the MAGIC regimen to four preoperative and four postoperative cycles of FLOT. In the study, 716 patients were randomized with significant improvement in median overall survival with the FLOT regimens (50 vs. 35 months).

The benefit of adjuvant radiation therapy is less clear. The Intergroup 0116 trial enrolled 556 patients for curative gastrectomy alone or surgery in combination with adjuvant 5FU and radiotherapy. This study revealed a significant benefit for adjuvant therapy for overall survival of 50% vs. 41% and recurrence-free survival of 64% versus 41%. Nevertheless, this study is often criticized for the high rates of inadequate lymphadenectomy potentially influencing the observed locoregional benefit. The ARTIST trial randomized patients with gastrectomy and D2 lymphadenectomy to adjuvant chemotherapy with capecitabine and cisplatin alone or with radiotherapy. There was no difference in disease-specific outcomes; however, in a subgroup analysis, radiotherapy did appear to improve disease-free survival in patients with any nodal metastases.

TARGETED THERAPY

Although surgery remains the only potentially curative treatment, the last decade has seen an evolution of cancer care with an increased focus in targeted therapy in an attempt to optimize and personalize care.

The CheckMate-649 phase III randomized trial showed that treatment with the PD-1 inhibitor nivolumab in combination with chemotherapy resulted in an improvement of survival in patients who had PD-L1 positive advanced gastric cancer, GEJ cancer, and esophageal cancer compared with patients receiving chemotherapy alone (13.8- vs. 11.6-month median survival). The results of this study lead to FDA approval of nivolumab for the initial treatment of patients with advanced disease in 2021. Additional targeted therapies under ongoing investigation include the tyrosine kinase inhibitors ramucirumab and bevacizumab that target the vascular endothelial growth factor (VEGF) receptors induced by tumor angiogenesis. Phase II studies have suggested these anti-VEGF antibodies may enhance efficacy of chemotherapy for advanced gastric cancer, although phase III trials remain conflicted. The human epidermal growth factor receptor (ErbB) family has been extensively investigated in gastric cancer. This includes ErbB-2 (HER2), which plays a critical role in regulating cell growth and proliferation and may be overexpressed in gastric cancer. A phase III trial evaluated 594 patients with HER2 overexpressing advanced gastric cancer comparing chemotherapy with or without the addition of trastuzumab and identified a better median survival in the group that included combination with the HER2 targeted monoclonal antibody. The armamentarium for advanced gastric cancer will likely continue to grow with the maturation of multiple ongoing clinical trials investigating different targets and combinations of chemotherapy and immunotherapy.

SURVEILLANCE

All patients with gastric cancer are recommended for systematic postoperative surveillance. This typically entails a complete history and physical examination, basic laboratory testing, and imaging with a CT scan every 3 to 6 months for 1 to 2 years, and then every 6 to 12 months until 5 years out from treatment. This recommendation is despite data that shows no survival benefit to routine CT surveillance. Unfortunately, recurrent gastric cancer is almost never curable. Most all cases of recurrent gastric cancer present within the first 4 to 5 years of initial treatment, and thus 5-year disease-free survival from gastric cancer is considered a cure. For those with recurrent disease, first-line therapy with two drug chemotherapy regimens is the preferred approach for patients, with three drug regimens offered to patients with good performance status. Second-line therapy regimens are recommended based on prior therapy and patient performance status. Although not supported by robust prospective data, surgery can be considered as an option for resectable locoregional recurrence in patients who are medically fit. Some clinical trials are open for recurrent and stage IV disease.

PALLIATION

Approximately 50% of gastric cancer patients initially present with locally advanced unresectable or widespread metastatic disease. With best supportive care, the median survival of these patients without the option for curative resection is only 5 months. Nevertheless, palliative care aims to prevent, reduce, and relieve suffering while maximizing quality of life. The goal can be described as helping patients live as strong as possible for as long as possible emphasizing quality of life in addition to longevity alone. Symptoms of progressive gastric cancer can include bleeding, obstruction, nausea, and pain. Endoscopic coagulation can assist with control of bleeding with adjuncts of external beam radiation or angiographic embolization for recurrent bleeding that is not controlled. The primary goals for patients with obstruction are to reduce nausea and, when possible, resume an oral diet. To accomplish this, a multidisciplinary approach is encouraged, and individual management strategies may include external beam radiation therapy, chemotherapy, placement of an endoscopic stent, surgical gastrojejunostomy, venting gastrostomy, or even palliative gastrectomy in selective patients. Indeed, a distal gastrectomy is a much simpler operation with less physiologic insult that is much better tolerated, which may be offered to some patients with distal tumors aiming to improve their quality of life. A total gastrectomy, however, is a much bigger operation with higher complication rates, including anastomotic leak, of up to 10%, even at high volume centers. Thus, it must be very carefully considered before being offered as a palliative procedure. One must weigh the expected recovery time of the potential procedure against the anticipated survival. A gastrostomy or jejunal feeding tube may be required to provide adequate hydration and nutritional support for patients who cannot tolerate an oral diet.

CONCLUSION

Complete surgical extirpation with appropriate lymphadenectomy remains the foundation of curative therapy for patients with operable gastric adenocarcinoma. The extent of gastric resection and selection of surgical technique depends on the location and extent of the tumor as well as the experience of the surgical team. Addition of neoadjuvant or adjuvant systemic chemotherapy improves survival over surgery alone. Newer biologic therapies target the molecular profile of the tumor allowing for personalized and biology-based therapy. The treatment armamentarium continues to grow as trials investigating HIPEC, immunotherapy, and targeted therapy begin to mature.

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Familial Gastric Cancer

Hamza Khan, MD, Juliet Siena Lumati, MD, and Fabian M. Johnston, MD

The World Health Organization (WHO) estimates that gastric cancer is the sixth most common cause of malignancy worldwide and is responsible for more than 1 million new cases and more than 750,000 annual deaths as of 2020. Unfortunately, late diagnoses with concomitant advanced disease and limited effective therapeutic options ultimately lead to high mortality. As with most cancers, gastric adenocarcinoma is most commonly sporadic in nature with a multifactorial etiology. Multiple risk factors have been extensively studied including *Heliobacter pylori* infection, smoked/processed foods, obesity, alcohol/tobacco consumption, long-term inflammation, and gastroesophageal reflux disease. However, up to 10% of these cases have a familial predisposition. The term *familial* is attributed to families who have two first- or second-degree relatives with gastric cancer diagnosed before 50 years of age or three first- or second-degree relatives diagnosed at any age.

Although there are multiple subtypes of gastric cancer, gastric adenocarcinoma is the most common subtype (90%–95%), followed by primary gastric lymphoma (2%–8%), gastrointestinal stromal tumor (<1%), and neuroendocrine tumor (<1%). For the purpose of clarity, we will focus on gastric adenocarcinoma in this chapter. Familial gastric cancer is most commonly associated as being identified in 1998 when Guilford et al. reported a high incidence of multigenerational diffuse gastric cancer affecting individuals at a young age within the indigenous Māori people of New Zealand. This family was found to have germline mutations within the gene coding for the calcium-dependent E-cadherin cell-cell adhesion molecule *(CDH1),* which was identified as a seminal mutation leading to the development of gastric cancer. This finding identified the need for physicians to have an understanding of the molecular profiles specific to familial gastric cancer, allowing them to identify individuals and family members at high risk who may benefit from early surveillance, prevention, or intervention.

PATHOLOGY OF GASTRIC CANCER

Per the Lauren classification, gastric adenocarcinoma is histologically divided into intestinal and diffuse subtypes. The intestinal subtype is composed of tumor cells that are arranged in a glandular formation, is commonly associated with environmental risk factors, and offers a more favorable prognosis. In contrast, the diffuse subtype lacks adhesion molecules and has poorly cohesive cells that are highly metastatic. It is associated with lesions that are transmural, poorly differentiated, and common in younger patients, overall offering a poor prognosis. Genetic mutations by random error at the cellular level accumulate to transform normal cells into a malignant state. Patients with familial gastric cancer syndromes are at increased risk of developing malignancy because they inherit the initial hit to the genome that allows development of the subsequent neoplastic phenotype more easily.

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant malignancy that composes about 1% to 3% of all gastric cancers. This syndrome was first identified in the Māori families of New Zealand. HDGC is associated with a loss-of-function mutation in the calcium-dependent adhesion protein *(CDH1)* gene on chromosome 16q. *CDH1* has an important role in cell-cell adhesion, thus the loss of function increases invasiveness and epithelial-to-mesenchymal transition. Families with a *CDH1* mutation are at an increased risk of developing diffuse, aggressive, signet ring gastric adenocarcinoma, lobular breast carcinoma, or cleft lip and palate.

The *CDH1* pathogenic variant lends a lifetime risk of 37% to 42% for men and 25% to 33% for women of developing gastric adenocarcinoma in carriers. Up to 60% of female patients are also at risk of developing lobular breast cancer along with 14% of the families reporting cleft lip and palate. Given the high degree of penetrance with this mutation, mapping out familial pedigree is imperative. Testing guidelines for *CDH1* are based on recommendations from the International Gastric Center Linkage Consortium (IGCLC) (Box 1). These guidelines suggest that testing begin at 18 years of age because the IGCLC recommends against testing in children. Typically, asymptomatic family members undergo testing 5 years before the earliest age of the family member with diagnosed invasive cancer or in their second decade of life.

Patients with HDGC can develop poorly differentiated diffuse gastric cancer on average by 38 years of age. Carriers are offered prophylactic total gastrectomy (PTG) as a risk-reducing procedure because it offers excellent outcomes in primary prevention of gastric cancer, even if carriers are asymptomatic. Before undergoing PTG, a preoperative workup including nutritional assessment, risks of intervention, and discussion about long-term sequalae such as dietary changes is of utmost importance. For individuals who decline surgery, annual endoscopic surveillance is offered starting at 20 years of age and includes multiple biopsies of any identifiable lesion and at least 30 random biopsies from all five anatomic zones of the stomach. However, endoscopy is a poor screening tool because early disease of the diffuse gastric cancer subtype can infiltrate the submucosa without endoscopically visible lesions, leading to a high false-negative rate. Following prophylactic gastrectomy, close pathologic inspection reveals multiple foci of intramucosal (T1a) diffuse signet ring cell carcinoma ranging from 0.1 to 10 mm in the overwhelming majority of cases. In a study on prophylactic total gastrectomy in patients with a *CDH1* mutation, 92% of patients were found to have T1N0

BOX 1 2020 Hereditary Diffuse Gastric Cancer Genetic Testing Criteria

Family Criteria (First- or Second-Degree Blood Relatives)

- ≥2 cases of gastric cancer in family regardless of age, with at least one DGC
- ≥1 case of DGC at any age and ≥1 case of lobular breast cancer at <70 years of age in different family members
- ≥2 cases of lobular breast cancer in family members before 50 years of age

Individual Criteria

- DGC before 50 years of age
- DGC at any age in individuals of Māori ethnicity
- DGC at any age in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate
- History of DGC and lobular breast cancer, both diagnosed before 70 years of age
- Bilateral lobular breast cancer, diagnosed before 70 years of age
- Gastric in situ signet ring cells or pagetoid spread of signet ring cells diagnosed before 50 years of age

DGC, Diffuse gastric cancer.

Modified from Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: Updated clinical practice guidelines. *Lancet Oncol.* 2020;21(8):e386–e397.

malignancy on histopathologic examination, whereas only 16% had a tumor diagnosed on endoscopic surveillance.

Given the high lifetime risk of developing lobular breast cancer, women carriers of *CDH1* are also offered annual surveillance with mammography or breast MRI starting at 30 years of age. Although data are insufficient, bilateral prophylactic mastectomy can be considered between 30 and 60 years of age. In patients with a family history of two or more individuals with lobular breast cancer or individuals with bilateral disease, *CDH1* genetic testing should be offered. Studies have shown that 3% to 6% of patients with lobular breast cancer have *CDH1* mutations, therefore it is necessary that physicians caring for patients with breast diseases are also familiar with familial gastric cancer syndromes so appropriate counseling can be performed.

Ideally, care for these patients is undertaken by a multidisciplinary team consisting of a surgical oncologist, gastroenterologist, dietician, pathologist, and genetic counselor who can provide the patient with the most up-to-date guidelines regarding surveillance, intervention, and long-term care. High-volume centers are better equipped with the resources that are necessary to provide longitudinal care for HDGC patients and their families.

Hereditary Nonpolyposis Colorectal Cancer

Henry T. Lynch initially discovered two families predisposed to develop colorectal cancer (CRC) in the 1960s and deemed it *hereditary nonpolyposis colorectal cancer* (HNPCC). The development of cancers other than CRC, including gastric cancer, has been identified and thus the term *Lynch syndrome* has gained popularity. HNPCC is a highly penetrant, dominantly inherited familial cancer syndrome with a molecular phenotype of DNA microsatellite instability. Accumulated germline mutations in mismatch repair (MMR) genes *MLH1, MSH2, MSH6,* or *PMS2* result in carcinogenesis in several organs including the colon, rectum, uterus, ovaries, stomach, and hepatobiliary systems. These mutations account for up to 3% of all newly diagnosed CRC cases, making it the most commonly inherited CRC disease. Mutations in the *hMSH2* gene on chromosome 2p and the *hMLH1* gene on chromosome 3p cause 90% of the microsatellite instability observed in CRC from HNPCC families and are believed to play a role in inherited gastric cancers.

The Bethesda criteria (Box 2) are used to identify patients with HNPCC but do not include gastric adenocarcinoma as a defining criterion. The criteria include (1) CRC diagnosed in an individual younger than 50 years of age; (2) presence of synchronous or metachronous CRC or other HNPCC-related tumors, irrespective of age; (3) CRC with high microsatellite instability histology diagnosed before 60 years of age; (4) individuals with CRC with at least one first-degree relative with CRC or HNPCC-related tumor diagnosed before 50 years of age; and (5) individuals with CRC with at least two first- or second-degree relatives with CRC or an HNPCC-related tumor, irrespective of age. Individuals who meet these criteria are referred for molecular and immunohistochemical testing for microsatellite instability because some individuals may meet the clinical criteria but are microsatellite stable on testing, which is an exclusionary characteristic.

Gastric malignancy is found in approximately 4% to 8% of patients with Lynch syndrome. Patients typically present before 50 years of age with gastric carcinoma, which is more commonly the intestinal phenotype. Endoscopic surveillance is recommended for patients with HNPCC and a family history of gastric cancer or carriers of *MLH1/MSH2* mutations. This surveillance is important given the rate of gastric cancer development and the importance of understanding that there is no role for prophylactic gastrectomy, and surgery is limited to cases with confirmed malignancy.

Li Fraumeni Syndrome

Li Fraumeni syndrome (LFS) is characterized by germline mutations in the *TP53* gene on chromosome 17. *TP53* encodes the tumor suppressor protein p53 that regulates apoptosis in cells with damaged DNA and is termed *guardian of the genome. TP53* mutations prevent cell cycle arrest and permit unregulated division of cells, with mutated DNA leading to an autosomal dominant cancer syndrome composed of various malignancies. Suppression or deletion of *TP53* are common mutations found in the majority of familial or sporadic gastric cancer cases. LFS is associated with *TP53* mutation, thus encompassing several tumor types such as sarcoma, breast tumors, or leukemia that generally develop before 45 years of age (Box 3). Gastric carcinoma is diagnosed in up to 4.9% of LFS carriers, and up to 40% of families with *TP53* mutations report gastric tumor in the pedigree. The median age of diagnosis for gastric malignancy is 36 years, but it has been seen as early as 12 years of age, with the majority of tumors in the proximal stomach and displaying the intestinal phenotype. Screening is focused on breast and CRC, however the phenotypic diversity of LFS complicates effective screening. Therefore periodic screening gastroscopy should be considered at an early

BOX 2 Clinical Criteria to Identify Individuals at Risk for Lynch Syndrome: Bethesda Guidelines

Revised Bethesda Guidelines

Tumors from individuals should be tested for MSI in the following situations:

1. CRC diagnosed in a patient who is younger than 50 years of age.
2. Presence of synchronous, metachronous colorectal or other HNPCC-associated tumors, regardless of age.
3. CRC with the MSI-H† histology diagnosed in a patient who is younger than 60 years of age.
4. CRC diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed before 50 years of age.
5. CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

Amsterdam Criteria II

1. There should be at least three relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis).
2. One should be a first-degree relative of the other two.
3. At least two successive generations should be affected.
4. At least one should be diagnosed before 50 years of age.
5. Familial adenomatous polyposis should be excluded in the CRC case(s) if any.
6. Tumors should be verified by pathologic examination.

CRC, Colorectal cancer; *HNPCC,* hereditary nonpolyposis colorectal cancer; *MSI,* microsatellite instability.

Modified from Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst.* 2004;96(4):261–268; Amsterdam Criteria II: Vasen, Hans FA, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999;116(6):1453–1456.

BOX 3 Diagnostic Criteria for Li Fraumeni Syndrome

Classic LFS criteria (must meet all three)
1. A proband with a sarcoma diagnosed before 45 years of age
2. A first-degree relative with any cancer diagnosed before 45 years of age
3. A first- or second-degree relative with any cancer diagnosed before 45 years of age or a sarcoma diagnosed at any age

Modified from Schneider K, Zelley K, Nichols KE, Garber J. Li-Fraumeni Syndrome. 1999 Jan 19 [updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Mirzaa GM, Amemiya A, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022. PMID: 20301488.

age for LFS carriers who have at least one family member affected by gastric cancer.

Polyp-Associated Gastric Cancer Syndromes

Familial gastric cancer syndromes can be subclassified broadly into those prominently associated with polyps and those that are not. Benign neoplasms and polyps of the gastric mucosa are made up of multiple taxonomies including adenomatous, fundic gland, hyperplastic, inflammatory, and hamartomatous polyps. In general, the inflammatory, hyperplastic, and hamartomatous polyps are considered benign, although occasionally malignant potential is appreciated. Gastric adenomatous polyps and fundic gland polyps are uncommon outside of familial syndromes and are more likely to behave as premalignant lesions. Despite displaying relatively indolent rates of neoplastic development, these subsets of polyps are associated with a significantly increased lifetime risk of developing gastric adenocarcinoma and are thus approached with greater caution. A number of inherited cancer syndromes are characterized by a higher frequency of these polypoid lesions yielding an increased risk of gastric cancer.

Familial Adenomatosis Polyposis and *MUTYH*-Associated Polyposis Syndromes

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome characterized by a loss-of-function mutation in the adenomatous polyposis coli *(APC)* tumor suppressor gene on chromosome 5q. Classic FAP is known for the presence of hundreds of colorectal polyps leading to 100% of affected individuals developing CRC. In contrast, attenuated FAP is characterized by fewer polyps, a later age of diagnosis for adenomas or cancer, and a lower risk of CRC (80%) compared with classic FAP. Adenomatous polyps are also manifested in the upper gastrointestinal tract in 50% to 88% of FAP cases. Gastric polyposis (>20 gastric polyps) may also be identified. In cases of gastric polyposis, the polyps are predominately located in the body/fundus, with adenomatous change most frequently identified near the body/antrum junction. The risk of developing dysplasia is proportional to the polyp size. Furthermore, although the overall risk of carcinoma is low (2%), polyps are more likely to harbor dysplasia in patients with familial polyposis compared with sporadic gastric polyps. In the West, up to 4% of patients with FAP are at risk of developing gastric carcinoma, which is mostly of the intestinal subtype.

FAP patients are recommended to undergo prophylactic total proctocolectomy with ileal pouch anal anastomosis because of the high penetrance of early CRC cancer. No standard guidelines, however, currently exist for gastric surveillance. The age of gastric manifestations is variable in FAP patients, although gastric adenocarcinoma is typically developed long after their colectomy. Current data suggest upper endoscopy initiated at 21 to 30 years of age and performed at intervals of 3 to 5 years with a decreased interval following finding of adenomatous polyps or dysplasia. Polyps larger than 1 cm should be removed to confirm the diagnosis and diminish the risk of malignant degeneration. If dysplasia is identified, low-grade dysplasia is most common, and the overall risk of carcinoma is low. Surgical intervention is typically reserved for patients with severe polyposis causing symptoms (i.e., bleeding) or in the case of confirmed malignancy on endoscopic biopsy. Prophylactic gastrectomy can be discussed for patients who have FAP or attenuated FAP and display diffuse fundic gland polyps, large polyps, or high-grade dysplasia polyps.

The *MUTYH* gene on chromosome 1p regulates DNA damage, and a loss-of-function mutation can lead to *MUTYH*-associated polyposis (MAP) syndrome. This is an autosomal recessive disease, and diagnosis requires evidence of a wild-type *APC* gene to rule out FAP. Clinical presentation, however, is similar to attenuated FAP, with the colon primarily affected along with multiple extracolonic manifestations, such as the development of breast, ovary, or skin cancers. In contrast, patients with MAP have gastric polyps in 11% of the cases compared with up to 90% in FAP. These polyps include both fundic polyps and adenomas with an overall lower risk (2%) of developing gastric cancer compared with patients with FAP.

For both FAP and MAP, surveillance is the mainstay of treatment. Surgical intervention is considered only when gastric carcinoma is established or in the presence of symptomatic polyps that typically present with bleeding or obstruction. For screening, current data suggest endoscopy starting after 25 to 30 years of age in 3- to 5-year intervals. Other therapies such as acid-suppression or nonsteroidal antiinflammatory drugs (NSAIDs) have been shown to reduce polyps, although the effect on overall survival is unknown. Minors have low risk for conversion to malignancy, hence screening is not recommended in this age group. Patients are also at significant risk of duodenal polyps with conversion to malignancy, hence continued endoscopic surveillance after gastric resection is prudent. Thus, surgeons should consider a wider Roux-en-Y anastomosis with a deliberately shorter biliary pancreatic limb to facilitate subsequent endoscopic surveillance of the duodenal stump. Surgeons also should recognize that this may lead to an increased risk of bile reflux.

Peutz-Jeghers Syndrome

Genetic mutation in the tumor suppressor gene *STK11* can lead to the development of Peutz-Jeghers syndrome (PJS). PJS is an autosomal dominant disease classically known for mucocutaneous pigmentation, multiple hamartomatous polyps along the entire gastrointestinal tract, and a high risk of developing various cancers, particularly gastrointestinal and breast tumors. Polyps are found throughout the gastrointestinal tract, more commonly in the small bowel, colon, and stomach (70%–90%, 50%, and 25%, respectively). Gastric polyps can involve the antrum and pylorus and can grow to large sizes, mimicking carcinoma. Because of their size, these polyps are occasionally associated with symptoms including bleeding, abdominal pain, intussusception, and even obstruction.

PJS is associated with the *PJS1* gene on chromosome 19p. Seventy percent of individuals with PJS also have germline mutations of *STK11* on chromosome 19p. The role of these genes as initiators of gastric cancer is poorly defined, but the association of gastric polyps and cancers implicates a potential role. Individuals with *STK11* mutations are more likely to develop gastric polyps and malignancies than their wild-type counterparts. Gastric polyps can present as early as 2 years of age, with a median age of onset of 16 years. Despite the early onset of disease, progression to carcinoma is rare and has a long latency period of greater than 20 years. The lifetime risk of developing gastric cancer in individuals is up to 30% along with an increased risk of malignancy in the pancreas, lung, breast, ovary, or cervix. Given the young age of disease onset, screening with upper and lower endoscopy is recommended to start by 8 years of age with subsequent surveillance based on endoscopic findings. In patients with

no evidence of polyps, surveillance is reinitiated by 18 years of age. Surgical intervention is reserved for histologically confirmed malignancy or symptomatic polyps. Annual CBC is also recommended to screen for anemia from chronic slow bleeding polyps. Select studies have shown some benefits of COX-2 or mTOR inhibitors (rapamycin) in controlling the polyp burden.

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

Extensive gastric polyposis limited to the body and fundus in the absence of duodenal or colorectal polyposis is termed *gastric adenocarcinoma and proximal polyposis syndrome* (GAPPS). It is a relatively new, autosomal dominant disorder with incomplete penetrance. Diagnosis requires exclusion of other polyposis syndromes by ruling out mutations in *CDH1, MUTYH*, and *APC*, among other genes. The precise genetic mutation leading to this syndrome is yet to be identified. Affected individuals have greater than 100 gastric polyps if they are the index case or greater than 30 polyps if they are a first-degree relative of the index case (Fig. 1). Polyps are typically smaller than 1 cm in size and can harbor dysplasia with progression to intestinal-type adenocarcinoma. The syndrome can present as early as the first decade of life, and up to 13% of patients can develop gastric malignancy. GAPPS appears to have an inverse association with *H. pylori* infection, and it is unclear whether it is because *H. pylori* is protective against the syndrome or because infection is rare given the altered gastric morphology from polyposis. Patients who are on proton pump inhibitors (PPIs) are recommended to stop the medication and repeat endoscopy because PPIs can increase the risk of gastric fundic polyps. Endoscopic surveillance is difficult in the presence of extensive polyposis, and total gastrectomy can be considered based on the individual patient's risk versus the morbidity of the surgery.

PREOPERATIVE WORKUP AND SURGICAL INTERVENTION

Although rare, familial gastric cancer syndromes have major implications for patients and their families. Better understanding of the biology of these hereditary syndromes will allow improved outcomes and quality of life. Among the many syndromes discussed (Table 1), once any of them is suspected, care is entailed by a multidisciplinary team. Family counseling is initiated to identify members at increased risk of disease so surveillance can be offered. Methods of surveillance, their frequency, and surgical intervention are discussed on a case-by-case basis depending on the individual's age, their relative's age at the time of diagnosis of cancer, family history, genetic mutation, and most importantly, personal preference. Large institutions can develop a specialized program that is equipped to deal with the complexity that is required for these patients.

Patients who are diagnosed with gastric carcinoma and require gastrectomy are preoperatively referred to a dietician for nutritional evaluation. Preoperative radiologic, endoscopic, and positron emission tomographic (PET) imaging allow adequate staging of the disease. In patients with a hereditary gastric cancer syndrome with a biopsy-proven gastric malignancy, care is similar to any patient with sporadic gastric cancer. Operative intervention with a goal for complete resection offers the only curative treatment option. Surgical margins of 5 cm from gross tumor along with frozen sections are recommended, particularly in cases of diffuse-type gastric cancer because the cells are highly infiltrative. Lymph node involvement and depth of tumor invasion are the most important prognostic indicators. For adequate staging, more than 15 resected lymph nodes are necessary, and a D2 lymphadenectomy is performed.

For patients undergoing a prophylactic total gastrectomy, an upper endoscopy is performed for evaluation of any visibly abnormal sections of the stomach along with random biopsies taken from visibly normal-appearing areas. In patients with no apparent pathology, a conservative approach to harvesting perigastric lymph nodes is taken because it is rare for the tumor to metastasize to the nodes in the setting of visibly unremarkable mucosa. In this scenario, minimally invasive techniques can also be employed, offering shorter hospital stays and possibly improved pain.



FIG. 1 Retroflexed view of gastric endoscopy showing diffuse polyposis covering the body and fundus. *(From Tacheci I, Repak R, Podhola M, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)—A Helicobacter-opposite point. Best Pract Res Clin Gastroenterol. 2021;50–51:101728.)*

POSTSURGICAL CARE

Because patients with familial gastric syndrome may undergo prophylactic gastrectomy at a time when they feel completely healthy, it is important to discuss expectations about postoperative recovery beforehand. Postsurgical recovery can be complicated by potential operative complications or infections. Within the first few weeks after surgery, it is common to have difficulty eating, and patients are also counseled to expect a 10% to 20% weight loss in the beginning as they adapt to a new lifestyle for meals. Derangement in intestinal motility occurs in about 20% of patients and can lead to early satiety, bloating, epigastric pain, and nausea. Dietary modifications like consuming multiple small meals throughout the day in most cases improves symptoms of dumping syndrome, and patients rarely need medical or surgical intervention. In the early recovery phase, well-cooked and soft meals that are high in protein are recommended. As patients improve, a return to their own regular diet in smaller amounts multiple times a day works well. A nutritionist is often an integral part of the team at this stage and can help patients with dietary modifications. Other known risks after total gastrectomy are vitamin B_{12} deficiency from loss of intrinsic factor and calcium, folic acid, iron, thiamine, or other trace mineral deficiencies from malabsorption. Additional supplementation by multivitamin pills or capsules is advised to meet daily requirements.

Long-term, large-scale studies on patient outcomes are lacking because familial gastric cancer syndromes are rare; however, quality of life indicators assessing psychological health and body image generally return to baseline by 12 months after surgery. In a survey conducted on 53 patients, 6% were dissatisfied with their decision to undergo surgical intervention. Because patients are asymptomatic at the time of operative intervention, it is normal that they experience remorse or regret for their choices, particularly in the face of a difficult postoperative recovery. In our experience, a support group composed of patients with a similar background is very helpful as it

TABLE 1 Familial Gastric Cancer Syndromes with Characteristic Molecular and Clinicopathological Features Along with Management

Syndrome	Gene Affected	Autosomal Inheritance	Risk of Gastric Cancer %	Age of Onset for Gastric Polyps	Endoscopic Surveillance, Initiation (Years)	Treatment
HDGC	*CDH1*	Dominant	56–70	–	20	Prophylactic gastrectomy
HNPCC	*MMR (MLH1, MSH2, MSH6, PMS2)*	Dominant	2–44	–	Advised for patients with *MLH1 or MSH2* mutation	*Heliobacter pylori* eradication
LFS	*TP53*	Dominant	3.1–4.9	–	Early age	Case-by-case
FAP	*APC*	Dominant	4	8	21–30	NSAID or acid-suppression
MAP	*MUTYH*	Recessive	2	14	30–35	NSAID or acid-suppression
PJS	*STK11*	Dominant	30	16	8	COX-2 or mTOR inhibitor
GAPPS	Unknown	Dominant	13	10	Case-by-case	Gastrectomy if severe polyposis

FAP, Familial adenomatous polyposis; *GAPPS,* gastric adenocarcinoma and proximal polyposis syndrome; *HDGC,* hereditary diffuse gastric cancer; *HNPCC,* hereditary nonpolyposis colorectal cancer; *LFS,* Li Fraumeni syndrome; *MAP, MUTYH*-associated polyposis; *NSAID,* nonsteroidal antiinflammatory drug; *PJS,* Peutz-Jeghers syndrome.

Modified from Setia N, Clark JW, Duda DG, et al. Familial gastric cancers. *Oncologist*. 2015;20(12):1365–1377.

allows them familiarity with the entire process. As such, it becomes important to maintain an institutional database of such families.

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Management of Gastrointestinal Stromal Tumors

Laurence P. Diggs, MD, and Miral Sadaria Grandhi, MD

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the gastrointestinal (GI) tract and the most common subtype of sarcoma overall; thus, a general surgeon should be familiar with the unique principles of management for this disease. Derived from mesenchymal cells of the GI tract known as interstitial cells of Cajal, GISTs generally present in the stomach followed by the small bowel, rectum, and colon. Over the last several decades, knowledge of the pathophysiology of GISTs has led to improved management and treatment of this disease process. In most cases, development of GISTs is a result of a gain of function mutation and subsequent activation of tyrosine kinase proteins. Mutations activating the KIT proto-oncogene are the most common, accounting for approximately 75% of these tumors. Platelet-derived growth factor receptor (PDGFR) α mutations account for another 10% of these tumors and is mutated in approximately 80% of KIT-wild type (WT) tumors. BRAF mutations have been reported in 13% of KIT-WT tumors. Certain familial syndromes associated with GIST, such as neurofibromatosis type 1 (NF1) and mutations to succinate dehydrogenase (SDH), also make up a percentage of the KIT-WT tumors. WT or sporadic GISTs, whereby a driver mutation has not been identified, are currently thought to account for no more than 5% of all cases.

Since the description of a gain of function mutation in the KIT proto-oncogene in 1998, targeted therapy against GIST has been

studied extensively. Imatinib mesylate (Gleevec), a tyrosine kinase inhibitor (TKI) of ABL, BCR-ABL, KIT, and PDGFR, has become a major component in the multidisciplinary management of patients with GIST. In patients with metastatic disease, imatinib prolongs median survival to more than 5 years from a historical median of 18 months. In the adjuvant setting, imatinib prolongs recurrence-free survival (RFS). Neoadjuvant imatinib therapy may improve resectability for tumors that are locally advanced or located in anatomically difficult areas and, in some instances, may allow organ-preserving resection. Imatinib therapy has also expanded the role of surgical therapy for metastatic GIST. The ability to estimate the risk of recurrence in GIST patients is increasingly refined. In addition to traditional stratification using tumor size, mitotic index, and organ site, specific mutations in KIT have a significant bearing on tumor behavior and sensitivity to TKIs. Although targeted therapy plays a major role in the management of patients with GIST, surgery remains the only potentially curative therapy for GIST.

CLINICAL PRESENTATION

GIST is typically a disease of adults, with a median presenting age of approximately 60 years and a slight male predominance. The incidence of GIST is estimated to be approximately 6000 new cases per year in the United States. According to autopsy studies, the incidence of micro-GISTs, smaller than 1 cm, is much higher. Although GISTs have been reported throughout the GI tract from esophagus to rectum, the majority are found within the stomach (>50%) followed by the small bowel (25%–35%). Within the small bowel, the majority are found in the ileum and jejunum with only 5% arising in the duodenum. Although other sites of GIST are rare, including rectum, colon, esophagus, and extraintestinal/indeterminate locations, an increasing number of GISTs have been discovered in the colon and the rectum due to the widespread use of screening colonoscopy. The median size of GIST at presentation is 5 to 7 cm but can grow to be larger than 30 cm in size. Often, GISTs are discovered incidentally by endoscopy or imaging during workup for other conditions or at time of unrelated surgery. Patients may have symptoms at the time of diagnosis, particularly with large GISTs, including pain, fullness, early satiety, nausea, vomiting, weight loss, or noticeable mass. Although GISTs are not mucosal-based lesions and grow from the muscle layer of the bowel wall, roughly one-quarter of patients present with GI bleeding secondary to erosion and ulceration of the underlying mucosa. Bleeding from tumor rupture into the peritoneal cavity is a rare but negative prognostic factor and may lead to life-threatening hemorrhage. Metastasis typically involves the liver or peritoneal cavity. Lymph node involvement, occurring in less than 5% of patients, is rare in adult GIST and usually reflects direct tumor extension.

Two subsets of GIST are worth noting. Pediatric GISTs, often associated with SDH deficiency, exhibit different biology compared with adult GIST. This disease is indolent with female predominance, multifocal disease, frequent lymph node metastasis, and universal imatinib resistance. Familial GISTs involving germline mutations in KIT or PDGFRα are rare. Typically, tumors are multifocal and indolent. For patients with an SDH mutation, certain constellations may be observed including Carney's triad (GIST, paraganglioma, and pulmonary chondroma) or Carney-Stratakis syndrome (GIST and paraganglioma). More rarely, patients with mutations in NF1 may develop GISTs and present with additional tumors including gliomas, malignant peripheral nerve sheath tumors, and the typical neurofibroma.

WORKUP

Cross-sectional imaging consisting of a computed tomography (CT) scan of the abdomen and pelvis with IV and oral contrast is the imaging modality of choice for initial evaluation of a GIST tumor. Typical features of a GIST include an enhancing mass arising in the wall of the stomach or small intestine. GISTs may be grossly categorized as exophytic, endophytic, or mixed/dumbbell shape (Fig. 1). Tumor heterogeneity is common in larger tumors due to tumor necrosis. Small masses may not be evident on CT scan depending on the level of distention of the bowel or stomach and if oral contrast was given or not. Alternatively, a large hypervascular mass arising from the lesser curvature of the stomach may be misinterpreted as a primary liver tumor. Determining whether adjacent structures are involved by large tumors can be difficult because of loss of plane interfaces on CT; however, most GISTs are found to be mobile at the time of operation and do not require multivisceral resection. For periampullary and rectal tumors, MRI can help further delineate anatomy. Although GISTs are typically glucose avid on [^{18}F] fluoro-2-deoxy-D-glucose positron emission (PET)/CT, this test is not necessary for initial assessment. PET/CT may be considered to assess for occult metastatic disease and to test for tumor response to TKIs. In addition, it may be useful in determining neurofibromas from GIST tumors in NF1 patients.

CT scan may be sufficient during workup of gastric or small bowel masses that exhibit classic features of GIST. However, many tumors require further evaluation to obtain a definitive diagnosis. Endoscopic evaluation including endoscopic ultrasound (EUS) and fine-needle aspirate (FNA) is the next step in evaluation. It is important to note that biopsies should be obtained endoscopically and that percutaneous biopsies of small bowel GISTs are never recommended due to the risk of peritoneal dissemination. Tissue analysis remains the gold standard to confirm the diagnosis and rule out other potential gastric and intestinal tumors, including adenocarcinoma, lymphoma, and leiomyoma. Pathology consistent with GIST will reveal a population of spindle cells that stains positive for CD117 (KIT) on immunohistochemistry. In addition, tissue analysis is essential to detect additional genetic mutations, including PDGFRα, BRAF, SDH, and NF1, and to help guide effective targeted therapy. In tumors that would require a potentially morbid operation, such as gastroesophageal junction (GEJ) tumors, periampullary duodenum, or rectum, tissue diagnosis is necessary to further determine the sequence of intended treatments with targeted therapy and surgical resection.

RISK STRATIFICATION

Three clinicopathologic parameters have been shown to independently predict risk of recurrence after complete resection of primary GIST: tumor size, mitotic rate, and tumor site. Size greater than 5 cm, mitoses larger than 5/50 high-powered field (HPF), and nongastric site are poor prognostic variables. Several different risk stratification systems have been developed based on these variables (Table 1). A nomogram that incorporates all three criteria (Fig. 2) provides an individualized estimate of 2- and 5-year RFS after complete resection of a primary GIST and can provide selection criteria for adjuvant imatinib.

Identification of the specific *KIT* or other gene (e.g., *PDGFR*, *SDH*) mutation in GIST, either after resection or even preoperatively, provides useful information regarding responsiveness to targeted therapy and progression-free survival (PFS) after resection. Specific mutations are associated with tumor biology and, most importantly, tumor response to imatinib therapy. Three-quarters of tumors harbor a KIT mutation, varying substantially in aggressiveness. Mutations of exon 11 are the most common, representing 65% of all GISTs. Among exon 11 mutations, codons 557 and 558 are hot spots for mutation, and tumors with deletions of this part of the gene are more likely to metastasize or recur compared with point mutations or insertions in this area. Of note, patients with KIT exon 11 deletions in the ACOSOG Z9001 study were responsible for nearly all the improvement in RFS achieved with 1 year of adjuvant imatinib, whereas other KIT mutations demonstrated little difference. KIT exon 9 mutations (about 10% of all GISTs) typically arise in nongastric tumors and carry unfavorable biology. Meta-analysis of two large trials of imatinib in metastatic unresectable GIST demonstrated that patients with exon 9 mutations require higher dose imatinib for

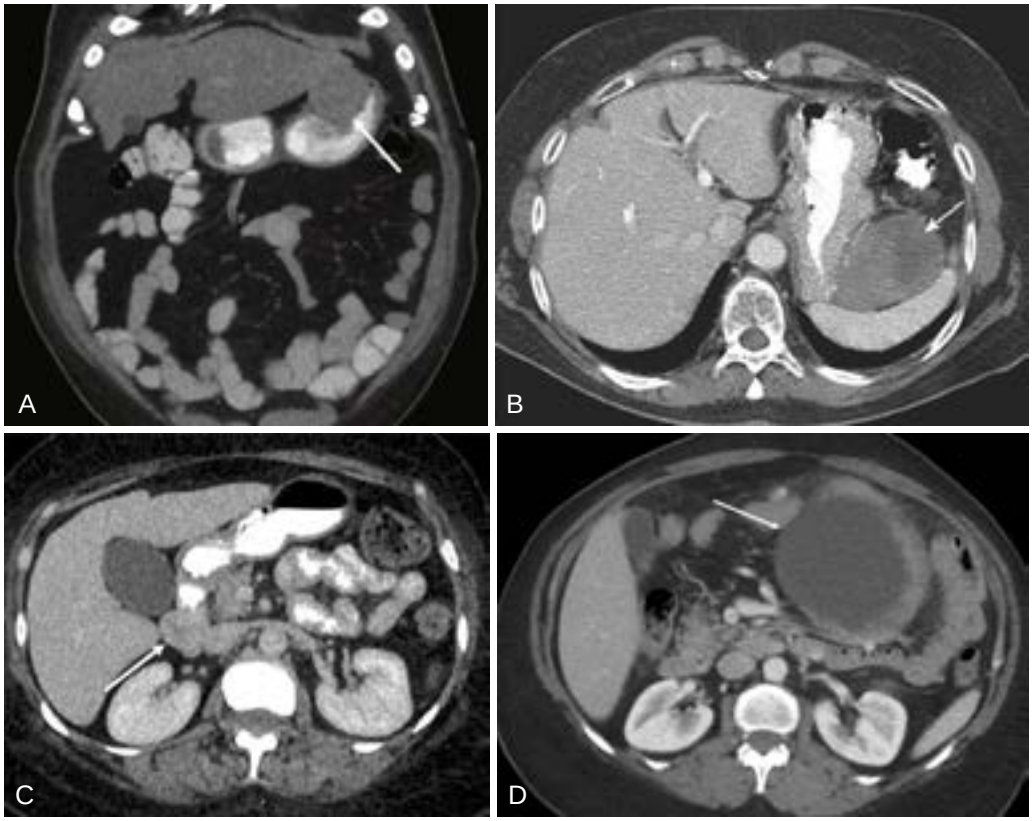


FIG. 1 Contrast-enhanced CT scan of a typical gastric and small bowel gastrointestinal stromal tumor (GIST). Gastric GIST may be **(A)** endophytic, **(B)** exophytic, or intramural (not shown). Small bowel GISTs can occur anywhere along the small bowel, such as the **(C)** duodenum or **(D)** jejunum.

TABLE 1 Risk Classification for Primary Gastrointestinal Stromal Tumor According to Mitotic Index, Tumor Size, and Tumor Site

Tumor Parameters		Risk of Disease Progression (% of Patients)			
Mitotic Index	**Size (cm)**	**Stomach**	**Duodenum**	**Jejunum or Ileum**	**Rectum**
≤5 per 50 HPF	≤2	None	None	None	None
	>2 to ≤5	Very low (1.9)	Low (8.3)	Low (4.3)	Low (8.5)
	>5 to ≤10	Low (3.6)	Insufficient data	Moderate (24)	Insufficient data
	>10	Moderate (10)	High (34)	High (52)	High (57)
>5 per 50 HPF	≤2	None	Insufficient data	High	High (54)
	>2 to ≤5	Moderate (16)	High (50)	High (73)	High (52)
	>5 to ≤10	High (55)	Insufficient data	High (85)	Insufficient data
	>10	High (86)	High (86)	High (90)	High (71)

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.
GIST, Gastrointestinal stromal tumor; *HPF*, high-powered field.
Modified from Miettinen M, Lasota J. Gastrointestinal stromal tumor: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23(2):70–83.

response (800 mg vs. 400 mg daily). PDGFRα-mutant tumors, representing 10% of GISTs, are almost always gastric and demonstrate comparably indolent biology. However, the most common *PDGFRα* mutation is exon 18 (D842V), which imparts imatinib resistance but does respond to avapritinib therapy, recently FDA-approved as first-line therapy for these patients. Thus, understanding the biology associated with a specific mutation and the expected response to imatinib can help plan treatment and follow-up.

SURGERY FOR PRIMARY DISEASE

Indications

Surgical resection remains the mainstay of treatment for most patients with GISTs. According to the National Comprehensive Cancer Network (NCCN), resection is indicated for all GISTs greater than 2 cm in size in patients who are otherwise acceptable candidates for surgery. Tumors less than 2 cm in size that

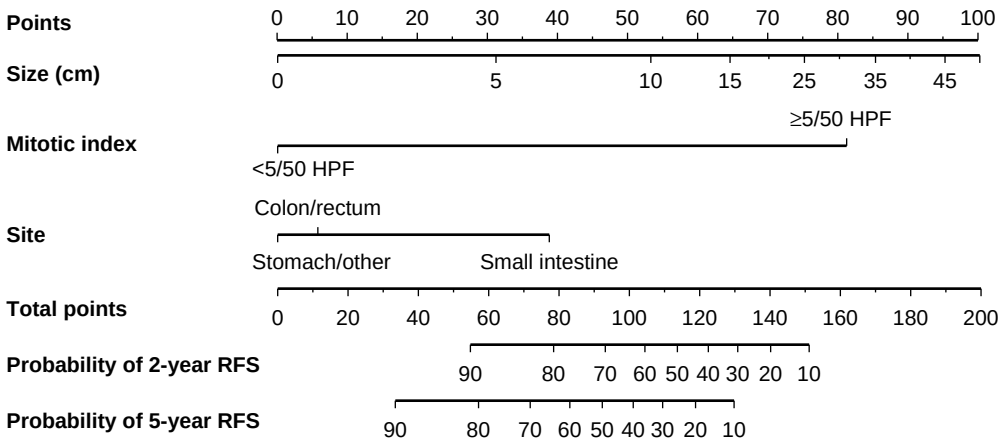


FIG. 2 Nomogram for predicting 2- and 5-year recurrence-free survival (RFS) after resection of primary gastrointestinal stromal tumor. Points are assigned on tumor size, mitotic index, and site by drawing a vertical line from each row to the "points" row. The sum is then located in the "total points" row, and a vertical line is drawn to the "probability" rows to estimate RFS. *HPF*, High-powered field. *(Modified from Gold JS, Gönen M, Gutiérrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol. 2009;10:1045–1052.)*

are asymptomatic, uncomplicated, and indolent in nature can be observed with surveillance imaging. In selected cases of tumors with locally advanced or low volume metastatic disease, surgical resection may also be considered as well as the role for neoadjuvant therapy. For those on neoadjuvant imatinib therapy, imatinib can be stopped right before surgery and restarted as soon as the patient tolerates oral medications. For all other TKIs, therapy should be stopped at least 1 week before surgery and restarted based on clinical judgment or recovery from surgery.

General Technical Principles

Upon entry into the abdominal cavity, whether open or minimally invasive, special attention should be given to the peritoneum, omentum, and liver to assess for metastatic disease. Exophytic anterior and greater curvature gastric tumors are immediately apparent. Posterior gastric tumors require mobilization of the stomach, which is facilitated by retracting the left lobe of the liver to the right and entering the lesser sac through the greater omentum or gastrocolic ligament. Small intramural, intraluminal, or endophytic tumors that are difficult to identify externally can be localized by intraoperative endoscopy with a gastroscope. Duodenal tumors beyond the first portion require extensive Kocher maneuver and possibly mobilization of the ligament of Treitz. Ileal and jejunal tumors are identified best by carefully running the small bowel from the ligament of Treitz to the terminal ileum. After the primary tumor is identified, all tumor manipulation should be done with great care because these tumors are friable and can rupture, especially after neoadjuvant therapy. Tumor rupture, whether spontaneous or iatrogenic, is associated with almost inevitable peritoneal recurrence. GISTs commonly have large arterial and venous collateral blood vessels, and care must be given to avoid potential significant blood loss. Although GISTs typically displace and do not invade adjacent organs, any tissue surface that is densely adherent to the tumor should be at least partially resected en bloc.

Although gastric adenocarcinoma requires a formal anatomic gastrectomy with wide margins, resection of GIST does not require wide margins or lymphadenectomy because they do not typically spread via lymphatics. The goal of surgery is to resect the entire tumor with microscopically negative margins (R0 resection). However, data from 819 primary GISTs 3 cm or larger resected in the American College of Surgeons Oncology Group Z900 and Z9001 trials demonstrated no difference in the RFS in the 72 (8.8%) patients who had microscopically positive margins (R1 resection) on final pathology compared with those who underwent R0 resection, irrespective of imatinib treatment. Gross circumferential resection margins of 1 cm will ensure an R0 resection.

Minimally Invasive Approach

In several studies, a minimally invasive approach, including both laparoscopic and robotic approaches, for the resection of gastric GISTs has been demonstrated to be safe and efficacious with equivalent oncologic outcomes in terms of R0 resection, tumor rupture rates, and recurrence rates. In addition, a minimally invasive approach offers the advantage of decreased length of stay and low morbidity. However, operative times for robotic resection tended to be longer. During a minimally invasive approach, surrounding tissue should be grasped, and a no-touch technique should be employed. If excessive tumor manipulation cannot be avoided during a minimally invasive approach, conversion to an open approach should strongly be considered. In addition to careful manipulation of the tumor during a minimally invasive technique, retrieval of the specimen in a securely fashioned retrieval bag is essential to mitigating the risk of rupture and peritoneal dissemination. For large gastric tumors, a minimally invasive approach is not well described. In addition, there is currently little data comparing minimally invasive approaches to open approaches for nongastric GISTs. Ultimately, surgeon expertise and comfort level should guide the surgeon's decision on the approach to surgical resection of both gastric and nongastric GISTs.

Site-Specific Considerations

The surgical approach to GISTs varies greatly depending on the location of the tumor. Although many exophytic gastric tumors with a narrow stalk or those on the greater curvature or fundus of the stomach can be removed easily with a wedge partial gastrectomy using surgical staples without compromising the lumen, direct visualization facilitates safe resection while minimizing luminal narrowing in more difficult areas, such as the antrum, incisura, lesser curvature, or GEJ. A unique technique of tumor excision with a small negative margin (usually 1 cm) under direct visualization using cautery is useful for gastric GISTs (Fig. 3). Direct visualization and excision facilitate safe resection while preserving gastric capacity and minimizing luminal narrowing in these more difficult areas. GISTs involving the GEJ should attract attention for neoadjuvant imatinib for tumor downsizing before

resection. Although open surgery is preferred by most surgeons for tumors along the posterior aspect of the GEJ (Fig. 4), these tumors can be approached minimally invasively. Once open, a gastrotomy is performed to resect the tumor with a 1-cm margin, and a hand-sewn closure is performed in the direction providing the widest lumen (see Fig. 3). A bougie (usually 50Fr) should be placed in the esophagus during reconstruction to avoid narrowing the GEJ. Minimally invasive, an anterior gastrotomy is created to visualize the posterior tumor and excise the tumor with small negative margin under direct visualization. The posterior gastrotomy is closed in the direction providing the widest lumen. A bougie (usually 50Fr) is placed in the esophagus, and then the anterior gastrotomy is closed primarily. This minimally invasive approach to a GEJ GIST again requires surgeon experience and expertise to minimally invasive surgery. Tumor excisions from the lesser curvature of the stomach will require careful dissection to preserve vagal nerve integrity. When the vagal trunks cannot be preserved, pyloroplasty or pyloromyotomy should be performed.

Total gastrectomy or esophagogastrectomy is rarely necessary but may be required for sizable tumors involving a large area of the lesser gastric curvature or GEJ, respectively. Massive tumors may be adherent to the spleen, distal pancreas, or colon, necessitating en bloc resection. When recognized preoperatively, preference lies with neoadjuvant imatinib to accomplish tumor downsizing and devascularization before an attempt at organ-preserving resection.

The next most common site of GIST is the small bowel. Jejunal and ileal tumors can be removed easily with either open or minimally invasive techniques. If employing a minimally invasive technique, the small bowel anastomosis can be performed intracorporeally or extracorporeally using a wound protector. Management of duodenal GISTs is complicated because of the relationship with the pancreas and bile duct. Consideration for neoadjuvant imatinib should occur for any duodenal GIST when pancreatoduodenectomy is deemed necessary for complete resection. When the tumor is near the ampulla, a cholecystectomy can be performed to cannulate the cystic

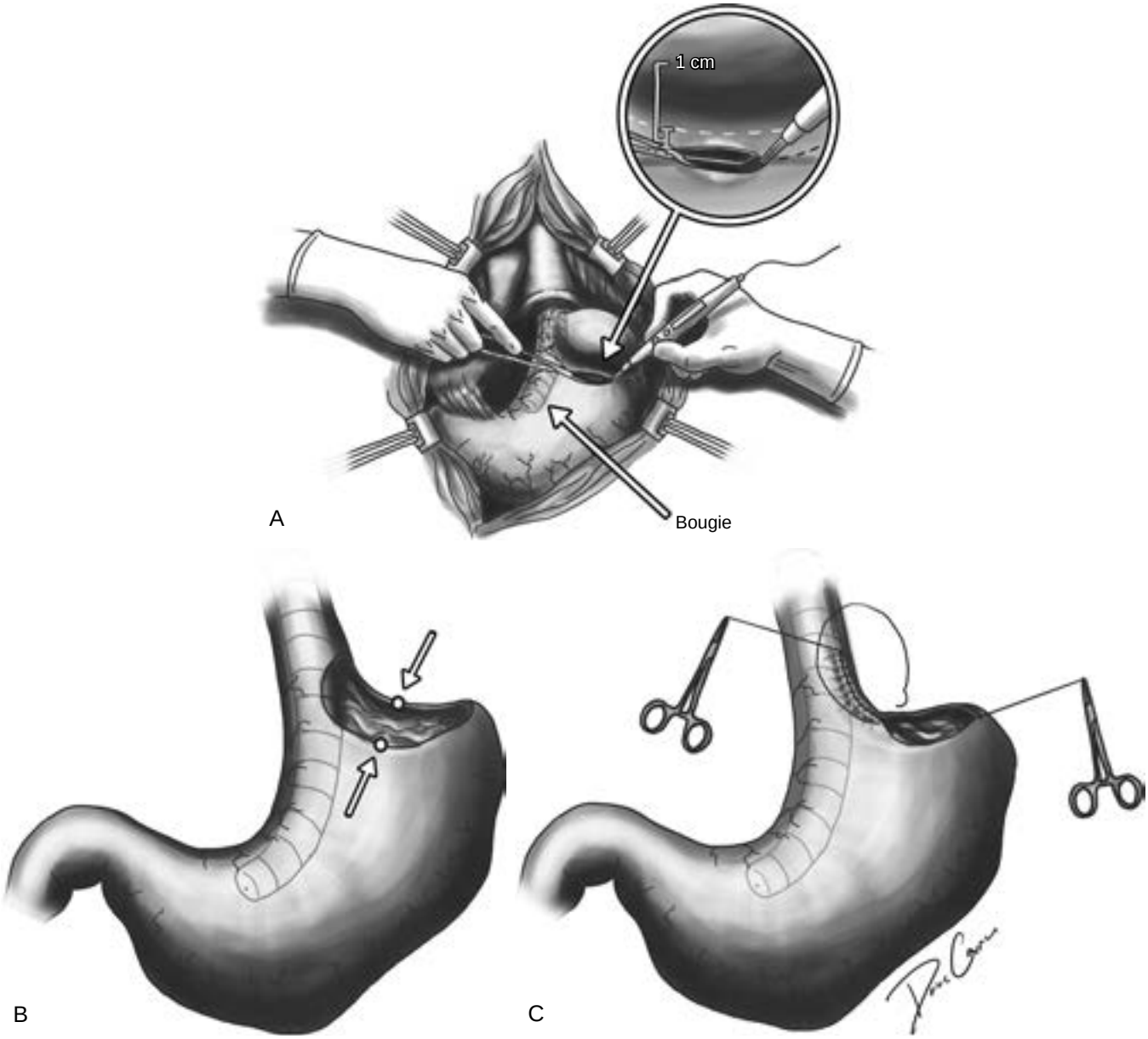


FIG. 3 Resection of a large gastrointestinal stromal tumor at the gastroesophageal junction. **(A)** After making a gastrostomy with cautery, the tumor is resected with a 1-cm margin. **(B)** The defect **(C)** is then sewn closed over a large bougie placed in the esophagus to prevent narrowing. *(Courtesy Dave Cavnar.)*



FIG. 4 Contrast-enhanced CT scan of a patient with a gastric gastrointestinal stromal tumor that is endophytic in nature and located along the posterior aspect of the gastric cardia just 2 cm beyond the gastroesophageal junction *(arrow)*.

duct with a 4Fr Fogarty catheter and enter the duodenum through the ampulla, facilitating localization of the ampulla. Small GISTs not involving the periampullary duodenum can be resected without pancreatectomy. Periampullary GISTs involving the medial duodenal wall generally require pancreatoduodenectomy even after neoadjuvant imatinib. Small GISTs arising from the lateral wall of the second portion of duodenum can usually be excised. The duodenal defect can be closed with suture duodenorrhaphy without compromising luminal caliber. Alternatively, the duodenal defect can be reconstructed with a Roux-en-Y duodenojejunostomy. Tumors in the third or fourth portion of the duodenum can be managed with segmental duodenectomy followed by primary duodenojejunostomy.

Rectal GISTs are rare but are much more common than colonic GISTs. Neoadjuvant imatinib treatment should be offered to patients with large rectal GISTs to accomplish tumor downsizing and sphincter preservation. Small GISTs involving the lower rectum can be excised transanally with possible need for transanal endoscopic mucosal surgery.

ENDOSCOPIC MANAGEMENT OF GIST

Although endoscopic management of GIST has not been incorporated as standard of care into the NCCN guidelines at this time, a body of literature focused on the endoscopic management of GISTs exists. Currently, guidelines advocate for gastric GISTs under 2 cm with no concerning risk factors undergo active surveillance. However, GIST can still have malignant potential, initially leading to the development of endoscopic treatment strategies for small GISTs <2 cm. At present day, endoscopic management of upper gastrointestinal tract GIST has been described as feasible and safe for lesions <5 cm in size after exclusion of high-risk features, such as high mitotic rate, enlarged lymph nodes, irregular margins, internal heterogeneity, and presence of cystic spaces within the mass on EUS. These procedures include endoscopic band ligation (EBL), endoscopic submucosal excavation (ESE), endoscopic submucosal dissection (ESD), endoscopic mucosal dissection (EMD), endoscopic submucosal tunnel dissection (ESTD), submucosal tunneling endoscopic resection (STER), endoscopic full thickness resection (EFTR), laparoscopic endoscopic cooperative surgery (LECS), nonexposed endoscopic wall-inversion surgery (NEWS), and a combination of laparoscopic and endoscopic approaches to neoplasia with a nonexposed technique (CLEAN-NET). When considering endoscopic enucleation, GISTs must be classified into four types based on their location in the gastric wall (Fig. 5). Endoscopic enucleation, including EBL, ESD, EMD, ESTD, and STER, is most suitable for types 1 and 2. Types 3 and 4 are not amenable to endoscopic enucleation, and EFTR, LECS, NEWS, and CLEAN-NET should be considered.

NEOADJUVANT THERAPY

For nonmetastatic GISTs, neoadjuvant imatinib treatment should be considered for tumors that are locally advanced, require multivisceral resections, and are in difficult anatomic locations where tumor downsizing may allow for a less morbid operation. For those with D842V mutation of exon 18 of the *PDGFRα* gene, avapritinib therapy should be used due to imatinib resistance in these patients. Although change in metabolic activity is evident on PET/CT within days of imatinib exposure, objective tumor downsizing may take many weeks or even several months on imatinib treatment. In addition, responding tumors may even swell temporarily. Treatment response is more reliably assessed by comparing tumor density and dimensions, particularly when evaluating early tumor response (Fig. 6). After initiation of neoadjuvant imatinib, a follow-up contrast-enhanced CT should be obtained within 6 to 8 weeks. Surveillance imaging is typically obtained at 3-month intervals thereafter. Beyond 6 months of neoadjuvant imatinib therapy, further tumor downsizing is unlikely to be observed. Unlike most cytotoxic chemotherapy regimens used in a neoadjuvant setting, neoadjuvant imatinib can be continued up until the time of surgery without compromising wound healing or causing immunosuppression. Likewise, it may be resumed when the patient is eating normally and has regained bowel function. Avapritinib or other TKI should be stopped at least 1 week before surgery and restarted based on clinical judgment or recovery from surgery.

ADJUVANT THERAPY

The initial large-scale studies of imatinib in metastatic unresectable GIST were highly successful, resulting in a dramatic improvement in survival from a historical median of 18 months to beyond 5 years. However, demonstrating similar improvement in survival from adjuvant imatinib after complete surgical resection has proven more difficult. Randomized adjuvant trials designed with cross-over treatment arms have demonstrated that placebo-treated patients who develop recurrence are usually salvaged with imatinib therapy followed by surgery and survive for extended periods of time. The benefits of adjuvant imatinib were first demonstrated in the American College of Surgeons Oncology Group Z9001 study, which was a phase III multicenter prospective randomized clinical trial of imatinib compared with placebo for 1 year after resection of primary GISTs of at least 3 cm size regardless of mitotic index. The study was stopped early at interim analysis when the imatinib group was noted to have significantly improved RFS over the placebo group (98% vs. 83% at a median follow-up of 19.7 months), resulting in approval by US and European regulatory agencies for imatinib treatment in GIST. Long-term follow-up of these patients revealed that relapse occurred within 5 years after completing 1 year of prescribed imatinib (Fig. 7). After 74 months of follow-up, the RFS curves of the placebo and imatinib treatment arms converged, demonstrating that imatinib controlled but did not eradicate residual disease. Most of the improvement in RFS from imatinib was primarily observed in the patients with exon 11 deletion but not other mutations.

The follow-up SSG XVIII phase III randomized study compared the benefits of 1 year versus 3 years of adjuvant imatinib. This study demonstrated improved 5-year RFS (66% vs. 48%) with a slight improvement in overall survival (92% vs. 82%) for 3 years of adjuvant imatinib over 1 year of adjuvant imatinib. The PERSIST-5 (Pacritinib versus Best Available Therapy for the Treatment of Myelofibrosis Irrespective of Baseline Cytopenias-5) trial was a phase II single-arm study of 5 years of adjuvant imatinib after resection of primary GISTs at high risk for recurrence (any site ≥ 2 cm with ≥ 5 mitoses/50 HPF or any nongastric GIST ≥ 5 cm). Five years of imatinib treatment for this group of GIST patients was effective in preventing recurrence in those with sensitive *KIT* gene mutations.

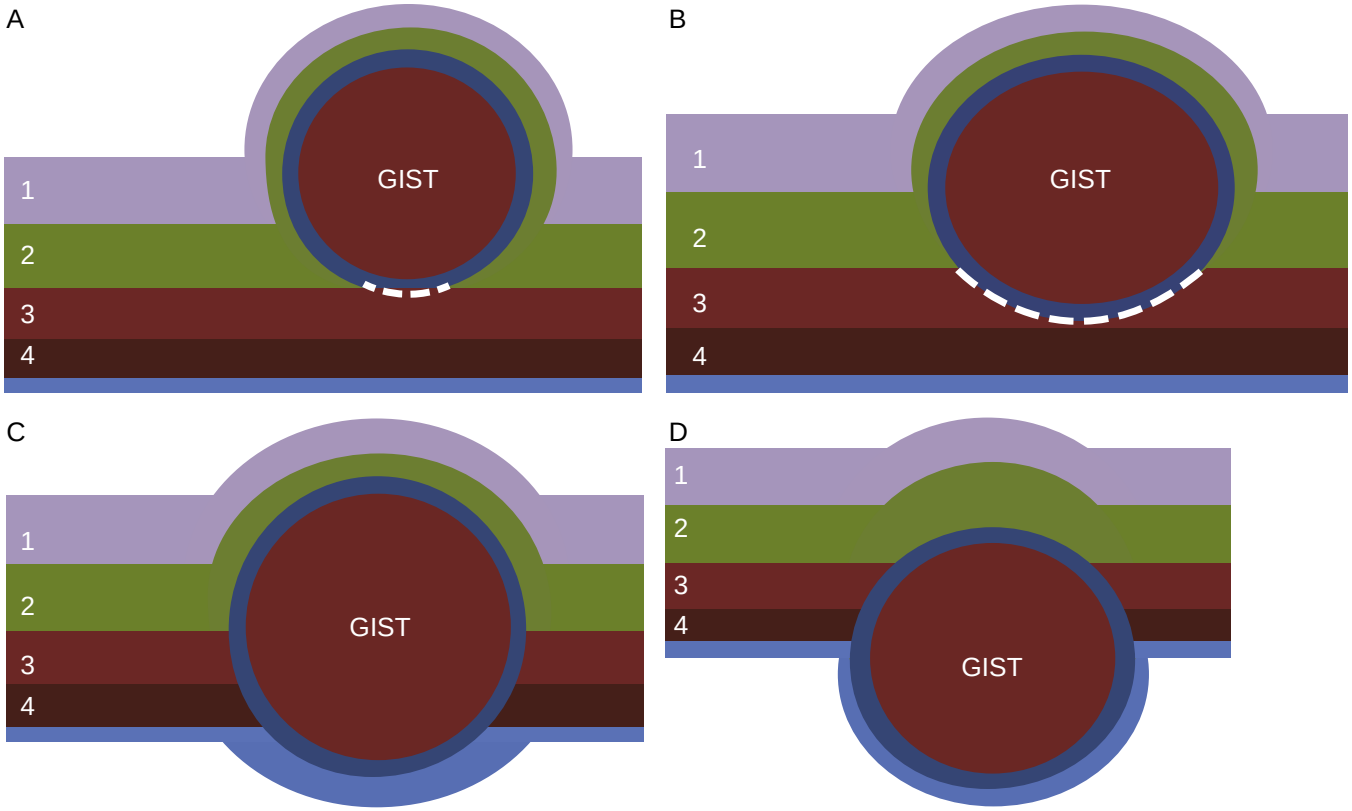


FIG. 5 Classification of gastrointestinal stromal tumor (GIST) according to the location in the gastric wall. **(A)** Type I is a GIST that has a very narrow connection with the proper muscle layer and protrudes into the luminal side like a polyp. **(B)** Type II has a wider connection with the proper muscle layer and protrudes into the luminal side at an obtuse angle. **(C)** Type III is located in the middle of the gastric wall. **(D)** Type IV protrudes mainly into the serosal side of the gastric wall. White dotted lines indicate the area dissected from the proper muscle layer. *1:* Mucosa; *2:* Submucosa; *3:* Circular layer of proper muscle; *4:* Longitudinal layer of proper muscle. *(From Kim HH. Endoscopic treatment for gastrointestinal stromal tumor: Advantages and hurdles. World J Gastrointest Endosc. 2015;7:192–205.)*

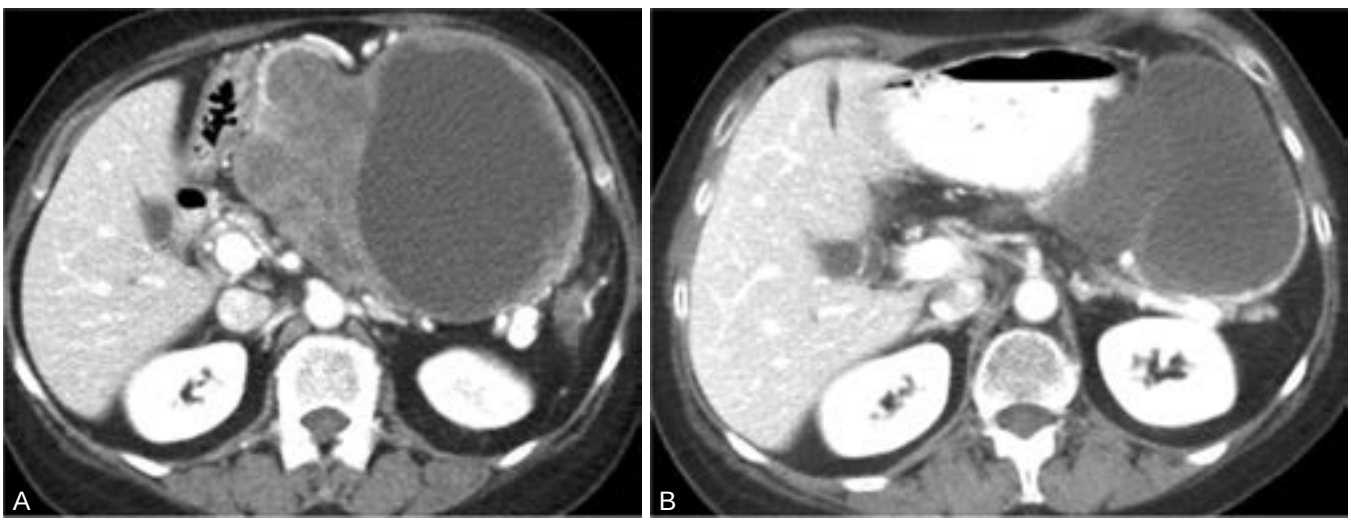
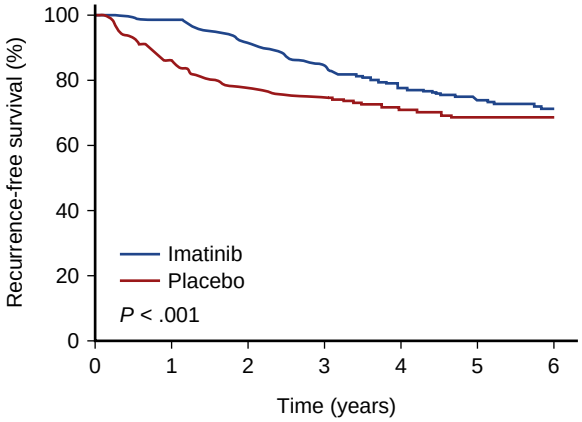


FIG. 6 Initial treatment response to neoadjuvant imatinib is best assessed by changes in tumor density. **(A)** A large gastric gastrointestinal stromal tumor at the time of diagnosis. **(B)** After treatment with 9 months of imatinib therapy, computed tomography scan demonstrated significantly decreased size with decreased density, demonstrating primarily cystic, necrotic tumor.



No. at risk							
Imatinib 400 mg	359	296	261	230	199	143	74
Placebo	354	278	243	218	186	132	64

FIG. 7 Recurrence-free survival in patients with primary gastrointestinal stromal tumor of 3 cm or greater after complete resection, randomized to 1 year of adjuvant imatinib versus placebo. *(Modified from Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial.* J Clin Oncol. *2014;32:1563–1570.)*

RECURRENT, METASTATIC, AND RESISTANT DISEASE

In patients with disease recurrence after primary resection without adjuvant therapy and those with metastatic disease, imatinib is highly effective with partial response or stable disease in the majority of patients. However, the median time to disease progression with imatinib therapy alone is on the order of 24 months, generally reflecting the development of secondary mutations in *KIT*, most commonly in exons 13, 14, or 17. Resistance to imatinib may be detected during radiographic surveillance with the appearance of enhancing nodules within a nonviable, necrotic, responding tumor (Fig. 8). These imatinib resistant tumors often demonstrate a partial response to second-line TKIs, with each further line of therapy providing sequentially diminishing returns. For example, second-line sunitinib improved PFS from 6 weeks to 27 weeks, whereas third-line regorafenib only improved PFS from 0.9 to 4.8 months. Of note, avapritinib should be used as first-line therapy for GISTs with the D842V mutation of exon 18 of the *PDGFRα* gene.

Patients with recurrent or metastatic GIST should be imaged on a 3-month basis. Operative resection can be considered when tumor resistance becomes apparent. Survival benefit from surgical therapy in these two situations is realized only in carefully selected patients with limited burdens of disease. Patients with partially responsive GISTs after TKI therapy will experience improved survival after surgery compared with patients who develop either rapid or multifocal tumor resistance patterns. Patients with multifocal sites of tumor resistance during TKI therapy should be referred for clinical trials.

Resection or ablation of hepatic GIST metastases should be planned to clear all detectable sites of tumor with attention to parenchymal preservation of the liver remnant. Resection of peritoneal GIST metastases may require removal of adjacent organs. After resection of hepatic or peritoneal metastases, adjuvant TKI therapy should be continued indefinitely or until tumor recurrence develops.



FIG. 8 Development of resistant tumor subclone growing on imatinib therapy within necrotic tumor in the setting of responding hepatic and peritoneal metastases.

CONCLUSION

GIST is a relatively rare sarcoma arising throughout the GI tract, most commonly in the stomach or small intestine, with activating mutations in the *KIT* or *PDGFRα* genes. GIST is a heterogeneous disease process that may present as a clinically irrelevant microtumor or a rapidly progressive malignancy with widespread metastatic disease. Surgery for GIST requires a no-touch technique to avoid tumor rupture and spillage. Tumor locations along the alimentary tract dictate the specific aspect of surgical therapy that will provide complete tumor clearance. Operative resection of larger tumors and tumors located at difficult anatomic locations, such as the GEJ, rectum, or duodenum, may be facilitated by neoadjuvant imatinib therapy. Risk for tumor recurrence is independently predicted by tumor size, mitotic rate, and site of disease. Specific mutations of KIT help to predict responsiveness to TKI therapy. Adjuvant imatinib should be used for at least 3 years in patients at high risk for disease recurrence predicted by individualized nomograms. Resection of recurrent or metastatic GIST should be considered for patients with limited burden of disease who are responding to TKI therapy or demonstrate only focal tumor resistance. An algorithm for multimodality therapy of GIST is shown in Figure 9.

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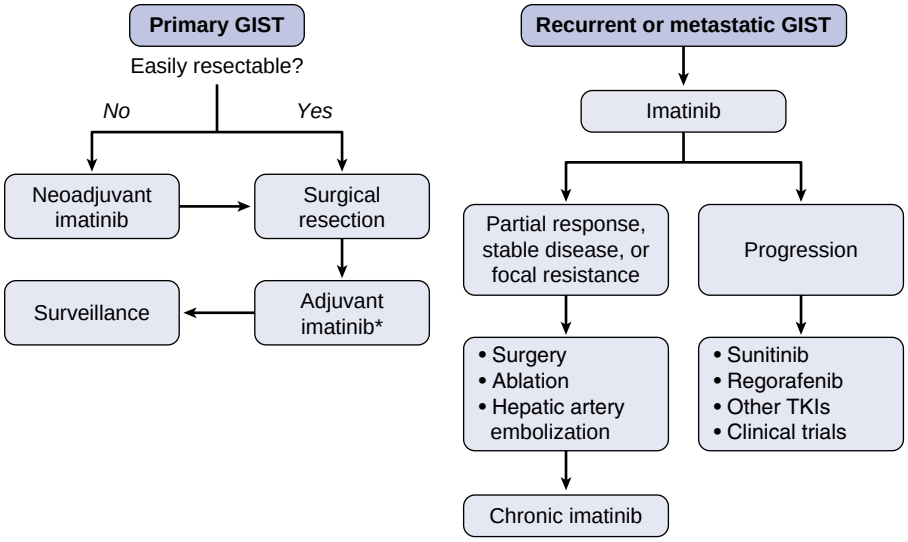


FIG. 9 Schematic approach to patients with gastrointestinal stromal tumor (GIST). For locally advanced primary tumors treated with adjuvant imatinib, tumor density should be assessed by CT at 4 weeks to document response to therapy. If GIST nomogram predicts a high or intermediate risk of recurrence, adjuvant imatinib *(*)* should be continued for at least 3 years, possibly chronically. Surveillance after resection of GIST should include a CT of abdomen and pelvis every 3 to 6 months for 3 to 5 years and then annually. *TKI*, Tyrosine kinase inhibitor. *(Modified from Gold JS, DeMatteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model.* Ann Surg. *2006;244:176.)*

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Gastrointestinal Tubes for Feeding and Decompression

Lawrence B. Brown, MD, MPH, MHS, and Susan L. Gearhart, MD

INTRODUCTION

The primary purposes for placement of upper gastrointestinal access tubes are gastric decompression, prevention of aspiration, and administration of medications or nutrition. Over the past decade, the importance of gastrointestinal access in the management of several conditions has been redefined. This chapter highlights the current indications and contraindications to the use of gastrointestinal access and outlines current knowledge regarding their safe placement and usage.

NASOGASTRIC TUBE

A nasogastric (NG) tube is a flexible tube with a single or double lumen that is passed through the nose, down the nasopharynx, and into the stomach. NG tubes are made of polyurethane, polyvinyl chloride (PVC), or silicone. They come in several sizes and vary based on patient size (pediatric or adult). The most common type of NG tube is the Salem-sump, and its primary function is gastrointestinal decompression (Fig. 1). This tube has two lumens; the larger lumen connects to wall suction to provide aspiration of gastric contents. When not connected to suction, this port can be used for medication delivery or enteral feeding. The smaller lumen is used to vent to the atmosphere to prevent the distal tip of the tube from adhering to the stomach wall. This equalization takes place in the stomach once the gastric contents have been emptied.

Unlike the Salem-sump tube, the Levin tube (Fig. 2) has a single lumen with multiple distal holes. Its advantage lies in its relatively large single internal diameter. However, because of its inability to vent, there is a high likelihood that without venting, the suction would cause the mucosa of the stomach to adhere to the tube, leading not only to poor decompression but also to potential mucosal ischemia. Because of this likelihood, the Levin tube is uncommonly used in practice. Finally, a tri-lumen long tube with the ability to intubate into the mid-jejunum has been described and found to have a reduced failure rate for conservative management of an acute small bowel obstruction (ASBO) in one study. However, the long tube can only be placed endoscopically and for this reason is rarely used.



FIG. 1 Salem-sump tube. In addition to a suction lumen for decompression, this tube has a second lumen that allows venting during continuous suction. Insertion depth markers are placed on the tube *(black dots)*.



FIG. 2 The Levin tube has a single lumen and multiple distal holes.

Indications for Nasogastric Tube Placement

Indications for NG tube decompression include management of acute gastrointestinal obstruction, management of prolonged ileus with vomiting, and prevention or treatment of intestinal perforation (Table 1). The successful removal of gastrointestinal contents decreases emesis and the chance of possible aspiration pneumonia. The NG tube is essential in the nonoperative management of an ASBO and is generally placed early in the treatment algorithm. In consensus statements regarding the management of ASBO, most societies agree that

TABLE 1 Indications and Types of Commonly Used Gastrointestinal Tubes

Indications	Type of Tube
Acute intestinal obstruction	NG tube, long enteric tube
Prolonged ileus with vomiting	NG tube
Decompression during minimally invasive surgery	NG tube, Levin tube
Long-term nutritional supplementation, medication delivery, decompression using gastric access	PEG
Long-term nutritional supplementation without gastric access	DPEJ

DPEJ, Direct percutaneous endoscopic jejunostomy; *NG,* nasogastric *PEG*, percutaneous endoscopic gastrostomy.

NG tube decompression is effective for up to 72 hours, after which the risks outweigh the benefits. Routine use of an NG tube for prevention of postoperative ileus in no longer recommended in adult or pediatric patients. In addition, a recent Cochrane review suggests that NG tube placement for postoperative ileus is associated with a slower return to bowel function and higher likelihood of pulmonary complications. The review found that use of an NG tube was only beneficial in patients who were experiencing vomiting.

During both minimally invasive and open abdominal surgery, an NG tube is often placed postintubation to decompress the stomach for safe port placement and to prevent emesis/aspiration caused by increased gastric distention following positive pressure/bag-mask-valve ventilation. The risk of gastric injury during port placement for minimally invasive surgery is reportedly 7%, although these data are from a study performed before the development of newer access ports with more safety features. Esophageal and gastric trauma is managed with NG tube decompression until healing of the injury is confirmed. For patients unable to swallow, an NG tube may be placed to administer medications or oral contrast for a computed tomography (CT) scan.

Contraindications

NG tube placement is contraindicated in patients with basilar skull fracture or facial fractures because of the risk of intracranial penetration and misplacement. Additionally, their blind placement should be avoided in patients with esophageal stricture or a history of alkali ingestion because of the risk of esophageal perforation. Because of the increased risk of bleeding, esophageal varices and coagulation abnormalities are relative contraindications to NG tube placement.

Placement of Nasogastric Tubes

NG tubes are often placed at the bedside in an awake patient, and the benefits and risks should be discussed. The head of the bed is raised so the patient is upright. An absorbent pad or emesis basin is placed on the patient's lap in case vomiting is induced by the procedure. The insertion distance should be estimated by measuring the distance between the tip of the nose to the earlobe and then to the xiphoid; 15 cm should be added to this number and noted on the tubing. One should visualize the nares for obstruction and ask the patient to sniff while occluding one nostril to determine the most patent nostril for placement. To reduce gagging and discomfort with insertion, the nares, nasopharynx, and oropharynx are anesthetized before NG tube placement. Typically, this is performed with lidocaine gels, Cetacaine (a combination of tetracaine, butyl aminobenzoate, and benzocaine), or nebulized or atomized lidocaine. Additionally, some

have administered antinausea medications before NG placement to reduce nausea and gagging. Gentle pressure should be applied if mild resistance is encountered in the posterior nasopharynx. Asking the patient to sip water through a straw will take advantage of the swallowing mechanism to facilitate the passage of the tube into the stomach. Additionally, flexing the patient's neck once the tube is in the nasopharynx aids in allowing it to traverse into the esophagus rather than the trachea. If too much resistance or bleeding is met upon initial passage into the nasopharynx, then one should attempt passage down the other naris. Gagging is a common occurrence during NG tube placement and should not be an indication to halt the procedure. However, excessive choking, coughing, voice changes, or condensation within the NG tube indicates tracheal placement, and the tube should be removed.

NG tube placement in patients who are incapacitated as a result of cognitive disorders or sedation and in patients on a ventilator can be challenging and is reportedly only successful 50% of the time. Airway protection is of primary importance, and securing the airway before NG tube placement may be required. Once secured, NG tube passage can be assisted with the use of a laryngoscope or a nasopharyngeal airway. One randomized study demonstrated that placement of a right nasopharyngeal airway in intubated patients increased first-time success rates to 80%. Furthermore, icing a PVC or silicone tube increases its stiffness, which may prevent coiling and assist in placement.

The NG tube should be secured with a commercial adhesive holder applied to the nose. Guidelines exist for proper securing and repeat assessment of the NG tube fixation method. For long-term insertion, bridling of the NG tube is a method that has been shown to significantly decrease inadvertent removal and pressure injury. NG tube bridle kits are available and assist in the safe passage of a bridle loop through the posterior nasopharynx from one nostril to the other.

Confirmation of Nasogastric Tube Placement

Before using an NG tube, one should confirm placement. Bedside confirmation can be accomplished by auscultation over the stomach for a rushing noise while one insufflates the stomach with air through the NG tube. Unfortunately, this method is unreliable. Literature also describes confirmation with ultrasound, litmus paper testing, pH paper testing, capnography/colorimetric capnometry, manometric techniques, and electromagnetic tracing; however, these tests are impractical. The goal standard method for confirming NG tube placement is performing a lower-chest/upper-abdominal x-ray. Based on imaging, the NG tube should be advanced or retracted so it is properly positioned in the middle of the stomach for best function. NG tube placement should be reassessed every 4 hours and before using for administration of medications or feeding.

Complications

The most common complication from NG tube placement is aspiration pneumonia. This may result from insertion of the NG tube directly into the airway during insertion or from occlusion of the tube during use, allowing for reflux and aspiration of gastric contents. Pressure injuries to the nares from prolonged NG tube insertion are most common among ICU patients, and the reported incidence is 0.13/1000 patient days. Gastric mucosa trauma has been shown to be reduced if continuous low-pressure wall suction is utilized compared with intermittent suction.

FEEDING TUBES

Current literature demonstrates that enteral nutrition is superior to parenteral nutrition. Indications for nutritional support are as follows: critical illness, poor caloric intake, oropharyngeal dysfunction, neurologic disorders, acute and chronic pancreatitis, short bowel syndrome, serious trauma and burns, and malnutrition before elective major surgery. Enteral feeding tubes are classified by the location of the tip of the tube, with termination in the stomach, proximal intestine, or both. Post-pyloric feeding has been shown to prevent aspiration of feeds and is largely recommended. Patients with diseases or who have had procedures associated with gastric atony (Box 1) may require enteral feeds that are beyond the ligament of Treitz. ICU patients have been found to have abnormal small bowel motility leading to retroperistalsis and increasing the risk of aspiration when fed directly into the stomach.

Nasoenteric Tubes

Nasoenteric tubes (NETs) are best suited for short-term (<6 weeks) use for nutritional assistance. NETs can be placed unassisted at the bedside or with endoscopic or fluoroscopic guidance. NETs are made of silicone or polyurethane and are commonly 12 or 14F in diameter (Fig. 3). If performed at the bedside, informed consent should be obtained before insertion. Like NG tube placement, the NET should be measured from the patient's nose to the xiphoid process. After lubrication, the NET should be inserted to the distance previously measured to the xiphoid process. Once secured, one should obtain a chest x-ray to confirm placement in the esophagus. If confirmed, the tube should be advanced slowly to 75 cm. Placing the patient and right lateral decubitus and insufflating the stomach can assist with tube advancement. If the stylet moves freely (slides back and forth by 5–10 cm), the tube is likely not coiled in the stomach, and the NET can be advanced to its furthest point (approximately 110 cm). NETs may also be placed via endoscopic means into the small intestine. Once an endoscope has traversed through the stomach into the small bowel, a guidewire is advanced through the accessory channel. The endoscope is then removed while the guidewire remains in place. The NET is placed over this guidewire. One should obtain an abdominal x-ray while the patient is lying in the supine position to confirm placement. Once post-pyloric placement is confirmed, the stylet or guidewire is removed, and the tube is used for enteral feeding.

Percutaneous Endoscopic Gastrostomy or Jejunostomy Tubes

Percutaneous endoscopic gastrostomy or jejunostomy (PEG or PEG/J) tubes are widely used for enteral nutrition. Common indications for PEG placement include disease processes that interfere with normal oral intake and swallowing, such as severe neurologic impairment, facial trauma, and oropharyngeal tumors. Jejunostomy tubes are required if the stomach is absent or nonfunctioning as a result of gastroparesis or tumor. Patients who are unable to maintain sufficient nutritional intake for more than 1 month, despite a functioning gastrointestinal tract, are candidates for a feeding tube placement.

Placement of PEG, PEG/J, or direct percutaneous endoscopic jejunostomy (DPEJ) tubes can be performed endoscopically (PEG, PEG/J, DPEJ), radiographically (PEG), and surgically (PEG, jejunostomy). For

BOX 1 Patient Groups, Diseases, and Procedures Associated with Gastric Atony

Diabetes with neuropathy
Gastrointestinal neuromuscular disorders
Abdominal surgery
Intraabdominal sepsis
Cerebrovascular accident
Hypothyroidism
Polytrauma, including head trauma
Acute pancreatitis
ICU patients on ventilators
Neuromotor deglutition disorders

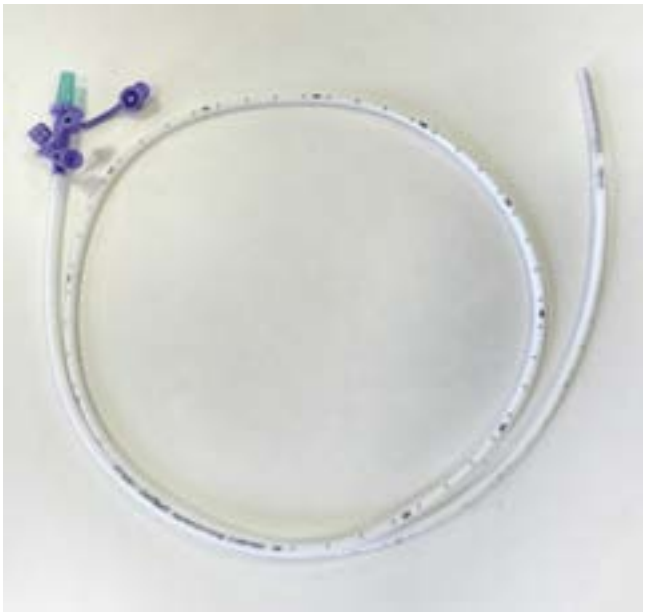


FIG. 3 Nasoenteric tube with stylet.

the purpose of this chapter, the endoscopic technique will be discussed as surgical placement usually occurs when the patient is going to the operating room for a separate procedure. On occasion, laparoscopy is used to guide placement when endoscopic placement alone is challenging; however, the technique does not differ greatly as endoscopic insertion techniques are used while laparoscopy is performed. Laparoscopic or endoscopic jejunostomy is rarely performed as there is a significant risk for tube leakage and failure. There are three main techniques: (1) Sachs-Vine push technique, (2) Ponsky pull technique, and (3) Russell external dilation. Antibiotics should be given before the procedure.

Contraindications to feeding tube placement are esophageal or oropharyngeal obstruction (i.e., unable to perform endoscopy), aspiration risk, gastric varices, severe coagulopathy, massive ascites, gastroparesis, gastric outlet obstruction, gastric resection, and hemodynamic instability.

Endoscopic Placement Technique

Once sedated, the left upper quadrant and mid-abdomen are prepped and draped in a sterile fashion. An endoscope is passed into the patient's mouth, down the esophagus, and into the stomach. For a jejunostomy, the endoscope must be passed to the jejunum. After inspection of the gastrointestinal tract, the antrum of the stomach or a dilated loop of proximal jejunum will be viewed through the endoscope. A double-balloon endoscopic technique may assist in performing DPEJ. An antiperistaltic medication can be given to reduce peristalsis of the small bowel. Transillumination must occur. The surgeon will use a finger to indent the external abdominal wall to determine the optimal puncture site where the abdominal wall and the stomach or jejunum are closest; this should be noted via the endoscope. If transillumination is possible, an introducer or seeker needle with a syringe attached is passed through the abdominal wall. This syringe is advanced until the needle tip is seen entering the gastric or jejunal lumen on endoscopic views. Upon aspiration, if air is seen and the needle tip is not visualized, then the needle is likely in another section of the gastrointestinal tract and not the stomach. Once correct intraluminal location has been confirmed, a guidewire is placed into the lumen and grasped by a snare via the endoscope. The needle is removed from the skin once the wire has been grasped. For PEG tube insertion using the pull technique, the endoscope is removed over the guidewire. The wire is then attached to the gastrostomy tube, and a small skin incision is made around the wire in the abdominal wall. The gastrostomy tube is then pulled through the mouth, into the stomach, and out of the incision created in the abdominal wall. The dilation technique and push technique are used for jejunostomy placement. A smaller jejunal tube can also be passed through one port of the PEG tube and endoscopically placed in the jejunum. However, one randomized trial suggested that the DPEJ tube as compared to the PEG/J clogged less due to the larger caliber.

It is important to note that the internal bolster of the feeding tube should contact the mucosa, and the external bolster (or crossbar) should be placed snugly against the abdominal wall. Endoscopic and radiologically placed tubes have a soft cupped bolster internally and a second bolster that is placed over the tube near the abdominal wall. This design allows for the internal bolster to deform and the tube to be removed by applying traction on the tube when necessary. It also avoids common issues such as inadvertent deflation of the balloon, which can happen with balloon-tipped gastrostomy tubes (Fig. 4). Immediately after placement, the tube can be placed to gravity drainage. After 4 to 6 hours, the tube can be used for medication delivery. Historically, enteral feeds start 12 to 24 hours following the procedure.

Routine Care

Routine care involves three considerations: positioning of the external bolster to avoid compression of the abdominal wall between the bolsters, flushing the tube to prevent clogging, and maintaining a clean feeding tube site. Compression of the tissues between the internal and external bolsters of a feeding tube can lead to pressure necrosis, breakdown of the gastrostomy tract, and buried bumper syndrome (where the internal bumper migrates alongside the tract of the stoma and lodges between the intestinal wall and the skin). The external bolster should be situated in such a manner as to allow 1 to 2 cm of in-and-out movement of the tube in the abdominal wall. Additionally, gauze pads



FIG. 4 Gastrostomy tube with balloon.

should not be placed underneath the feeding tube as this may allow for pressure on the tract. During daily care, the feeding tube should be pushed forward into the wound slightly and rotated to ensure that the internal bumper does not become buried in the mucosa.

Feeding tubes tend to clog as a result of the interaction of protein-based formulas with an acidic environment and medications. Tubes with a smaller diameter clog more frequently, and all feeding tubes should be flushed with 20 mL of water every 4 to 6 hours and after administration of medications or enteral feeds. If the tube becomes clogged, and water flushing does not open the tube, the installation of pancreatic enzymes is efficacious in relieving more than 50% of occluded tubes. Mechanical devices, such as a Fogarty balloon, biopsy brush, or commercially available tube decloggers, may be used if prior measures fail. Tube replacement is reserved as a last resort to tube clogging. Bulking agents (e.g., psyllium) and resins (e.g., cholestyramine) should not be placed through feeding tubes as they are prone to clogging.

Complications

Immediate complications of enteral access include aspiration, hemorrhage, perforation, and the risk of sedation/anesthesia. Aspiration risks can be minimized by avoiding excessive sedation, aspiration of gastric contents preprocedure, suctioning insufflated air from the stomach postprocedure, and reducing the procedure time. A particularly morbid complication is inadvertent perforation of the stomach, small bowel, or colon during percutaneous insertion leading to peritonitis. This harm may be reduced by maximizing endoscopic transillumination and using discrete finger palpation on the abdominal wall to identify a safe entry site. In addition, laparoscopic assistance can be used. Delayed complications of feeding tube insertion include peristomal leakage or irritation, site infection, intraabdominal leakage, herniation of omentum, jejunal volvulus, gastric ulceration or hemorrhage, fistulous tracts, inadvertent tube removal, fungal tube infection, "buried bumper syndrome," and tumor tract seeding.

Tube Deterioration and Replacement

Deterioration of the feeding tube is a common problem that is recognized by the presence of discoloration, irregular beading of the tube, and foul odor. Though deterioration presents no direct risk to the patient, a leak or break in the tube would disallow tube feeding. Replacement tubes have a balloon at the distal tip. These should only be placed in the tract once the site has matured (approximately 4 weeks). A Foley catheter may serve as a temporary replacement tube, particularly in situations in which a tube has been inadvertently removed and a replacement tube is unavailable.

Gastrostomy or Jejunostomy Tube Removal

Methods for removing a feeding tube vary by the type of tube (i.e., removal with traction on the tube, removal after deflating a balloon at the distal tip, and tubes that required endoscopic visualization before removal). One should know the type of tube and how it was placed before an attempt to remove a tube. Endoscopic and radiologically placed tubes have a soft cupped bolster within the lumen. This design allows for the tube's internal bolster to deform and the tube to be removed by applying traction on the tube when necessary. Endoscopic visualization should be performed if the type of tube cannot be confirmed with the patient's medical record. Once removed, the feeding tube site should be covered with a dressing until the tract closes. Generally, the tract closes within 24 to 72 hours following removal.

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Management of Morbid Obesity

Michael A. Schweitzer, MD, and Vivek Kumbhari, MD

The prevalence of morbid obesity has continued to increase in the United States and throughout the world. The Centers for Disease Control and Prevention (CDC) estimates that 42.4% of US adults are classified as obese with a body mass index (BMI) greater than 30 kg/m^2, with more than 9.2% being severely obese (BMI >40 kg/m^2). Bariatric surgery continues to be the only durable method to obtain sustained weight loss and improvement of obesity-related medical disease for most patients. New flexible endoscopic (intragastric balloon [IGB], endoscopic sleeve gastroplasty [ESG]) and pharmaceutical therapies (e.g., GLP-1 analogs) have recently shown better weight loss than any previous medical therapy; however, there is a lack of long-term follow-up studies.

Weight loss surgery first came into prominence in the 1970s, but early procedures were abandoned largely because of unacceptable complications and poor long-term results. In the late 1990s, weight loss surgery saw a resurgence, largely because of the development of improved bariatric procedures and application of minimally invasive surgical techniques. Currently, more than 250,000 bariatric procedures are performed in the United States annually. Over the last decade, numerous well-designed clinical trials have demonstrated the safety, efficacy, and durability of weight loss surgery. The most common bariatric operations performed in the United States include vertical sleeve gastrectomy, Roux-en-Y gastric bypass, and duodenal switch with biliopancreatic diversion. The American Society of Metabolic and Bariatric Surgery (ASMBS) estimates that laparoscopic adjustable gastric band represents less than 1% of bariatric surgeries in the United States in 2019. Weight loss surgery also has been demonstrated to have significant metabolic and neurohormonal effects (independent of restriction and malabsorption), which play an important role in the long-term success of these procedures.

PATIENT SELECTION

The National Institutes of Health issued a consensus statement in 1991 regarding the effectiveness of bariatric surgery and outlined patient selection criteria that are still being used today by most insurers. Patients are considered candidates for bariatric surgery if they have a BMI of 40 kg/m^2 or greater or a BMI between 35 and 40 kg/m^2 if an obesity-related comorbidity such as diabetes or hypertension is present. The ASMBS position statement on class one obesity (30–35 kg/m^2) patients with obesity-related comorbidities states, "bariatric surgery should be considered after a patient fails nonsurgical treatment methods and should be strongly considered for patients with type 2 diabetes." An alternative to bariatric surgery for patients with a BMI of 30 to 40 kg/m^2 could be IGB or ESG. These flexible endoscopic therapies are especially worthy of consideration in patients who have a contraindication to bariatric surgery (e.g., hostile abdomen, large incisional ventral hernia, etc.) or are simply unwilling to undergo bariatric surgery despite being aware of its effectiveness. In general, appropriate candidates for surgery should demonstrate prior attempts at nonsurgical weight loss options that may include dietary intervention, pharmacologic therapy, or behavioral modification. Patients should also have realistic expectations regarding the long-term outcomes achieved with surgery (Box 1). Relative contraindications include inability to comply with postoperative requirements, active alcohol or substance abuse, and uncontrolled psychiatric disease.

The evaluation of potential patients for bariatric surgery should involve a multidisciplinary team approach. This team should include a dietician and a mental health professional familiar with bariatric surgery. Their purpose is to obtain a complete past dietary and behavioral eating history, educate the patient on postoperative dietary expectations, examine social support structure, and ensure that any psychiatric or behavioral disorders are optimally controlled. At the Johns Hopkins Center for Bariatric Surgery, all patients are asked to attend an online preoperative education seminar. Participation in postoperative support group meetings also is encouraged.

The age limits for surgery have expanded considerably over the last two decades. Select centers now offer surgery to adolescent patients and to patients over the age of 70 years, with overall good results.

OPERATIVE PROCEDURES

Most bariatric surgical procedures are performed laparoscopically, or robot-assisted, with a hospital length of stay of 1 day or less. Staged operations may be used in select cases for high BMI patients where a laparoscopic sleeve gastrectomy is performed first followed by a Roux-en-Y gastric bypass or duodenal switch with biliopancreatic diversion at a later time, usually over a year out, if further weight loss is desired. An alternative approach for patients with a relatively lower BMI could be to commence with a flexible endoscopic approach and then proceed to bariatric surgery, though data on this are limited.

BOX 1 Indications for Bariatric Surgery for Morbid Obesity

1. BMI of 40 kg/m^2 or greater
2. BMI 35 to 39 kg/m^2 with significant obesity-related comorbidities (diabetes, hypertension)
3. BMI 30 to 35 kg/m^2 and obesity-related comorbidities who have failed nonsurgical treatments
4. Clearance by a dietitian and mental health professional
5. No medical contraindications to surgery

On the morning of surgery, all patients should receive appropriate antibiotics as well as subcutaneous unfractionated or low-molecular-weight heparin to help minimize venous thromboembolic complications. Laparoscopic surgery involves the use of reverse Trendelenburg position, and the patient must be placed appropriately on the operating room table with use of a footboard and arms and legs secured. Initial laparoscopic entry in a morbidly obese patient can be difficult. We have found that the safest way to enter the peritoneal cavity is in the left upper quadrant with direct vision, while using a device that allows visualization of the abdominal wall layers during entry with a zero-degree laparoscope. Alternatively, we may use a Veress needle, placed in the left upper quadrant, to insufflate the peritoneal cavity and then place our midline optical trocar first, followed by the remaining trocars under direct view with the laparoscope inside the peritoneal cavity.

Laparoscopic Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (Fig. 1) is the second most common bariatric procedure performed in the United States (~20% of all bariatric surgery cases). Numerous articles have shown that gastric bypass results in durable long-term weight loss and remission of metabolic disease with a reasonably low complication rate.

A 45-degree angled laparoscope is inserted into the peritoneal cavity through the midline trocar, and the operation is performed using a total of five laparoscopic trocars. The omentum and transverse colon are retracted cephalad until the ligament of Treitz is visualized. The jejunum is then transected approximately 40 to 75 cm distal to the ligament of Treitz with a 60-mm white stapler cartridge. The mesentery is then divided with a gray stapler cartridge or ultrasonic shears. The proximal biliopancreatic limb of jejunum is then anastomosed to the distal segment of jejunum 75 to 100 cm distal from the point of division. We perform this anastomosis in a side-to-side fashion using a white 60-mm-length laparoscopic stapler cartridge. The common enterotomy is then closed with a white 60-mm-length laparoscopic stapler cartridge. The resulting mesenteric defect is closed with a running suture to help minimize the risk of internal hernia.

Next the patient is placed in reverse Trendelenburg position, and the gastric pouch is created. The left lateral segment of the liver is retracted using a Nathanson retractor (Cook Medical, Bloomington, IN) through a subxiphoid 4-mm puncture and is held in position with a movable arm that attaches to the bed. We next dissect the peritoneal attachments at the angle of His to expose the left crus, which is then followed by opening the bare area of the gastrohepatic ligament with the ultrasonic shears to enter the lesser sac. Division of the neurovascular bundle on the lesser-curve side of the stomach just distal to the left gastric artery and vein is accomplished using a gray vascular cartridge or ultrasonic shears. Multiple 60-mm blue staple cartridges are then used to transect the stomach up to the angle of His, creating a vertically oriented, 20-mL proximal gastric pouch. A 40 French bougie can be placed down into the stomach along the

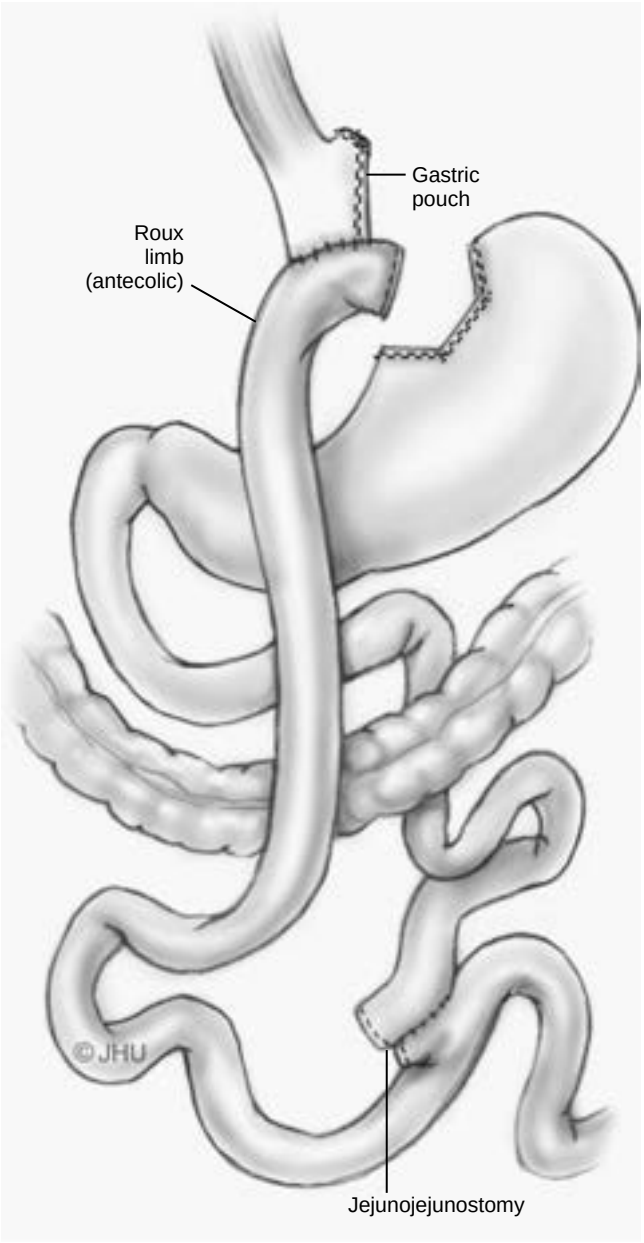


FIG. 1 Antecolic-antegastric Roux-en-Y gastric bypass. *(Courtesy Corinne Sandone, Johns Hopkins University.)*

lesser curve after the first firing of the stapler to assist in transecting the stomach where the bougie is used as a guide to the angle of His. The 40 French bougie is then removed. Any bleeding from the staple lines is controlled with clips or suture ligation.

We routinely bring the Roux limb up to the gastric pouch in an antecolic-antegastric orientation. This seems to reduce the incidence of internal hernias, gives excellent exposure, and is simpler to perform than a retrocolic retrogastric approach. The side of the Roux limb is sutured to the gastric pouch staple line. A small enterotomy is made just proximal to the end of the Roux limb, and a similarly sized gastrotomy is made in the gastric pouch for the placement of the stapler. The stapler is loaded with a 60-mm blue cartridge to create the gastrojejunostomy, using only the first 40 mm of the staple cartridge. After the stapler is fired, a stay suture is placed on the lesser curve (right) side of the opening. A 32F, blunt, round-end bougie then is passed from the mouth and through the gastrojejunal anastomosis and into the Roux limb. The bougie can then be seen through the opening that was formed after the stapler was removed. This stay suture and the stay suture on the left (angle of His side) are used to elevate the tissue so that the 60-mm length blue load cartridge can be used to close the opening. The stapler is brought down on top of the bougie while the tissue to be transected is retracted and then fired. The gastrojejunostomy is completed by running a 2-0 absorbable suture as a second layer. The resultant anastomosis is approximately 12 mm in diameter. A leak test may be performed if the surgeon desires by clamping the Roux limb just distal to the anastomosis and insufflating air (via endoscope or orogastric tube), whereas the gastric pouch and anastomosis are submerged in saline. The mesenteric defect then is closed between the Roux limb mesentery and the transverse mesocolon, up to the transverse colon.

Laparoscopic Vertical Sleeve Gastrectomy

Laparoscopic vertical sleeve gastrectomy (LVSG) (Fig. 2) is currently the most performed weight loss operation in the United States (~60% of all bariatric surgery cases).

The LVSG is primarily restrictive, as the lateral aspect of the stomach is removed to create a sleevelike tube or reservoir. The gastric resection also may assist with weight loss by causing hormonally assisted satiety. The fundus produces the proappetite hormone ghrelin, and because the fundus is removed, these hormone levels are reduced after LVSG. Although this bariatric procedure is not reversible, it can be converted into a Roux-en-Y gastric bypass or duodenal switch if greater weight loss is desired. It may also need to be revised to a Roux-en-Y gastric bypass if postop complications were to occur, for example, gastric stricture or severe gastroesophageal reflux disease.

The VSG typically is performed with one 5-mm, two 12-mm, and one 15-mm trocar. With the liver retracted with the Nathanson, the short gastric vessels are divided along the greater curve of the stomach. A LigaSure device (Covidien, Norwalk, CT) typically is used to accomplish this. A 40F blunt-tip bougie is placed in the

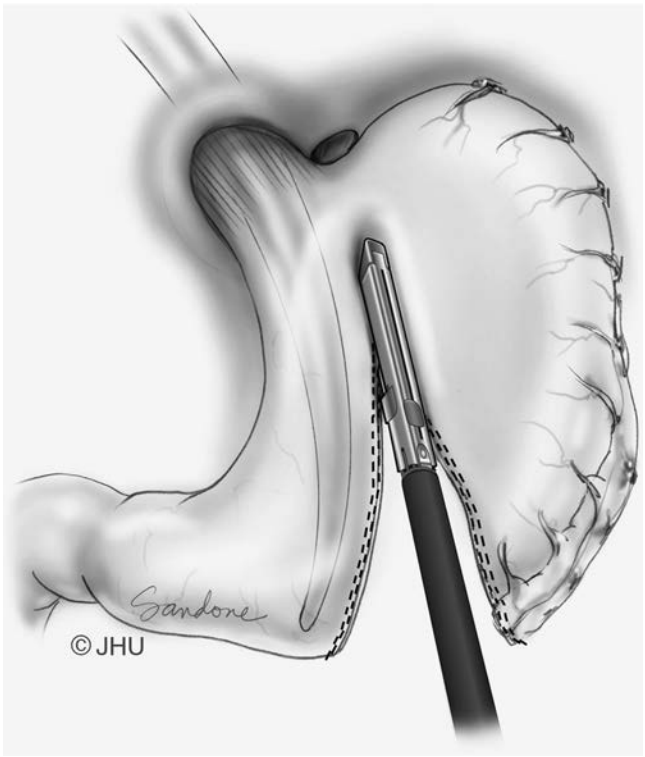


FIG. 2 Creation of the gastric sleeve. *(Courtesy Corinne Sandone, Johns Hopkins University.)*

stomach and directed along the lesser curve. The stomach is divided at the greater curvature, beginning 4 to 6 cm proximal to the pylorus. Green and blue staple loads are used adjacent to the 40Fr bougie and extending to the angle of His. When stapling, it is important to avoid stapling too close to the incisura angularis of the stomach since this may lead to a gastric stricture. The staple line can be oversewn or an absorbable buttress material can be used with the clips to assist with hemostasis of the gastric staple line.

The partial gastrectomy specimen is removed through the 15-mm trocar site. Care should be taken to suture close the fascial opening of this enlarged trocar site to prevent postoperative herniation. As with Roux-en-Y gastric bypass, a limited upper gastrointestinal study is performed only if clinically indicated.

Laparoscopic Duodenal Switch with Biliopancreatic Diversion

The laparoscopic duodenal switch with biliopancreatic diversion (DS-BPD) is primarily a malabsorptive operation that involves preservation of the pylorus and creation of a short, 100-cm ileal "common channel" (Fig. 3). The DS-BPD is the least common bariatric procedure performed because of its surgical complexity, potential for severe malabsorptive nutritional deficiencies, and possible diarrhea.

This procedure can be performed in a single operation or in two stages if the patient has a high BMI (>70). The first stage is similar to a VSG operation with the creation of a gastric sleeve. After approximately 1 to 2 years, patients can be revised to DS-BPD and the malabsorptive second stage performed. This is performed by dividing the small bowel 250 cm from the ileocecal valve. The proximal end of bowel then is anastomosed to the distal ileum 100 cm from the cecum.

The patient is placed in steep reverse Trendelenburg position, and the liver is retracted. If the sleeve gastrectomy portion has not been performed previously, then partial gastrectomy proceeds as previously described. The duodenum is then divided approximately 3 cm distal to the pylorus with a blue Endo GIA 60-mm stapler.

The Roux limb is directed in an antecolic fashion, and a side-to side anastomosis is performed with the first part of the duodenum. Finally, the mesenteric defect is then closed between the Roux limb mesentery and the transverse mesocolon.

Laparoscopic Single Anastomosis Duodenal Switch

The laparoscopic single anastomosis duodenal switch (Fig. 4), also referred to as loop duodenal switch or single-anastomosis duodenoileal bypass with sleeve gastrectomy (SADI-S), was recently approved by the American Society of Metabolic and Bariatric Surgeons (ASMBS). When compared with duodenal switch with biliopancreatic diversion, SADI-S is easier to perform with possibly a lower rate of internal herniation than DS-BPD. However, it does not divert the biliopancreatic fluid since there is no Roux limb but instead there is a loop anastomosis that, if there is a leak, may potentially be more difficult to treat since biliopancreatic fluid is flowing through where the small bowel is anastomosed with the duodenum. Controversy exists with the size of the bougie for creating the sleeve

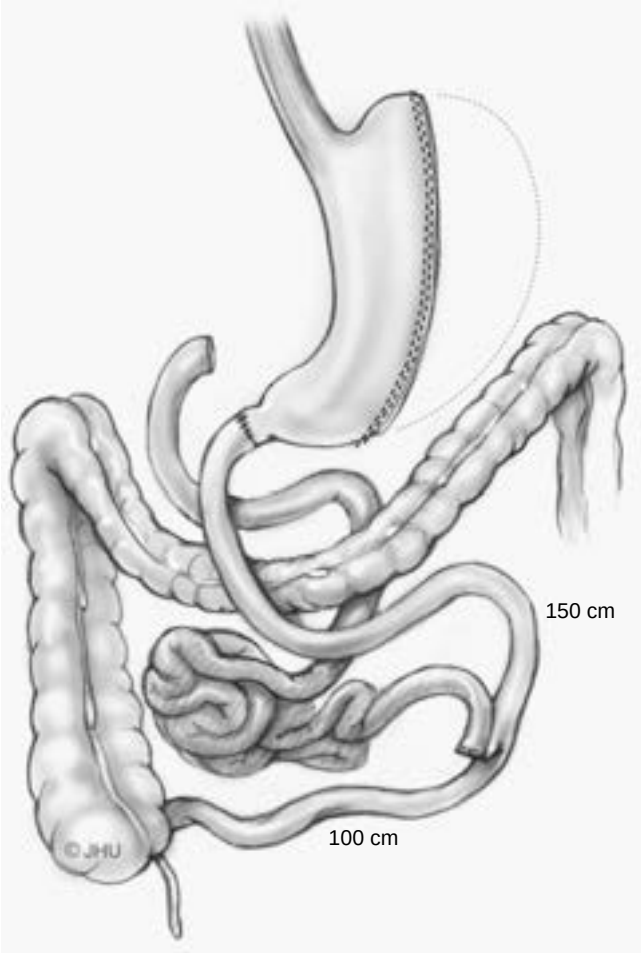


FIG. 3 Antecolic duodenal switch with biliopancreatic diversion. *(Courtesy Corinne Sandone, Johns Hopkins University.)*

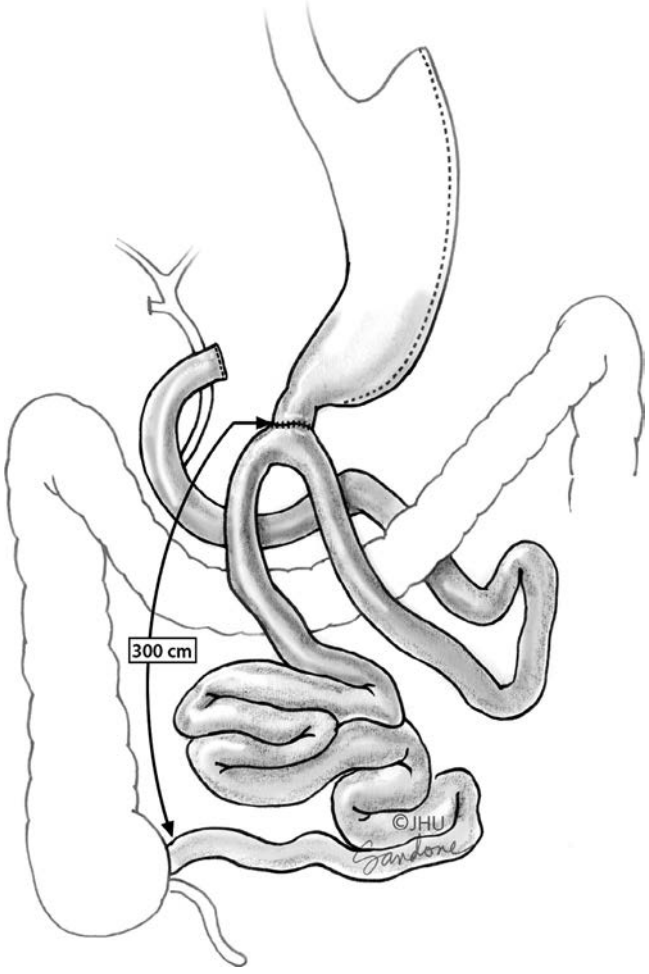


FIG. 4 Laparoscopic single anastomosis duodenoileal bypass with sleeve gastrectomy (SADI-S). *(Courtesy Corinne Sandone, Johns Hopkins University.)*

gastrectomy and length of the efferent or absorptive limb. Bougie size has decreased down to a size of 40 French by many surgeons, and the absorptive channel has increased from 200 to 300 cm to decrease protein and vitamin deficiencies while maintaining excellent weight loss. Diarrhea can be troublesome after DS-BPD and SADI-S, but by increasing the length of the absorptive channel, this may become less of a problem for most patients.

The sleeve gastrectomy is performed as previously described. The dissection is then continued a few centimeters past the pylorus where the duodenum is divided with the endoscopic linear stapler. The omentum is then divided with the energy device at a point where the path of the small bowel is unobstructed as it travels to be anastomosed to the first part of the duodenum.

The surgeon then measures the absorptive limb by starting at the ileocecal valve and walking back the bowel 300 cm. This point on the bowel is then carefully brought up to the duodenum and stay sutures are then placed while making sure there is no twisting nor tension present before creating the anastomosis.

The anastomosis may be formed using a stapler technique, in which an endoscopic stapler is used to join the small bowel to the duodenum and then the common enterotomy opening is closed with either a suture or another stapler firing, taking care not to make the open channel too tight. The anastomosis can also be formed by using handsewn two-layer suturing technique.

It is recommended to place a stitch from the afferent limb, just before the anastomosis, to the gastric antrum to prevent an obstruction from the limb rotating. The mesenteric defect between the small bowel mesentery and transverse colon mesentery can be sutured closed to prevent possible internal herniation, but in the SADI-S operation this is still controversial when it is discussed, with many surgeons finding that it is unnecessary. Hopefully, future analysis of long-term outcomes data will help resolve the need for this step.

Intragastric Balloon

IGBs are gas- or fluid-filled devices that are deployed in the stomach for a period of 6 to 12 months. As a result of being a temporary implant, they require two endoscopic procedures (one for insertion and another for removal of the IGB). Though initially appealing to patients, IGBs have been plagued by poor tolerability and concerns regarding safety. Furthermore, as a result of the device needing to be removed, weight regain is somewhat expected. The mechanism of action is unclear with theories ranging from that of effective volume reduction due to space occupation to alterations in gastric emptying; some believe there are even neurohormonal benefits. Notably, regardless of the IGB type, weight loss seems to taper at 3 months, and this appears to be the result of an accommodation phenomenon. Therefore, newer space-occupying devices attempt to circumnavigate this by being adjustable. There is even a capsule that is taken twice a day before meals that dissolves, releasing hundreds of hydrogel beads that result in temporary space occupation.

Endoscopic Sleeve Gastroplasty

ESG was first reported in 2013 and, since then, has disseminated globally, being performed by gastroenterologists and surgeons alike. It attempts to recapitulate laparoscopic greater curvature plication through an over-the-scope attachment of the OverStitch (Apollo Endosurgery, Austin, TX) and 2-0 nonabsorbable monofilament sutures. A running suture pattern is performed using a tissue helix such that plications are made to the distal gastric fundus (a small residual fundal pouch is inevitable). The procedure is performed on an outpatient basis with 5 to 9 running full-thickness sutures being placed with a total procedure duration of 1 hour. The current technique results in a stomach with decreased gastric volume and reduced compliance. Published data demonstrate outcomes that it is more effective than even high intensity diet and lifestyle program, but it is less effective than laparoscopic sleeve gastrectomy. ESG has been used not only as a primary weight loss therapy but in patients who have had weight regain and dilation of the stomach after surgical sleeve gastrectomy.

ENHANCED RECOVERY AFTER SURGERY

We implemented an Enhanced Recovery After Surgery (ERAS) program for bariatric surgery at our center in 2017 and published a decrease in length of stay from 2.77 days to 1.77 days (P <0.001) with a reduced 30-day readmission rate from 7.94% to 2.86% (P = 0.011). On the day of surgery, patients have a scopolamine patch placed if there is no contraindication. During the operation, opioids are minimized, acetaminophen 1000 mg IV is given, no Foley is placed, and no drains are used for routine bariatric surgery operations. Dexamethasone 4 to 8 mg IV is given after induction, and postoperatively, we give our sleeve gastrectomy patients a second dose of dexamethasone IV 8 hours after leaving the operating room. Ondansetron is used intraoperatively and postoperatively to prevent nausea as well as treat it. Metoclopramide is used if ondansetron is not enough to treat a patient's postoperative nausea complaints. Patients are instructed to walk soon after surgery. Clear liquids are started that evening and increased the following morning, with discharge on postoperative day number one. Oral acetaminophen is used for pain control as well as oral narcotics for breakthrough pain, but it is stressed to the patient to try and avoid narcotics if possible. IV narcotics are discouraged and avoided if possible. The patient is discharged once they are drinking enough to maintain hydration at home.

OUTCOMES AND COMPLICATIONS

After any of the bariatric procedures, patients are seen in follow-up at 2 weeks to ensure that they are well-hydrated, tolerating oral intake, and without wound complications. They are then seen at 3, 6, 12, 18, and 24 months and then annually thereafter to follow weight loss and nutritional issues. For patients who undergo flexible endoscopic techniques, more rigorous surveillance in the first 24 months is necessary as there is a greater propensity for weight regain. Regardless of the procedural technique, patients are encouraged to meet with dieticians and remain with their support groups indefinitely.

For 1 month after surgery, patients are all maintained on a high-protein puree consistency diet; after that they gradually are advanced to solid food. They also receive multivitamins, calcium, and vitamin B_{12} supplements. This is especially important for patients with gastric bypass and DS-BPD who are at higher risk for malabsorption and possible malnutrition. Supplemental iron should be considered for menstruating women.

Weight loss after gastric bypass and DS-BPD occurs primarily in the first 12 to 18 months after surgery and averages approximately 70% and 80% excess weight loss (EWL), respectively. Sleeve gastrectomy patients typically have less EWL, on average 50% to 60% over a 2-year period.

One of the most important outcome measures after bariatric surgery is remission of obesity-related metabolic diseases, such as type 2 diabetes. More than 70% to 80% of patients with diabetes experience complete remission after undergoing gastric bypass or DS-BPD. The restrictive operations have a 50% remission rate of diabetes. Hypertension, sleep apnea, hyperlipidemia, and fatty liver disease have similar remission rates after surgery. Flexible endoscopic approaches confer less weight loss than their surgical counterparts and do not appear to induce the weight-independent metabolic benefits seen with bariatric surgery.

Overall complication rates after bariatric surgery are less than 15% in most reports. Like most surgeries, there are early and late complications for bariatric surgery. Early or perioperative complications include bleeding, anastomotic leakage, and deep venous thrombosis. The mortality rate is less than 0.5% and is usually attributable to a pulmonary embolus or sepsis from anastomotic leak. Persistent

unexplained tachycardia higher than 120 beats/min may be an early sign of sepsis, and an appropriate workup should be considered.

Vitamin B_{12}, calcium, iron, vitamin D, and protein deficiencies are long-term complications that can occur within the first year after surgery. Rigorous monitoring of nutrition status is necessary. Vitamin B_1 deficiency also can occur in patients with protracted vomiting after surgery, and they may experience extremity paresthesias, confusion, and nystagmus. Lower extremity weakness and paresthesias also can be seen with vitamin B_{12} deficiency. Anastomotic stenosis and obstruction at the gastrojejunostomy in the first few months after surgery occur in less than 5% of patients after gastric bypass and usually can be managed with endoscopic dilation.

Internal hernias are also a possible complication and can occur at any time after surgery. The symptoms of internal hernia can be similar to an acute bowel obstruction or become chronic and described as postprandial periumbilical cramping pain. If internal hernia is suspected, operative intervention may be required to avoid possible bowel ischemia.

In general, the results of weight loss surgery are excellent, with most patients losing more than 50% of their excess weight with dramatic improvement or remission of metabolic disease. Approximately 10% to 15% of patients either do not achieve significant weight loss or partially regain their weight after 2 to 3 years. Ideally, these patients respond to dietary counseling, although some may need operative revision or conversion to a more malabsorptive procedure, such as the DS-BPD.

Unfortunately, no perfect method exists for choosing the best operation for each individual patient. Certainly, a multidisciplinary team approach is helpful in providing patient support throughout the preoperative and postoperative course. Reducing obesity-related diseases should be the major goal, not merely cosmetic improvement. Patients must understand that bariatric procedures are a tool to assist with weight loss, and it must be combined with lifelong changes in dietary, exercise, and lifestyle habits.

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Management of Small Bowel Obstruction

Charudutt Paranjape, MD, and George Velmahos, MD

INTRODUCTION

Small bowel obstruction (SBO) accounts for 2% to 4% of emergency department (ED) visits for abdominal pain and accounts for as many as 16% of surgical admissions and more than 300,000 operations annually in the United States. The associated cost is over $2 billion in inpatient costs annually. Although some obstructions occur in the large intestine, close to 80% of bowel obstructions occur in the small intestine. Unfortunately, patients may experience a high complication rate including strangulation. The overall mortality rate associated with SBO is less than 3%, but the rates escalate to 7% to 14% in the elderly.

CAUSES

Postoperative adhesions account for 75% to 80% of all cases of SBO. Adhesive small bowel obstruction (ASBO) represents a common entity among emergency surgical diseases, accounting for 4.6% for all types of operations. Among patients operated on for prior ASBO, the incidence of operative intervention increases to 15.6%. Other causes of SBO include congenital anatomic abnormalities (e.g., midgut volvulus, ileal atresia, de novo adhesions), disorders of the bowel wall (e.g., intussusception, stricture, tumor), extrinsic compression (e.g., compression from mass), intraluminal disorders (e.g., meconium ileus, gallstones, foreign body, bezoar), strangulated hernias (most common cause of SBO in undeveloped countries), foreign bodies (e.g., bezoars, swallowed objects, gallstones), radiation, endometriosis, and infection (a common cause in undeveloped countries, such as tuberculosis). In the absence of previous intraabdominal surgery, abdominal wall hernia with small bowel incarceration is the most common cause of bowel obstruction. Older patients with suspected SBO but no prior abdominal surgery and the absence of a hernia on examination should be evaluated for malignancy.

CLINICAL PRESENTATION

The diagnosis of SBO is not always straightforward, as many patients have variable symptoms at onset, and some cases may initially be misdiagnosed. Patients may describe nausea and vomiting, intermittent abdominal pain, abdominal distension, hyperactive bowel sounds, and inability to keep food and fluids down. Symptoms may then progress to continuous pain, hypoactive bowel sounds, and worsening vomiting. However, these signs and symptoms are not specific for diagnosis, and patients with SBO may continue to pass stool and flatus. Specific historical elements that should be discerned include previous bowel obstructions and their management, abdominal operations, radiation, and other abdominal disorders (e.g., inflammatory bowel disease [IBD], neoplasm).

The physical examination should begin with evaluating for systemic toxicity necessitating resuscitation, followed by abdominal examination and evaluation for the presence of any hernia causing the obstruction. Peritonitis, localized tenderness, hypotension, or tachycardia suggest strangulation and bowel ischemia. Fever, leukocytosis, decreased urine output, altered mental status, and metabolic acidosis are also concerning for systemic toxicity and bowel ischemia. Persistent pain that continues to worsen or pain out of proportion to examination is suggestive of ischemia or closed-loop obstruction and should be evaluated without delay. Palpation of the abdomen of patients with SBO is critical and a learned art. Significant pain to light percussion, focal tap tenderness, and guarding are potential signs of peritonitis and merit close attention and possible surgical exploration. Rectal examination is mandatory because it can identify fecal impaction, rectal masses, blood, or the rare obturator hernia, all of which would critically alter management.

DIAGNOSIS

Although the history and physical examination can guide the clinician toward a diagnosis of SBO, they are not sufficiently sensitive or specific for the diagnosis of SBO and its potential complications; thus, imaging has become essential for a diagnosis.

Laboratory Testing

There are no laboratory tests that are sensitive or specific for the diagnosis of SBO or that can reliably predict ischemic bowel. Recommended tests in patients with abdominal pain, nausea, and vomiting include a basic metabolic panel with magnesium and phosphate, a complete blood count with differential, and if bowel ischemia is suspected, a lactic acid level. A basic metabolic panel can identify electrolyte imbalances and renal dysfunction caused by hypovolemia. Patients with SBO may have hypokalemia, contraction alkalosis, or metabolic acidosis. A CBC (with differential) can assess leukocytosis. Leukocytosis with a left shift is a nonspecific indicator of inflammation and/or infection; it does not correlate with disease severity. An elevated lactic acid level can be seen with bowel ischemia, but notably, a normal lactate level does not rule it out. An elevated lactic acid level can also be a nonspecific indicator of inadequate perfusion of any number of organs.

Imaging

Plain Radiography

Plain radiographs may have a role in the initial diagnostic evaluation because of their widespread availability, low cost, and ability to follow

disease progression serially; however, the sensitivity of plain films is 66% to 85%. In addition, over 20% of abdominal radiographs in patients with SBO are nonspecific or normal. The typical gas pattern for SBO on plain film demonstrates dilated gas- or fluid-filled loops of small bowel in the setting of a gasless or nondistended colon (Fig. 1). However, a patient with SBO may demonstrate more subtle findings on x-ray study, and a plain film can simply show air-fluid levels with a normal or slightly distended colon. Small bowel perforation may be diagnosed with upright radiography, although not with an optimal level of accuracy. The severity of SBO can be underestimated on abdominal radiography if the dilated bowel loops are predominantly fluid-filled. If a strong suspicion for SBO is present, other testing is recommended as a negative radiograph cannot exclude the diagnosis.

Computed Tomography

CT is the imaging modality of choice and currently considered the standard of care for imaging SBO in most cases. Per the Eastern Association for the Surgery of Trauma (EAST) guidelines, level 1 evidence recommends the use of CT for diagnosing SBO. Intravenous contrast is desirable in the absence of contraindications. Although oral contrast may not be used in the initial CT scan as it causes delays and possible aspiration, Gastrografin may be given in partial adhesive SBO at a later point to expedite resolution of the obstruction. CT identifies the site of obstruction (transition point between distended and collapsed bowel) with a 93% sensitivity and 67% specificity and can detect bowel ischemia or closed-loop obstruction. Findings concerning for bowel wall compromise include bowel wall edema or hemorrhage, altered bowel wall enhancement, interloop ascites, mesenteric edema/fat stranding, vascular engorgement, and/or vessel occlusion. As in abdominal radiographs, pneumatosis of the bowel wall, mesenteric and/or portal venous gas, and extraluminal free air are late signs of bowel wall compromise and indicate bowel wall necrosis in the setting of SBO. Despite the sensitivity of CT in detecting direct and indirect signs of bowel compromise, it cannot be used alone for the decision to operate. Such a decision is always based on a combination of clinical, laboratory, and imaging findings.

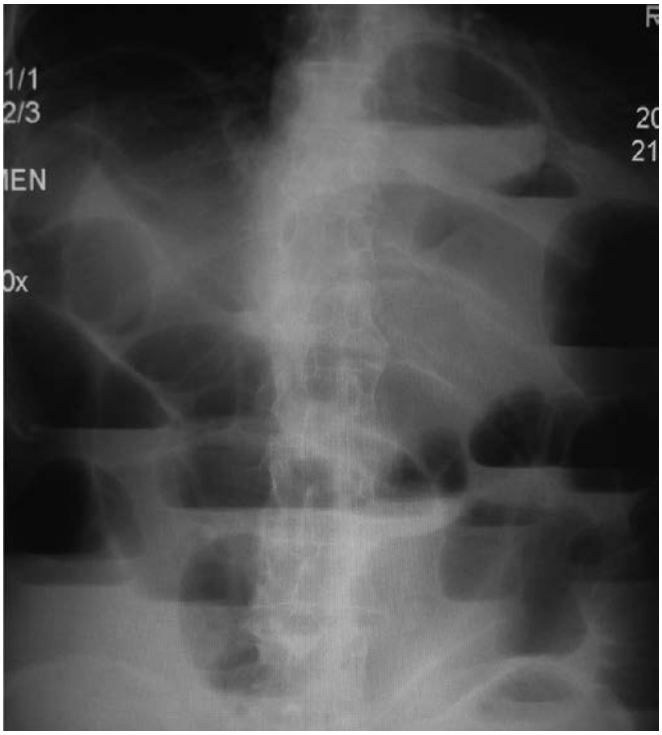


FIG. 1 Plain x-ray of the abdomen showing many distended small bowel loops caused by a distal obstruction.

Magnetic Resonance Imaging

Advantages of MRI over CT include lack of ionizing radiation, improved soft tissue contrast, the ability to provide dynamic information regarding bowel distention and motility, and relatively safe intravenous contrast agents. MRI possesses high sensitivity and specificity for diagnosis. MRI possesses limitations, including limited availability, long scan times, high cost, variability in examination quality, and lower spatial and temporal resolution compared with CT. At this time, except for pregnant women and children, CT is preferred over MRI.

CLASSIFICATION

The aforementioned diagnostic process will allow the patient to be categorized into one of three groups (Fig. 2).

Partial Small Bowel Obstruction

Patients with partial small bowel obstruction (pSBO) have incomplete obstruction with luminal narrowing, but some contents continue to pass through the intestine. Clinically, this is recognized when patients exhibit the signs, symptoms, and radiographic findings consistent with SBO, but exhibit a benign abdominal examination and continue to pass bowel movements and flatus.

Complete Small Bowel Obstruction

These patients have obstruction with no passage of luminal contents beyond the point of obstruction. Clinically, this is recognized when patients exhibit the signs, symptoms, and radiographic findings consistent with SBO and are not passing bowel movements or flatus.

Complete Small Bowel Obstruction with Bowel Compromise

The bowel is considered compromised when there is ischemia or injury that has led or may lead to necrosis and/or perforation of the bowel wall. There is a high risk of morbidity and mortality if compromised bowel is not treated in an expedient manner. Signs, symptoms, and imaging findings of bowel compromise are shown in Table 1.

MANAGEMENT

The initial goal of evaluating a patient with SBO is to immediately identify hemodynamic instability, the presence of strangulation or bowel ischemia, and the need for urgent operative intervention. These decisions should be made concurrently with resuscitation. Patients with SBO should be provided intravenous fluid resuscitation and electrolyte replacement, symptomatic control with antiemetics and analgesics, and bowel rest by nil per os. Decompression via nasogastric tube (NGT) is necessary in most but not all cases. Early evaluation by a surgical service is desirable.

Nonoperative Management

Expectant therapy and symptomatic management are typically recommended for patients without peritonitis or hemodynamic instability, with high success rates.

The use of NGT decompression is based on old and often debated evidence. Supposedly, proximal decompression facilitates relief of the obstruction, but the pain and discomfort to the patient is not negligible. The exact population that can be managed safely without it has not been accurately determined, although it exists.

Patients with partial adhesive SBO without strangulation are good candidates for water-soluble contrast medium such as Gastrografin

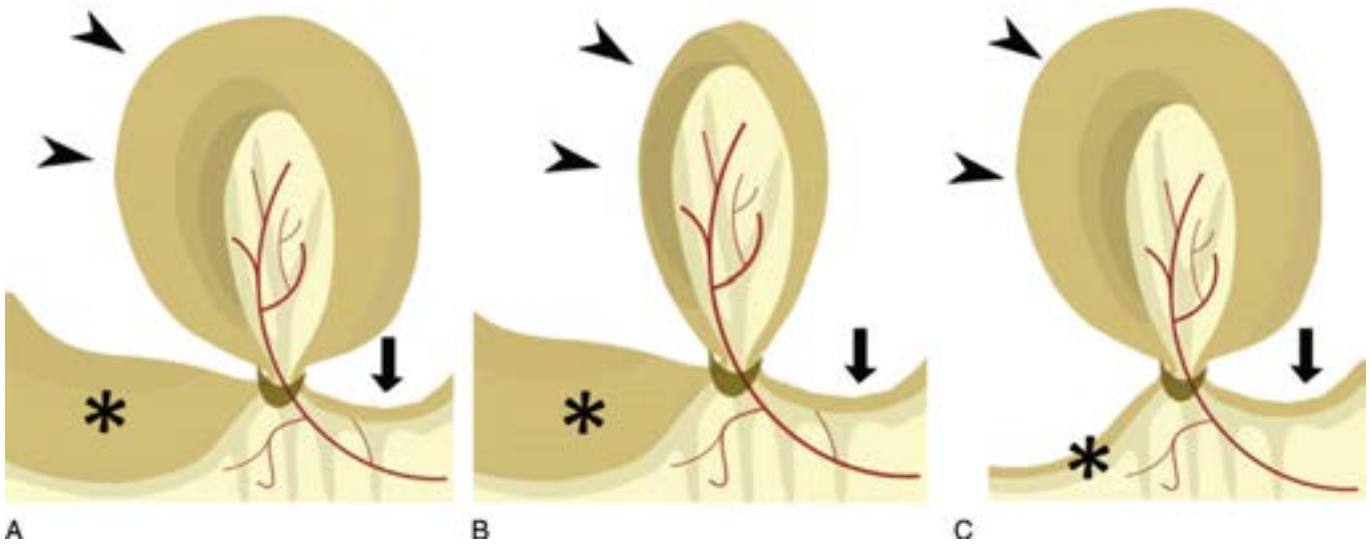


FIG. 2 Diagram of the three CT patterns of closed-loop small bowel obstruction, which is defined as obstruction of the bowel lumen at two sites located next to each other, creating a closed loop. **(A)** In typical closed-loop obstruction, the afferent loop *(asterisk)* and closed loop *(arrowheads)* are dilated and the efferent loop *(arrow)* is collapsed. **(B)** In collapsed closed-loop obstruction, the closed loop *(arrowheads)* is collapsed, the afferent loop *(asterisk)* is dilated, and the efferent loop *(arrow)* is collapsed. **(C)** In flat-belly closed-loop obstruction, the closed loop is dilated *(arrowheads)* and the afferent *(asterisk)* and efferent *(arrow)* loops are collapsed. *(From Rondenet C, Millet I, Corno, L., et al. CT diagnosis of closed loop bowel obstruction mechanism is not sufficient to indicate emergent surgery. Eur Radiol. 2020;30:1105–1112.)*

TABLE 1 Findings Consistent with Small Bowel Compromise

Clinical Presentation of SBO	Concerning Radiographic Signs
• Severe abdominal pain • Fever • Hypotension • Tachypnea • Tachycardia • Mental status changes • Peritoneal signs (guarding on examination, rebound tenderness) • Nonreducible hernia with severe pain and overlying skin changes (erythema and/or dark discoloration) • Decreased urine output • Leukocytosis • Elevated lactate	**Abdominal x-ray or CT abdomen/pelvis:** • Pneumatosis, mesenteric and/or portal venous gas, and extraluminal free intraperitoneal air are late signs and indicate bowel necrosis in the setting of SBO. **Other signs:** • Bowel wall edema or hemorrhage • Altered bowel wall enhancement (decreased, absent, or delayed hyperenhancement) • Interloop ascites • Mesenteric edema/fat stranding, ascites, vascular engorgement or occlusion • Multiple transition zones: Closed-loop obstruction demonstrates radial small bowel arrangement with a U- or C-shaped configuration, converging at the site of obstruction. • Swirling of mesenteric vessels (also known as the *swirl sign* or *whirl sign*) may indicate volvulus and/or closed-loop obstruction.

SBO, Small bowel obstruction.

for both diagnostic and therapeutic purposes. Gastrografin is administered orally or most commonly by NG tube in doses of 100 mL in 50 mL of water, either immediately at admission, or if conservative therapy with decompression fails, after 48 hours. After administration, Gastrografin appearing in the colon within 24 hours on x-ray study predicts resolution without surgical intervention. The radiograph can be repeated every 8 to 12 hours as long as the patient's examination, symptoms, laboratory tests, and vital signs improve or remain stable. Literature suggests that this intervention is safe and can reduce the need for surgery, SBO time to resolution, and hospital stay. Nonoperative techniques can be utilized for 2 to 3 days, but if the patient demonstrates no improvement or no passage of Gastrografin into the colon, operative therapy should be strongly considered.

Operative Management

Patients with signs of strangulation or generalized peritonitis, evidence of clinical deterioration (continuous or worsening pain, fever, hypotension, tachycardia, metabolic acidosis), or concern for bowel compromise based on imaging should undergo surgical exploration (level 1 recommendation per EAST guidelines). Nearly all other patients can be offered a trial of nonoperative management. Close monitoring during nonoperative management allows identification of patients with worsening symptoms who should be explored. A greater point of debate presents the time of surgery for those who have a benign abdominal examination but remain with a persistent obstruction. From the old dictum of "never let the sun rise or set on a small bowel obstruction," we now accept that nonoperative treatment can continue for days. The likelihood for spontaneous resolution

TABLE 2 Eastern Association for the Surgery of Trauma Practice Management Guideline for Managing SBO

Management	Recommendation Level
Patients with generalized peritonitis or other evidence of clinical deterioration (fever, leukocytosis, tachycardia, acidosis, continuous pain) should undergo timely surgical exploration.	1
Patients with no evidence of clinical deterioration can safely undergo nonoperative management initially.	1
CT findings consistent with bowel ischemia require a low threshold for operative intervention.	2
Laparoscopic treatment of SBO is a viable option compared with laparotomy in selected cases.	2
Water-soluble contrast should be considered for patients with partial SBO that has not resolved in 48 hours.	2

SBO, Small bowel obstruction.

decreases after the third day, and a number of studies suggest that the likelihood of complications increases. However, the evidence is poor and controversial. The EAST guidelines for general operative management are shown in Table 2.

Laparoscopic Management

Historically, abdominal exploration through laparotomy was the standard treatment for SBO, but laparoscopy has been used with a higher frequency over recent years. In a systematic review and meta-analysis of 14 nonrandomized studies, laparoscopic adhesiolysis reduced the risk of morbidity, in-hospital mortality, and surgical infections. Predictors for successful laparoscopic treatment of SBO are the following: a history of ≤2 laparotomies, appendectomy as the sole previous operation and cause of the obstruction, no previous median laparotomy incision, and a single adhesive band.

SBO WITH CONFOUNDING CONDITIONS

Closed-Loop SBO

Patients with closed-loop SBO are at increased risk for both strangulation and failure of nonoperative treatment (Fig. 3). The threshold for surgical exploration lowers significantly, and vigilance increases. However, it must be emphasized that not all closed-loop obstructions automatically need an operation. As stated earlier, the decision to operate is a combination of various factors, including clinical presentation and imaging findings, and not just a picture on CT.

SBO with a Transition Point at the Site of a Hernia

Patients presenting with a transition zone at the site of an abdominal wall hernia require special attention. These obstructions should only be reduced by the surgical team. Assessment for ischemic bowel is required to be performed by a member of a surgical team. If ischemic bowel is suspected (severe pain, tense hernia, overlying skin changes), urgent surgical exploration should be performed. The surgical team admitting the patient may decide to reduce the bowel and monitor post–hernia reduction (typically at least 24 hours) if there are no concerns for bowel compromise.



FIG. 3 Closed loop small bowel obstruction.

Geriatric Patients

Because of medical comorbidities, especially in the emergency setting, patients older than 60 years and 80 years have twice and thrice the risk of adverse outcomes after surgery, respectively, relative to younger adults. Preoperative cardiac risk stratification and physiologic optimization is desirable when not leading to undue delays. Overall, the decision to operate in geriatric patients should balance the desire to intervene early and before fragile physiologic reserves are exhausted, while not liberalizing major abdominal surgery on frail individuals. Goals of care, code status, and discharge disposition should ideally be discussed at the time of admission.

Pregnancy

SBO in pregnancy is rare; it is estimated that a practicing surgeon may manage 1 to 2 cases in a career. One-half of reported SBO cases during pregnancy are caused by adhesions. Fetal mortality averages 21% and is more likely with surgery in the first trimester. An urgent MRI is advised absent immediate indications for surgery. Pregnancy is not an absolute contraindication to ionizing radiation from radiographs or CT scans; however, the risks and benefits of fetal exposure to radiation must be carefully weighed. Overall, the same rules of operative versus nonoperative management that are used in the general population apply also to pregnancy.

Obstruction Due to Inflammatory Bowel Disease

Although most IBD patients are admitted to a medical service, early surgical consultation is recommended in the presence of an acute SBO. Evidence of intestinal obstruction represents one of the defining characteristics for severe/fulminant IBD. Although there is no strong evidence in support of specific treatment algorithms on the acute management of intestinal obstruction associated with IBD, a number of evidence-based recommendations have been made. It has

been recommended that the treatment plan be based on factors such as the location and length of the stricture, degree of concomitant inflammation, degree of upstream bowel dilation, and other accompanying features, such as abscess or phlegmon. Early cross-sectional imaging with a CT enterography (CTE) protocol is essential as is the early involvement of both gastroenterology and colorectal surgery in the treatment team. The team should determine early surgery versus neoadjuvant antiinflammatory therapy and the need for antibiotics and/or abscess drainage.

Malignancy

Unlike nonmalignant etiologies, these patients tend to have a subacute clinical picture with a slow insidious onset that is typical of partial SBO. For patients who present with SBO caused by a nonmetastatic or locally advanced primary small bowel tumor, an operative intervention with curative intent remains the principal tenet of management. The differential for these tumors typically includes small bowel neuroendocrine tumors, adenocarcinomas, lymphomas, and gastrointestinal stromal tumors. For such patients, oncologic principles should include a resection of the involved segment of bowel along with a 5- to 10-cm margin proximally and distally as well as removal of all associated mesentery. Small bowel resection is a preferable approach when the site of obstruction is isolated, the tumor causing the obstruction is intrinsic to bowel, negative margins are a possibility, and the postoperative outcome is potentially curative. A small bowel bypass is preferable if the tumor causing the obstruction cannot be completely resected and multiple sites of bowel obstruction exist. The goal with bypass is palliation. For patients who present with obstruction from incurable advanced disease, the factors affecting the final treatment plan include established goals of care set forth by the patient with the guidance of the surgeon and the medical oncologist. It is beneficial to involve a palliative care specialist at this juncture as well.

Virgin Abdomen

Based on findings in recent reviews, SBO in virgin abdomen (VA) has a mostly benign cause; this is in contrast with older literature and surgical textbooks that suggest malignancy as the main cause of obstruction in VA patients. Etiology and treatment results for patients with SBO in VA are largely comparable to the results in patients with SBO after previous abdominal surgery. CT has a pivotal role in the assessment of SBO in VA to assess the etiology and to evaluate if the bowel is compromised, demanding early surgery. Moreover, modern high-resolution CT is also useful in minimizing the risk of failure to detect a malignant cause. As with ASBO in general, the majority of cases with SBO in VA can be treated by nonoperative trial initially. Nevertheless, a laparotomy remains indicated in case of a nonresolving obstruction. The need to perform surgical exploration in every patient with SBO in VA can be waived. Noninvasive diagnostics with high accuracy for detection of malignancy and a close follow-up are mandatory.

Bariatric Surgery

Bariatric patients can present with obstruction from the same causes as all other patients, but also carry a greater risk of internal hernia, intussusception, and closed-loop obstructions resulting from surgical creation of mesenteric defects. CT results for patients with a history of laparoscopic Roux-en-Y gastric bypass may be subtle. A significantly dilated small bowel with a transition point is often a late finding. Elevated amylase and/or lipase may be a significant finding in this patient population, especially with acute obstruction of the biliopancreatic limb. Reviewing the CT scan with the radiologist to discuss any subtle findings and having a lower threshold to proceed to the operating room for any suspicious findings is recommended. Early intervention is necessary to prevent the loss of significant portions of bowel to ischemia with resulting increased morbidity and mortality. Laparoscopic enterolysis is feasible and safe. Careful bowel handling and clearly identifying all three limbs is essential because mesenteric or internal hernia can occur at multiple sites.

Early Postoperative Small Bowel Obstruction

Pivotal problems in the management of obstruction in the early postoperative period (3–4 weeks after surgery) are differentiation of ileus from mechanical obstruction and distinction between simple and strangulating obstruction if mechanical obstruction is present. Early postoperative small bowel obstruction (ESBO) poses an interesting dilemma for the surgeon. Although some ESBOs will resolve with nonoperative/conservative treatment, waiting beyond the 2-week period after the index surgery can result in forcing the surgeon to operate in a "hostile abdomen" because of significant inflammatory/postoperative adhesions. The decision to reoperate should account for clinical and radiographic signs suggesting impending strangulation or closed-loop obstruction, elapsed length of time of nonoperative management, and the nature of the index operation. Early reoperation should be considered after certain laparoscopic procedures. Surgeons managing SBO can benefit from understanding the unique features of ESBO after Roux-en-Y gastric bypass.

CONCLUSION

Small bowel obstructions remain an exceedingly common reason for emergency/unplanned admissions. SBO is a significant burden to the healthcare system, accounting for over 300,000 admissions per year and $1.3 billion per year in US healthcare costs. They present a management dilemma for clinicians and, most importantly, are a significant burden to patients because of the use of nasogastric tubes, need for operative intervention, and the often recurrent nature of the disease process. Unique variations of SBO pose challenging clinical decision dilemmas. The management of SBO is based on clinical evaluation, biological tests, and CT imaging. The goal of the initial assessment of a patient with SBO is to quickly identify signs of bowel ischemia that would necessitate urgent surgical intervention with concurrent resuscitation. The challenge for the emergency general surgeon is identifying as quickly as possible the minority of patients presenting with SBO who will not resolve without surgery. In the absence of any "alarming" signs, the patient can be managed with a trial of nonoperative management. Incorporation of a water-soluble contrast agent challenge early in the treatment algorithm can efficiently predict the success of nonoperative management and potentially hasten the return of bowel function, reducing hospital length of stay. Absence of passage of contrast into the cecum or interval deterioration of clinical examination suggests the need for operative intervention. Adhesive SBO can lead to small bowel strangulation, which is considered a major cause of morbidity and mortality. Therefore, surgery is indicated in patients with clinical deterioration or with radiologic evidence of strangulation and/or persistent obstruction. Laparoscopic surgery is becoming more common in the management of SBO and has distinct advantages in selected patients.

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Management of Crohn's Disease of the Small Bowel

John Peter Ricci, MD, and Mark A. Talamini, MD

Crohn's disease is a chronic inflammatory transmural disease that can affect the entire gastrointestinal (GI) tract. As often is stated in medical school lectures, it can present anywhere from "the mouth to the anus." Most commonly, it occurs in the small intestine with the terminal ileum being the most common location. Its incidence is increasing worldwide and now is noted to be present in 201 of 100,000 adults in the United States. Its exact cause is unclear and continues to be an enigma despite intense investigation. A complex interaction of genetics, environment, and the microbiome with the host's immune system appears central in understanding the origin of Crohn's disease. Clinically, it tends to be a cyclical disease in symptoms and pathophysiology. There are episodes of alternating active inflammation and relative dormancy that contribute to the overall difficulty in management. There is a large spectrum of severity in presentation ranging from mild inflammation to significant complications including strictures, perforations, hemorrhage, abscess formation, and malignant degeneration.

The clinical hallmark of Crohn's disease is abdominal pain and diarrhea. The broader spectrum of associated symptoms may include hematochezia, fever, anorexia, weight loss, fatigue, nausea, emesis, malnutrition, vitamin deficiency, and stunted growth in younger patients. Most patients are diagnosed between 15 and 30 years of age, but a second spike in diagnosis has been noted in the sixth decade of life, largely in females. In its early presentation, Crohn's disease must be differentiated clinically from acute GI conditions such as appendicitis and bowel obstruction. Definitive diagnosis is not always easily obtained and depends on a detailed family history, environmental history, and physical examination. CT enterography and MRI enterography have become essential in the initial evaluation of these patients as have blood tests to monitor and follow inflammatory markers. Endoscopy and colonoscopy are performed for direct visualization of bowel mucosa and to obtain tissue diagnosis. Capsule endoscopy can be employed for further direct evaluation of the small bowel mucosa. At initial presentation, 40% of patients will have terminal ileal disease, 20% colonic disease, 10% proximal small bowel disease, 10% perianal disease, and 20% will have involvement of more than one anatomic location.

Over the past 20 years, medical management of inflammatory bowel disease has improved significantly with the development of tumor necrosis factor (TNF) inhibitors and other biologic therapies. Despite this fact, surgery remains a significant treatment option in the management of a large cohort of patients, and approximately one-half of Crohn's patients will require some surgical intervention within 10 years of diagnosis. Surgery for Crohn's disease is not curative; therefore its application in patient management can be challenging. Overall, the goals of surgical treatment are alleviating symptoms, improving quality of life, and preserving bowel length. Surgery can provide remission of active inflammation that cannot be obtained with medical therapy alone. It can also be used to treat strictures, abscesses, and fistulas that also will not respond to medicine.

MULTIDISCIPLINARY MANAGEMENT

The optimal management of the Crohn's disease patient requires a team approach. This team is anchored by the surgeon and gastroenterologist. A multidisciplinary group will also require input from radiology, pathology, social work, nutrition, enterostomal therapy, and associated specialties. Complex cases often are reviewed in a formal organized setting in which a member from each specialty is represented so the best treatment plan can be formulated.

MEDICAL TREATMENT

Mild to moderate disease is noted in the majority of patients at initial presentation. Standard initial management, in these cases, will usually include 5-aminocalycylates or budesonide depending on the location of disease. Acute flares can be treated with short courses of corticosteroids with transition to maintenance therapy once an adequate remission has been achieved. TNF inhibitors have drastically changed the approach to patients with moderate to severe disease. Studies have shown fistula resolution and combination therapy with methotrexate has demonstrated high mucosal healing rates. Newer biologic agents including anti-interleukin12/23 antibody (ustekinumab), anti–alpha-4 beta-7 integrin antibody (vedolizumab), and JAKs-based therapies (tofacitinib) continue to be developed with new molecular targets to decrease inflammation.

These new medications have been shown to decrease the need for surgical intervention in milder forms of the disease. They also provide the gastroenterologist a means of delaying surgery for prolonged periods. However, surgery remains an important treatment option for severe disease and disease that is otherwise refractory to medical management.

INDICATIONS FOR SURGERY

The main indications for surgery in Crohn's disease are obstruction, perforation, and failure of medical management. Emergency surgery is infrequently required as free perforation and massive bleeding are rare and obstruction is usually gradual in presentation. Acute appendicitis can occur, but this often is treated with antibiotics as associated small bowel and colonic inflammation are usually noted before intervention on CT imaging. Patients with long-standing Crohn's disease are at increased risk of developing adenocarcinoma. Principles of surgical management would be the same as a patient with de novo adenocarcinoma of the small bowel. However, diagnosis is commonly an incidental finding after standard Crohn's disease surgery.

Obstruction

Obstruction is the most common indication for surgery in Crohn's disease. The natural history is that of gradual onset in the setting of

chronic relapsing disease. The cycling of inflammation and repair over time in an affected segment eventually converts soft pliable bowel into a constricted "stovepipe." Clinically as this process progresses, the symptomatology evolves from intermittent partial obstruction experienced during episodes of transmural inflammation to chronic partial obstruction that exists between episodes of acute inflammation. The latter situation is commonly referred to as a *fibrostenotic stricture*. Once this stricture has developed, minimal acute inflammation can lead to obstructive symptoms and an acute flare. On imaging, proximal bowel to the stricture is noted to be dilated, prompting treatment frequently with corticosteroids and antibiotics. All strictures have some component of chronic scarring, and it can be difficult to differentiate a stricture that is largely inflammatory versus one that is largely fibrostenotic. Both MRI and CT enterography have improved significantly over the past decade, making this differentiation somewhat clearer. In the authors' practice, once the patient is treated acutely with anti-inflammatory medication and is noted to be asymptomatic, imaging is repeated. If persistent dilation of the bowel proximal to the stricture is appreciated, predominant fibrostenotic disease is assumed to be present. This is a clear indication for surgical intervention as medication will not be effective in the treatment of chronic scar tissue. If the bowel is noted to be decompressed, medical therapy should be optimized.

Perforation

Perforation is the next most common indication for surgery. As a transmural inflammatory process, Crohn's disease can cause localized perforation with abscess formation leading to fistulization. The pathophysiology is that of the inflammatory process in the affected bowel perforated into the peritoneal cavity, usually forming a walled off abscess. This abscess can become chronic requiring long-term antibiotics or percutaneous drainage. If an abscess persists, it ultimately will require surgical intervention. If the abscess can be treated nonoperatively, a multidisciplinary approach should be used to determine ongoing treatment on an individual basis. A small resolved abscess on a patient on minimal medical therapy would likely benefit from medical escalation and optimization, whereas a resolved abscess in a patient who has failed three biological medications would likely be offered surgery.

Frequently, these abscesses can "burrow" to adjacent "innocent" structures, creating a fistula. The structures most commonly involved are pieces of bowel (enteroenteric/enterocolonic fistula), the bladder (enterovesical fistula), or the skin (enterocutaneous fistula). When the process creates a clean fistula into another portion of the GI tract without an associated abscess, the decision regarding surgery depends on the impact of this connection. Thus, enteroenteric or enterocolonic fistula are not in themselves a definite indication for surgery. Only when the fistula causes worsening clinical symptoms or nutritional deficiencies should surgery be performed. In addition, studies have shown that TNF inhibitors have some effect in treating GI tract fistula. Enterovesical fistulas are usually not life-threatening, but they lead to recurrent urinary tract infections, pyelonephritis, and, in rare cases, urosepsis. In addition, the symptoms of pneumaturia and fecaluria are generally intolerable to most patients. Surgical repair should be pursued in this situation. Similarly, enterocutaneous fistulas require surgical intervention because of chronic drainage from the abdominal wall, chronic abdominal wall wounds, dehydration, and frequent nutritional deficiencies.

Failure of Medical Management

Failure of medical management is probably the most difficult indication to determine as it is largely patient dependent. The surgeon, gastroenterologist, and patient must work closely together to determine when during the treatment process surgical intervention is most appropriate for "medical refractory" disease. As medical therapies have advanced, new treatments continually become available that have allowed some patients to avoid surgery while only delaying it for others. Clearly, given their long-term consequences, inability to wean steroids after an acute flare and transition to maintenance therapy is an absolute indication for surgery. It is less clear how to proceed when a patient remains symptomatic and has tried multiple medications, but additional options exist. In these instances, attempting additional second- and third-line therapies can take several months to determine success and possibly delay the inevitable need for surgery. It should also be noted that eliminating the burden of active disease and inducing remission surgically can provide patients with a "fresh start" off all agents and allows previously failed medications to be reattempted.

PREOPERATIVE CONSIDERATIONS

Timing

The timing of surgery is important in maximizing the clinical outcome. The patient's willingness or resistance to surgery affects decision making. The input of the surgeon and gastroenterologist regarding recommendations is imperative. Operating too soon when the bowel is intensely inflamed is technically challenging and puts non-diseased bowel at risk. Allowing an acute flare time to resolve, at least partially, can greatly affect outcome. Every effort should be made to convert more emergent situations to urgent and elective scenarios. Active abscesses should be drained percutaneously. Conversely, these patients frequently have some aspect of malnutrition, and waiting too long for intervention can worsen this situation. In rare instances when a significant length of bowel is at risk, bowel rest and total parenteral nutrition may be required.

Once a decision regarding elective surgery has been made, the patient's current disease state must be assessed to inform preoperative planning. The patient's general medical condition must be assessed and optimized. If nutritional deficits exist and time allows, nutritional improvement should be pursued. The authors follow a strict enhanced recovery protocol and surgical site infection bundle. A standard mechanical bowel preparation with oral antibiotics is given unless a prolonged high-grade bowel obstruction is present. In this case, an extended period of clear liquid diet is employed. Patients are maintained on a clear liquid diet until 2 hours before surgery and are given a carbohydrate-rich beverage preoperatively. If bowel diversion is anticipated, the patient is evaluated by an enterostomal therapist for preoperative stoma siting.

Medications

Prolonged and chronic use of corticosteroids has clearly been shown to adversely affect wound healing and to increase the risk of surgical site infection. This is especially an issue as dosages increase from lower to higher daily prednisone equivalents. All efforts should be made to wean or discontinue steroids before surgery, but this is frequently not an option in the actively inflamed patient. In addition, patients may require perioperative steroid supplementation depending on duration of use and dosage to prevent acute adrenal insufficiency. More recently, the question of TNF inhibitor impact on wound healing has come into question. Unfortunately, the literature provides no definitive guidance on this matter. Some studies have shown no effect, with others showing a significantly increased incidence of infectious complications when patients have taken the medications within 6 to 8 weeks before surgery.

Consideration of bowel diversion with stoma creation must be entertained when patients are on long-term steroid treatment. This is likely true to a lesser extent when a patient has taken a TNF inhibitor in the perioperative period. Malnutrition and bowel quality also must be taken into account when considering stoma creation. This ideally will be discussed with the patient preoperatively and the patient will be referred to enterostomal therapy for evaluation.

TECHNICAL CONSIDERATIONS FOR SURGICAL INTERVENTION

Once it has been determined that surgery is the next step in treatment for a patient, meticulous preparation is required. This is necessary to plan the possible extent of resection and identify all areas of active disease. The entire small bowel should be evaluated, and the exact state of the disease should be elucidated. Usually this involves a current axial imaging study (CT or MRI enterography). If questions remain regarding the small bowel anatomy or disease state, capsule endoscopy or small bowel push enteroscopy can be pursued. The colon should be evaluated via colonoscopy. The cecum and the terminal ileum in particular merit examination because the state of colonic disease can be more difficult to evaluate intraoperatively than small bowel disease. Endoscopy should be performed for disease in the duodenum and proximal jejunum. Despite extensive workup, intraoperative assessment can sometimes alter the surgical plan.

Preoperatively, findings of the workup and contingencies must be reviewed with the patient. The possible nutritional effects of surgery and the possible role of a stoma should be discussed, as previously noted. The more information the patient and family understand regarding the plan, the better.

Resection

The mainstay of surgical therapy for Crohn's disease of the small intestine is resection. The most commonly faced initial operative scenario is a tight, but reasonably short segment of chronically obstructed and scarred terminal ileum. The most common operation, therefore, is an ileocecectomy. This accounts for approximately half of the surgery for Crohn's disease on the small intestine. Additional ascending colon may need to be included with the resection specimen depending on the disease activity noted on colonoscopy. Consideration of isolated terminal ileal resection should be considered only if 15 centimeters or more of normal small intestine is present just proximal to the ileocecal valve. A short, isolated segment of terminal ileum is extremely susceptible to recurrent inflammation.

In virtually all cases, the authors attempt laparoscopic access, dissection, and mobilization of the targeted diseased tissue. The laparoscope is placed in a periumbilical or umbilical position with a Hassan port via a direct cut-down technique. A 10-mm 30-degree scope is used to maximize visualization from a variety of angles. Generally, three 5-mm ports are employed on the left side of the abdomen as working ports. Upon entrance into the abdomen, full evaluation of the GI tract should be performed. This should be correlated with the visual information from the preoperative evaluation. If isolated mid small bowel disease is noted, this can be identified and easily externalized through extension of the umbilical port for resection and re-anastomosis. If a fistula exists, it must be identified. Enteroenteric fistula of the terminal ileum to itself can usually be preserved as the entire segment of bowel usually requires en bloc resection as an inflammatory mass. If the terminal ileum is fistulizing to otherwise "innocent" portions of the GI tract, the fistula must be transected and the healthy bowel must be assessed. This situation typically occurs with a small bowel to sigmoid colon fistula. In this scenario, the fistula opening in the sigmoid colon must be debrided to healthy tissue and can be closed primarily. The author prefers a handsewn two-layer approach in this situation, but a stapled repair can also be performed. In some instances, colonic resection will be required given associated inflammation in the area. A similar approach to fistulas must be employed for "innocent" small bowel involvement. A fistula to the bladder is usually taken down with primary repair of the bladder if a definite opening is noted, and prolonged Foley catheter drainage is performed. The catheter is removed after CT cystogram confirms healing of the bladder.

Sufficient mobilization of tissue for resection must be performed. This almost always involves some mobilization of the cecum, right colon, and terminal ileal mesentery from the retroperitoneum. This can be performed in a lateral-to-medial or medial-to-lateral approach. However, the medial-to-lateral technique cannot always be performed because of significantly thickened mesentery. Care must be taken in this dissection to ensure that the proper plane is identified and retroperitoneal tissue is preserved. The ureter should be identified clearly. In rare cases of extreme inflammation, this is not possible. In this situation, dissection of the ureter should be performed in the pelvis to better evaluate its course. In addition, if this inflammation is noted and expected, preoperative ureteral catheter placement should be performed.

As stated earlier, the specimen is generally extracted through an extended umbilical incision. If extensive pelvic inflammation is noted, the incision may need to be extended inferiorly. Vascular transection can be performed intracorporeally, however frequently the bowel mesentery is significantly foreshortened and thickened from chronic inflammation. Transecting this mesentery can be tortuous and may require proximal vascular control to prevent extensive blood loss. Attempt at laparoscopic transection should be considered carefully.

The basic principle of small bowel resection for Crohn's disease is to remove all of the grossly involved disease while preserving as much bowel length as possible. The authors attempt to measure pre-resection and post-resection bowel length so it will be notated if additional surgery is performed in the future. Grossly involved bowel is best determined by visual and tactile evaluation. Fat creeping should not be present, and the mesenteric margin should be palpable in unaffected intestine. Division of the mesentery, as previously noted, can be difficult. The authors generally use a combination of approaches including a vessel-sealing energy device, vascular staplers, and sutures to control bleeding from exceptionally thickened mesentery. When at all possible, transection of mesentery distally should be attempted so as not to compromise the vascular supply of otherwise healthy bowel.

The worst complication in any bowel surgery is anastomotic dehiscence, and this is no different for the Crohn's disease patient. Anastomotic techniques have been studied at length with no definitive determination on the superiority of stapled or handsewn anastomosis. It is the authors' opinion, however, that the technique employed should be that which is most comfortable for the primary surgeon. This should hopefully maximize reproducibility and quality. The mesenteric defect is closed, when possible, to prevent internal herniation but is left fully open for large defects that cannot be reapproximated.

Ileostomy

As previously noted, sometimes patients will require temporary bowel diversion after surgery for Crohn's disease of the small intestine. This usually is required when the bowel or the patient is not healthy enough to undergo primary anastomosis. This can occur with extensive contamination from a drained abscess or if the bowel is noted to be significantly dilated precluding healthy anastomosis. High-dose steroid use and severe malnutrition can also create such an environment. Rarely, a proximal diversion is required when significant inflammation of long segments of small intestine are noted. In this situation, too much bowel is involved to resect, and proximal diversion is performed as a last-ditch effort to induce remission. Unfortunately, this diversion will undoubtedly be accompanied by a high-output stoma requiring parenteral nutrition.

Disease of the Duodenum

Crohn's disease of the duodenum frequently presents with nausea, epigastric fullness, and emesis. It is easily diagnosed with imaging

and upper endoscopy. Initial attempts at management can be performed with endoscopic balloon dilation. However, recurrence is common. When surgery is indicated, strictureplasty is the procedure of choice. Frequently, the disease is too diffuse, making a bypass procedure necessary. Gastrojejunostomy is most commonly employed. It is recommended that the patient undergo a pH study before the procedure to determine the need for associated vagotomy. In addition, when possible, gastroduodenal bypass is recommended for proximal disease of the duodenum to prevent marginal ulceration in the future.

Strictureplasty

Bowel-sparing procedures and strictureplasty are discussed directly in a separate chapter in this text, but we will discuss them briefly as they are a critical tool in the inflammatory bowel disease surgeon's armamentarium. In patients with small bowel Crohn's disease, 20% to 30% can be managed with some form of strictureplasty. Technically, a strictureplasty can be performed laparoscopically, but because of the extensive suturing required, it is often performed through a small laparotomy after identification of strictures laparoscopically. The most challenging operative situation involving structuring disease is the case of diffuse jejunoileitis. In this situation, multiple strictures separated by inches throughout the small intestine are encountered. Deciding what requires resection, what will resolve with strictureplasty, and what can be left alone requires careful consideration and judgment. It has been described that inflating a Foley catheter with 3 mL to 10 mL of saline and inserting it into the bowel through an enterotomy can be used to determine clinically significant strictures. Once it has been determined that a strictureplasty is to be performed, the mucosa of the affected bowel must be examined once opened to evaluate for underlying pathology. Biopsies with possible frozen section must be performed if malignancy is suspected.

Heineke-Mikulicz Strictureplasty

The Heineke-Mikulicz strictureplasty is the most commonly employed technique and the simplest to perform. It is generally used for strictures less than 7 cm in length. An incision is made parallel to the bowel on the antimesenteric border. It should extend approximately 2 cm past the active inflammation on either side. The incision is then reapproximated transversely. This can be performed with a running or interrupted suturing technique in one or two layers.

Finney Strictureplasty

The Finney strictureplasty is generally used for medium-length strictures between 8 and 15 cm. Once again, a longitudinal incision is made on the antimesenteric border of the actively inflamed bowel. The defect is then closed as a U-shaped enterotomy with the bowel folded on itself at the midpoint of the enterotomy. This is usually performed in two layers with interrupted sutures on the outside and running or interrupted sutures on the inside.

Side-to-Side Isoperistaltic Strictureplasty (Michelassi Strictureplasty)

The Michelassi strictureplasty is a specialized technique that should only be employed by the most experienced Crohn's disease surgeons. It allows for preservation of long segments of diseased small intestine. It entails transection of actively inflamed portions of small intestine and aligning them in isoperistaltic side-to-side fashion. The bowel is usually anastomosed by a two-layer handsewn technique while spatulating the ends for full closure.

POSTOPERATIVE CARE

Postoperatively, patients continue on the hospital's enhanced recovery pathway. Preoperative blocks and spinal anesthesia are used to initiate postoperative pain control. Nasogastric tubes are not employed. Narcotics are minimized, mobilization is initiated as early as possible, and diet is started immediately. Patients are discharged once there is clear evidence of sufficient bowel function to maintain hydration and nutrition independent of the hospital. Once home, patients are provided with information regarding warning signs of complications and given a quick and clear pathway back to the team should concerns arise. They are contacted by the team directly for the first three days post-discharge.

It is well known and even assumed that Crohn's disease will recur and that it will do so at a microscopic level early at the anastomotic site. How to address and survey these patients is imperative to their long-term success and prevention of additional surgical interventions. A recent and important advance in the team management of surgical Crohn's patients is early postoperative medical therapy, according to logical protocols. This is an active area of investigation worthy of monitoring.

Suggested Readings

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Use of Strictureplasty in Crohn's Disease

Lea Lowenfeld, MD, and Fabrizio Michelassi, MD

Crohn's disease (CD) is a chronic, full-thickness, inflammatory bowel disease. It can affect any site along the gastrointestinal tract and may present with one of three phenotypes: (1) nonpenetrating/nonstricturing disease characterized by inflammatory masses, (2) penetrating disease characterized by fistulae and abscesses, or (3) fibrostenotic disease characterized by fibrotic strictures. Strictures are defined as "a constant luminal narrowing with prestenotic dilation or obstructive signs without penetrating disease" (Satsangi et al., 2006). Fibrostenotic Crohn's strictures most commonly affect the small bowel, leading to small bowel obstruction. To date, there is no medical therapy that prevents or reverses stricturing disease; therefore, endoscopic and surgical treatments are the mainstays of treatment to palliate symptoms and treat complications. Endoscopic approaches include dilation, stricturotomy, and endoscopic stenting. Surgical options include proximal diverting stoma, resection, intestinal bypass, and strictureplasty. This chapter focuses on strictureplasties, specifically on indications, technical aspects of different strictureplasty techniques, and outcomes.

CLINICAL PRESENTATION

Patients with strictures may develop progressive luminal narrowing over time and only become symptomatic when a critical degree of narrowing has been reached. Patients with gastroduodenal strictures typically present with early satiety, postprandial fullness, burping, and vomiting. Patients with strictures of the small intestine initially notice postprandial bloating, crampy abdominal pain, obstipation, and constipation and may progress to nausea, vomiting, and high-grade intestinal obstruction. Patients with colonic strictures present with bloating, distension, obstipation, constipation, and abdominal pain. Patients with stricturing disease may develop a single stricture or a series of strictures with intervening healthy intestine. In the presence of multiple strictures, symptoms originate from the most proximal critical stricture.

Noninvasive imaging modalities, including computed tomography enterography (CTE) and magnetic resonance enterography (MRE), are useful in showing luminal narrowing, intestinal wall thickening, and prestenotic bowel dilation to map the number, degree, length, and location of strictures and also to estimate overall small-bowel length in preoperative planning. Endoscopic evaluation with or without biopsy is important to evaluate for extension and severity of luminal disease and presence of malignancy, but it may be limited by tight strictures or luminal narrowing secondary to angulations caused by adhesions from previous surgical procedures or localized sepsis.

Resection remains the most common approach for patients undergoing operative treatment for obstruction caused by stricturing CD. The initial presentation of a patient with a single stricture or a series of strictures in a relatively short segment of intestine is most often best managed with surgical resection. However, patients with multifocal, extensive, and recurrent disease are at risk of short gut syndrome, especially following prior extensive bowel resections. In these cases, bowel-sparing procedures offer an alternative to resections by enlarging the lumen of the bowel while maintaining the overall absorptive surface area of the intestine.

INDICATIONS AND CONTRAINDICATIONS FOR STRICTUREPLASTY (BOXES 1 AND 2)

Strictureplasty is indicated for fibrotic strictures in the duodenum and small bowel, particularly if multiple strictures are present over an extensive length of intestine or when recurrent strictures develop in a patient with previous bowel resections at risk for short bowel syndrome. Relative contraindications include malnutrition; the presence of a fistula, unless the fistulous opening is devoid of acute inflammation and located on the antimesenteric side of the bowel, where it can be debrided as part of the strictureplasty; a stricture close to an area of resection, which is usually included in the resection unless the patient is affected by or at risk for short bowel syndrome; or a long stricture with thick, unyielding intestinal wall. Absolute contraindications include acute or chronic hemorrhage; a stricture within an inflammatory mass or in proximity to a perforation or abscess; or the presence of dysplasia or malignancy. If there is concern for malignancy, the intestinal segment must be resected according to standard oncologic principles.

Asymptomatic strictures should not be resected, but they can be strictureplastied or included in a strictureplasty for an adjacent symptomatic stricture to prevent progression of the stricture to a critical narrowing. If left untouched, disease progression requiring subsequent surgical treatment occurs in one-fourth of cases over the ensuing 3 to 4 years.

Patients requiring surgical intervention for obstructive symptoms are frequently malnourished. Patients who are nutritionally compromised should undergo nutritional repletion with a liquid enteral diet or parenteral diet supplementation, if needed, to reverse their catabolic state before surgery.

OPERATIVE PLANNING

Careful preoperative patient evaluation is critical to operative planning. The nature of the patient's past and current disease activity (obstructive, septic, hemorrhagic, or neoplastic) should be evaluated and documented. Obtaining a thorough history of prior operations

BOX 1 Indications for Strictureplasty

- Fibrotic small bowel stricture without associated inflammation
- Multiple strictures throughout the small bowel
- Recurrent small bowel stricture(s) following previous resection

BOX 2 Contraindications for Strictureplasty

Absolute Contraindications
- Hemorrhage
- Evidence of dysplasia or malignancy
- Stricture at a site of uncontrolled sepsis (perforation, abscess, or inflammatory mass)

Relative Contraindications
- Malnutrition, albumin level <2
- Fistula involving the stricture
- Stricture in close proximity to a segment planned for resection
- A long stricture with a thick, unyielding intestinal wall
- Multiple strictures within a short segment of small bowel in a patient who has not had a prior resection

and operative reports is helpful to understand the patient's current gastrointestinal anatomy. Imaging with CTE or MRE and endoscopic evaluation provide a preliminary "road map" of the distribution of disease activity as well as any unsuspected entero-enteral fistulae, contained perforations, and an overall estimate of small bowel length. The optimal stoma site should be marked preoperatively when a temporary or permanent stoma is likely.

The first step in any CD abdominal procedure is to thoroughly examine the entire bowel. The bowel can be examined laparoscopically or via laparotomy, with the preoperative imaging and endoscopic evaluation in mind, matching the preoperative findings to the visual appearance of the bowel. The bowel must be visually inspected, palpated digitally or through laparoscopic instruments, and, if necessary, the lumen can be evaluated by passing a well-lubricated Foley or Fogarty balloon through the bowel and then retracting the partially inflated balloon to identify more subtle luminal narrowings. Areas of small bowel disease usually display creeping fat, wall thickening, and mesenteric thickening. Disease in the colon may manifest more subtle external changes: mucosal disease can be present with the external wall looking normal, hence preoperative endoscopic evaluation is useful.

At the end of the examination, the surgeon should have a mental road map of the gastrointestinal tract, with the total length of the small bowel, the length and location of the diseased bowel, the phenotypic appearance of the disease, and the presence of previous resections and strictureplasties. Each diseased segment should be evaluated to determine whether it is a candidate for strictureplasty, resection, or no intervention in the case of a noncritical narrowing. The relationship of multiple fibrostenotic strictures to one another must also be noted to see whether they would need multiple simple strictureplasties, a single intermediate or complex strictureplasty, a resection, or a combination of strictureplasties and resections. If abscesses or fistulae are present, they must be computed in the surgical plan.

Gastroduodenal strictures are most often endoscopically accessible and can be treated with endoscopic dilation. When surgery is indicated, short strictures throughout the first three portions of the duodenum may be treated with the Heineke-Mikulicz strictureplasty, and strictures of the fourth portion of the duodenum may be treated with the Finney strictureplasty by recruiting the first loop of jejunum. These procedures are discussed later in this chapter. To treat a duodenal stricture, the duodenum must be fully mobilized to allow for a strictureplasty without tension. If a strictureplasty is not feasible, a gastrojejunal bypass is a viable alternative.

Jejunal-ileal strictures may be addressed with a combination of resection and strictureplasty techniques. Heineke-Mikulicz strictureplasty is the procedure of choice for short-segment strictures. Finney strictureplasty is performed for longer-segment strictures. The Michelassi strictureplasty is used for multiple sequential strictures. These procedures are discussed later in this chapter.

Terminal ileum and colon strictures are usually the result of inflammatory, nonpenetrating/nonstricturing or penetrating disease. Therefore, a segmental resection is usually preferred. Occasionally, Crohn's terminal ileitis can be addressed with a modified Michelassi strictureplasty.

Anastomotic strictures may be addressed with endoscopic dilation if endoscopically accessible. Anastomotic strictures that are not amenable to endoscopic treatment can be addressed with resection or strictureplasty. To perform a tension-free strictureplasty at the site of a prior anastomosis, adequate mobilization of the intestinal loop and lysis of adhesions must be performed. Anastomotic strictureplasty is safe and efficacious, but it is associated with a high rate of recurrence (57%) when followed long term.

STRICTUREPLASTY TECHNIQUES (BOX 3)

The technical difficulty of strictureplasty varies from simple (Heineke-Mikulicz) and intermediate (Finney) to complex (Michelassi). Certain overarching principles are shared by all strictureplasty techniques:

BOX 3 Strictureplasty Operative Strategy

- An incision is made along the length of the stricture.
- Examine the mucosa, and perform a biopsy on any areas suspicious for dysplasia or carcinoma.
- Obtain excellent hemostasis.
- Close the enterotomy with absorbable or nonabsorbable suture in one or two layers.

- After opening the bowel during the performance of a strictureplasty, the mucosal surface of the affected and neighboring bowel must be evaluated for disease severity and presence of dysplasia/carcinoma. Suspicious areas must be biopsied for frozen-section analysis. If dysplasia or malignancy is confirmed, the strictureplasty is aborted in favor of an oncologic resection.
- Excellent hemostasis is critical. Bleeding from a strictureplasty site is one of the most common and troubling postoperative complications. Bleeding is usually self-limited, but occasionally requires blood transfusions. For persistent bleeding originating from a strictureplasty within reach of an endoscope, endoscopic techniques can be employed to achieve hemostasis. Selective mesenteric angiography with intraarterial vasopressin infusion effectively controls most episodes of bleeding originating from strictureplasties that are not accessible with endoscopic techniques. In the presence of multiple suture lines (strictureplasties, anastomoses), India ink blue dye can be injected at the time of selective mesenteric angiography for subsequent intraoperative localization of the bleeding.
- Minimally invasive approaches to surgery can be utilized during the performance of a strictureplasty either completely intracorporeally with effective laparoscopic or robotic suturing skills or in a hybrid fashion by mobilizing and exteriorizing the affected segment through a small incision in the abdominal wall.

Heineke-Mikulicz Strictureplasty (Fig. 1)

Short strictures are best treated with a Heineke-Mikulicz strictureplasty, a technique derived from the Heineke-Mikulicz pyloroplasty performed for pyloric stenosis. The Heineke-Mikulicz strictureplasty is appropriate for strictures up to 5 cm in length.

First, two 3-0 sutures, either nonabsorbable or absorbable, are placed on each side of the bowel at the midportion of the stricture to act as stay sutures. A longitudinal enterotomy is made over the stricture on the antimesenteric side of the bowel, extending 1 to 2 cm beyond the length of the stricture proximally and distally into

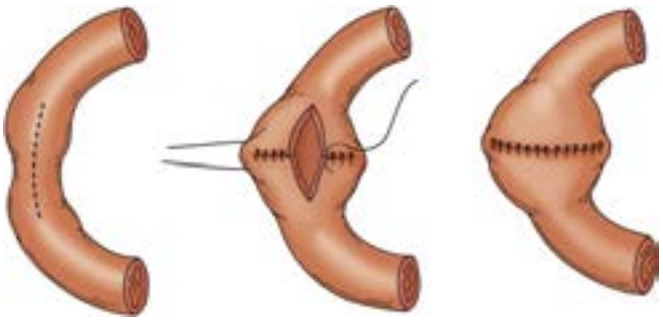


FIG. 1 Heineke-Mikulicz strictureplasty. The longitudinal enterotomy is closed transversely to reconstruct a more widely patent lumen.

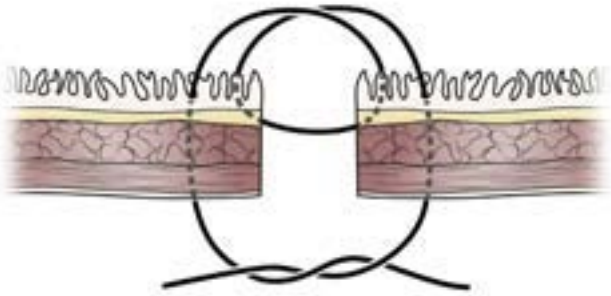


FIG. 2 Modified Gambee stitch. First the stitch penetrates all layers of the bowel wall from the serosa to the luminal mucosa approximately 0.5 cm from the cut edge. The mucosa of the other limb is traversed out of the bowel lumen, and then the mucosa of the first side is traversed back into the bowel lumen. Finally, on the other limb, the stitch penetrates all layers of the bowel wall from the luminal mucosa to the serosa approximately 0.5 cm from the cut edge. *(From Shureih SF, Wilson TH Jr, Howard WH. Modified Gambee stitch. Safe, easy and fast modification. Am J Surg. 1981;141:304.)*

nondiseased bowel. The stay sutures are then pulled perpendicular to the long axis of the bowel, lining up the enterotomy to be closed transversely. The closure may be performed in one or two layers. For a one-layer closure, the Gambee stitch (Fig. 2), using an absorbable suture, ensures appropriate approximation of the mucosa and serosa while leaving the blood supply intact between sutures and is particularly well-suited to strictureplasty. For a two-layer closure, a running absorbable inner layer is followed by an interrupted Lembert nonabsorbable suture outer layer.

A Sasaki modification of the Heineke-Mikulicz strictureplasty technique (Fig. 3) can be applied to two short-segment strictures in very close proximity. The enterotomy is created along the antimesenteric border through both strictures and the intervening healthy segment of intestine. The resulting longer enterotomy is then closed transversely after tailoring the end of each transected stricture.

The Moskel-Walske-Neumayer strictureplasty (Fig. 4) is another modification of the Heineke-Mikulicz strictureplasty that applies a V-Y advancement flap closure to address the disparity in size between a very dilated proximal bowel and a nondilated distal bowel. The enterotomy is created along the antimesenteric border of the stricture extending into a *Y* shape on the antimesenteric border of the dilated bowel just proximal to the stricture. The *Y*-flap of the proximal dilated bowel is advanced into the strictured area and closed in a transverse fashion.

The Judd strictureplasty is a variation of the Heineke-Mikulicz strictureplasty used when the strictured segment also includes a fistula opening. This technique can be used when the fistula opening is located on the antimesenteric side of the bowel. The anti-mesenteric longitudinal incision is made to include the fistula opening. The fistula opening is debrided, leaving healthy tissue, and the enterotomy is closed transversely using the described Heineke-Mikulicz technique.

Finney Strictureplasty (Fig. 5)

The Finney strictureplasty is also derived from the homonymous pyloroplasty technique. The Finney strictureplasty is appropriate for strictures 5 to 12 cm in length or for a similar-length segment with multiple short strictures closely grouped together with intervening short segments of dilated bowel.

The strictured segment is folded creating a U-shape loop. A rigid stricture that lacks the pliability to fold onto itself may require folding normal bowel onto diseased bowel. The two limbs of the *U* are sutured together in a side-to-side fashion. Interrupted Lambert

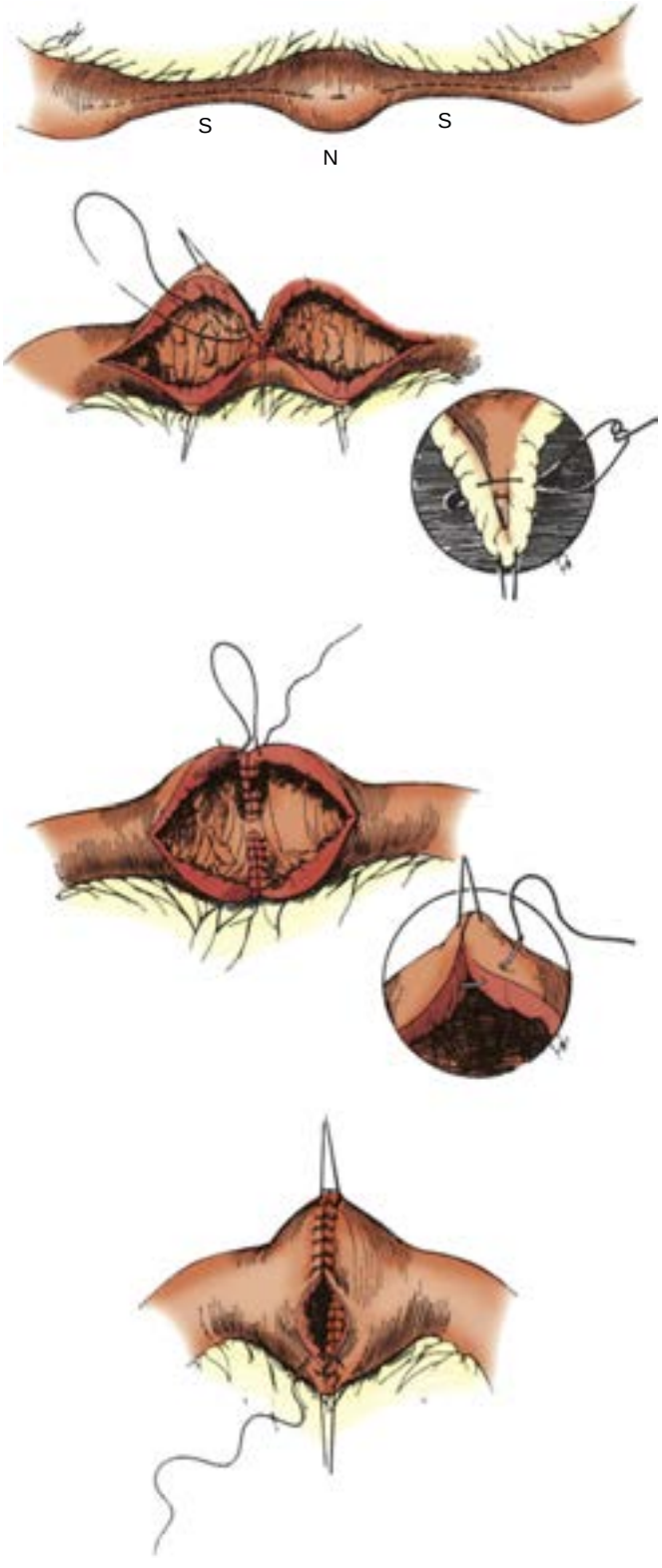


FIG. 3 Sasaki modification of the Heineke-Mikulicz strictureplasty can be applied to a segment that contains two short segment strictures *(S)* with a short intervening segment of normal *(N)* or dilated bowel.

sutures are placed close to the facing mesenteric borders forming the posterior outer layer, extending 1 to 2 cm beyond the length of the stricture proximally and distally. A longitudinal enterotomy is created just above the stitches. The side-to-side anastomosis is

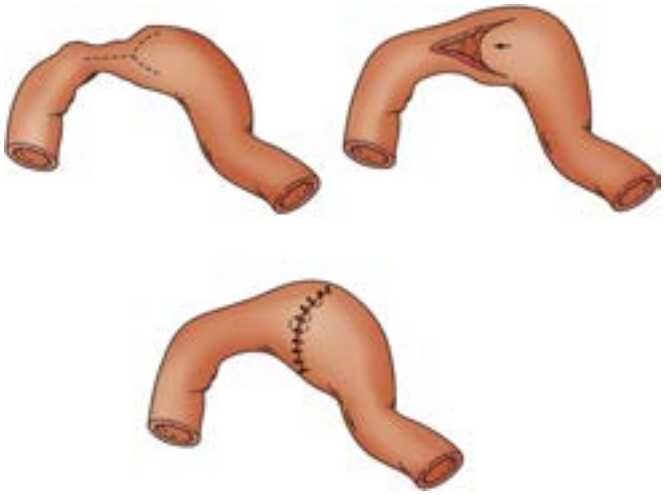


FIG. 4 Moskel-Walske-Neumayer strictureplasty is a modification of the Heineke-Mikulicz strictureplasty that can be used to address a size mismatch of the dilated proximal segment of small bowel and the strictured segment of small bowel. The longitudinal enterotomy along the stricture is extended into a Y-shaped enterotomy on the dilated proximal bowel and closed transversely by advancing the apex of the *Y* into the most distal point of the enterotomy. *(From Tichansky D, Cagir B, Yoo E, et al. Strictureplasty for Crohn's disease: meta-analysis. Dis Colon Rectum. 2000;43:911–919.)*

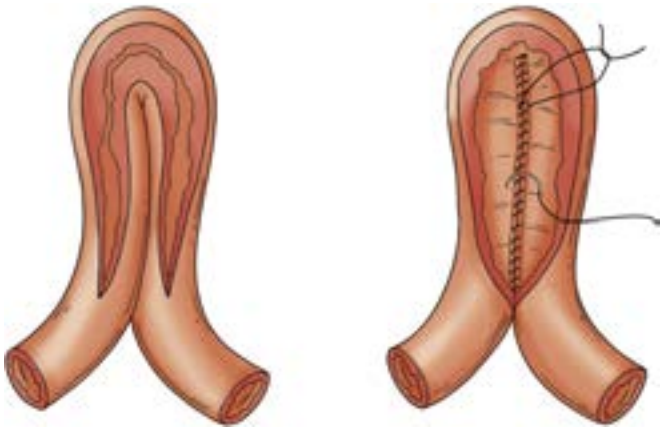


FIG. 5 Finney strictureplasty. The stricture is folded into a U-shape, and a side-to-side anastomosis is created between the proximal and distal portions of the stricture.

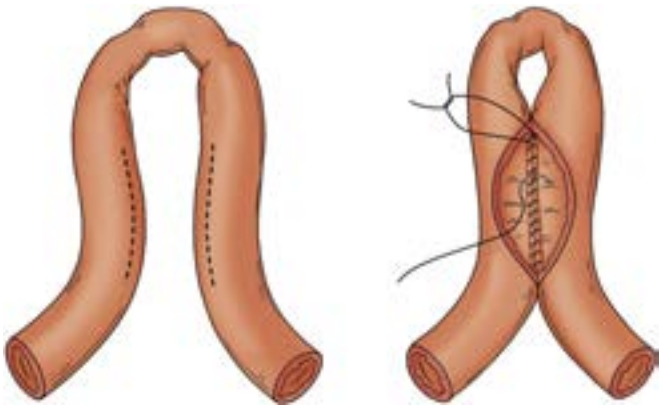


FIG. 6 The Jaboulay strictureplasty is a modification of the Finney strictureplasty that excludes the segment of the stricture that is not amenable to suturing.

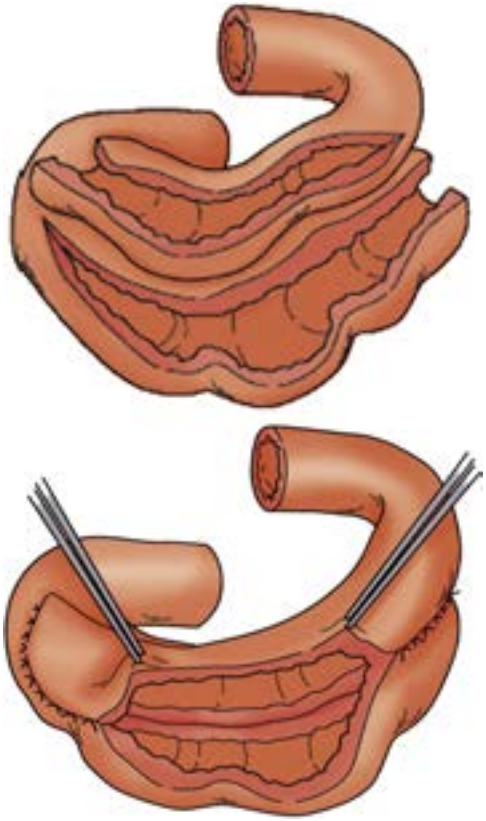


FIG. 7 Michelassi strictureplasty (side-to-side isoperistaltic strictureplasty). Long strictures or multiple consecutive strictures can be treated with side-to-side isoperistaltic strictureplasty. The involved segment and associated mesentery are divided to allow for the two segments to align alongside one another and create an isoperistaltic side-to-side anastomosis. *(From Tichansky D, Cagir B, Yoo E, et al. Strictureplasty for Crohn's disease: meta-analysis. Dis Colon Rectum. 2000;43:911–919.)*

constructed with an inner layer of running absorbable suture, reinforced by an anterior outer layer of interrupted Lambert sutures.

If the bowel quality of the stricture is not suitable for suturing, a Jaboulay strictureplasty (Fig. 6) is a modification of the Finney strictureplasty in which a side-to-side anastomosis is created between the uninvolved healthy bowel proximal and distal to the stricture, leaving the strictured segment in place as a short bypassed segment. This side-to-side anastomosis can also be created using a stapler device. One concern specific to the Jaboulay strictureplasty is that the short-bypassed segment may lead to long-term issues of bacterial overgrowth, septic complications, and malignant degeneration.

Michelassi Strictureplasty or Side-to-Side Isoperistaltic Strictureplasty (Fig. 7)

The side-to-side isoperistaltic strictureplasty (SSIS) preserves long segments of bowel that otherwise would be resected leading to major loss of intestinal absorptive capacity. Segments of bowel greater than 12 cm containing a single long stricture or a series of shorter strictures in close proximity to one another over a long intestinal segment may be addressed with SSIS.

The bowel and the mesentery are divided at the midpoint of the segment of bowel intended for the strictureplasty. The proximal and

distal loops of the diseased bowel are brought alongside each other to overlap in a side-to-side isoperistaltic fashion, lining up the stenotic areas of one loop against the dilated areas of the other loop as much as possible. The two limbs are approximated with interrupted non-absorbable Lambert sutures, forming the posterior outer layer of the ultimate closure. A longitudinal enterotomy is then made just above the sutures along the length of each of the two intestinal loops. The ends of the bowel are spatulated to avoid creating blind ends. Luminal hemostasis is obtained with suture ligation and electrocautery. The inner layer of running full-thickness absorbable sutures starts with two sutures at the middle of the posterior suture line and each progresses anteriorly as a continuous Connell stitch. An anterior outer layer of interrupted seromuscular sutures completes the two-layer closure. Thick and friable mesentery may restrict the mobility of the small bowel and thereby limit the ability to transect and slide the proximal intestinal loop alongside the distal intestinal loop, precluding creation of an SSIS.

If the transection of the intestine and the mesentery cannot be performed at the midpoint of the diseased loop and one resulting loop is shorter than the other, normal bowel can be recruited into the anastomosis when aligning the two limbs. The Michelassi strictureplasty can also be combined with resection of very severely diseased segments. If the middle of the diseased loop of intestine is severely affected by a long, rigid stricture that is not amenable to creating a safe anastomosis, that segment can be resected before sliding the proximal and distal loop alongside each other and creating the SSIS (Fig. 8A). Similarly, if one end of the diseased loop of intestine is severely affected, that segment can be resected, and

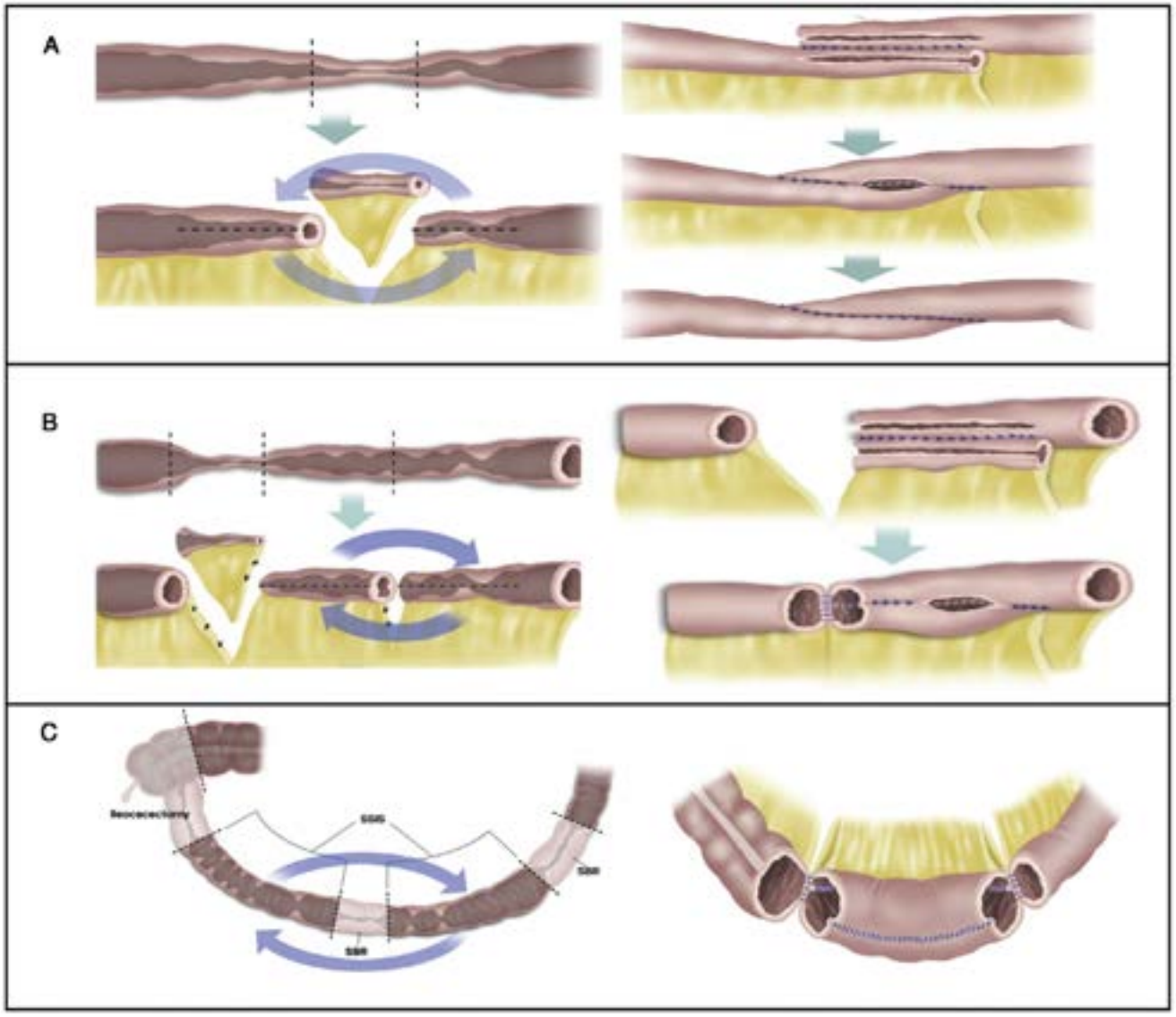


FIG. 8 **(A)** Resection side-to-side isoperistaltic strictureplasty (SSIS). The severe stricture located in the middle of the diseased loop can be resected before sliding the proximal and distal loops alongside each other and performing the SSIS. (**B**) Side-to-side-to-end SSIS. The severe stricture located at one end of the diseased loop can be resected, and the SSIS can be anastomosed to the uninvolved bowel in an end-to-end fashion. (**C**) End-to-side-to-side-to-end SSIS (SSIS with two discontinuous bowel loops). Severe strictures located in the middle and at either end of the diseased loop can be resected before performing the SSIS using the discontinuous diseased loops and then creating an end-end anastomosis at each end of the SSIS (Michelassi II). *SBR*, small bowel resection. *(From Lowenfeld L, Michelassi F. Managing stricturing Crohn's disease: Resect? Strictureplasty? Dilate? J Laparoendosc Adv Surg Tech A. 2021;31[8]:881–889.)*

the side-to-side strictureplasty can be anastomosed to the distal or proximal uninvolved bowel (Fig. 8B). When three severely fibrotic and deformed bowel segments are separated by two strictured segments, the Michelassi II strictureplasty can be employed (Fig. 8C). After resection of the three severely diseased segments located in the middle and at either end of the diseased loop, the remaining two discontinuous segments are used to perform an SSIS, according to the original description. Finally, each of the two ends of the SSIS is then anastomosed with the proximal and the distal bowel fashioning an end-to-side-to-side-to-end strictureplasty.

Results

In one of the largest systemic reviews and meta-analysis of 23 series on strictureplasty, including 1112 patients and 3259 strictureplasties, Yamamoto et al. reported that the most commonly performed strictureplasty was the Heineke-Mikulicz strictureplasty (81%), and strictureplasties are most often performed in the jejunoileal region (94%). The mean number of strictureplasties performed during one operation was 3 (range 1–21). The majority of patients underwent simultaneous resection and strictureplasty (61%). These observations have remained constant despite the widespread use of biologics and the development of complex strictureplasty techniques to address extensive CD in the past two decades (Heineke-Mikulicz 82.6%, jejunoileal 99.7%, simultaneous resection 73.7%). In a paper reviewing the 25-year experience with SSIS, Michelassi et al. found that 24% of patients who underwent strictureplasty for jejunoileitis underwent one or more SSIS procedures, and of the patients who underwent SSIS, 47% required additional small bowel resection away from the site of strictureplasty, and 45% required at least one synchronous conventional strictureplasty.

Yamamoto et al. reported a 13% overall complication rate following jejunoileal strictureplasty.[6] Septic complications occurred in 4% of cases, with 78% of septic complications related to the strictureplasty site and 44% of patients experiencing postoperative sepsis requiring laparotomy. The risk of postoperative hemorrhage requiring at least 2 units of packed red blood cells was 3%, probably as a result of creating a suture line in thick, diseased bowel. Most were successfully managed nonoperatively, only 6% requiring laparotomy. Only 2% of patients developed postoperative ileus, and 1% developed postoperative bowel obstruction. Of the patients who developed bowel obstruction, 27% required laparotomy. Emergency surgery, intraabdominal abscess, low hemoglobin, hypoalbuminemia, preoperative weight loss, and older age were significant risk factors for postoperative complications. In a meta-analysis including 32 studies with a total of 1616 patients and 4538 strictureplasties, Campbell et al. found that the incidence of early or late complications after a conventional (Heineke-Mikulicz, Finney) or nonconventional (SSIS) strictureplasty was similar (early complications 15% vs. 8% and late complications 29% vs. 17%, respectively).

Large studies and meta-analyses support strictureplasty as at least an equivalent alternative to resection in the treatment of CD. For extensive CD, use of the Michelassi strictureplasty may help avoid postoperative short gut syndrome. In the paper reviewing the 25-year experience with SSIS, Michelassi et al. showed that the median length of spared bowel was 52.5 cm (range: 20–280), equal to 17% of bowel length (range, 4.3%–40%).

In terms of disease recurrence following strictureplasty, Yamamoto reported a 5-year recurrence rate following strictureplasty of 28%, with only a 3% site-specific recurrence rate. Comparing recurrence rates after strictureplasty and resection is challenging because these operations are usually performed in two different groups of patients who may have a different risk for recurrence: strictureplasties are performed in fibrostenotic CD, while resections are performed in all types of CD (fibrostenotic, inflammatory, and penetrating). How much the phenotype of the disease influences the recurrence rate is poorly understood. Yet, from available data, it seems that the site-specific operation-free interval is similar for patients who undergo resection or strictureplasty.

SUMMARY

No treatment is curative in CD, and there is no medical therapy to prevent or reverse stricturing disease. Stricturing CD most commonly occurs in the small intestine and, over time, can lead to small bowel obstruction. While small bowel resection appropriately addresses a first incidence of obstruction at a single site, bowel preservation must be prioritized in the treatment of recurrent, extensive, and multifocal CD to avoid or delay the occurrence of short gut syndrome. Strictureplasty techniques alleviate strictures and preserve small bowel absorptive surface. Different strictureplasty techniques have been developed to address the variety of disease presentations. The safety profile of strictureplasty is good, making the technique safe. In terms of disease recurrence, the site-specific operation-free interval is similar for patients who undergo resection or strictureplasty. Strictureplasty can be used as a complement to medical therapy, endoscopic treatments, and surgical resection. These treatments may be used simultaneously, sequentially, and repeatedly.

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Management of Small Bowel Tumors

Ramy El-Diwany, MD, PhD, and John W. Harmon, MD

Small bowel malignancies are rare, difficult to diagnose, and have few treatment guidelines. Because small bowel tumors present with vague and common symptoms, it is imperative that the surgeon keep them on the differential for abdominal pain, obstruction, and gastrointestinal (GI) bleed. However, the majority of patients referred to surgeons for small bowel tumors have a suspicious mass on imaging. Evidence-based guidelines on management of small bowel malignancy are difficult to find, and given the rarity of these lesions, there is little information in the literature to provide reference for clinical decision making.

PRESENTATION

The typical presenting symptoms of small bowel tumors are vague and highly variable. Many patients with a known mass, discovered following workup for GI bleeding or encountered incidentally on imaging, present to surgeons as a referral from a primary care provider or a gastroenterologist. Others will present with colicky pain from obstruction, either partial or complete, and will be found to have a small bowel tumor during surgery. The mass itself can be intraluminal or circumferential, directly responsible for obstruction, or can have surrounding fibrosis that results in stricture and adhesion to the mesentery or retroperitoneum. GI stromal tumors (GIST) are frequently asymptomatic but can present with bleeding or obstruction.

Paraneoplastic symptoms such as weight loss and vague abdominal pain are concerning for malignant neoplasms like adenocarcinoma and lymphoma, particularly in the context of a known small bowel mass; however, these nonspecific symptoms should prompt broad investigations, as small bowel tumors are one of the rarer malignancies. Neuroendocrine tumors (NETs) that are productive of vasoactive amines can present with a wide range of symptoms, from epigastric pain and ulcerations to flushing, sweating, and diarrhea. However, most are asymptomatic and are found incidentally on imaging workup for other conditions.

Predisposing Conditions

Familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer (HNPCC) and Peutz-Jeghers syndrome (PJS) are genetic cancer syndromes that predispose to small bowel malignancy. Crohn's disease and celiac sprue, chronic inflammatory conditions involving the small bowel, also predispose to small bowel malignancy, and risk increases with increased severity and longer duration of disease. Patients with cystic fibrosis have 19-times higher incidence than the general population, with an additional 2- to 5-fold higher risk following lung transplantation. Obesity, tobacco use, and high dietary intake of red meat, smoked foods, alcohol, and refined sugar have all been shown to have an association with small bowel tumors, but the links between these risk factors and tumorigenesis are not clear. In fact, the etiology of small bowel tumors that are not associated with either chronic inflammatory diseases or genetic cancer syndromes is poorly understood.

Examination and Diagnostics for Patients Found to Have Small Bowel Tumors

On physical examination, it is only rarely possible to palpate an abdominal mass. Laboratory workup should include the standard complete blood count to look for anemia or elevated white blood cell count in the acute setting if signs of perforation are present. Elevated liver enzymes or amylase suggest possible duodenal mass or obstruction. Carcinoembryonic antigen (CEA) is often elevated in small bowel adenocarcinoma but is not sensitive or specific. Serum 5-HIAA and chromogranin A should not be routinely tested unless there is a strong clinical suspicion of NET based on symptoms or imaging features.

Imaging

Upon presentation with obstructive symptoms, a computed tomography (CT) scan with IV contrast allows clinicians to visualize the location of obstruction and possibly even the mass itself (Fig. 1). Masses can be constricting, occasionally demonstrating an "apple core" appearance with a circumferential constriction of the lumen. Some masses are polypoid, projecting intraluminally, and are better visualized with oral contrast. Close evaluation of the contour of the bowel is necessary to find submucosal lesions, and the keen surgeon should also thoroughly evaluate the mesentery for associated enlarged nodes or a mesenteric-based mass. Occasionally, enlarged nodes are the only sign of a nearby small tumor. A negative CT should not rule out small bowel tumor, as they are not particularly sensitive in this condition. However, CT does detect abnormalities in up to 80% of patients who do have a small bowel tumor. CTs are also valuable for staging nodes and metastatic lesions. Additional specialized imaging modalities such as octreotide or PET/DOTATATE scans are helpful in localization of NETs and identification of multifocal and metastatic disease (Fig. 2). In some institutions, these scans are routine before operative intervention.

Endoscopy

Esophagogastroduodenoscopy (EGD) can detect tumors into the third portion of the duodenum and is an excellent tool to begin the workup for GI bleed or other symptoms that are suspicious for GI masses. Endoscopic ultrasound is a useful adjunct to standard EGD

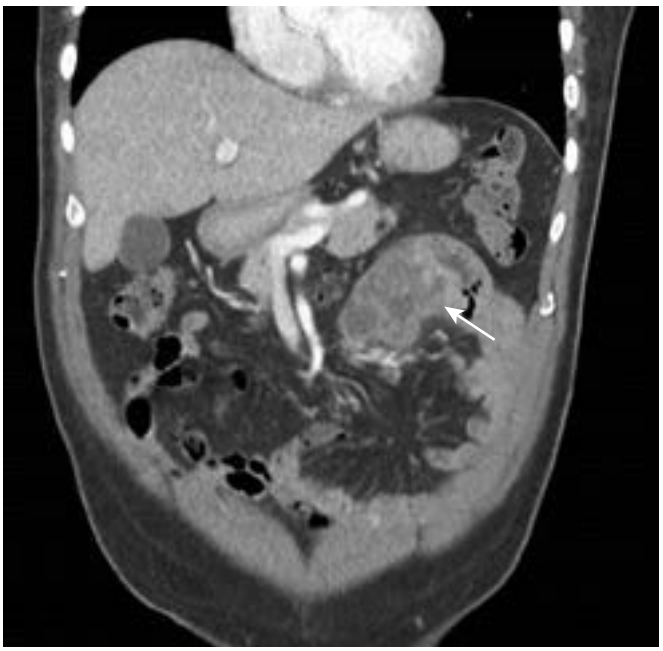


FIG. 1 Adenocarcinoma in the fourth portion of duodenum *(arrow)*.

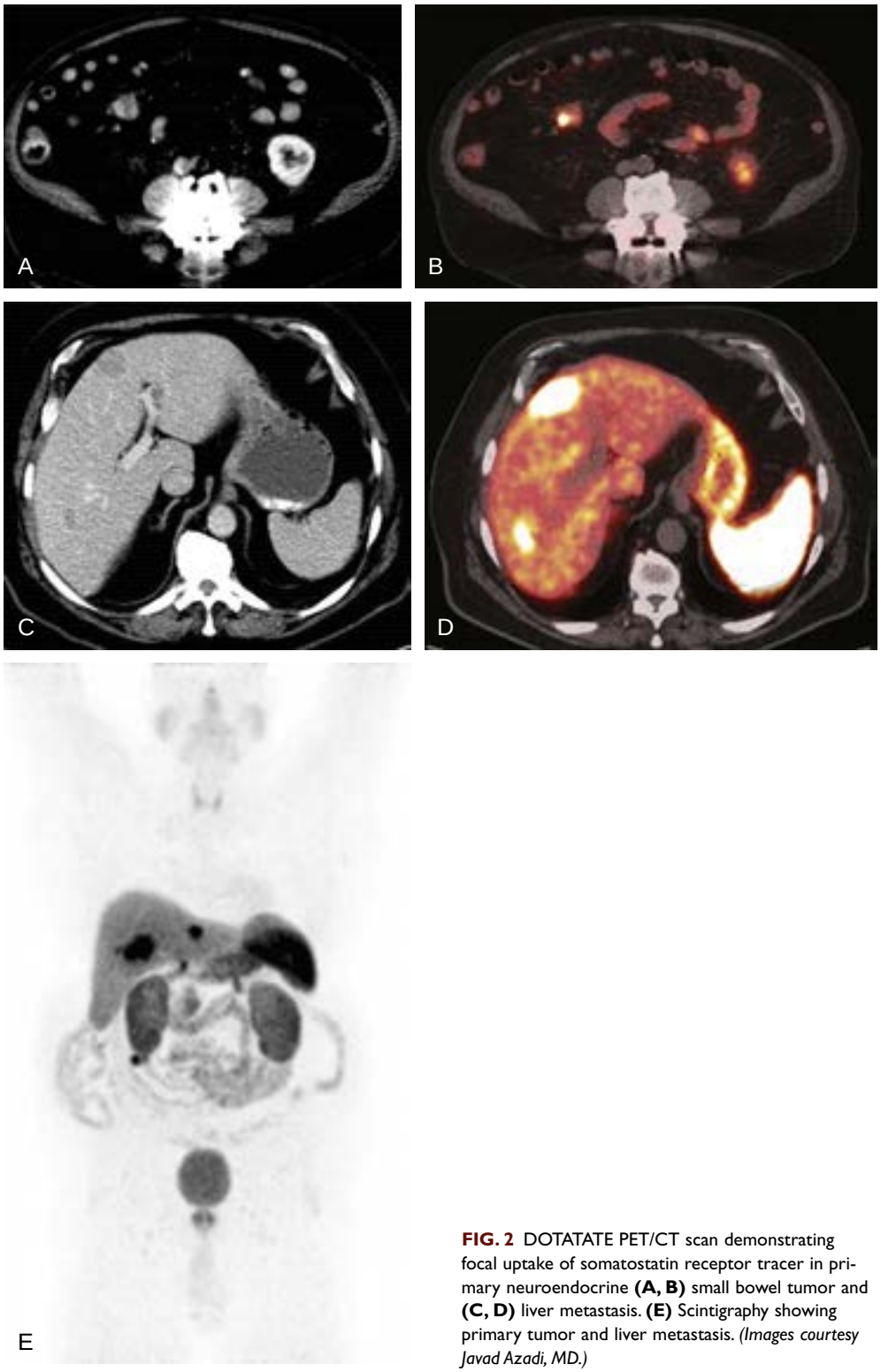


FIG. 2 DOTATATE PET/CT scan demonstrating focal uptake of somatostatin receptor tracer in primary neuroendocrine **(A, B)** small bowel tumor and **(C, D)** liver metastasis. **(E)** Scintigraphy showing primary tumor and liver metastasis. *(Images courtesy Javad Azadi, MD.)*

but in the discussion of small bowel tumors is limited to evaluation of duodenal lesions. For more distal evaluation, balloon-assisted deep enteroscopy or push endoscopy techniques can be performed by expert gastroenterologists and allow for visualization of most or even all of the small bowel lumen. This, however, is only rarely employed and only available in specialized centers. Video capsule endoscopy (VCE) also affords the ability to evaluate the mucosal surface of the entire small bowel, with an average of 30,000 images captured in the small bowel alone during an examination. With the assistance of neural networks and machine learning, the interpretation of these studies is becoming more sensitive and specific, making them an increasingly helpful tool for the investigation of small bowel tumors. VCE does not allow for tissue diagnosis and is contraindicated in patients with obstructive symptoms.

MANAGEMENT

Benign

Several types of benign small bowel neoplasms exist, and all are quite rare. Adenomas can be categorized as either villous, tubular, or Brunner's gland associated. As in colorectal cancer, some adenomas have malignant potential. There are no firm guidelines regarding management of these masses, but conventionally, the colorectal cancer pathway is followed with endoscopic resection if possible. Adenomas have increased malignant potential when associated with FAP. The number, size, histology, and dysplastic characteristics of the polyps should guide management using the Spigelman classification.

Surgical resection is warranted for large adenomas that are not amenable to endoscopic resection, particularly if biopsy reveals villous features. Additionally, patients should be screened for synchronous colorectal lesions with colonoscopy.

Leiomyomas are small tumors that are present in the submucosa of the small bowel. They are routinely small, firm, and well circumscribed. While they may cause obstruction and require resection for this reason, their presence alone is not an indication for surgery. Differentiating between leiomyosarcoma and leiomyoma can be difficult, and often these lesions are surgically resected to rule out malignant disease.

Lipomas are diagnosed relatively easily on CT due to their characteristic fatty density. Hamartomas associated with PJS should be resected only if causing bleeding or obstructive symptoms. In addition to lipomas and hamartomas, fibromyxomas and ganglioneuromas do not require resection, although biopsy may be necessary for diagnostic confirmation. Hemangiomas can be present along the length of the small bowel. Fortunately, these are easily differentiated on CT with IV contrast or magnetic resonance (MR) enterography obviating the need for biopsy.

Malignant

Malignant tumors of the small bowel are rare, with an estimated 10,470 cases and an estimated 1450 mortalities in the United States in 2018. Small bowel cancer comprises only 1% to 2% of GI malignancies. Because of the rarity of these cases and available retrospective data, there are very few guidelines available even worldwide for treatment of small bowel malignancy, and those are routinely derived from expert opinion based on analogous management of colon cancer. For this reason, each case should be evaluated on an individual basis and overseen by a multidisciplinary oncology team including a surgical oncologist.

Neuroendocrine Tumors

Derived from enterochromaffin cells, known as Kulchitsky cells, NETs are found throughout the crypts of Lieberkühn and are the most common small bowel tumor. They are histologically characterized by cytoplasmic core granules most commonly containing chromogranin A, synaptophysin, and neuron-specific enolase (Fig. 3). They often have the capacity to secrete clinically relevant vasoactive monoamines, peptides, and hormones. Neuroendocrine tumors are commonly referred to as carcinoid tumors and are the most common tumors of small bowel, accounting for more than 20% of the malignant tumors in the small bowel. Although small bowel NETs are often incidentally identified, many individuals present with advanced disease. At presentation, 40% of individuals will have multifocal tumors >2 cm, 70% will have invasion into the muscularis propria and regional lymph nodes, and 50% will have liver metastasis. Five-year cancer-specific survival in local staged small bowel NETs is 95%; however, with nodal and distant disease, this falls to 84% and 51%, respectively, with an overall survival of 32% in individuals with distant disease. Well-differentiated NETs are characterized as grade 1 to 3 based on Ki-67 index (%) and mitotic index/10 high-powered field (Table 1). GI NETs can occur anywhere in the GI tracts; however, 35% to 45% of them occur in the small intestine, and most are found within 60 cm of the ileocecal valve. On CT scan, carcinoid lesions are hyperenhancing in contrast to adenocarcinomas that are only moderately enhancing. They tend to extend through the serosa and can cause foreshortening of the mesentery secondary to a desmoplastic reaction. Frequently, the primary small bowel lesion is not visualized on imaging, and the presenting finding is bulky mesenteric adenopathy.

The regional spread of carcinoid tumors necessitates en bloc resection of the mass and mesentery, including an extensive lymphadenectomy, which is often more amenable to an open exploration (Fig. 4). During the operation, it is important to inspect for multicentric disease and liver metastases. However, even if these are present, it is still recommended to resect the primary lesion both for local control and longevity. Evidence indicates that 90% of the disease burden should be removed to yield the most durable symptomatic improvement, so any disease that seems resectable should be targeted at the time of surgery. In patients with liver metastasis, occasionally a staged approach to resection is implemented. Operative manipulation of carcinoid tumors has been associated with hemodynamically significant surges in vasoactive peptides known as carcinoid crisis, which is generally managed with high-dose somatostatin analogues in addition to hemodynamic stabilization. There is mixed evidence supporting the use of prophylactic somatostatin analogues for the prevention of carcinoid somatostatin crisis, and the practice varies substantially among surgeons and institutions. For duodenal carcinoid, endoscopic resection may be possible for small lesions. Anterior wall duodenal lesions may be directly excised with laparoscopic or open surgery. For select posterior lesions, local excision through an anterior duodenotomy to expose the posterior wall is an excellent approach. When both an anterior and posterior duodenotomy are performed, a gastrojejunostomy is recommended to avoid obstruction from narrowing of the duodenum. A Fogarty balloon, introduced through the gallbladder or cystic duct and passed proximally through the ampulla, can provide guidance during resection of tumors in the second portion of the duodenum. A cholecystectomy is then performed. This avoids opening the common bile duct. If the tumor is too close to the ampulla to be safely resected, a pancreaticoduodenectomy may be the only recourse.

Typical small bowel carcinoid resection removes 1 to 2 feet of small bowel, with wide lymphatic mesenteric clearance. The mesenteric involvement of this disease is often underestimated and can be misleading, necessitating more bowel resection than originally anticipated in some cases. It is imperative that patients are counseled about the risks of extensive resection preoperatively. Cases in which there is extensive involvement of small bowel mesentery require careful deliberation, and in some cases, leaving mesenteric disease behind is a disconcerting but necessary consideration to avoid short-gut syndrome. The authors would like to emphasize that while extensive resection should be considered for debulking symptomatic, multifocal, or metastatic disease, the consequences of a near-complete enterectomy, if less than 120 cm of small bowel remained, certainly outweigh the benefits of resection for these cases. Similarly, if the disease is extensive but relatively asymptomatic, with heavy mesenteric involvement to the root, the OR may best be left out of the treatment plan and systemic medical treatment with a somatostatin analogue is warranted.

Both multiple endocrine neoplasia type I (MEN1) and neurofibromatosis predispose patients to small bowel NETs; however, these occur primarily in the foregut, presenting as gastrinomas or somatostatinomas. The diagnosis and management of individual NETs is discussed elsewhere in this textbook.

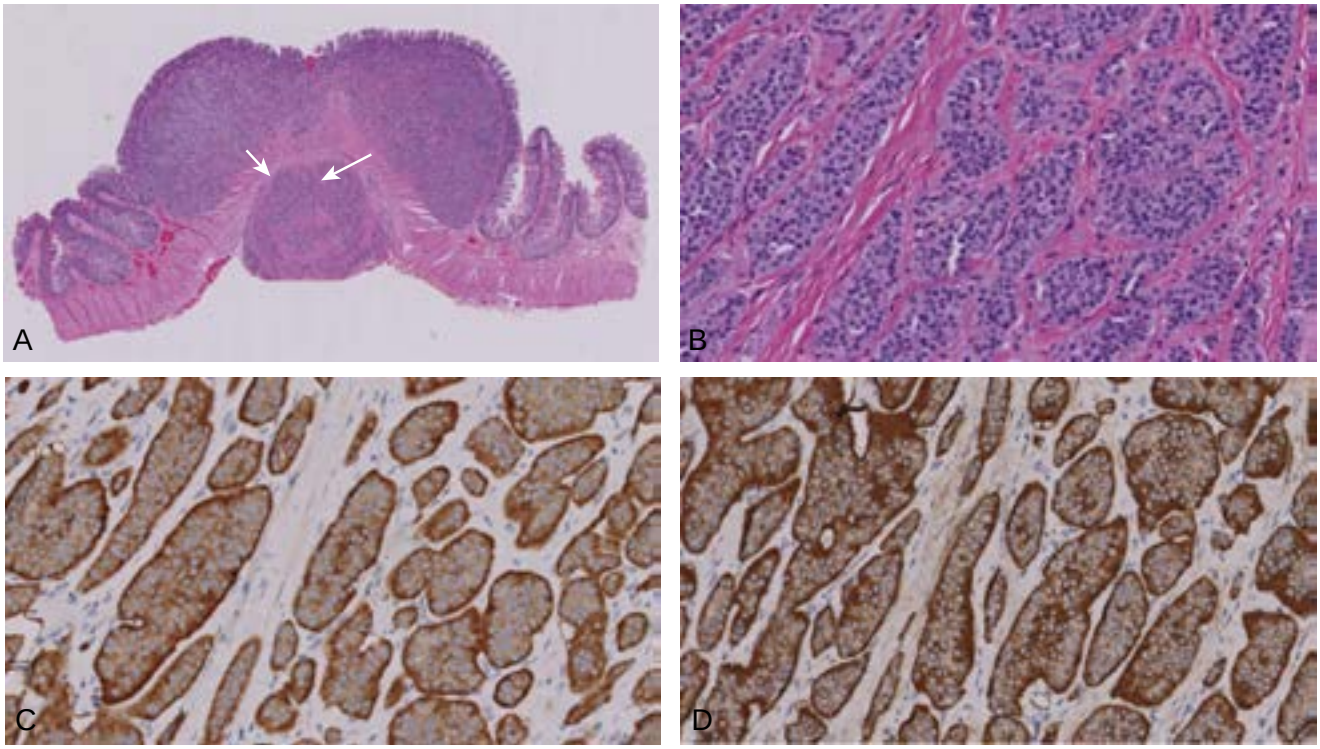


FIG. 3 Histology of NET. **(A, B)** Small bowel serosal invasion with surrounding normal small bowel mucosa (H&E, 2× and 20× magnification). **(C)** Synaptophysin (20× magnification). **(D)** Chromogranin (20× magnification). *(Images courtesy Neil Neumann, MD, PhD, and Sarah Umetsi, MD, PhD.)*

Adenocarcinoma

More than a third of small bowel cancers are adenocarcinoma and occur primarily in the duodenum. Unfortunately, because they are relatively asymptomatic until they are large enough to be obstructive or cause clinically evident bleeding, more than half of these tumors present at advanced stages, a third with nodal spread, and a quarter with distant metastases. Because of this, the 5-year survival following diagnosis is only 20% to 40% in most cases. Surgical resection is the mainstay of therapy, with a segmental resection and accompanying wide local excision of the mesentery to collect the nodal basin (Fig. 5). For those at the terminal ileum, an ileocolectomy should be performed. For duodenal lesions at the ampulla, a pancreaticoduodenectomy is necessary.

For unresectable primary disease, it is reasonable to perform a palliative surgical bypass of the obstructive lesion. Palliative radiation for unresectable disease is usually not beneficial. Clinical trials are ongoing to improve local and systemic control of unresectable disease, and surgeons are encouraged to help patients seek out these resources if possible.

TABLE 1 Gastrointestinal Neuroendocrine Neoplasm Classification System

	KI-67 INDEX (%)	MITOTIC INDEX/10 HPF
WELL-DIFFERENTIATED		
NET GRADE 1	<3	<2
NET GRADE 2	3–20	2–20
NET GRADE 3	>20	>20
POORLY DIFFERENTIATED		
NET GRADE 3	>20	>20
SMALL CELL TYPE	N/A	N/A
LARGE CELL TYPE	N/A	N/A
MIXED NEUROENDOCRINE NEOPLASMS		

Data from WHO classification of Tumors of Endocrine Organs, Fourth edition (2017).



FIG. 4 Ileocecal resection specimen with carcinoid tumor extending into serosal surface with regional lymph node metastasis. *(Image courtesy Neil Neumann, MD, PhD, and Sarah Umetsi, MD, PhD.)*

GIST

Mesenchymal tumors such as GISTs are most often found in the stomach (>50%) but also develop in the small bowel, with 25% in the jejunum. Derived from the interstitial cells of Cajal, they comprise approximately 10% of small bowel tumors. About 20% to 30% of GISTs are malignant at presentation, more often malignant when involving the small bowel. On CT scan, they appear as smooth, well-defined masses arising from the small bowel wall demonstrating exophytic growth patterns and internal heterogeneity. They may have areas of central hemorrhage or necrosis (Fig. 6). GIST rarely metastasize to nodes or spread outside of the abdominal cavity but can be aggressive. Metastases to the liver can present with multiple serosal-based nodules. The primary lesions are known for causing ulceration through the mucosa, presenting with bleeding. GIST can be differentiated from other sarcomas of smooth muscle by immunostaining for c-KIT. Activating mutations of the KIT oncogene can be seen in over 80% of GISTs. CT-guided biopsy is usually not necessary as radiographic appearance is distinctive and resection is indicated.

A laparoscopic approach for resection of GIST is often ideal. These tumors are exophytic, making them easier to locate than other small bowel tumors during laparoscopic exploration, and as they do not spread via lymphatics, lymphadenectomy is not required. A short segmental enterectomy with only 2 cm margins is recommended. If the tumor is bulky or adjacent organ involvement is suspected, preoperative imatinib can aid in shrinking the mass to facilitate resection. Unfortunately, more than 50% of these masses recur within 5 years. To prolong disease-free survival, high-risk patients should be treated postoperatively with a minimum of 12 to 24 months of imatinib, and studies are ongoing regarding longer or even indefinite treatment to prevent recurrence. High-risk features include tumor size >2 cm, high mitotic index, poorly differentiated cell type, presence of metastasis, and positive margin.

Sarcoma

Sarcoma, typically leiomyosarcoma, is rare, occurring most often in the ileum. Five-year survival is approximately 50%. Radical surgical excision is recommended if the primary disease is resectable. Similar to adenocarcinoma, if the disease is deemed unresectable, surgical bypass should be considered. Palliative radiation has a greater role in sarcoma management compared with other small bowel tumors.

Lymphoma

The small bowel is the most frequently encountered extranodal site for lymphoma. This tumor is usually non–Hodgkin-type lymphoma and involves the small bowel mesentery more commonly than the luminal surface. It is most common in the ileum, the most lymphoid-rich region of the small bowel. Clinicians should maintain a high suspicion for other sites of involvement, as a solitary small

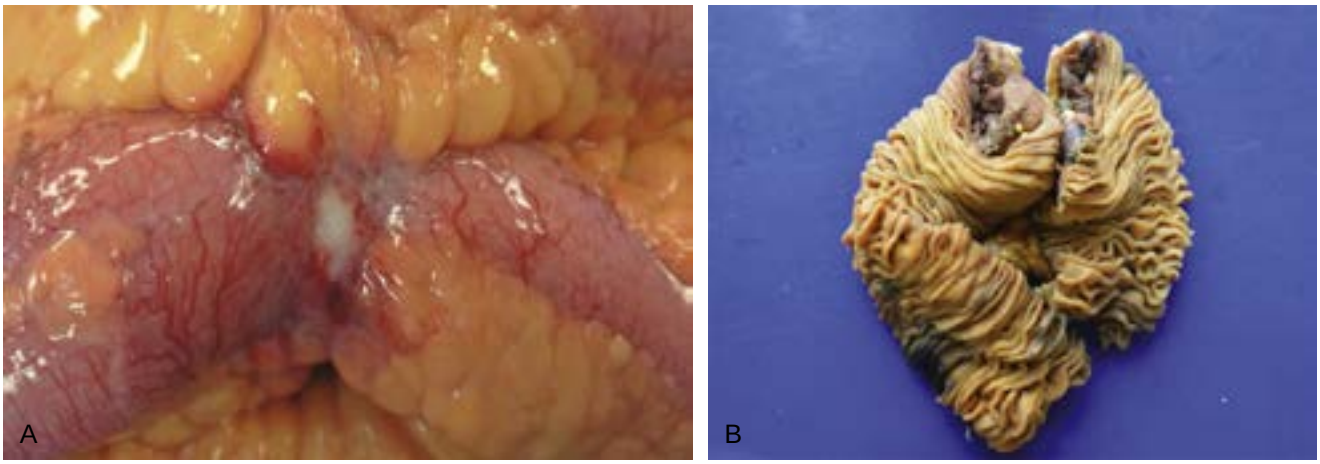


FIG. 5 Small bowel adenocarcinoma **(A)** intraoperative photo and **(B)** gross pathology. *(**B** courtesy of Neil Neumann, MD, PhD, and Sarah Umetsi, MD, PhD).*



FIG. 6 **(A)** Gross pathologic appearance high-grade GIST invading distal pancreas. **(B)** Gross pathologic appearance of intraluminal portion of GIST. *(Images courtesy Neil Neumann, MD, PhD, and Sarah Umetsi, MD, PhD.)*



FIG. 7 Small bowel lymphoma.

intestinal lesion is a rare presentation for lymphoma. Patients with Celiac disease have a 20-fold higher risk of GI lymphoma, and patients with chronic immunosuppression including transplant recipients and those with HIV are also at an increased risk. On CT with IV contrast, the mass often appears well circumscribed and homogeneous (Fig. 7).

A tissue diagnosis is required for lymphoma, and as there are a variety of non-Hodgkin subtypes, it is imperative that enough tissue is harvested to perform the full battery of cytopathology and flow cytometry. The subtype dictates the tumor behavior, treatment, and prognosis. Most small bowel lymphomas do not require resection and rather are best treated with multidrug chemotherapy. The 5-year survival is 50%, with poorer prognosis in males and the elderly. Surgery may be necessary for obstruction, or the diagnosis of lymphoma may be made postoperatively after surgical intervention for small bowel obstruction (SBO) has already taken place. In patients without signs and symptoms of SBO, CT-guided or endoscopic biopsy is appropriate to guide therapy. Indeed, the main role of biopsy in small bowel tumors is to distinguish lymphoma, as most other small bowel masses require resection as the primary management.

Metastatic Disease

Secondary involvement of the small bowel from other metastatic lesions presents as multifocal advanced cancer and not as an isolated small bowel lesion. Lung, melanoma, breast, colon, and cervical cancers can all spread to the small bowel. Sarcomas and adenocarcinomas can also impact the small bowel, either through direct erosion or carcinomatosis of overlying peritoneum. As an innocent bystander, the small bowel may need to be resected or bypassed depending on the type and stage of primary tumor.

SUMMARY

Small bowel tumors are rare and present with a constellation of common symptoms. Late diagnosis makes the prognosis of small bowel malignancy particularly poor, and a thorough workup to rule out small bowel tumors should be undertaken in anyone with vague abdominal pain and paraneoplastic symptoms with no other apparent source. Aside from small bowel lymphoma, most other suspicious small bowel masses do not require biopsy and should be resected. Nuanced management of these malignant lesions has room for investigation, and surgeons should feel compelled to lead efforts to discover optimal treatment paradigms and create guidelines.

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Small Bowel Diverticulosis

Jonathan B. Greer, MD

INTRODUCTION

Although small bowel diverticulosis is a rare clinical entity, all general surgeons should be comfortable with its diagnosis and management. The true prevalence is unknown, but a busy practitioner will frequently encounter these in clinical practice. Less than 4% of all small bowel diverticula will become overtly symptomatic. The duodenum is the most common site, while Meckel's diverticula are the most well-known. Small bowel diverticula can be congenital or acquired. These can be classified as either true or false, based on whether all three walls of the bowel are involved. Meckel's diverticula are the most well-known true diverticula of the small bowel. They are further classified by location (duodenal or jejunoileal), but they are best delineated by those that are asymptomatic and therefore incidentally detected versus those that present with clinical symptoms (usually bleeding or diverticulitis) and rarely as a cause of obstruction or perforation. Many manuscripts have been published on this topic, mostly single-center studies or case reports. There is a paucity of high-level evidence, however. Nonetheless, improvements in both axial imaging and advanced endoscopic techniques will likely lead to the increased detection of small bowel diverticulosis over time. This chapter will review the diagnosis and management of this clinical entity.

DETECTION AND MANAGEMENT OF ASYMPTOMATIC (INCIDENTALLY DISCOVERED) SMALL BOWEL DIVERTICULOSIS

The increasing frequency of high-quality cross-sectional imaging and endoscopic procedures has led to an increase in the detection of asymptomatic small bowel diverticulosis. However, this has not led to an increase in symptomatic cases. There are three principal groups of asymptomatic small bowel diverticula: duodenal, jejunoileal, and Meckel's diverticula, a subset of jejunoileal diverticula that are always congenital and true diverticula.

Duodenal Diverticula

The most common diverticula of the small bowel are duodenal diverticula, comprising 45% to 79% of cases. In terms of prevalence, a true number is difficult to ascertain, but these have been reported in 2% to 5% of upper gastrointestinal contrast studies, 7% of endoscopic retrograde cholangiopancreatography, and as high as 20% in one autopsy series. The only known risk factor is age. Duodenal diverticula are most commonly located in the second portion of the duodenum (60% to 95% of cases). They are much more commonly asymptomatic. These can be congenital or acquired, and extraluminal or intraluminal. The vast majority are acquired and extraluminal. The mechanism is thought to relate to weakness of the bowel wall where perforating vessels are found. There are rare congenital duodenal diverticula that are intraluminal, called *windsock diverticula,* and are lined with duodenal mucosa on the entirety of the diverticulum, both inside and outside, from a failure of canalization of the embryonal foregut.

Diagnosis is made by the discovery of an outpouching of the duodenum on cross-sectional imaging, fluoroscopic contrast studies, endoscopy, or at the time of an abdominal operation. Though duodenal diverticula can be quite large, asymptomatic diverticula are, by definition, asymptomatic; therefore, no treatment is required. Particularly in cases that would require a pancreaticoduodenectomy, surgical resection is associated with significant morbidity and therefore is not recommended for an incidentally discovered diverticulum.

Jejunoileal Diverticula

Jejunoileal diverticula are less common than duodenal diverticula, comprising less than 20% of small bowel diverticulosis in most series, although they are more likely to cause complications than their duodenal counterparts. The actual prevalence is unknown, but autopsy series have reported a prevalence as high as 7%. The vast majority are asymptomatic. These can be single or multiple, with 80% in the jejunum, 15% in the ileum, and 5% found in both. False diverticula are the most common. These are likely caused by the gradual weakening of the wall of the intestine from increased intraluminal pressure that can be generated by dysfunction of the migrating motor complexes. As such, age is the most widely reported risk factor. Other risk factors include intestinal dysmotility disorders. The most common location is the proximal jejunum, and these are frequently multiple.

Jejunoileal diverticula can be discovered on laparotomy, although they are commonly also diagnosed on radiographic or endoscopic studies. Enteroclysis is the best radiographic study to evaluate jejunoileal diverticula, though CT and MR enterography are increasingly used as techniques improve. Capsule endoscopy may be useful as well. There is no role for the surgical management of incidentally discovered jejunoileal diverticula.

Meckel's Diverticulum

Meckel's diverticula are the most common congenital diverticula of the small bowel and account for 25% of small bowel diverticula (Fig. 1). A prevalence estimate in an autopsy study was 1.23%.



FIG. 1 Common presentation of a Meckel's diverticulum projecting from the antimesenteric border of the ileum. *(From McKenzie S, Evers BM. Small intestine. In: Townsend CM Jr, ed. Sabiston Textbook of Surgery. 19th ed. Philadelphia: Elsevier; 2012.)*

They are, by definition, true diverticula of the ileum and represent a remnant vitelline (omphalomesenteric) duct that connects the embryonic midgut to the yolk sac. This duct is normally obliterated during embryologic development. As a true diverticulum, it involves all three layers of the bowel wall and is always antimesenteric. The classic "rule of two" for Meckel's diverticula is thus: They are located approximately 2 feet from the ileocecal valve, contain two types of heterotopic tissue (gastric or pancreatic), occur twice as commonly in males, in 2% of the population, are symptomatic in about 2% of cases, tend to be diagnosed within the first 2 years of life, and can extend over 2 inches in length. Additionally, there are two types of symptoms that can arise: bleeding and obstruction.

Given their small size, most asymptomatic Meckel's diverticula are discovered during surgery for another indication. They are less frequently found on axial imaging. Meckel's diverticula have a low lifetime risk of complications related to the diverticula itself, and mortality is extremely rare. Therefore, in most cases, there is no compelling indication for surgical resection of an incidentally discovered Meckel's diverticulum in an adult. Some authors advocate for prophylactic resection in children, and in adults in cases of palpable ectopic tissue, prior history of diverticulitis, hemorrhage, intussusception, or the presence of a mesodiverticular band. This is in contradistinction to the management of clinically significant Meckel's diverticula, which will be discussed later in this chapter.

DETECTION AND MANAGEMENT OF SYMPTOMATIC SMALL BOWEL DIVERTICULOSIS

The minority of small bowel diverticula present with clinical manifestations, which can be infection (diverticulitis), bleeding, or obstruction. Unlike the incidentally discovered and therefore asymptomatic versions, symptomatic small bowel diverticula require treatment.

Duodenal Diverticula

Only about 5% of patients with duodenal diverticula present with complications. The most commonly reported symptom is postprandial epigastric abdominal pain, which can be associated with nausea and vomiting. Obstruction from a duodenal diverticula is quite rare but can occur, particularly in cases in which the diverticula is large. This can result in extraluminal compression of the duodenum. There can also be extrinsic compression of the biliary tree or pancreatic duct, thus resulting in a rare cause of obstructive jaundice or recurrent pancreatitis. More commonly, infectious complications may develop, such as diverticulitis +/– abscess, perforation, and rarely, fistula. Bleeding may also occur secondary to diverticulitis as inflammatory erosion into a neighboring vessel may result in fairly significant bleeding, with hematemesis and melena as the presenting signs.

After initial nasogastric tube decompression for duodenal obstruction, diagnosis of a duodenal diverticula as the underlying cause is usually one of exclusion, as a malignancy would be far more common. This diagnosis can be made by axial imaging, usually CT, although an upper gastrointestinal contrast study may also be helpful. These can be challenging in an obstructed patient. In conjunction with these radiographic studies, endoscopy is necessary to rule out mucosal-based lesions as the etiology. In cases of biliary tree or pancreatic duct obstruction from duodenal diverticula, axial imaging (CT or MRI) in concert with endoscopy, including ERCP, are essential to make the diagnosis. Duodenal diverticulitis will usually be diagnosed on CT with characteristic findings similar to the vastly more common colonic diverticulitis. CT angiography may be necessary to identify a bleeding vessel related to a duodenal diverticula, although endoscopy may also be helpful. The patient's clinical condition should dictate whether purely diagnostic studies (e.g., CT angiography or endoscopy) can be safely done, rather than diagnostic and therapeutic modalities, such as mesenteric angiography in interventional radiology.

Management of duodenal diverticulosis in the asymptomatic patient is straightforward (nothing to do) but can be more nuanced in symptomatic patients and varies greatly with the clinical scenario. The rare case of duodenal obstruction secondary to a duodenal diverticula may require surgical intervention. This may include resection of the diverticula alone with transverse closure of the duodenum, use of a serosal small bowel (Thal) patch, a Roux-en-Y duodenojejunostomy, or potentially a segmental duodenal resection. Assessment of the anatomic relationship between the ampulla of Vater and the line of transection is crucial for segmental resection of the duodenum. Involvement of the medial side of the duodenum that results in obstruction will require a pancreaticoduodenectomy. The more common case involving biliary or pancreatic obstruction should be temporized first via endoscopic means, usually with stenting. Surgical resection, which would be a pancreaticoduodenectomy, should be reserved for patients who fail endoscopic management. As with all complex hepatobiliary procedures, surgeon familiarity and comfort with these techniques along with well-delineated anatomic relationships between the duodenal diverticula and important neighboring structures is critical. Most cases of duodenal diverticulitis, even with contained perforation, can be managed conservatively with nil per os, placement of a nasogastric tube, antibiotics, and occasionally percutaneous drainage. Surgical management in the acute setting is almost never indicated and can be quite challenging. Bleeding duodenal diverticula are managed similar to other causes of upper gastrointestinal bleeding, either via endoscopy or interventional radiology. Surgical management is rarely indicated.

Jejunoileal Diverticula

Symptomatic false jejunoileal diverticula are rare, but about 10% of all jejunoileal diverticula will become symptomatic. Patients can present with nonspecific symptoms such as abdominal pain, early satiety, bloating, and malabsorption (diarrhea and/or steatorrhea) secondary to small intestinal bacterial overgrowth (SIBO). The complications that can arise and therefore lead to detection are diverticulitis, bleeding, obstruction, or perforation. The clinical presentations associated with each of these complications are similar to their large bowel counterparts, although the pain is typically epigastric or periumbilical in location. Cross-sectional imaging is the most common means of detection as these patients will usually present with abdominal pain or melena.

SIBO is treated with antibiotics. The treatment of jejunoileal diverticulitis is identical to that of colonic diverticulitis: bowel rest, intravenous fluids, and antibiotics. Surgical intervention is not always needed, particularly in isolated cases. Recurrent or complicated episodes may mandate segmental resection, although rare. Management of perforated jejunoileal diverticula depends greatly on the condition of the patient. Conservative management may be appropriate in cases in which the perforation has walled off and the patient is minimally symptomatic. Conversely, critically ill patients warrant urgent exploration and segmental resection. Enterocutaneous fistulae secondary to jejunoileal diverticulitis have been reported. A bleeding jejunoileal diverticulum can be found on push or double-balloon enteroscopy or on capsule endoscopy, and it should be considered in cases of gastrointestinal bleeding in which both esophagogastroduodenoscopy and colonoscopy are negative. Endoscopic management of bleeding can be difficult, and interventional radiology angioembolization is not typically attempted. After a trial of conservative management, surgical intervention is warranted. Small bowel obstructions secondary to jejunoileal diverticula are managed like adhesive small bowel obstructions. Resection of the diverticula would be warranted in cases of failure of conservative management. An uncommon clinical scenario is bowel obstruction secondary to an impacted fecalith. These can be treated surgical by enterotomy and stone extraction.

Meckel's Diverticula

The risk of a complication that leads to discovery of a Meckel's diverticulum is estimated to be in the 2% to 6% range. The most common mechanism of a symptomatic Meckel's diverticulum is thought to relate to acid production by heterotopic gastric mucosa within the diverticulum leading to ulceration. The symptoms/complications that can arise are bleeding, obstruction, or abdominal pain. These usually occur in the pediatric population. The relative proportion of each of these findings is not fixed, but one single-center series of known Meckel's diverticula in pediatric patients had 19% discovered incidentally, whereas the remaining patients presented with the following: 35% gastrointestinal bleeding, 20% diverticulitis or perforation, 14% obstruction, and 12% intussusception.

Gastrointestinal bleeding that is caused by a Meckel's diverticulum may be acute or chronic. It is frequently associated with heterotopic gastric mucosa, much more so than an asymptomatic Meckel's diverticulum. The suspicion of a bleeding Meckel's diverticulum should be higher in young patients with no evidence of an inflammatory explanation for the bleeding, such as infectious illnesses or inflammatory bowel disease, or in adults <30 years of age in whom an exhaustive workup for gastrointestinal bleeding is otherwise negative. Algorithms for gastrointestinal bleeding should be followed in the appropriate clinical setting. A Meckel's scan, which is a scintigraphic study, or mesenteric angiography may localize the Meckel's diverticulum as the source of the bleed, as can advanced endoscopic techniques such as double-balloon or capsule endoscopy (Fig. 2). CT angiography has been shown to play an increasing role as a sensitive test, but in a young, hemodynamically stable patient, the Meckel's scan is the test of choice as it will detect heterotopic gastric mucosa in 85% to 97% of cases. Rarely, if all other studies are negative, in the setting of ongoing bleeding leading to hemodynamic compromise, surgical exploration may be warranted to exclude a bleeding Meckel's diverticulum.

There are multiple mechanisms by which a Meckel's diverticulum can lead to a small bowel obstruction, including hernia formation. In

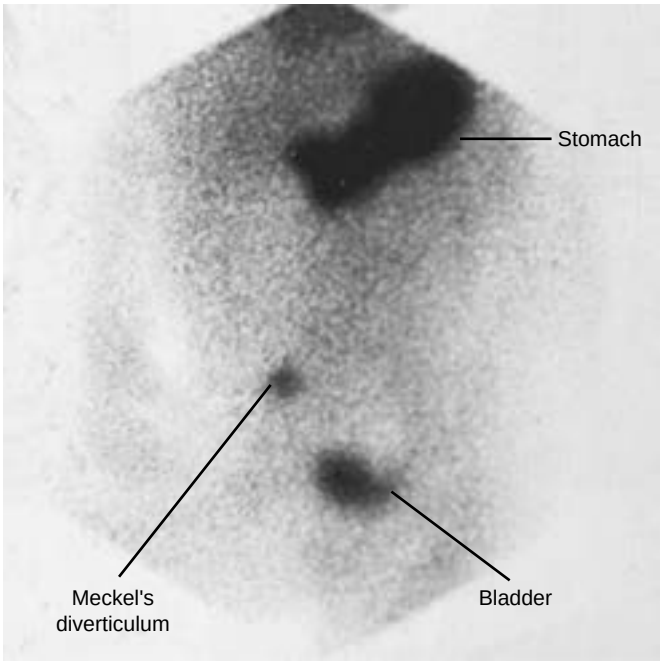


FIG. 2 Technetium-99m pertechnetate scintigram from a child with a Meckel's diverticulum clearly differentiated from the stomach and bladder. *(From McKenzie S, Evers BM. Small intestine. In: Townsend Jr CM, ed. Sabiston Textbook of Surgery. 19th ed. Philadelphia: Elsevier; 2012.)*

children, volvulus and intussusception can occur, whereas these are rare in adults. Symptoms are similar to non–Meckel's-related small bowel obstruction. Diagnosis can be made by CT scan, but often it is made at exploration.

Diverticulitis or perforation secondary to a Meckel's diverticulum will lead to abdominal pain and tenderness on physical examination. Although the location of tenderness secondary to Meckel's diverticulitis may be variable, perforation will lead to lower abdominal tenderness.

The treatment of a clinically significant Meckel's diverticulum is first to address the clinical scenario in a standard fashion. For example, in the case of a bowel obstruction secondary to a Meckel's diverticulum, nasogastric tube decompression and volume resuscitation are the first steps. Following this, surgical resection should be undertaken. Surgical resection can be either via a diverticulectomy or segmental bowel resection and reconstruction. A segmental resection is recommended in cases in which the base of the diverticulum is broad or there is a palpable abnormality. Furthermore, in bleeding secondary to a Meckel's diverticulum, segmental resection is recommended because the ulcer is commonly on the mesenteric side of the ileum, sometimes downstream of the diverticulum. Some authors advocate for appendectomy at the time of operation for a symptomatic Meckel's diverticulum so as to avoid diagnostic dilemmas in the future.

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Diagnosis and Management of Motility Disorders of the Stomach and Small Bowel in the Current Era

Omar M. Ghanem, MD, and Michael G. Sarr, MD

INTRODUCTION

Unlike in the duodenal ulcer/vagotomy era of the 1950s–1980s, motility disorders of the upper gut are currently quite uncommon. When present, this spectrum of disorders is difficult to both diagnose and treat effectively. To suspect these disorders, it is necessary to understand the overall control of motility of the stomach and small bowel; thus, we will present a very brief review of the physiology of motility.

In brief, the contractile activities of the stomach and small intestine are controlled by the enteric (autonomic) neuromuscular system in the wall of the gut. This is important to remember, because the extrinsic innervation to the gut (parasympathetic/vagal nerves and sympathetic/paravertebral nerves) do not control or initiate motility; but rather, they can only influence motor patterns as can some hormones. Basically, contractile activity is generated by spontaneously active neuromotor cells within the wall of the gut. When the stomach and small intestine are completely separated from the central nervous system (as after a small intestinal transplantation), relatively normal motility still occurs.

Contractile activity has two basic patterns, one during fasting (the so-called interdigestive period) and another after feeding (the postprandial period). Also, all contractile activity is oriented in a distal, downstream direction of propagation that leads to distal transit of ingested foods.

The stomach and small intestine, however, do differ in their contractile patterns. During the interdigestive period when there is no food ingested, the stomach and small intestine cycle through a recurrent pattern of intense contractions that travel peristaltically but only up to about 30 cm; this band of contractions begins in the stomach and then moves slowly down the small intestine over about 90 minutes. These contractions are of very high amplitude to clear the lumen of undigested food and debris. In contrast, during the postprandial period after ingestion of food, the contractile patterns

maximize contact of ingested foodstuffs with the mucosa. In the stomach, the contractile pattern mixes and mechanically breaks down (triturates) the bigger food particles to maximize digestion (indeed, larger food particles do not leave the stomach during this period, because the so-called antropyloric pump controls the size of the pylorus to only allow food particles <1 cm to leave the stomach), while the small intestine slows transit through the gut to maximize absorption.

Although we talk about "peristalsis" of the gut, the contractions of the stomach and small intestine do NOT peristalse as does the esophagus, where a contraction that starts in the proximal esophagus propagates down the entire length of the esophagus in a very orderly, peristaltic fashion (indeed the motor activity of the esophagus is designed only to transport food into the stomach). In contrast, the stomach and the small intestine are designed to move content distally but in doing so to maximize digestion and absorption.

Contractile activity of the stomach differs considerably from the esophagus, and understanding these differences is absolutely crucial to diagnose gastric motility disorders. The proximal and distal stomach have different contractile activity with the proximal stomach controlling emptying of liquids and the distal stomach the emptying of solids. The proximal stomach has a nonphasic, slow continuous tonic activity that gradually relaxes the proximal stomach increasing its volume for the ingestion of food, the so-called vagally mediated "receptive relaxation" that allows that full plate of spaghetti we eat to enter the large volume reservoir of the proximal stomach. Later, the proximal stomach slowly contracts tonically, thereby decreasing the volume reservoir, increasing intraluminal pressure, and leading to gastric emptying of liquids. In contrast, the mid to distal stomach has definite physic contractions (2–4 per minute) that arise from a pacemaker region in the mid stomach (similar in principle to the pacemaker in the heart). These contractions then propagate in a peristaltic manner distally from the distal mid stomach to the antrum and down to the pylorus. Why is this important to understand? Nearly all current motility disorders of the stomach are related to injuries of the vagus nerves that control both the relaxation of the proximal stomach (emptying of liquids) as well as modifying the coordination of contractions of the distal stomach with the pylorus (emptying of solids).

The small bowel also has a pacemaker region in the proximal duodenum that drives the rate and distal direction of contractions in the small bowel. But peristalsis as we know it in the esophagus is NOT present in the small bowel despite our use of the term "peristalsis" of the small bowel. Although contractile activity is phasic (6–12 per minute) and always oriented distally, the length over which a true peristaltic contraction migrates after a meal is only 5 to 10 cm, leading to the small areas that tend to move content distally but only for a short distance; this pattern of contractions leads to a segmenting appearance that we readily see on contrast fluoroscopy. This pattern increases contact of luminal content with the mucosa, slows transit, and increases absorption. Control of this activity is not vagally dependent, but the sympathetic system does have modulatory effects (primarily inhibitory) on small intestinal contractions as evidenced both by postoperative ileus (POI) and especially by the condition of adynamic ileus that can occur with retroperitoneal trauma, infection, or "irritation." (We will expand on this later.)

In summary, most true gastric motility disorders that currently occur are related to inadvertent operative injury to the vagus nerves or vagal neuropathies, whereas small intestinal motility disorders are much less common and are related either to congenital/hereditary abnormalities in the enteric nervous system or to sympathetic neural effects.

MOTILITY DISORDERS OF THE STOMACH

In our current era, objective dysmotility of the stomach (with either documented delayed gastric emptying or dumping with accelerated gastric emptying) occurs more typically after upper gut operations that purposely or inadvertently cut or injure the vagus nerves or occur as a result of damage to the vagus nerves (neuropathy) from chronic illness, such as poorly controlled diabetes. Surgeons see gastric dysmotility most often after operative interventions that disrupt vagal nerve function, such as after a gastrectomy, after an esophagectomy that necessitates transection of the vagus nerves, or after a hiatal herniorrhaphy that injures the branches of the vagus nerves at the esophageal hiatus. In the past when duodenal ulcer operations centered around a truncal vagotomy, the loss of vagally mediated receptive relaxation of the proximal stomach leads to rapid emptying of liquids leading to dumping syndrome and/or disruption of emptying of solids. Less commonly, after creating a Roux-en-Y limb to drain the gastric remnant or the esophagus, gastric emptying can be delayed. The obligate transection of the jejunum disrupts myoelectric continuity (which controls orderly coordination of contractions) of the Roux limb with the duodenal pacemaker; this leads to erratic, noncoordinated contractions in the Roux limb with some contractions actually going upstream, thereby delaying gastric emptying (the so-called Roux stasis syndrome). There is also a spectrum of idiopathic gastroparesis syndrome that usually occurs in young females that is poorly understood and is often not associated with any objective delay in gastric emptying; yet because of the symptoms, this has been termed "gastroparesis-like syndrome." Overall, true gastric motility disorders involve either delayed emptying (mild or severe gastroparesis) or too rapid emptying (dumping).

When functioning normally, the proximal stomach is responsible for vagally mediated relaxation (receptive relaxation) to accommodate the entry of solids and liquids by providing a reservoir necessary for temporary storage and the start of enzymatic and mechanical breakdown of the ingested content. This relaxation is mediated by the vagus nerves. In addition, some protein and fat digestion in the stomach begins by way of pepsin and hydrochloric acid; the presence of amino acids in the duodenum will lead to hormonal signaling that causes a slow tonic contraction of the proximal stomach. This tonic contraction increases the intraluminal pressure in the proximal stomach, thereby leading to emptying of chyme into the duodenum. In contrast, fats in the duodenum can slow gastric emptying by prolonging the relaxation of the proximal stomach. Gastric emptying mediated by the enteric nervous system can be disrupted by surgical procedures as previously listed. Little is known about specific causes that lead to altered gastric emptying after gastroesophageal surgery, but it appears to be multifactorial. The surgical process itself, in addition to patient-related factors, such as the presence of diabetes, hypothyroidism, chronic narcotic use, or cancer, can contribute to this process. As aging occurs, the rate of gastric emptying decreases, so older patients are more susceptible to this syndrome. This section focuses on motility disorders after surgical interventions, postsurgical gastroparesis syndrome, and rapid gastric emptying. There is also a separate section on gastroparesis-like syndrome.

Delayed Gastric Emptying/True Gastroparesis

Although uncommon, delayed gastric emptying can occur after operations on the distal esophagus or stomach that include a known or inadvertent vagotomy, Roux-en-Y gastrojejunostomy, or even after an antireflux procedure. The risk of delayed gastric emptying after a gastrectomy that includes a truncal vagotomy increases twofold and can plague patients undergoing a classic pancreatoduodenectomy (which includes an antrectomy) with the Roux-en-Y reconstruction with a rate of up to 30%. The exact causes are unknown, but certainly vagus nerve dysfunction is a key contributor as is the disruption of the continuity of the proximal jejunum with the duodenal pacemaker after duodenal resection leading to incomplete emptying or gastric stasis. Truncal vagotomy causing the disruption of afferent vagal signaling to the brain also may lead to stasis or even gastric atony.

Clinical Presentation and Diagnosis

Symptomatically, patients found eventually to have an objective delay in gastric emptying (i.e., true gastroparesis) and not the

gastroparesis-like syndromes (see later, Gastroparesis-Like Syndromes) often describe epigastric fullness or pain and complain of early satiety that may or may not be accompanied by nausea and vomiting, usually of solids more than liquids. Look for delayed vomiting of undigested food, hours or even the day after ingestion of the solid food; this delayed vomiting of undigested food is virtually pathognomonic of gastroparesis provided there is no mechanical gastric outlet obstruction. Liquid intake will be better tolerated than solids but may be limited by early satiety, anorexia, or the inability to ingest enough calories because of symptoms of gastric fullness; this situation can be severe enough that patients may develop dehydration, weight loss, or malnutrition.

A detailed history is necessary to evaluate risk factors, such as prior upper abdominal surgery (esophageal, gastric, or duodenal), or metabolic disturbances, such as diabetes or rarely hypothyroidism. The physical examination is often not helpful, but a succussion splash will be evidence of delayed emptying of the stomach but most probably from a mechanical obstruction. During the diagnostic phase, it will be necessary to exclude any type of mechanical obstruction, such as an efferent limb syndrome, anastomotic stricture, or rarely an intussusception after a gastroenterostomy. Once mechanical obstruction is excluded, clinicians must exclude metabolic derangements that can be observed from persistent vomiting or contributing causes, such as diabetes and hypothyroidism. It is important to evaluate the nutritional state with nutritional parameters such as serum albumin levels. Because albumin levels may be normal (they take a week or more to decrease substantially), ordering a prealbumin that has a shorter half-life may help determine a more acute or subacute process. If patients have a mechanical obstruction at the gastroenteric anastomosis identified as an anastomotic stricture or a stricture immediately downstream from the anastomosis, ensure that they are not abusing aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) and thereby contributing to ulceration and anastomotic inflammation. Unfortunately, patients will not always admit this, so if you suspect it, check a urinary level of aspirin, not a serum level that is more transient.

Imaging can begin with abdominal x-rays with contrast to rule out a mechanical obstruction. One caveat to remember: most cases of a gastric motility disorder leading to gastroparesis do NOT have gastric distension, because as stated earlier, most cases are related to vagal dysfunction and the loss of proximal gastric relaxation; there may, however, be solid matter retained in the remnant. In contrast, if there is a markedly dilated gastric pouch of stomach, it is much more likely due to a mechanical obstruction. One exception is the transient POI or a generalized adynamic ileus in which the stomach may very well be distended.

Upper endoscopy will allow visualization of undigested food in the stomach (always an abnormal sign if present more than 2 or at most 3 hours after ingestion), elimination of the possibility of anastomotic stricture, and the means by which to obtain biopsies if necessary. Remember, postvagotomy gastroparesis and most other forms of gastroparesis are NOT associated with a dilated, distended stomach.

Currently, there are three potential tests to demonstrate delayed gastric emptying objectively: scintigraphy, wireless motility capsule (WMC), and carbon breath testing. The gold standard for evaluation of delayed gastric emptying, and thus the diagnosis of gastroparesis, is the 4-hour scintigraphic gastric emptying of solids. The most reliable parameter for the diagnosis is gastric retention of solids is based on the percent retention at 4 hours, graded as mild (<15%), moderate (16%–35%), and severe (>35%) gastroparesis. The WMC, though new and a technique that avoids the (minimal) radiation exposure of a scintigraphic technique, is not well standardized and relies on the emptying of just this one capsule; this test is used primarily under experimental studies. Carbon breath testing has been used in Japan and elsewhere but is still experimental in the United States and is not used except in selected centers. Barium swallow is not a good measure of gastric emptying, and gastric manometry, when available, has not really become a go-to diagnostic test. With the presence of retained solid food in the gastric reservoir, these studies attempting to quantify the rapidity of gastric emptying are usually not necessary.

Nonoperative Treatment

Treatment begins with the management of contributing factors, such as obtaining tighter glucose control or treatment of hypothyroidism. The mainstay of treatment is directed at modifying the diet. One should focus on encouraging the ingestion of liquids more than solids and adapting to smaller and more frequent meals (ideally six or even more if necessary while awake). If well-tolerated, some of the high-calorie, high-protein, low-fat, so-called small particle liquid formulations, though often not as palatable, can provide the necessary calories for patients with nutritional challenges; if associated dumping (see later) is problematic, the high-calorie liquids may not be a good option, but the high-protein formulations may help. The authors recommend a low-residue diet (i.e., lower fiber content) and softer foods that do not require mechanical breakdown. Remember, this will be the mainstay of treatment. Having the patient develop a relationship with an informed dietician can be extremely beneficial.

Pharmacologic agents: If dietary modification does not manage symptoms, a trial of a prokinetic drug, such as metoclopramide, domperidone (if the patient still has an antrum, which is where domperidone takes effect), or low-dose erythromycin (125 mg) that activates the prokinetic motilin receptor, may help stimulate emptying, but NOTE not the usual antibacterial doses of 250 or 500 mg (Table 1). Be aware that these medications do not work in most patients, and if after a short trial no results occur, there is no benefit of continuing their use. The medications used most commonly are metoclopramide and domperidone. As with any D2 receptor antagonist that penetrates the blood-brain barrier, extrapyramidal side effects can occur. Metoclopramide should be started at 5 to 10 mg three times daily but needs to be administered 30 minutes before each meal; the use of >40 mg per day is associated with a not-insignificant risk of extrapyramidal effects, both acute (spasmodic dystonias) and chronic (tardive dyskinesia), especially in the elderly. As the prescribing physician, you will need to explain and warn patients of this very alarming side effect and stop the medication if any such symptoms occur. The latter risk has led to the US Food and Drug Administration (FDA) to issue a black box warning that has effectively decreased its use as an antinausea medication as well as a prokinetic agent. Domperidone, although not approved in the United States, is a closely related D2 receptor antagonist that does not cross the blood-brain barrier. This agent is used widely outside the United States and still is recommended frequently by US physicians (with patients obtaining this medication from other countries such as Canada). Recently, however, concerns about cardiovascular proarrhythmic risks (QT prolongation and tachyphylaxis) are the most concerning adverse effects from domperidone that has led to warnings in Europe and has had some feedback in the United States. Erythromycin is useful for improving gastric emptying in the short term (e.g., in hospitalized patients) but has never been rigorously evaluated for symptomatic relief with its long-term use; its tachyphylaxis requires "drug holidays."

Several newer, highly selective 5HT3 antagonists and 5HT4 receptor agonist medications may help selected patients with the nausea and vomiting, but do not expect these agents to increase effective gastric emptying. Total parental nutrition (TPN) or, if tolerated, enteral nutrition may be required in severe and life-threatening cases of malnutrition; indeed, enteral delivery of nutrition should always be tried before TPN. Finally, tricyclic antidepressants have been suggested and may be considered for especially refractory nausea and vomiting, but the data are quite controversial, because the anticholinergic component of it could potentially worsen symptoms and it might actually retard gastric emptying. Therefore, these agents should be considered only with close monitoring and only after failure of prokinetic agents.

TABLE 1 Medications for Gastroparesis

Drug	Indication	Mechanism	Dose	Side Effects
Metoclopramide	Gastroparesis (FDA-approved for this indication)	Central/peripheral dopamine receptor antagonist, 5HT3 receptor antagonist, 5HT4 receptor agonist (prokinetic and antiemetic)	5–10 mg 3 times daily 30 min before meals	Up to 30% CNS symptoms to some extent: most serious is Parkinsonian, tardive dyskinesia (FDA black box warning)
Domperidone	Gastroparesis (not available in the United States except under FDA IND); often can be bought in Canada	Peripheral dopamine receptor antagonist (prokinetic and antiemetic)	10–20 mg 4 times daily	Rarely can cause QTc prolongation, with risk of arrhythmia; hyperprolactinemia
Erythromycin	Gastroparesis (off-label)	Motilin receptor agonist (prokinetic)	50–125 mg given 30 minutes before a meal; note the dose is considerably less than that used for an infection	May worsen nausea, vomiting, abdominal pain; tachyphylaxis with long-term use requires drug holidays; can cause QTc prolongation with risk of arrhythmia, greater doses can cause vomiting and nausea
Mirtazapine	Gastroparesis (off-label)	Alpha adrenergic, 5HT2, 5HT3, and H1 receptor antagonist (prokinetic, antiemetic)	15–30 mg every day at bedtime	This is an antidepressant, can cause somnolence, increased appetite, and weight gain
Prucalopride	Gastroparesis POI, CIIPO (off-label)	Highly selective 5HT4 receptor agonist (prokinetic, secretagogue)	1–2 mg daily	Headache, nausea, abdominal pain, diarrhea

CIIPO, Chronic idiopathic intestinal pseudo-obstruction; *CNS*, central nervous system; *FDA*, US Food and Drug Administration; *GI*, gastrointestinal; *IND*, investigational new drug; *POI*, postoperative ileus.

Operative Treatment of Delayed Gastric Emptying

Operative intervention should be limited to patients with severe, medically refractory symptoms affecting quality of life and challenging the patient's nutritional health. First, we will discuss those patients with objective evidence of delayed gastric emptying (true gastroparesis). A jejunal feeding tube (percutaneous or open or as one of the authors prefers a duodenostomy) may be indicated, but only after a trial of nasoenteric feeding to evaluate for tolerance of such feedings; NOTE: such a trial is absolutely essential, because some patients have a poorly understood postvagotomy small bowel dysmotility and cannot tolerate these feedings. This is especially true for patients who also complain of substantial abdominal pain, which is another indication that a trial of feedings is absolutely crucial before placing a J tube. The inability to tolerate enteric feedings, either because they cannot tolerate the volume related to severe bloating or the feedings exacerbate the abdominal pain, is a very bad sign for the optimistic hope of a good response to enteric feedings. In some situations of severe refractory gastroparesis, TPN may be the only viable option. A venting gastrostomy tube may assist with the feeling of gastric fullness or persistent vomiting; one just needs to be careful to monitor how much volume is lost via such a gastrostomy tube, because the volume will have to be replaced. Also, if the gastric drainage is voluminous and bilious, loss of bile salts will be a distinct possibility and may even require reinfusing the gastric drainage; as might be expected, this is quite cumbersome and not at all appealing, and thus placement of a gastrostomy tube alone may not be the best option. If the enteric feeding trial is successful, then some form of direct, enteric placement of a feeding tube is best. Placement can be done either via a laparoscopic, open, or direct percutaneous placement (PEJ) rather than a PEG tube with a jejunostomy extension, the latter of which all too often flips back up into the stomach and requires replacement via gastroscopy.

In a small subset of patients with objective gastroparesis and who had undergone an operation with a postoperative total vagotomy or a defined vagal injury, a near total (>95%) gastrectomy (with a cardiojejunostomy leaving no effective volume reservoir) or even a completion gastrectomy may be an option. A multidisciplinary discussion is mandatory before recommending this controversial strategy. An examination of 20 years of Mayo Clinic's experience of providing near total or completion gastrectomy in patients with severe postsurgical gastroparesis after a prior partial gastrectomy with truncal vagotomy showed that only about half the patients were able to maintain their nutrition orally. A similar trial of near total gastrectomy after a prior Nissen fundoplication in patients with postsurgical gastroparesis who had also had a pyloroplasty (remember the vagus nerves also help to coordinate antropyloric function presumed to be related to vagal nerve injury) found no benefit; the majority of this unusual subset of patients had persistent symptoms and required supplemental nutrition (enteral or parenteral) after the gastric resection. *Please Note!* We learned early on that a trial of enteric feedings was absolutely necessary with any type of operative intervention designed to deliver food by mouth, because as stated before, if the patient cannot tolerate enteric feedings, then the delivery of ingested foods into the jejunum via the esophagus will also not be tolerated. Therefore, the authors do not recommend near or total gastrectomy as a routine strategy for postsurgical gastroparesis, except in selected patients who are demonstrated to tolerate enteric feedings.

In recent years, there has been a new interest in various stomach-specific treatments that might appear to help with gastric emptying, including pyloroplasty, either done as a formal operation (laparoscopic or open) or via an endoscopic approach titled per-oral pyloromyotomy (POP) or gastric per-oral endoscopic myotomy (G-POEM; also known as POEM or endoscopic POP) based on the rationale that pyloric dysfunction could result in gastric outlet obstruction. If any of these procedures are to be considered, a preoperative trial of injection of botulinum toxin into the pylorus should be considered strongly. This temporizing approach relaxes the pylorus similar to a pyloroplasty; if no symptomatic relief occurs, then an operative procedure on the pylorus is probably not indicated. Sleeve gastrectomy (with or without pyloroplasty) has received quite a bit of interest recently. This operation decreases the reservoir capacity of the stomach because it resects all the fundus and the lesser curvature tube has no substantial reservoir capacity; when combined with a pyloroplasty, there should be no resistance at the pylorus, and thus there is some theoretic interest in its potential efficacy. The operation might increase gastric emptying and thus have an emerging role in the treatment of gastroparesis, especially in patients suffering from obesity and/or diabetes. The data are still scarce and not yet well accepted, and gastroesophageal reflux disease in the setting of a sleeve anatomy and nonresolving gastroparesis remain of concern without even midterm postoperative data. Acupuncture has been shown anecdotally to have some symptomatic benefit in the management of selected patients with gastroparesis.

Finally, implantation of an electrical gastric stimulator (Fig. 1) into the stomach wall has been suggested with increasing frequency by some groups; this approach of gastric electrical stimulation (GES) may be an option for patients with severe and refractory gastroparesis and who have diabetes or with predominant symptoms of nausea or vomiting. Although these nerve stimulators might help with nausea and vomiting, they are very controversial, with quite radically different success reported by various groups. Because GES does not reliably increase effective gastric emptying (see later, Gastroparesis-Like Syndromes), be aware that patients may consider these like a cardiac pacemaker that will "pace" the stomach and increase the rate of contractions, but no one has been able to show that gastric stimulation can actually "pace" the stomach.

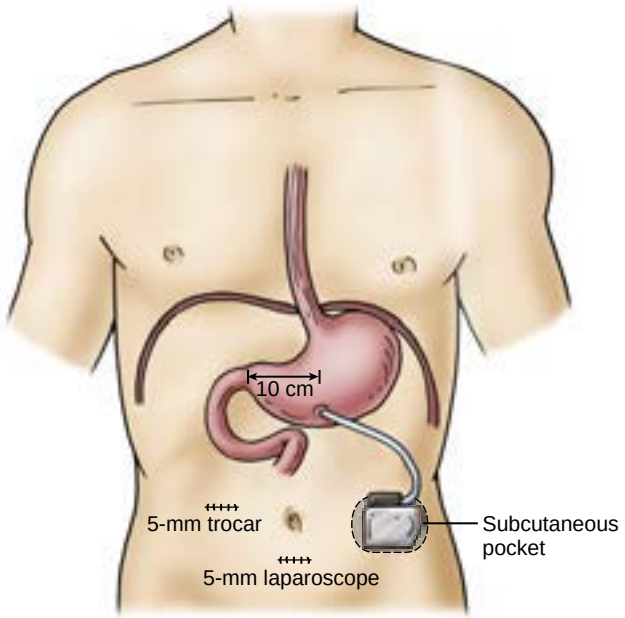


FIG. 1 Laparoscopic approach for gastric electrical stimulator: placement of gastric wall electrodes and subcutaneous battery.
(Modified from Ginsburg GG, et al. Clinical Gastrointestinal Endoscopy. 2nd ed. Philadelphia: Saunders; 2012.)

GASTROPARESIS-LIKE SYNDROMES

In recent times, symptoms suggestive of gastroparesis but often without any objective delay in gastric emptying have received considerable attention in the literature. It remains unknown whether these syndromes have always been present or whether this spectrum of disorders are related to a more focused, increased interest in symptomatic functional disorders without objective evidence of delayed gastric emptying. These syndromic conditions present with early satiety, nausea, and often vomiting, mimicking true gastroparesis and are most often seen in young females in their 20s or 30s. Although gastroparesis by definition implies a delay in gastric emptying, it has become clear that there is poor correlation between the severity of delay and symptoms in these patients. A substantial percentage of these patients have normal emptying, although their symptoms are indistinguishable from those in patients with overt delay; this syndromic presentation is likely part of a clinical spectrum that has been termed *chronic unexplained nausea and vomiting* or *gastroparesis-like syndrome*. In these patients, other mechanisms (e.g., impaired gastric accommodation with increased tension in the proximal stomach wall, sensitization of vagal afferent pathways, etc.) may account for the symptomatology.

Symptomatic treatment for this spectrum of complaints first revolves around excluding true gastroparesis, often requiring a formal radionuclide gastric emptying study. Because there is little association of symptoms with the rate of gastric emptying, the focus on these patients is to treat the symptoms of nausea and vomiting. Some modification of diet as for true gastroparesis can help, but treatment begins with antiemetics and antinausea medications. The usual approach is to start with the classic antinausea medications, like metoclopramide or the 5HT3 receptor antagonists, typically beginning with ondansetron (which is also available in an orally disintegrating tablet form) or granisetron, which is available as a subcutaneous delivery patch. A more general approach to nausea has been in the form of neuromodulators (e.g., tricyclic antidepressants such as nortriptyline). Although most of these agents have prominent anticholinergic activity, these drugs generally do not affect motility when used in low doses. Several anecdotal reports suggested substantial relief, but a randomized controlled study showed no improvement in nausea. A more promising agent is mirtazapine, which is being used increasingly to treat nausea (due to its 5HT3 receptor antagonism), improve appetite, and to a lesser extent modulate functional pain. Buspirone is an anxiolytic that is an agonist of the 5HT1A receptor, which may also be responsible for its ability to improve gastric accommodation. It may prove useful in patients with prominent early satiety.

Over the past 15 to 20 years, the still not fully accepted treatment of neuromodulation by various forms of GES has been recommended with increasing frequency. GES is a technique in which serosal electrodes are implanted onto the gastric antrum via an open or laparoscopic approach (see Fig. 1). The accepted use for GES includes the indication approved by the US FDA of "drug refractory disease," but there are no defined criteria for the diagnosis of this condition. Because under the FDA statute for the Practice of Medicine, any FDA-approved device can be used off-label with an adequate justification, GES can be used in the "off-label" setting. Because the current devices for GES require a Humanitarian Use Device (HUD) approval, any centers employing these devices should have some form of Institutional Review Board (IRB) oversight. Some investigators have advocated that multiple uses of GES are allowed under certain conditions. Randomized crossover trials have shown no or only modest symptom relief with the device when on versus off, although many prospective, open label trials have rather aggressively suggested impressive benefit, particularly in patients with diabetic gastroparesis. Putative mechanisms of action are presumed

to be via modulation of vagal signaling and not via improved gastric emptying. The bottom line is that the role of GES in gastroparesis, despite its now relatively frequent use, remains unclear.

The problems with this spectrum of gastroparesis-like syndromes are that we do not understand their etiology, it appears to be in the spectrum of functional disorders of the gut, and the response to different medications varies considerably. These patients are best managed by a thoughtful, considerate, and understanding gastroenterologist.

DIABETIC GASTROPARESIS

Diabetic gastroparesis should be discussed as a separate entity. Most investigators agree that this disorder is related primarily to poor glucose control and its effects on vagal nerve function. One important aspect of this disorder is that although it is associated with a true delay in gastric emptying, the clinical symptomatology waxes and wanes in severity, and thus any attempt to intervene in an irreversible way is usually to be avoided. Many times, the symptoms are more cumbersome than any problems with caloric intake or nutrition aside from the underlying diabetes mellitus.

This intermittent nature of diabetic gastroparesis should weigh into any therapeutic considerations. Attempts to obtain better control of glucose intolerance are definitely appropriate. Some reports suggest that the use of insulin pumps in patients with type 1 diabetes can lead to fewer hyperglycemic events, a decrease in HbA1c, and considerable improvement in the symptoms of gastroparesis. Of course, the initial therapeutic suggestions should concentrate on dietary modifications as discussed earlier and trying the various pharmacologic agents as for other forms of gastroparesis. A true venting gastrostomy may be advantageous in these patients for relief from bloating symptoms, but as with any gastrostomy, it should not be open to continuous drainage for fear of dehydration, bile salt wasting, and so on. Specific counseling of patients with such a venting gastrostomy is imperative. Also, this may be a potential avenue for a somewhat safer jejunal extension tube to allow intrajejunal feedings if the patient can tolerate them. In terms of a gastric resection, the senior author of this chapter performed a near total gastrectomy in one highly unusual patient with chronic, unrelenting diabetic gastroparesis of 5 years' duration who could also tolerate jejunal feedings. Although this patient did well for 8 years after which follow-up was lost, we want to stress that this approach (tailored after treatment of vagal dysfunction in selected patients as described before) should not be considered in the overwhelming majority of patients with diabetic gastropareses.

Because diabetic gastroparesis can lead to considerable symptomatology of vomiting and nausea, GES might have benefit in this population and should be entertained in the highly symptomatic patient. Whether it will augment gastric emptying is not necessarily to be expected, but it may help with symptoms.

RAPID GASTRIC EMPTYING

The overly rapid early emptying of gastric contents from the stomach into the duodenum or the jejunum, also known as *dumping,* can result from gastric operations that almost universally involve a vagotomy; this condition leads to the dumping of a bolus of liquid or hyperosmolar chyme into the proximal gut. Approximately 10% to 15% of patients experience some extent of dumping after gastric surgery. If the contents are of high osmolarity, such as a carbohydrate-rich bolus, then the resultant symptoms can be very unpleasant for the patient. Because of increased osmolality, some have suggested that the rapid shift of fluid into the lumen of the small bowel can lead to feelings of bloating. The old theory that dumping may result in a relative hypovolemia from the fluid shift into the gut has been disproven and is not the primary cause of the symptoms; indeed, the majority of the symptoms arise from the release of vasoactive substances related to the high osmolality of the intraluminal content. Also important to remember is that many physicians relate dumping to diarrhea; this is neither appropriate nor accurate, because many patients with dumping have no diarrhea. The symptoms of dumping are abdominal bloating, nausea, and the feeling of a need to lie down early after eating; diarrhea may occur but not always.

Dumping can be seen after virtually any operation on the distal stomach but usually those involving a vagotomy; the greatest frequency is after subtotal gastrectomy with vagotomy and the least frequent is after pyloroplasty alone. Patients who have undergone a truncal vagotomy (or an inadvertent or necessary vagotomy) and pyloroplasty will experience dumping at greater rates than those who had pyloroplasty alone. The symptoms occur early, usually within 30 minutes of eating. Symptoms are likely to be elicited after a large, rapidly ingested meal and are much worse with liquid meals of high osmolarity. In the past, dumping was a very common feature after truncal vagotomy and pyloroplasty, but in the current era, dumping is observed primarily after Roux-en-Y gastric bypass surgery. Thankfully, dumping rarely is a permanent state, especially after gastric bypass, in which the majority of patients will not have prominent or persistent symptoms after the first 3 months. Predicting who will develop dumping is challenging.

There is also a form of dumping called *late dumping*, in which the symptoms occur 90 minutes to 3 hours after eating. This symptomatology is believed to be related to the delivery of high-calorie meals to the more distal intestine, whereby a different neurohormonal milieu occurs. The initial symptoms are quite similar to early dumping, but also often involve diarrhea, which is not a part of early dumping. Some of the symptomatology of this late dumping appear to be related to the entry of high caloric value into the duodenum or jejunum overwhelming the regulatory mechanisms for insulin release, resulting in a delayed continuous increase in the levels of serum insulin leading to the rapid "reactive" development of hypoglycemia; this rapid onset of hypoglycemia then causes symptoms very similar to early dumping along with the symptoms of hypoglycemia. Indeed, the hypoglycemia can be quite severe (<20 mg/dL) and can even lead to disturbed thinking, seizures, and even coma. Although some have described this late hypoglycemia as a new postbariatric syndrome called noninsulinoma postprandial pancreatogenous hypoglycemia syndrome (NIPPS) that can occur after a Roux-en-Y gastric bypass, quite frankly, this syndromic complex was well-recognized in the past era of duodenal ulcer operations as "late dumping" after gastric resections.

Clinical Presentation and Diagnosis

The majority of patients, about 75%, will present with early rather than late symptoms of dumping. The differential diagnosis must exclude the afferent loop syndrome, pancreatic insufficiency, and bowel obstruction after prior gastric surgery. A detailed history will help to differentiate between dumping and these other potential complications. With *early dumping,* patients will complain of early satiety, abdominal pain, nausea, and evidence of autonomic dysfunction, such as a racing heartbeat, sweating, dizziness, and tremors. Unlike with late dumping, diarrhea is not common with early dumping symptoms. The symptoms may last for about an hour, because the high osmolarity causes release of vasoactive substances. Patients often are self-immobilized and want to lie down because of the severity of the ill feeling they experience. *Late dumping* has similar symptoms but generally occurs approximately 90 minutes to 3 hours after a meal. Additional features include fatigue, mental changes, or even fainting associated with reactive hypoglycemia. Recognition of this unfortunate sequela is important for patients to understand so that they can seek appropriate care if needed.

Provocative testing to help confirm the diagnosis of late dumping involves giving 50 g of orally administered glucose followed by serial measurements of glucose and plasma insulin levels as well as heart rate and determining any symptoms of dumping experienced by the patient. Some suggest a concomitant, hydrogen breath test; an

increase in the heart rate greater than 12 beats per minute and an increase in hydrogen breath excretion allegedly has a sensitivity of 94% and a specificity of 92%. An upper gastrointestinal (GI) series may help to define anatomy but is often not necessary. Usually, however, the diagnosis is evident by the patient's symptoms and the clinical setting.

Treatment

The primary treatment of dumping syndrome is dietary modification. Avoiding simple sugars (which includes alcohol and most dessert-type food items) and the intake of calorie-dense carbohydrates helps minimize symptoms. Simple measures, such as avoiding drinking 30 minutes before, during, and after a meal also may help. Adding fiber supplements and complex carbohydrates may help to slow transit; in addition, drinking plenty of water at other times during the day, especially if concomitant diarrhea is present, serves to avoid dehydration as a result of the dumping. Patients should avoid an upright posture while eating and instead recline if possible after eating, because upright posture may accelerate gastric emptying in some patients. Although diarrhea is not the main presenting symptom of dumping, patients may have a late onset of diarrhea. As before, eating small, frequent meals and having proteins and fats with meals may help to slow gastric emptying.

Dietary modifications alone may not relieve the dumping symptoms; 3% to 5% of patients will have refractory symptoms. A trial of octreotide in these patients may offer great relief of the dumping symptoms but in only about 20% of patients. In several randomized, controlled trials, octreotide improved symptoms in some patients when compared with controls. If octreotide is effective, then a longer-acting formulation of octreotide should be used. The timing of administration of subcutaneous octreotide is important and should be given 30 minutes before a meal. For patients on long-acting octreotide, steatorrhea can be a problem, because octreotide inhibits pancreatic enzyme secretion, but the resulting steatorrhea can be ameliorated with pancreatic enzyme replacement. Increasing the viscosity of the intraluminal contents by adding pectin and guar may slow the emptying process and alleviate symptoms.

The role of any operative interventions to manage dumping is limited. Distant literature describes the use of a 10-cm, reversed jejunal limb at 100 cm distal to the ligament of Treitz in patients who have severe diarrhea associated with rapid gastric emptying. There are, however, many complications with these reversed limbs, and studies have not shown any substantial benefit; this often quoted but outdated procedure should be relegated to history and no longer used currently. For the late form of dumping and the hypoglycemia associated with Roux-en-Y gastric bypass (NIPPS), endoscopic transoral outlet reduction (TORe) might be of benefit in some patients. With this procedure, the diameter of the gastrojejunostomy is decreased via endoscopic suturing, but consistently good results across different practices are lacking. Operatively reversing the gastric bypass or redirecting the Roux limb into the duodenum may be the only option. A prior high visibility suggestion of subtotal pancreatectomy to treat any associated hypoglycemia has proven to be ineffective in long-term outcomes.

MOTILITY DISORDERS OF THE SMALL INTESTINE

True motility disorders of the small intestine are actually quite unusual and represent a spectrum from transient, reversible problems of motility, such as generalized adynamic ileus to the rare and progressive familial disorders of chronic idiopathic intestinal pseudo-obstruction and the acquired disorder of scleroderma. There are also several unique, albeit rare, clinical scenarios that involve motor abnormalities, such as the bypass enteropathy of the defunctionalized jejunoileum in patients after the original bariatric operation of the jejunoileal or "small bowel" bypass, small intestinal intussusception, and the dysmotility that can complicate small bowel function in patients who were born with intestinal atresia. This section, however, will focus on the two forms of adynamic ileus and the pseudo-obstructions of the small bowel.

Adynamic Ileus

A true small intestinal "ileus" after intraabdominal operations actually is very unusual. In contrast, the "physiologic ileus" that occurs in the early postoperative period (first 1 to 4 days) after a laparotomy is often talked about and called "postoperative ileus." This form of transient ileus, or the inability to eat and have bowel movements, is primarily a gastric and colonic response to the abdominal wall trauma of a laparotomy. Interestingly, it is not a small bowel ileus or even a dysmotility of the small bowel; indeed, small intestinal contractile activity is present during the operation as can be seen and demonstrated by "tweaking" the small bowel and observing it contract (in contrast to the stomach and colon, which have no spontaneous or stimulated contractile activity intraoperatively). Also, intraintestinal feeding can be administered immediately postoperatively. In essence, the small intestine works relatively normally, whereas the motor activity leading to gastric emptying and colonic emptying is delayed for 2 to 4 days. Thus, POI is not a small bowel dysmotility. The absence of "bowel sounds" early postoperatively is due to the loss of gastric emptying of swallowed gas; it is the gas/liquid interface that leads to bowel sounds.

Adynamic ileus, however, is a rare, generalized motor disorder of the entire gut, involving the small intestine as well as the stomach and colon. Adynamic (generalized) ileus involves a secondary, neurally mediated blockade of effective contractile activity in response most commonly to a systemic inflammatory disorder (such as sepsis), after retroperitoneal operations (e.g., kidney transplantation), or with retroperitoneal conditions (e.g., trauma, hematoma), all believed to interfere with the autonomic nervous innervation to the gut. True adynamic ileus should not be confused with isolated colonic ileus (colonic pseudo-obstruction) that can complicate a total hip arthroplasty or retroperitoneal operations; this form of localized ileus involves only the colon but not the stomach or small bowel.

Clinical Presentation and Diagnosis

Diagnosis is based on the presence of symptoms similar to those of a small bowel obstruction that occur in the appropriate clinical setting: vomiting, bloating, abdominal distention, obstipation of stool and gas, and the physical findings of tinkling bowel sounds and generalized bowel distention (small and large bowel) on diagnostic imaging. Crampy abdominal pain as occurs with a mechanical small bowel obstruction, however, is distinctly unusual. With a heightened clinical suspicion, a simple abdominal radiograph will suffice showing the dilation of the stomach, small intestine, and entire colon. The differential diagnosis includes the exclusion of an obstructing rectal lesion, which may require proctoscopy or a transrectal contrast radiograph.

Treatment

Treatment should be directed at the cause of the ileus, most commonly sepsis. Specific pharmacologic or operative intervention is neither needed nor effective in an attempt to treat or reverse the ileus. Management is otherwise conservative, often including a nasogastric tube. Prokinetic agents are not effective. Adynamic ileus is transient and resolves when the systemic cause of the ileus has been controlled.

Postoperative Ileus

We want to differentiate POI from adynamic ileus; these represent two distinct and different entities. The former is a physiologic response to abdominal wall trauma, while the second is a pathologic response to infection, etc. Also, to be clear, POI involves the stomach and colon but not the small intestine as stated earlier, whereas

adynamic ileus involves the entire gut: stomach, small intestine, and colon.

A far too great emphasis has been devoted to POI when it is a transient condition that resolves spontaneously; the term itself has been magnified out of proportion to its importance. Although speeding discharge by at most 1 day is important after an open, full laparotomy for colonic or other operations that can delay early discharge within the first 3 days or so, laparoscopic operations are much less susceptible to POI as shown numerous times recently after laparoscopic colectomy. Much of this misunderstanding of POI stems from the inaccurate belief that POI is related to the extent of handling of the intestine; indeed, an excellent study in dogs showed that extensive handling of the small bowel was not associated with more POI than a simple laparotomy. This and other studies show that POI is related to the abdominal wall trauma of the laparotomy in combination with other factors such as opioid medications. Remember, POI does not affect small bowel motility, rather just the stomach and colon.

Thus, with so many operations now being performed laparoscopically, POI is no longer that relevant or problematic. Moreover, recent work with enhanced recovery after surgery (ERAS) has improved our understanding of early postoperatively feeding of either the stomach directly, even after major resections (e.g., pancreatoduodenectomy), or the small intestine such as after a Roux-en-Y gastric bypass where essentially all oral intake bypasses the stomach and enters the jejunum directly; this experience reinforces the lesser importance of POI currently.

There is one exception to these observations. On occasion after a distal gastrectomy when there has been mechanical obstruction of the gastric outlet and the stomach is dilated, recovery of gastric emptying can be delayed markedly, the exact cause of which remains poorly understood. With this quite rare condition, most so-called prokinetic medications, such as erythromycin, domperidone, prucalopride, acetylcholinesterase inhibitors, and alvimopan (a peripheral mu opioid receptor antagonist shown to speed discharge somewhat after open colonic operations), have been of minimal or no benefit, and watchful waiting without reoperation to "redo" the gastroenteric anastomosis because of concerns of its anatomic lie should be avoided at all costs.

Chronic Idiopathic Intestinal Pseudo-Obstruction

This family of heritable disorders is quite uncommon, and the diagnosis, which closely mimics a mechanical small bowel obstruction, can be confusing and difficult to recognize preoperatively, especially if there is no prior family history and if the patient has had no prior intraabdominal operation. The three most common forms of chronic idiopathic pseudo-obstruction, all of which are progressive, are the following: a histopathologic myopathy of smooth muscle, a histopathologic neuropathy, and a less well-characterized form of neuromotor dysmotility that lacks any definitive histopathologic findings. Another extremely rare genetic cause of GI pseudo-obstruction includes mitochondrial neurogastrointestinal encephalopathy disease, a multisystem disorder with peripheral as well as prominent GI dysfunction and an associated neurologic phenotype (ptosis/ophthalmoplegia, peripheral neuropathy, leukoencephalopathy); this disorder affects teens and young adults and is caused by a mutation in the gene encoding for thymidine phosphorylase. All these disorders lead to disorganized patterns of motility with ineffective, uncoordinated contractile activity resulting in intestinal distention and stasis of intestinal content.

Familial Visceral Myopathy

With this disorder of visceral smooth muscle, the amplitude of contractions is markedly abnormal, as is the coordination of propulsive contractile activity along the gut. This myopathy eventually affects the esophagus, stomach, small intestine, and colon, as well as the genitourinary system. The most common organs affected first (and often isolated) by this myopathy can be the esophagus (megaesophagus), the duodenum (megaduodenum), the colon (megacolon), or the urinary system (megaureter). With time, however, all smooth muscle of the gut and genitourinary system becomes involved to some varied extent.

Familial Visceral Neuropathy

This disorder involves the autonomic nervous system of the gut, leading to discoordinated contractile activity with ineffective transit. Histologic findings are subtle and require special expertise not only in the reading of the slides (which require a full thickness biopsy, not just an endoscopic biopsy) but also in the staining of the tissue. Currently there are very few histopathologists who have access to the appropriate staining techniques or experience in reading the biopsy slides, making the need for a transmural biopsy less important.

As Yet Undefined Neuromotor Dysmotility

This form of chronic, truly "idiopathic" pseudo-obstruction mimics the primary visceral neuropathy form but lacks any discernible histopathologic findings. It is rare but possible for a patient to develop a form of this dysmotility as a paraneoplastic phenomenon mediated by an as yet noncharacterized humoral agent released by the neoplasm.

Clinical Presentation

Many times, the symptoms of the hereditary dysmotility syndromes begin initially in one organ. A common presentation is severe constipation, which then progresses over a variable time (months to years) to also involve the small intestine. Some of these patients have been treated (inappropriately) by colectomy for a diagnosis of colonic inertia. Others present with initially isolated megaesophagus, mimicking achalasia in some respects; but over a variable time interval, the disease eventually involves the distal gut as well. In teenagers, one of the more common presentations of pseudo-obstruction is that of megaduodenum of the first and second portion of the duodenum, often confused with superior mesenteric artery (SMA); the latter itself is very rare and virtually always follows a marked weight loss rather than preceding or causing the weight loss as with pseudo-obstruction. Because these disorders are a familial, heritable disorder, for patients other than the proband, there should be a family history of esophageal, colonic, or genitourinary problems unless, of course, it is a new mutation.

The age of onset varies with the site of intestinal pseudo-obstruction. Often the symptoms begin insidiously during late childhood/early teenage years with vague, chronic GI complaints. Other forms of onset appear in the 20s and 30s in patients with a prior history of complaints, such as substantial constipation, dysphagia, gastroesophageal reflux, or intermittent abdominal distention/cramping. A clue to the clinical presentation/diagnosis is that, all too frequently, these patients have been operated on for a prior, presumed, mechanical "small bowel obstruction" secondary to a presentation of abdominal pain, distention, and markedly dilated small intestine, usually with no really objective or convincing site of mechanical obstruction found at the time of exploration. The disease and symptoms often wax and wane, which raises the question if the current symptoms are secondary to adhesions from prior abdominal operation(s) rather than to the dysmotility itself.

Diagnosis

The diagnosis of these forms of chronic idiopathic intestinal pseudo-obstruction is most often one of exclusion (unless, of course, there is a strong family history). Because of their rarity, the diagnosis often is not even considered initially, and patients are treated operatively as if they have a mechanical small bowel obstruction, a colonic obstruction, or colonic inertia. Even when there is no definitive site

of obstruction, all too often the assumption by the operating surgeon is that the obstruction was related to a transient kinking or twist that resolved; interestingly, this "obstruction" in the postoperative course may resolve without a protracted postoperative "ileus." A key here is that the small intestinal dilation occurs right down to the cecum, making a transient obstruction unlikely. Because the disease is intermittent at first, when the patient presents again with abdominal distention after a prior negative laparotomy and a clinical picture of a mechanical small bowel obstruction, the concern of an adhesive obstruction is always present, even in patients in whom a concern of pseudo-obstruction remains from the prior operation. This presentation makes the diagnosis and treatment very difficult.

Marked small intestinal distention (and often gastric as well) is the hallmark of diagnosis on radiographic imaging, and the distention of the small bowel extends all the way to the cecum without a transition point. Early in the course of the disease, megaesophagus or megaduodenum may be the first sign, but later in the course, the entire small bowel is dilated, mimicking a very distal mechanical small bowel obstruction. A prior history of a negative exploration in the past, a history of multiple recurrent complaints as a child with abdominal distention or constipation, or a presentation without any history of a potential cause of a mechanical obstruction, such as a prior intraabdominal operation or hernia, should at least raise suspicion of the diagnosis, especially in the younger patient; however, no one wants to mismanage or delay definitive treatment of a mechanical obstruction by delaying necessary definitive operative intervention, which makes the diagnosis difficult.

There is no definitive or objective means of preoperative diagnosis other than a well-defined family history or a known problem with genitourinary problems related to megaureter. A prior operation(s) without a defined site of obstruction (and often it is necessary to read between the lines of the previous operative note by the surgeon trying to convince themselves that there was a site of obstruction) should raise suspicion of pseudo-obstruction, but nevertheless, there is always the worry of a mechanical cause being present.

Multiple attempts at diagnosis by characterizing the motor (contractile) pattern have been largely unsuccessful. Although the amplitude of contractions is decreased markedly in the visceral myopathic form, measuring true amplitude in the presence of gastric and/or intestinal distension is not reliable whatever the cause. The most reliable method of diagnosis in those highly suspected of idiopathic pseudo-obstruction is best carried out by a "diagnostic" laparoscopic exploration, which allows for a less-invasive visualization of the distended bowel with the least risk of subsequent adhesion formation. The finding of intestinal distention of the entire small intestine all the way down to the cecum without any convincing site of concurrent or prior obstruction (adhesions, hernia, localized thickening of the bowel, or intraluminal mass that may have caused a transient intussusception) should confirm the suspicion of this motility disorder.

Treatment

Treatment of intestinal pseudo-obstruction is only symptomatic and supportive. Being a progressive disorder that eventually involves the entire small intestine, any resections or internal bypasses should be avoided. Similarly, repeated laparotomies should be avoided, if at all possible, because of the subsequent development of more adhesions, which only confuses the clinical picture concerning the etiology of the intestinal distension and complicates future decision making, especially by another surgeon. When the diagnosis is suspected, laparoscopic exploration rather than laparotomy should be used to confirm the diagnosis. Yes, these patients can develop a true mechanical obstruction from adhesions related to prior laparotomies, so the differentiation of mechanical from functional obstruction is a consideration. Whether a full-thickness biopsy is indicated or not is debatable, because there usually is no definite recognizable pathology evident, and most centers do not have the expertise to really identify abnormalities of the autonomic nervous system with the specialized neuromuscular staining needed; moreover, it requires an enterotomy because a full thickness biopsy is needed. Similarly, for patients operated on previously, a laparoscopic exploration may allow the least invasive confirmatory approach as opposed to open laparotomy.

Because the symptoms and severity tend to wax and wane early in the course of the disease, any nonreversible treatment should be avoided. As the disease progresses, if the primary area is the esophagus, stomach, and/or duodenum, intrajejunal feedings may be possible initially and will put off the need for chronic parenteral feeding, but chronic parenteral nutrition eventually becomes the mainstay of treatment. In the latter stages of the disease, when the abdominal distention becomes chronic and symptomatic, a decompressive tube enterostomy (not a formal enterostoma because of the inordinate risk of stomal prolapse) may provide some benefit for the small intestinal distention. These venting tubes should be considered cautiously because of the known complications of any enterostomy tube, such as discomfort, fluid loss, or infection. Similarly, if vomiting is problematic, a venting tube gastrostomy also can be entertained, but again, all fluid loss from these decompressive tubes will need to be replaced, making intravenous support more difficult. In the authors' opinion, chimney stomas are not indicated as a decompressive procedure, because they can serve as a large drain of enteral fluids and can lead to retrograde prolapses.

Intestinal transplantation is a therapeutic possibility in highly selected individuals. This approach obligates its own problems, such as immunosuppression and infections. Whether intestinal transplantation is state-of-the-art currently is a quality judgment for each individual patient. With improvements in immunosuppression, transplantation represents the best potential alternative for this progressive and otherwise untreatable disease.

Scleroderma

Scleroderma can involve the small bowel and colon with severe symptoms in about 10% of patients. The onset of small bowel involvement is usually later in the course of the disease. Involvement of the esophagus with gastroesophageal reflux is much more common, but the small bowel dysmotility when present is difficult to treat. Although most assume that involvement of the small bowel wall involves a fibrosis, usually the most prevalent finding is a myopathy with hypoplasia of the muscles of the intestinal wall. This myopathy leads to poor amplitude contractions as well as an overall dyscoordination of contractile patterns leading to poor propulsion of luminal content. While the presentation and findings are very similar to chronic idiopathic pseudo-obstruction, the underlying cause is a bit different. Most treatment is symptomatic, but while some have tried pyridostigmine (an acetylcholinesterase inhibitor), octreotide, and even oral antibiotics for bacterial overgrowth due to luminal stasis, most of these treatments are only marginally helpful at best.

Postvagotomy Diarrhea

Postvagotomy diarrhea is a very rare form of dysmotility that is poorly understood and has no known effective treatment. Now that the era of vagotomy for duodenal ulcer disease is over, this rare disorder should be even rarer.

Clinical Presentation

Although presenting as diarrhea, the underlying pathophysiology is believed to be a dysmotility, causing a rapid transit through the small intestine and not a malabsorption as such. The symptoms are diarrhea and cramping after eating, but specifically and importantly in the differential diagnosis, there is no diarrhea or cramping between meals. There is no real malabsorption as such in terms of fat (steatorrhea), protein (azotorrhea), or vitamins or minerals, but instead pain and fluid and electrolyte balance predominate. When analyzed, the diarrhea is a watery form, but the presence of undigested foodstuffs is evidence of rapid transit.

Diagnosis and Treatment

The diagnosis is rare, often not thought of, and is one of exclusion. Most physicians and currently most surgeons will never see such a patient in their career. Endoscopies show normal mucosa confirmed on biopsy. Every form of diarrhea should be excluded before this diagnosis is made. A detailed evaluation by an insightful gastroenterologist or surgeon is very important because there is no effective treatment. Pharmacologic attempts at slowing transit with opiates and even octreotide have been uniformly unsuccessful. Prior attempts to slow transit by operative means such as reversed segments of small intestine are also not indicated, because they just do not work. Once all other forms of diarrhea have been excluded, the treatment is supportive. The senior surgeon working in a major referral center for motility disorders has seen three such patients in his 30-year career; these patients are miserable and very unsettling to manage.

Suggested Readings

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Management of Short Bowel Syndrome

Jon S. Thompson, MD

Short bowel syndrome (SBS) is characterized by malabsorption and malnutrition, which generally occur when less than 180 cm of functional intestine remains in adults. The severity of the clinical features of SBS depends on several factors, including not only the extent of resection but also the site of resection, the underlying intestinal disease, the presence or absence of the terminal ileum and ileocecal valve, the functional status of the remaining digestive organs, and the adaptive capacity of the intestinal remnant. Three-fourths of these instances result from massive intestinal resection, and one-fourth result from multiple sequential resections of the small intestine. Approximately two-thirds of patients who develop SBS survive from that hospitalization, and a similar percent are alive 1 year later. Long-term outcome is primarily determined by the patient's age and underlying disease. However, a number of deaths are caused by complications directly related to the management of SBS.

The pathophysiologic changes that occur in SBS relate to the loss of intestinal absorptive surface and more rapid intestinal transit. Malabsorption of nutrients results in malnutrition and weight loss, diarrhea and steatorrhea, vitamin deficiency, and electrolyte imbalance. Other specific complications include an increased incidence of nephrolithiasis from hyperoxaluria, cholelithiasis secondary to altered bile salt and bilirubin metabolism, and transient gastric hypersecretion. Bacterial overgrowth can also occur secondary to mechanical obstruction or primary motor abnormalities. In patients dependent primarily on parenteral nutrition (PN), liver disease remains an important factor in mortality. Functional and structural adaptation of the remaining intestine occurs after massive intestinal resection, resulting in improved absorption of nutrients and a decrease in diarrhea within the first few months after resection. The degree of adaptation that occurs depends on the extent and site of resection, the provision of enteral nutrients, and the response to gastrointestinal hormones and other regulatory polypeptides.

Early management of the patient with SBS is that of the critically ill surgical patient having recently undergone intestinal resection and other concomitant procedures. Thus, controlling sepsis, maintaining fluid and electrolyte balance, and initiating nutritional support are important in the early management of these patients. Beyond this phase, the primary goals of management of SBS are to maintain adequate nutritional status, maximize the absorptive capacity of the remaining intestine, and prevent the development of complications related to both the underlying pathophysiology and the nutritional therapy itself. Surgical approaches have become increasingly important and generally include preserving the intestinal remnant, maximizing or improving the function of the intestinal remnant, and augmenting intestinal length via transplantation.

THERAPEUTIC GOALS

Maintain Nutritional Status

The most important therapeutic objective in the management of SBS is to maintain the patient's nutritional status. By necessity, this is achieved primarily by PN support in the early postoperative period. Enteral nutrition support can be started early after operation when the ileus has resolved. With time, an increasing amount of nutrients will be absorbed via the enteral route; this is important for maximizing intestinal adaptation and for preventing complications related to PN. As their conditions improve and intestinal adaptation occurs, many patients are able to absorb the necessary nutrients entirely via the enteral route. Intestinal remnant length has important prognostic implications in this regard. Patients with more than 180 cm of small intestine remaining generally require no PN, those with more than 90 cm of small intestine and particularly with colon will generally require PN for less than 1 year, and those with less than 60 cm of small intestine will likely require permanent PN.

During the transition from parenteral to enteral nutritional support, the primary objectives are to maintain a stable body weight and prevent large fluctuations in fluid balance. Metabolic monitoring is necessary to detect and correct any metabolic abnormalities and micronutrient deficiency. A marked increase in gastrointestinal fluid loss is a sign that further increases in enteral feeding will not be tolerated. As parenteral requirements diminish, intermittent PN can be instituted, reducing hours of therapy during the day and eventually alternating days. Some patients will require ongoing fluid supplementation.

Maximize Enteral Nutrient Absorption

Dietary management for an individual patient with SBS is determined by a variety of factors, including intestinal remnant length and location, any underlying intestinal disease, and the status of

the remaining digestive organs. The existence of a stoma is also an important consideration because diarrhea and perianal complications may markedly diminish oral intake. Thus, patients with stomas may be more likely to take a greater percentage of their calories enterally. Patients with SBS, in fact, may develop hyperphagia to overcome their inefficient absorption. Continuous rather than intermittent enteral feeding may permit greater absorption of nutrients in patients with remnants less than 90 cm.

The optimal diet for patients with SBS is determined primarily by whether or not the colon is in continuity. Initially a high-carbohydrate, high-protein diet is appropriate to maximize absorption. Fat absorption requires more digestion unless the fat is supplied in the form of medium-chain triglycerides. Stool fat increases markedly, however, with remnants less than 60 cm. The ability to absorb these nutrients does improve with time; thus, the diet should be continually modified. Other problems, such as lactase deficiency, may also be present. Patients with colon in continuity should have fat restricted to 20% to 30% of caloric intake and should have oxalate restricted to prevent nephrolithiasis. Because jejunal mucosa is relatively permeable, isotonic feedings are particularly important with jejunal remnants. Ingestion of a glucose-electrolyte oral rehydration solution with a sodium concentration of at least 90 mmol/L optimizes water and sodium absorption in the proximal jejunum and prevents secretion into the lumen. The role of specific nutrients (e.g., glutamine) remains controversial.

Another important aspect of the dietary management is to provide a diet that will maximize the intestinal adaptive response. Provision of fat, particularly long-chain triglycerides, and dietary fiber may be particularly important in this regard. Glutamine may be trophic to the gut. Although these nutrients may act directly to stimulate intestinal adaptation, the meal may also stimulate intestinal adaptation via endocrine or paracrine effects. Growth factors (e.g., growth hormone and glucagon-like peptide 2 [GLP-2]) may also stimulate intestinal adaptation.

Minimizing gastrointestinal secretion and controlling diarrhea are also important goals for maximizing absorption (Table 1). The addition of dietary fiber is useful in patients who are not fluid secretors. Several agents are useful for improving absorption via their antisecretory and antimotility effects, including narcotics such as codeine and diphenoxylate-atropine (Lomotil) and the peripherally acting narcotic loperamide. The long-acting somatostatin analogue octreotide improves diarrhea by increasing small intestinal transit time, reducing salt and water excretion, and reducing gastric hypersecretion. However, it may not remain effective long term and has potentially deleterious effects, including steatorrhea, inhibition of intestinal adaptation, and increased incidence of cholelithiasis. Thus, octreotide should not be used routinely for the management of chronic diarrhea. Both H_2 receptor antagonists and proton pump inhibitors have been shown to be effective in controlling gastric hypersecretion. Cholestyramine may also be beneficial when the diarrhea is related to the cathartic effect of unabsorbed bile salts in the colon and less than 100 cm of ileum has been resected.

Pharmacologic therapy for SBS is a rapidly expanding area of investigation. A variety of growth factors and hormones have been identified that promote intestinal growth or enhance absorptive function. Growth hormone has trophic and pro-absorptive effects on the gut as well as other metabolic effects. However, growth hormone alone has not had a consistent beneficial effect in clinical trials. Teduglutide, a GLP-2 analogue, is approved for use in SBS and promotes intestinal absorption and adaptation. Studies suggest that this therapy reduces the need for supplemental fluids and nutrients. Liraglutide and other GLP-1 analogues are currently being used off-label to slow gastric emptying and intestinal motility.

TABLE 1 Medical Treatment of Short Bowel

Slow transit	Loperamide, Lomotil, narcotics
Reduce gastrointestinal secretion	H_2 receptor antagonists Proton pump inhibitors Octreotide*
Treat bacterial overgrowth	Antibiotics Probiotics Prokinetics
Pharmacologic treatment	Growth hormone Teduglutide Liraglutide*

*Off-label use.

Prevent Complications

Metabolic complications are common in SBS patients (Table 2). Patients are at risk for dehydration and renal dysfunction. Hypocalcemia is a common problem related to poor absorption and binding by intraluminal fat. Maintaining adequate levels of calcium, magnesium, and vitamin D supplementation are important to minimize bone disease. Hyperglycemia and hypoglycemia are frequent complications of patients receiving a large amount of their calories parenterally. Both metabolic acidosis and alkalosis can occur.

Specific nutrient deficiencies must be prevented and monitored closely. These include iron and vitamin deficiencies as well as micronutrients such as selenium, zinc, and copper. Because fat is poorly absorbed, fatty acid deficiency can also occur. Serum free fatty acid levels and triene-to-tetraene ratios may need to be monitored periodically to determine the need for supplementation and response to treatment. In general, the enteral intake must greatly exceed the absorptive needs to ensure that these needs are being met.

Catheter-related sepsis is an important problem that often necessitates rehospitalization and replacement of catheters. Attention to technique and meticulous patient education are important to prevent this complication. Ethanol and antibiotic lock therapy may also be preventative. Catheter thrombosis is another frequent problem. In patients who require total parenteral nutrition permanently, this may become an important factor in the patient's survival because vascular access may not be achievable indefinitely.

PN-induced liver disease is another potential long-term problem. This appears to be a multifactorial process that is often reversible but may lead to severe steatosis, cholestasis, and eventually cirrhosis. It occurs more frequently in children and accounts for one-third of deaths in patients on long-term PN. It can be minimized by providing as large a portion of the calories as possible enterally, avoiding overfeeding, using mixed fuels (<30% fat), minimizing lipids (especially soy based), and preventing specific nutrient deficiencies. Treating bacterial overgrowth and preventing recurrent sepsis are also important.

Bacterial overgrowth may result from impaired motility or stasis caused by obstructive lesions. Depending on the bacterial species present, secretory diarrhea may also occur. Bacterial overgrowth requires a high degree of suspicion for diagnosis. This complication

TABLE 2 Complications in Short Bowel Syndrome

Therapy Related	Physiologic
Metabolic	Bacterial overgrowth
Nutritional	Cholelithiasis
Infectious	Nephrolithiasis
Liver disease	Gastric hypersecretion

should be suspected when a patient's absorptive capacity and stool habits change acutely. This may result from a mechanical obstruction or a blind loop, which can be relieved by operation. However, it is often a primary motor abnormality, which requires intermittent therapy with antibiotics. Colonization of the lumen with probiotics is another potential therapy.

Cholelithiasis occurs in 30% to 40% of SBS patients. Long-term PN causes both altered hepatic bile metabolism and gallbladder stasis. Biliary sludge forms within a few weeks of initiating PN if there is no enteral intake but rapidly disappears when enteral nutrition is resumed. Patients receiving PN are at risk for both cholelithiasis and hepatocellular dysfunction and thus require careful clinical evaluation. Intestinal mucosal disease and resection, particularly of the ileum, cause bile acid malabsorption, leading to lithogenic bile and the formation of cholesterol stones. The risk for cholelithiasis is significantly increased if less than 120 cm of intestine remains after resection, the terminal ileum has been resected, and PN is required. The incidence of cholelithiasis can be minimized by providing nutrients enterally whenever possible and using therapies to intermittently stimulate gallbladder emptying. Cholelithiasis is more likely to be complicated in patients with SBS and requires more extensive surgical treatment. Prophylactic cholecystectomy should be considered when laparotomy is being undertaken for other reasons.

Nephrolithiasis, primarily calcium oxalate stones, also occurs with some frequency. Oxalate is normally bound to calcium in the intestinal lumen and is not absorbed. Decreased availability of calcium secondary to reduced intake or binding by intraluminal fat leaves free oxalate in the lumen. Thus, the oxalate is absorbed in the colon and forms calcium oxalate in the urine. Nephrolithiasis is unusual in patients with intestinal resection and jejunostomy but occurs in one-fourth of such patients with an intact colon within 2 years of resection. Nephrolithiasis can be prevented by maintaining a diet low in oxalate, minimizing intraluminal fat, supplementing calcium orally, and maintaining a high urinary volume. Cholestyramine, which binds oxalic acid in the colon, is another potential treatment.

Gastric hypersecretion is a potential problem in patients with SBS. Massive intestinal resection can cause gastric hypersecretion as a result of parietal cell hyperplasia and hypergastrinemia. This phenomenon is usually transient, lasting several months, and presumably involves loss of an inhibitor from the resected intestine. The associated hyperacidity exacerbates malabsorption and diarrhea. About one-fourth of patients undergoing massive resection develop peptic ulcer disease. Treatment of gastric acid secretion may improve absorption but also prevents peptic ulcer disease. Control of acid secretion by H_2 receptor antagonists or proton pump inhibitors should be initiated in the perioperative period after resection and maintained until the increased acid production resolves. A few patients eventually require surgical intervention, but gastric resection should be avoided when possible.

SURGICAL STRATEGIES

Preserve the Intestinal Remnant

Abdominal reoperation is required in approximately 50% of patients with SBS after discharge from the hospital. Intestinal problems are the most frequent indication. An important goal in any reoperation in patients with SBS is to preserve the intestinal remnant length. Resection can often be avoided by using intestinal tapering to improve the function of dilated segments, employing strictureplasty for benign strictures, and using serosal patching for certain strictures and chronic perforations. Resection should be limited in extent when it cannot be avoided. Depending on the previous operations performed, patients will occasionally have intestinal segments that can be recruited into continuity at the time of reoperation. Often reconstruction of the proximal gastrointestinal tract is beneficial (e.g., previous Roux-en-Y gastric bypass). It is always important to document the length of intestine remaining during any operation on a patient with SBS.

An important clinical issue is whether to establish intestinal continuity in patients who have a colonic remnant. There are both advantages and disadvantages to restoring continuity. The colon may in fact improve intestinal absorption by increasing the absorptive surface area, deriving energy from short-chain fatty acids and prolonging transit time. It also improves quality of life by avoiding the stoma. However, the response of the colon to luminal contents is somewhat unpredictable. Bile acids may in fact cause a secretory diarrhea. Perianal problems can be disabling and decrease the patient's oral intake. Oxalate is absorbed primarily in the colon, and patients are thus at increased risk for the formation of calcium oxalate stones. Historically, only one-fourth of patients who initially had a stoma formed ultimately had continuity restored with a satisfactory outcome. However, we have become more aggressive about restoring continuity. This decision should be considered on an individual basis, depending on the length of the intestinal remnant and other anatomy and the patient's overall condition. Generally, at least 60 cm of small intestine are required to prevent severe diarrhea and perianal complications.

Surgical Therapy for Short Bowel Syndrome

There are several goals of surgical therapy for short bowel syndrome (Fig. 1). One has been to slow intestinal transit by reversing intestinal segments, interposing colonic segments into the small intestine, and other innovative approaches. Another goal has been to improve the function of existing intestine. For example, stenotic segments cause partial obstruction, which could lead to malabsorption. This can be managed by relieving the obstruction, often with a simple approach such as a strictureplasty. Furthermore, dilated dysfunctional segments aggravate malabsorption. These can be treated by tapering enteroplasty. For patients with particularly short remnants, increasing intestinal surface area is the best option for improving nutrient absorption. Intestinal lengthening procedures combine tapering with lengthening and are applicable in some patients. However, intestinal transplantation may be the final solution to this problem.

The surgical approach to the patient with SBS depends on several factors. The nature of nutritional support is obviously the primary determinant as to whether operation should be considered. In our experience, one-half of patients with SBS are able to sustain themselves on enteral nutrition alone. Operation should be considered cautiously and generally performed in these patients only if they demonstrate worsening malabsorption, are at risk for requiring PN, or have other symptoms related to malabsorption. Almost one-half of patients who are stable on long-term PN are candidates for operation, with the goal in this group being primarily to get the patient off PN. Patients who develop significant complications while dependent on PN have more compelling reasons to undergo operation. Most of these patients should undergo intestinal transplantation because many will die. Although liver disease is a frequent indication for transplantation, difficult vascular access and recurrent sepsis are also considerations. Patient age and underlying disease are also important factors. Children are much more likely to adapt to enteral nutrition but are also more likely to be candidates for operative treatment. In our experience, adult patients with mesenteric vascular disease and malignancy undergo operation less frequently.

The choice of operation for SBS is influenced by intestinal remnant length, intestinal function, and the caliber of the intestinal remnant (Fig. 2). These factors allow identification of several patient groups that might be treated by specific surgical procedures.

Adequate Remnant Length with Dilated Bowel

Adult patients with intestinal remnants greater than 120 cm are likely to be sustained on enteral nutrition alone, particularly if the ileocolonic junction is intact. However, these patients may develop

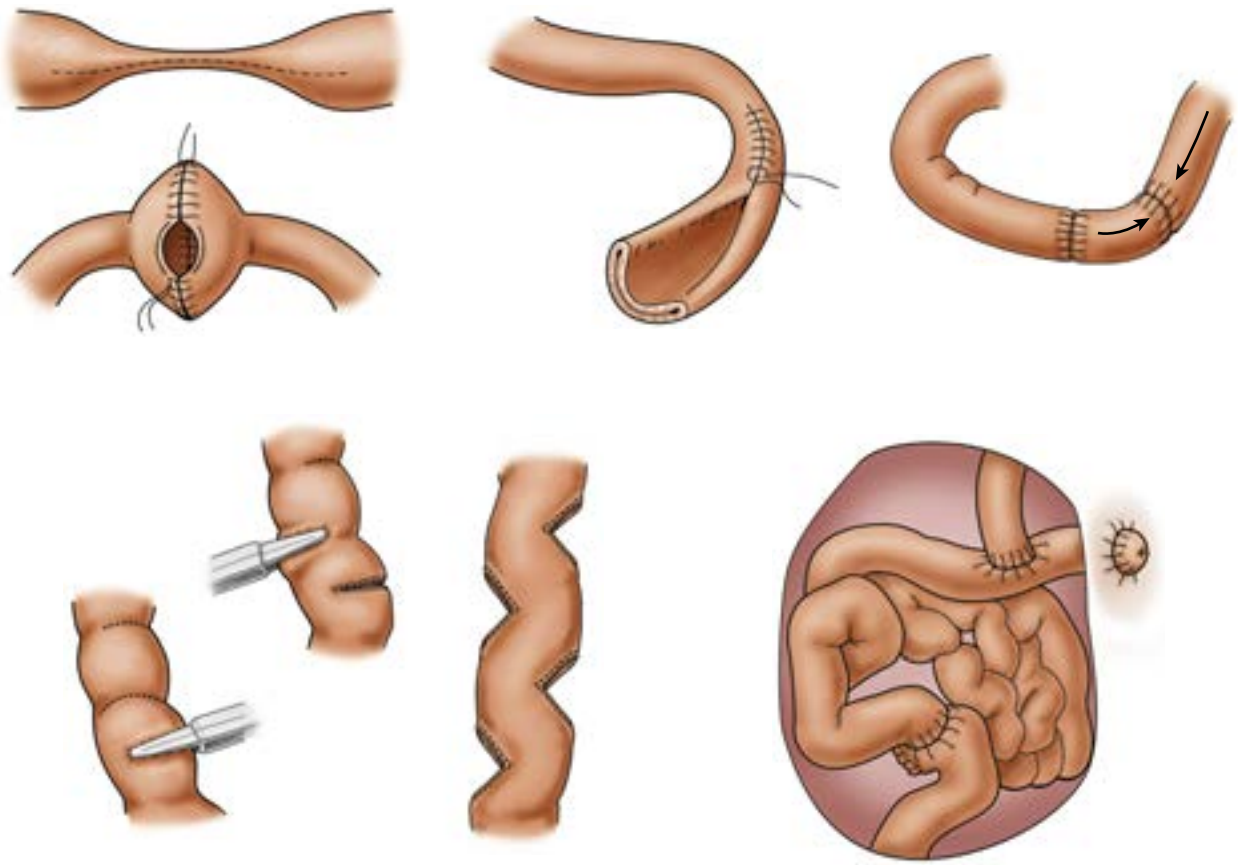


FIG. 1 Surgical procedures for improvement of intestinal function in short bowel syndrome. *(Modified from Thompson JS, Langnas AN, Pinch LW, et al. Surgical approach to short-bowel syndrome. Experience in a population of 160 patients. Ann Surg. 1995;222:605–607; Kim HB, Fauza D, Garza J, et al. Serial transverse Enteroplasty [STEP]: a novel bowel lengthening procedure. J Pediatr Surg. 2003;38:425–429.)*

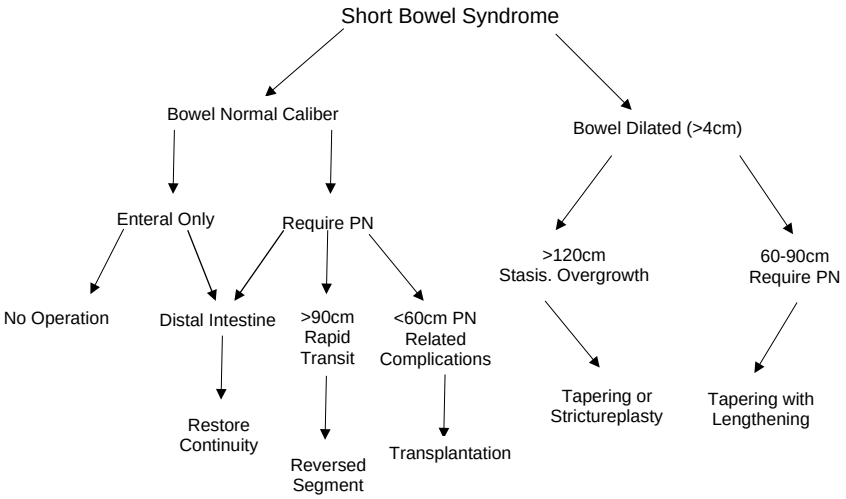


FIG. 2 Surgical management of short bowel syndrome. *PN,* Parenteral nutrition.

dilated bowel secondary to obstruction, often at the site of a previous anastomosis. A useful approach to these patients is to relieve the intestinal obstruction, often with a strictureplasty, although other procedures may be necessary. Children with remnants greater than 60 cm usually are sustained on enteral nutrition alone. Dilation of the intestinal remnant occurs more frequently in children and appears to have a different pathophysiologic basis. This may be a variant of intestinal pseudo-obstruction. Only one-fourth of children with a significantly dilated bowel have mechanical obstruction, but they routinely have bacterial overgrowth. Thus, for children, a tapering enteroplasty is often the appropriate therapy and also deals with any obstructive component present. This can be accomplished either by excising the redundant bowel along the antimesenteric border or simply imbricating it; the latter is our preferred approach. Motility is

generally slow to return. Recurrent dilation is a concern, but repeat tapering may be feasible.

Moderate Remnant Length with Rapid Transit

A challenging group of patients are those who have a shorter remnant (90–120 cm in adults) and signs of rapid transit. Slowing the rapid intestinal transit may permit these patients to be supported by enteral means alone. There are several possible approaches to this problem. Reversing 10- to 15-cm intestinal segments has been used most frequently in SBS. Longer reversed segments are more likely to be associated with chronic obstruction, whereas the shorter segments have less influence on intestinal transit and function. Almost 100 patients have been reported in the literature, and although documentation is usually not extensive, clinical improvement has been reported in at least one-half of patients. Some concerns have been raised about long-term function with the procedure. Both isoperistaltic and antiperistaltic colon interposition have been attempted. Although it appears that transit time may be prolonged because of the intrinsic differences in motility between the colon and small intestine, actual benefit has been difficult to show in a few anecdotal reports. Creation of various artificial valves to replace the ileocecal valve has been attempted. We have performed the valve procedure by creating a sphincter similar to that used in the continent ileostomy procedure but of shorter length (2 cm). We have had a favorable result in one adult and one child with this valve, but outcomes have not been as successful in the few other reports.

Patients with a Short Remnant and Dilated Bowel

Patients with short remnant length (<90 cm in adults and <30 cm in children) and dilated intestinal segments represent a more difficult problem. Even though the dilated segment could be tapered, this still does not result in enough functional bowel to avoid PN. In this situation, we and others have found intestinal lengthening to be the optimal treatment. The initial technique involved longitudinal intestinal tapering and lengthening, the Bianchi procedure. This involves dissection along the mesenteric edge of the bowel to allocate terminal blood vessels to either side of the bowel wall. Longitudinal transection of the bowel is then performed, usually with a stapling device that creates two parallel limbs of a smaller caliber. These can then be anastomosed to lengthen the intestinal remnant. More than 100 cases have been reported, mostly in children. Segments have been lengthened up to 55 cm, and overall improved nutrition resulted in approximately 90% of patients. This is a technically challenging procedure. Complications have been reported in 20% of procedures, which not surprisingly include ischemia and anastomotic leaks. Recurrent dilation has been a concern. However, follow-up for longer than 10 years suggests that this procedure has long-term benefit.

More recently, longitudinal lengthening has been supplanted by the *serial transverse enteroplasty procedure* (STEP) (see Fig. 1). This involves serial transverse applications of a linear stapler from opposite directions, dividing the bowel from either the mesenteric and antimesenteric sides or transversely. The length of the transverse division is determined by the intestinal diameter. This procedure avoids the difficult dissection along the mesenteric border of the Bianchi procedure and the end-to-end anastomosis. The bowel may have to be more dilated to use this technique. lt is more feasible in challenging areas such as near the ligament of Treitz. There are fewer complications with this technique. This procedure can be repeated if recurrent dilation occurs. Thus, the technique has become the procedure of choice for intestinal lengthening.

One of the limitations of intestinal lengthening procedures is that they can be applied only to a fairly select group of patients who have both a short intestinal remnant and an intestinal diameter greater than 3 to 4 cm. To improve the applicability of this technique, surgeons have used sequential operations employing first a procedure such as inserting an artificial valve to produce intestinal dilation and then performing the lengthening at a later time.

Short Remnant Length and Parenteral Nutrition–Related Complications

Patients with short intestinal remnants (<60 cm in adults and <30 cm in children) who develop complications related to PN represent a challenging group. For these patients, intestinal transplantation is the ideal solution. Patients with liver failure and SBS have been candidates for combined liver and small intestine transplantation. Patients who have reversible liver dysfunction or who have adequate liver function but other complications such as difficult vascular access and recurrent infection are candidates for solitary intestinal transplantation. More recently, isolated liver transplantation has been advocated for patients with irreversible liver failure and SBS that can be rehabilitated. The significant mortality rate among patients developing PN-induced complications justifies what continues to be a formidable operative approach.

More than 3000 intestinal transplantations have been performed worldwide. These have included primarily isolated small intestinal grafts (50%), combined liver and small intestinal grafts (25%), and multivisceral grafts (25%). The majority of transplant recipients are children. Although the morbidity and mortality rates remain significant, 80% of patients who survive the procedure long term have been able discontinue PN and return to more normal function. Long-term graft loss remains an important issue. Reported patient survival is 76% at 1 year, 56% at 5 years, and 43% at 10 years.

It is hoped that with greater experience and improved results, this therapy can be extended to other patients with SBS. The more successful recent outcome has been related, in part, to the use of new immunosuppressive agents and other innovative approaches to modifying the immune response. Of all of the surgical approaches, intestinal transplantation has the greatest potential for treating these patients, both in terms of the number of patients who would benefit and the functional improvement derived. Transplantation is clearly appropriate for individuals with anticipated survival of less than 12 months related to PN-induced complications. A more aggressive approach to the use of intestinal transplantation, particularly solitary transplantation, is justified in patients with signs of early liver dysfunction and other severe complications of nutritional therapy.

MULTIDISCIPLINARY APPROACH

Comprehensive care of intestinal failure patients requires a multidisciplinary approach. A physician leader with expertise in gastrointestinal disease should coordinate the efforts. Gastrointestinal surgical expertise in both adult and pediatric patients is required, and the presence of a transplant surgeon broadens the therapeutic options. Administrative support to coordinate the process and database is essential. A nurse coordinator is indispensable in day-to-day management. A nutritionist is essential. Psychologists and social workers are important for addressing psychosocial issues. This multidisciplinary effort can optimize patient outcome.

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Management of Enterocutaneous Fistulas

Grace C. Lee, MD, and Richard A. Hodin, MD

OVERVIEW

Enterocutaneous (EC) fistulas are among the most challenging, morbid conditions that general, gastrointestinal, and colorectal surgeons face. EC fistulas are abnormal connections between the lumen of the gastrointestinal tract and the skin. This term also includes enteroatmospheric (EA) fistulas, which are direct communications between the bowel and a nonepithelialized granulating wound that occur after nearly 10% of temporary abdominal closures. The majority of EC fistulas (75%–85%) are iatrogenic or postoperative in etiology, caused by anastomotic leaks (50%), missed enterotomies (45%), missed traumatic injuries, puncturing of bowel by percutaneous catheters, and/or erosion of foreign material such as mesh into adjacent bowel. The 15% to 25% of EC fistulas that develop spontaneously are often due to inflammatory bowel disease, malignancy, or prior radiation (Box 1).

Patients with EC fistulas can have severely impaired quality of life with malnutrition and chronic wounds that can be difficult to manage. Despite significant improvements in our knowledge of how to care for patients with EC fistulas, the overall mortality rate remains 15% to 25%, usually due to sepsis, malnutrition, and electrolyte imbalances.

This chapter focuses on the management of EC fistulas, which involves the multidisciplinary care by surgeons, wound and ostomy nurses, nutritionists, pharmacists, radiologists, and occasionally gastroenterologists. Through a stepwise approach that includes sepsis control, fluid and electrolyte repletion, nutritional optimization, control of effluent, wound care, and potential delayed operative intervention, outcomes have improved, though patients must be counseled that the process is resource-intensive and can take months to years.

PRESENTATION

The classic presentation of an EC fistula is in a patient anywhere from several days to several weeks out from surgery who develops fever, leukocytosis, and erythema around their incision. Opening the infected part of the incision generally releases purulent fluid, which then continues to drain and becomes a bilious green or brown color in appearance. EC fistulas can also be found in postoperative patients who develop abdominal pain, fever, and leukocytosis, and are found to have intraabdominal fluid collections on CT scans. An image-guided percutaneous drain initially produces purulent output, which then turns bilious or feculent.

Patients who develop EC fistulas can range from floridly septic with localized or diffuse peritonitis, which is less common, to having more mild symptoms of abdominal discomfort and leukocytosis. Surgeons must have a high index of suspicion for EC fistulas, as early recognition is key to starting appropriate treatment and preventing the development of sepsis.

BOX 1 Causes of Enterocutaneous Fistula Formation

Postoperative or iatrogenic (75%–85%)
- Anastomotic leak
- Missed enterotomy
- Missed traumatic injury
- Bowel injury from percutaneous catheter placement
- Erosion of foreign material (i.e., mesh) into adjacent bowel

Spontaneous (15%–25%)
- Inflammatory bowel disease
- Malignancy
- Prior radiation

CLASSIFICATION

EC fistulas are primarily classified based on daily output (Table 1). After recognition of an EC fistula, patients should be made nil per os (NPO) so that baseline fistula output, without any oral or enteral stimulation, can be ascertained. Low-output fistulas drain <200 mL per day, moderate-output fistulas drain 200 to 500 mL per day, and high-output fistulas drain >500 mL per day. This classification influences how fistulas are managed because low-output fistulas are much more likely to spontaneously close, whereas high-output fistulas are associated with dehydration, electrolyte disturbances, and malnutrition.

Fistulas are also classified based on location of the origin of the gastrointestinal leak. These include gastric, duodenal, enteric (small intestine), and colonic, the latter of which is called a *colocutaneous fistula.*

STABILIZATION AND SEPSIS CONTROL

The first step in management of EC fistulas is stabilization and sepsis control. Septic patients must be treated as per the Surviving Sepsis Guidelines, with fluid resuscitation, hemodynamic assessment, transfer to an intensive care unit if necessary, and initiation of broad-spectrum antibiotics. This step is critical because more than 70% of the mortality associated with EC fistulas is due to sepsis and uncontrolled infection.

Once the patient has been stabilized, the next step is to obtain source control by draining any intraabdominal abscesses. Abdominal axial imaging should be obtained to identify and characterize any abscesses (Fig. 1). For superficial abscesses that are already draining spontaneously, a small incision and debridement bedside procedure can be done to ensure continued egress of the effluent. Deeper intraabdominal or pelvic abscesses can be drained with image-guided percutaneous catheter placement by interventional radiology. These drains should be upsized and replaced as needed, with the goal of converting an uncontrolled enteric leak into a controlled EC fistula.

Operative intervention at this stage is rarely indicated; however, the occasional patient with peritonitis or evidence of free perforation on imaging should be taken urgently to the operating room for exploration. Abscesses and enteric contamination should be washed out. Oftentimes, the degree of inflammation and friability of tissues

TABLE 1 Classification of Enterocutaneous Fistulas Based on Daily Output

Classification	Daily output (mL/day)
Low output	<200
Moderate output	200–500
High output	>500

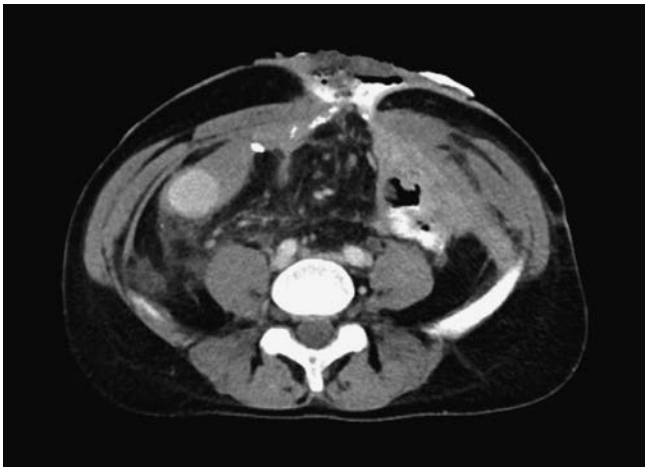


FIG. 1 CT scan shows enterocutaneous fistula with no drainable abscesses.

precludes safely running the bowel and identifying the leak. Performing an extensive lysis of adhesions in this state is fraught with danger, as healthy loops of bowel can be injured, leading to unnecessary bowel resections or missed enterotomies. If the source of the leak is identified, bowel resection can be performed; however, an anastomosis should not be created, as the risk of a recurrent leak is substantial. Similarly, primary repairs tend to not be durable solutions. Surgeons should have a low threshold to perform fecal diversions and/or leave drains to create a controlled fistula. It is important to remember that these are damage-control operations to address intraabdominal sepsis, not to definitively repair the enteric leak.

Once a patient has been stabilized and abscesses have been drained, antibiotics can be stopped in 4 to 7 days, pending clinical improvement. Longer courses of antibiotics are unnecessary for controlled EC fistulas and could lead to multiresistant organisms, which could make further antimicrobial management difficult. If a patient develops recurrent fevers, leukocytosis, or abdominal pain, clinicians should have a low threshold to reimage, as new abscesses could develop even after initial source control has been obtained.

LONG-TERM MANAGEMENT

As soon as the patient is stabilized and sepsis is controlled, then long-term management begins, usually starting within 2 days of diagnosis and lasting months to years. This chronic management consists of fluid and electrolyte repletion, nutritional optimization, pharmacologic control of effluent volume, and wound care, all of which are performed in parallel, using multidisciplinary expertise (Fig. 2). With this treatment, approximately 30% to 35% of EC fistulas will heal spontaneously within 5 to 6 weeks of diagnosis. Therefore, long-term management aims to increase the likelihood of spontaneous closure while also optimizing the patient for possible operative intervention.

Fluid and Electrolyte Repletion

Patients with EC fistulas, particularly high-output EC fistulas, can develop severe dehydration and electrolyte derangements. Quantifying fistula output and resuscitating adequately are crucial for the acute and long-term management of these patients. Many patients with high-output EC fistulas utilize total parenteral nutrition (TPN) for not only nutrition but also volume resuscitation. These patients often have long-term central access (such as peripherally inserted central catheters) for TPN, which enables them to also administer extra intravenous fluid infusions at home if needed based on fistula output.

The most common electrolyte abnormalities are hyponatremia, hypokalemia, and hypomagnesemia. Hyponatremia often normalizes with fluid resuscitation, and potassium and magnesium should be aggressively repleted. Patients with duodenal fistulas can develop metabolic acidosis requiring sodium bicarbonate replacements. After starting parenteral nutrition or resuming enteral nutrition, patients must be closely monitored for refeeding syndrome, with frequent serum phosphorus checks and phosphorus repletion.

Nutritional Optimization

Patients with EC fistulas can develop profound malnutrition, as they can lose up to 500 g of protein daily. Markers of nutritional status such as prealbumin, albumin, and transferrin should be monitored closely. Patients with low-output fistulas require 20 kcal/kg per day of carbohydrates and fat and 1 g/kg per day of protein, which can increase to 30 kcal/kg per day and 1.5 to 2.5 g/kg per day for patients with high-output fistulas.

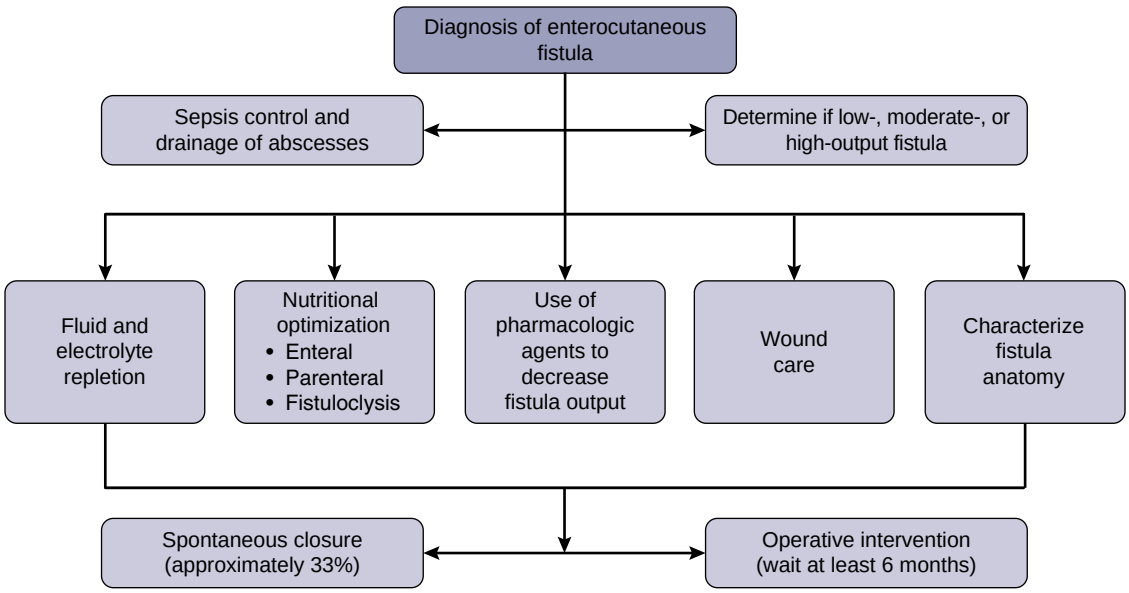


FIG. 2 Algorithm for the management of enterocutaneous fistulas.

Enteral feeding is preferred to parenteral nutrition because it promotes mucosal integrity, maintains intestinal function, and supports immune function. However, oral intake can often increase fistula output substantially, which can be a problem for wound care in some patients. TPN is usually needed as a bridge to enteral feeding or for longer-term nutrition in patients who cannot tolerate oral intake.

A common approach for patients with newly diagnosed fistulas is to attempt a few days of bowel rest, with or without TPN depending on the patient's nutritional status, to see if the fistula spontaneously closes or if the output decreases. If the output persists, then an oral diet is gradually introduced. If the fistula output increases significantly and there are concerns for malabsorption, then TPN is started. Pharmacologic measures, as discussed later, should be used to slow fistula output. As long as fistula output is controlled and wound care is manageable, most patients are able to continue an oral diet, with or without TPN for nutritional support. This holds true even for high-output fistulas, assuming that ostomy appliances are well seated and capture the output, and assuming that patients can provide themselves with additional IV fluids as needed.

Fistuloclysis

Fistuloclysis has become a popular method of enteral feeding distal to the EC fistula. With this technique, the distal limb of the EC fistula is identified using a fistulogram, which can be performed by interventional radiology or in the operating room using fluoroscopy (Fig. 3). The interventional radiologist or surgeon cannulates the distal limb with a catheter, which can then be used to instill tube feeds. Ideally, the surgeon tunnels the catheter under the skin, which enables securing of the catheter more firmly in place and facilitates easier wound care. For patients with high-volume liquid output, their effluent can be collected, strained, and then refed into the distal feeding tube. This method should only be used in patients who have fistulas that are not expected to close spontaneously, as cannulating the distal limb of the fistula will prevent it from closing.



FIG. 3 Example of a fistulogram, in which a catheter is inserted into the fistula, enteric contrast is injected, and the bowel is opacified.

Fistuloclysis enables maintenance of mucosal integrity and promotes intestinal adaptation and lengthening, which is beneficial for patients who will likely require operative intervention. It also enables patients to wean off parenteral nutrition. Furthermore, fistuloclysis has been shown to activate an "ileal brake," in which refeeding of succus leads to decreases in gastric acid secretion, pancreatic enzyme secretion, and peristalsis, thereby decreasing EC fistula output.

The careful balance between oral intake, distal tube feeds, succus refeeding, and parenteral nutrition requires collaboration with nutritionists who follow these patients closely as inpatients and outpatients and whose expertise is key to the long-term optimization of these patients.

Pharmacologic Management of Fistula Output

Another key component to the long-term management of EC fistulas is controlling effluent volume. First-line pharmacologic agents include opiate receptor agonists such as loperamide, diphenoxylate/atropine, codeine, and distilled tincture of opium, which act on the circular and longitudinal intestinal muscles to decrease peristalsis. These medications can be titrated up as needed to slow fistula output. Proton pump inhibitors and histamine-2 receptor antagonists are also part of the first-line treatment of high-output EC fistulas, as they lower the acidity of fistula output, while also decreasing volume due to their antisecretory effects.

Other agents can be added to the first-line pharmacologic therapies. Amitriptyline is a tricyclic antidepressant that causes constipation via anticholinergic pathways. Clonidine, an alpha 2-adrenergic agonist, increases mucosal absorption of fluids and electrolytes. Bulking agents such as psyllium or banana flakes can also be helpful to thicken enteric contents. Cholestyramine, a bile acid sequestrant, is useful in decreasing the output of more proximal EC fistulas, such as those originating from the duodenum or proximal jejunum. Octreotide, a somatostatin analog, has been recommended for use in high-output fistulas. It acts by reducing gastric acid and pancreatic enzyme secretions, as well as enhancing fluid and electrolyte absorption by prolonging intestinal transit time. Numerous studies have demonstrated that octreotide does not increase the likelihood of spontaneous fistula closure; however, it does decrease fistula output and the time it takes for fistulas to close.

With these pharmacologic agents, even high-output EC fistulas can be slowed to the point that many patients resume oral intake while keeping fistula output within a goal of <1 to 1.5 L per day.

Wound Care

The skin surrounding EC fistulas often becomes excoriated due to spillage of acidic succus, similar to ileostomies that are difficult to pouch (Fig. 4A). Patients with EC fistulas benefit from the expertise of wound and ostomy nurses who develop plans for isolating the fistulas and protecting the surrounding skin. These complex wounds usually require a combination of stoma paste and powders, barrier rings, and hydrocolloid dressings, as well as specialty ostomy appliances that can be cut to fit the fistulas (Fig. 4B and 4C). Pouches need to accommodate fistuloclysis catheters that directly enter the wound, which is why catheters that tunnel under the skin and come out away from the wound are preferred. EA fistulas sometimes require sump drains to collect the effluent and divert it away from the surrounding skin.

Vacuum dressings can be used to promote granulation of the surrounding tissues and protect those tissues from effluent. However, they must be used with caution. If vacuum dressings are placed

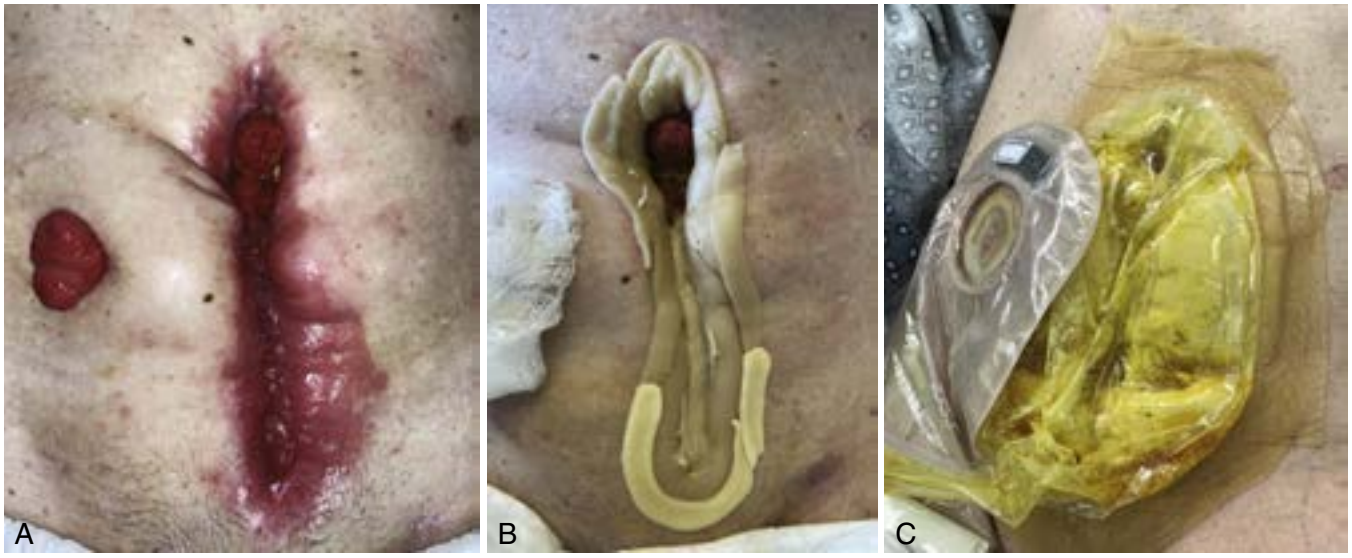


FIG. 4 A patient with multiple enterocutaneous (EC) and enteroatmospheric (EA) fistulas along a prior midline incision. **(A)** Note the skin excoriation around the fistulas. There is an ileostomy in the right lower quadrant that was distal to the fistulas. **(B)** The wound care plan included protecting the surrounding skin with stoma paste and barrier rings molded to the shape of the wound, thus also isolating the main fistulas. **(C)** Stoma appliances were then placed over the fistulas and the ileostomy to catch the effluent. Note that the main stoma appliance is further secured by adhesive dressings.

on granulation tissue directly over bowel or on a skin graft directly over bowel, the suction force could promote the development of new fistulas. Nevertheless, numerous small studies have demonstrated that, when used appropriately, vacuum dressings can promote wound healing and may even accelerate spontaneous closure.

Wound care plans often change over time as the wounds ideally heal and contract. Wound and ostomy nurses work very closely with patients and their families, teaching them tips and tricks to care for their wounds during the months- to years-long process.

Define the Fistula Anatomy

Next, it is critical to characterize the anatomy of the EC fistula, utilizing imaging studies such as CT scans with oral contrast, upper gastrointestinal swallow studies with small bowel follow through, contrast enemas, and fistulograms in which the proximal and distal limbs of the fistula are cannulated and injected with oral contrast under fluoroscopy (see Fig. 3). The goal of these studies is to delineate the location of the fistula, how much bowel is proximal and distal to the fistula, and assess if there are multiple fistulas. They can also determine if fistuloclysis will be possible. Furthermore, these studies can assess for distal obstructions, which would make spontaneous closure unlikely, and can help with operative planning.

SPONTANEOUS CLOSURE

Approximately 30% to 35% of EC fistulas will close within 2 months of diagnosis without operative intervention (Box 2). Fistulas with tracts longer than 2 cm, defect sizes of <1 cm^2, and decreasing output are more likely to heal spontaneously. Distal obstructions, ongoing sepsis or abscess, and malnutrition are all predictors of requiring operative intervention. EC fistulas caused by Crohn's disease, malignancy, radiation, or a foreign body are also less likely to close spontaneously.

OPERATIVE INTERVENTION

EC fistulas that have not spontaneously closed within 2 months will likely require operative management. Most surgeons recommend waiting at least 6 months after the diagnosis of the fistula before considering an operation. Over this period of time, intraabdominal adhesions soften and become more filmy, thus making the operation easier and less prone to causing enterotomies. The "pinch test" for EA fistulas, in which tissue or skin graft overlying bowel is pinched to see if the underlying bowel separates easily, can also be used to determine readiness for surgery. Surgeons should wait until the patient is nutritionally optimized, sepsis is controlled, and the patient is at or close to their baseline functional status.

In the operating room, surgeons should prepare for a difficult, lengthy procedure. Ideally, the case should start in the morning, and, for complex fistulas, no other operations should be planned for the same day. Anesthesiologists should be prepared for high insensible losses and should resuscitate accordingly, using a urinary catheter for

BOX 2 Characteristics Predictive of Spontaneous Closure of Enterocutaneous Fistulas

Increased Likelihood of Spontaneous Closure
- Postoperative etiology
- Fistula tract longer than 2 cm
- Fistula defect <1 cm^2
- Healthy surrounding bowel
- Good nutritional status
- Low fistula output

Decreased Likelihood of Spontaneous Closure
- Non-postoperative etiology (inflammatory bowel disease, cancer, radiation)
- Distal obstruction
- Presence of a foreign body
- Continued sepsis or abscess present
- Epithelialized fistula tract
- Steroid use
- Malnourished
- High fistula output

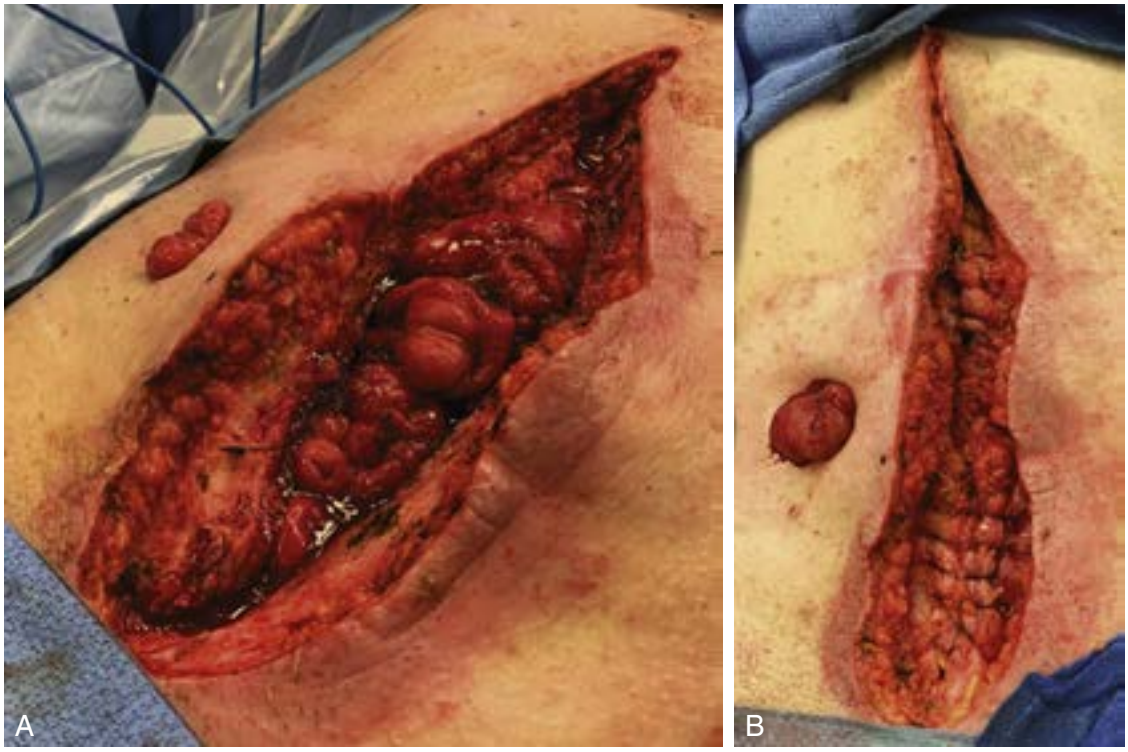


FIG. 5 The same patient from Figure 4 was taken to the operating room for an enterocutaneous (EC) fistula takedown. **(A)** Opening the wound revealed multiple loops of small bowel densely adhered to the prior incision, which were the sources of the numerous EC and enteroatmospheric (EA) fistulas. **(B)** At the conclusion of the case, a unilateral anterior component separation was used to close the fascia primarily. The loop ileostomy was converted to an end ileostomy.

accurate recording of urine output. Epidural catheters or transversus abdominis blocks should be considered for postoperative pain management. The incision should be made away from prior incisions, if possible, usually subxiphoid, and dissection should be started away from the EC fistula. An extensive lysis of adhesions with sharp dissection should be performed and the bowel should be fully mobilized, such that the exact location of the fistula, the amount of bowel involved in the fistula, and the presence of any other enterotomies can be identified. It is not uncommon for multiple loops of bowel to be involved in the inflammatory mass surrounding EC fistulas (Fig. 5A). Any foreign material such as previous mesh should be removed. The surgeon should look for any distal obstruction so that it can be fully addressed. At this point, the amount of bowel to resect can be determined with the goal of preserving as much small bowel as possible to prevent future short-gut syndrome. Fistula defects should not be repaired primarily, as it will likely lead to recurrent leaks. The amount of remaining bowel should be documented.

Most of these operations require closure of a large abdominal wall defect. Due to the contamination of the wound, many surgeons would not recommend placing synthetic mesh to aid in abdominal closure. Instead, component separations should be used to close the fascia if simple primary closure is not possible (Fig. 5B). Biologic mesh can be placed in an underlay fashion if needed. Involving general surgeons or plastic surgeons who specialize in abdominal wall reconstruction can be beneficial, particularly for large and complex abdominal wall defects.

Surgeons and patients must be prepared for the possibility of a frozen abdomen. If it becomes clear that the EC fistula itself cannot be resected safely, other options include creating a diverting stoma, if one is not already present, or placing a venting gastrostomy tube and/or a distal feeding jejunostomy tube.

Though the morbidity and mortality rates of EC fistula takedowns have been improving over time, patients must still be counseled preoperatively on the risks of the procedure and the long postoperative recovery. Approximately 16% to 36% of EC fistulas will recur after surgery, though some recent studies quote operative success rates as high as 92%. Mortality has decreased from approximately 40% in the 1970s to approximately 20% currently, with some studies citing mortality rates as low as 2%. Nevertheless, 30-day morbidity rates have been reported to be nearly 50% based on analysis of the American College of Surgeons National Surgical Quality Improvement dataset. Although significant improvements have been made over the years, EC fistula takedowns remain complex, morbid operations, and patient expectations should be set preoperatively.

The postoperative recovery period typically lasts for several months. Parenteral nutrition can be weaned off as enteral nutrition improves. Many patients benefit from postoperative physical therapy, and some require stays in rehabilitation facilities.

SUMMARY

EC fistulas are complex, debilitating conditions that require multidisciplinary, long-term management. By using the algorithm of sepsis control followed by simultaneous fluid and electrolyte management, nutritional optimization, decreasing the volume of effluent, and wound care, approximately one-third of EC fistulas will close on their own. For patients who require operative intervention, waiting at least 6 months to allow for preoperative optimization and softening of adhesions has led to decreasing mortality rates and increasing rates of operative success.

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Management of Radiation-Induced Injury to the Small and Large Bowel

Sophia Y. Chen, MD, MPH, and Chady Atallah, MD

INTRODUCTION

Radiation therapy plays an important role in the multimodal management of anorectal, gynecologic, and urogenital pelvic malignancies. Approximately 70% of cancer patients undergo radiation therapy for the treatment of these malignancies to prolong their disease-free survival and reduce local recurrence. Although radiation delivery is directed at the target tissue for maximum benefit, radiation fields required to treat these malignancies may nevertheless include normal small intestine, colon, and/or rectum, leading to potential injury of otherwise healthy tissue. Radiation-induced injury to the bowel therefore remains a critical issue requiring careful management considerations and preventative strategies.

PATHOPHYSIOLOGY AND HISTOPATHOLOGY

Radiation therapy is most commonly delivered via external beam radiation therapy (EBRT), which uses a linear accelerator to produce ionizing radiation. EBRT can directly or indirectly damage DNA within malignant and normal cells through its interaction with water and the release of free radicals. Depending on the extent of DNA damage, EBRT can result in mitotic inhibition or cellular apoptosis. Brachytherapy is another method of radiation delivery and involves the placement of a radiation source within the body, often in the form of pellets or beads.

The pathophysiology of radiation damage to the bowel has been described in the literature via the "target cell" theory, in which acute effects of radiation-induced injury target cells of the bowel epithelium, whereas chronic effects of radiation-induced injury target cells with slower turnover, such as endothelial cells and fibroblasts. Rapidly dividing cells like those in the gastrointestinal (GI) tract are most susceptible to radiation injury; as such, radiation affects the cells of the mucosa first, followed by the submucosa, muscularis, and serosa. Chronic radiation injury to the bowel is often associated with ischemic injury. Reaction of fibroblasts to cytokines, growth factors, and chemokines leads to fibrosis. Cellular death leads to intestinal atrophy and subsequent malabsorption and stricture formation. Radiation can also result in vascular damage, leading to dilatation of small blood vessels presenting as telangiectasias. Furthermore, arteriolar constriction can result in bowel ischemia and necrosis.

Histopathologically, acute radiation injury to the bowel is often characterized by extensive mucosal inflammation, crypt atrophy/abscesses, nuclear atypia with bizarre mitoses, and eosinophilic submucosal infiltration. Chronic radiation injury to the bowel is often characterized by obliterative enteritis (irregularly shaped endothelial cells, fibroblasts, myofibroblasts, and foamy cells within arteries), small-vessel vasculopathy (dilated, thickened, hyalinized blood vessels), ulceration, fibrous induration, and superimposed episodes of ischemic changes (Fig. 1).

RISK FACTORS

Risk factors associated with radiation-induced bowel injury include both patient factors and radiation treatment-related factors. Patient comorbidities associated with an increased risk for radiation-induced injury include smoking, diabetes mellitus, hypertension, vascular and collagen disorders, atherosclerosis, coronary artery disease, inflammatory bowel disease, and prior intestinal surgery. Chemotherapy such as fluoropyrimidines, taxanes, platinum agents, mitomycin C, gemcitabine, methotrexate, actinomycin D, topotecan, and doxorubicin can act as radiosensitizers and potentiate the effects of radiation. Low body mass index (BMI) has also been associated with increased risk for radiation injury due to higher rate of radiation toxicity.

Radiation treatment-related factors associated with increased risk for radiation-induced injury include higher radiation dose, longer length of bowel irradiated, fewer dose fractionation, and larger radiation field size.

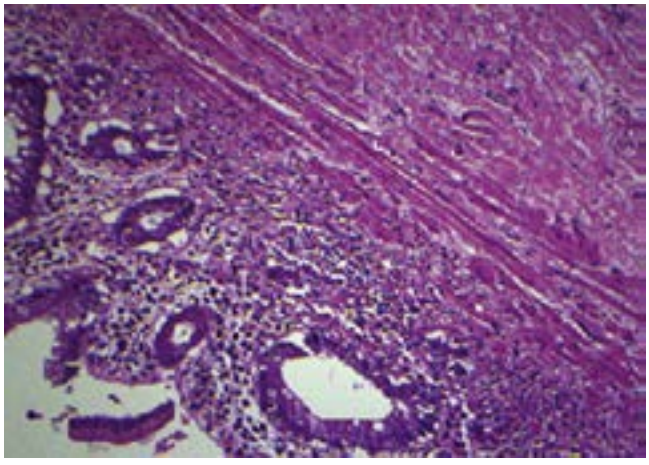


FIG. 1 Histopathology (magnification ×20) showing submucosal fibrosis with atypical fibroblasts, endothelial cells, and increased inflammatory cell infiltrate. *(From Theis VS, Sripadam R, Ramani V, Lal S. Chronic radiation enteritis. Clin Oncol. 2010; 22[1]:70–83.)*

RADIATION THERAPY TOXICITY GRADING SYSTEMS

Although various radiation toxicity grading systems exist in the literature, the Radiation Therapy Oncology Group (RTOC) and the European Organization for Research and Treatment of Cancer (EORTC) grading system is one of the most commonly used (Table 1). The RTOC/EORTC grading system differentiates acute radiation morbidity (day 1 through 90) from chronic radiation morbidity (after day 90) on a scale from 0 to 5 based on presenting symptoms. Although these grading systems provide a standardized assessment based on patient symptoms, they do not include endoscopic and histopathologic information. Other available grading systems include the Late Effects Normal Tissue (LENT) system; the Subjective, Objective, Management, and Analytic (SOMA) grading system for chronic radiation injury; and the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

CLINICAL FEATURES

Acute radiation-induced bowel injury can occur from the time of radiation treatment up to 6 months after treatment completion. Because acute radiation damage leads to mucosal inflammation and damaged mucosal surface, diarrhea is one of the most common symptoms. Injury to the mucosal barrier also increases the risk for bacterial translocation and subsequent bacteremia and sepsis. Other symptoms of acute radiation-induced bowel injury include nausea, bloating, cramping, abdominal pain, and GI dysmotility. Acute radiation colitis and proctitis can present with additional symptoms of bleeding, mucus discharge, urgency, and tenesmus.

Chronic radiation-induced bowel injury can continue from the acute phase or present after a latent period. Chronic radiation injury symptoms typically present 8 to 12 months after treatment completion; however, symptoms have been reported up to 30 years after a latent period. Like acute radiation-induced injury, diarrhea is one of the most common symptoms. Chronic radiation proctitis can also commonly present with rectal bleeding due to telangiectasias. Patients with chronic radiation-induced bowel injury can also have ulcerations from ischemia, abscesses, and fistula formation. Chronic ischemic changes can lead to stricture formation and subsequent bowel obstruction. Full thickness necrosis of the bowel can result in fistulae or free perforation.

DIAGNOSIS

Acute radiation-induced injury to the small intestine, colon, and rectum is generally diagnosed based on the patient's presenting symptoms and history. Chronic radiation-induced bowel injury is diagnosed not only by symptoms but also may require additional imaging such as a CT scan or MR enterography to evaluate the anatomy and assess for strictures, fistulae, or bowel wall thickness abnormalities. Patients with suspicion for radiation colitis or proctitis may occasionally undergo barium and water-soluble contrast enemas, which can reveal shortening, narrowing, lack of distensibility, and absent haustral/mucosal folds of the bowel. Fistulae may need to be further evaluated with MRI, fistulograms, cystograms, and pelvic examinations.

Definitive diagnosis can be made endoscopically with biopsies demonstrating histologic features pertaining to radiation injury, as described previously. Upper endoscopy may be considered for suspected radiation injury to the duodenum; however, lower endoscopy may not be effective in reaching more distal areas of radiation enteritis. Capsule endoscopy should only be considered if intestinal strictures have been excluded. Lower endoscopy via colonoscopy or sigmoidoscopy is beneficial in diagnosing radiation colitis and proctitis. These are characterized by neovascularization with fragile vessels on lower endoscopy (Fig. 2). Other features of radiation-induced bowel injury include pallor and friability. Rectal biopsies should be performed judiciously, as they have been associated with increased risk of rectal fistula formation.

MANAGEMENT STRATEGIES

Medical Management

Between 50% and 75% of patients with acute radiation-induced bowel injury present with symptoms. Fortunately, these symptoms are often self-limited and can be managed medically. Diarrhea can be managed with antidiarrheal medications such as loperamide and fiber supplements, and with dietary modifications (e.g., lactose-free diet, low-fat diet, low-residue diet, or elemental diet). Patients with severe diarrhea, dehydration, and nutritional deficits may need to be admitted to the hospital for intravenous fluids and/or parenteral nutrition. If first-line antidiarrheals are ineffective, octreotide may be given. Nausea can be managed with antiemetics. Anticholinergics,

TABLE 1 RTOG/EORTC Radiation Toxicity Grading System

Grade	1	2	3	4	5
Acute radiation morbidity (Days 1–90)	• Increased frequency or change in bowel habits • Rectal discomfort • No medication	• Diarrhea requiring parasympatholytic drugs • Mucus discharge not requiring sanitary pads • Rectal or abdominal pain requiring analgesics	• Diarrhea requiring parenteral support • Severe mucus or blood discharge requiring sanitary pads • Abdominal distension	• Acute/subacute obstruction, fistula, or perforation • GI bleed requiring transfusion • Abdominal pain or tenesmus requiring tube decompression or bowel diversion	• N/A
Late radiation morbidity (Days >90)	• Mild diarrhea and cramping • Bowel movement ≤5 times daily • Slight rectal discharge or bleeding	• Moderate diarrhea and cramping • Bowel movement >5 times daily • Excessive rectal mucus or intermittent bleeding	• Obstruction or bleeding requiring surgery	• Necrosis, perforation, or fistula	• Death

RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer

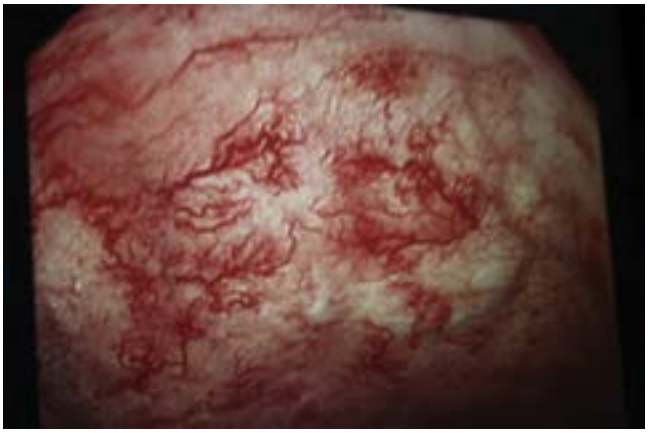


FIG. 2 Endoscopic appearance of radiation proctitis showing telangiectasias. *(From Hogan NM, Kerin MJ, Joyce MR. Gastrointestinal complications of pelvic radiotherapy: medical and surgical management strategies. Curr Probl Surg. 2013; 50[9]:395–407.)*

antispasmodics, bile acid–binding agents like cholestyramine, and antisecretory agents can also be considered.

Butyrate enemas have been shown to provide some benefit for the management of acute radiation proctitis due to the provision of short chain fatty acids as nutrient for colonocytes; however, they have had mixed results for the management of chronic radiation proctitis. Recent Multinational Association of Supportive Care in Cancer (MASCC) guidelines for patients with chronic proctitis in patients with rectal bleeding recommend the use of sucralfate enemas, given sucralfate's ability to evoke a protective barrier and promote epithelial healing. Other enemas such as mesalamine (5-ASA) enemas, short-chain fatty acid enemas, and steroid enemas have had mixed findings and require further investigation.

Formalin therapy has been found to be an effective form of topical treatment for bleeding from chronic radiation proctitis by chemically cauterizing telangiectasias and ulcers. Formalin (4%–10% concentration) can be delivered via irrigation with aliquots of 20 to 50 mL for a total volume of 400 to 500 mL or via direct application of formalin-soaked gauze onto mucosa via rigid proctoscopy. Washout with formaldehyde is typically recommended after application of formalin. Although formalin therapy is effective, multiple application sessions may be required. It is important to avoid direct contact of formalin to the anoderm because this may cause irritation and pain. Potential complications of formalin therapy include anal/pelvic pain, stricture, rectal wall necrosis, and fistula formation.

Other medical treatments that can be considered for radiation-induced bowel injury include antioxidants (vitamins E and C), probiotics, and hyperbaric oxygen to facilitate angiogenesis. A few studies have suggested that a 4-week course of oral metronidazole may be associated with decreased bleeding, ulceration, and diarrhea in radiation proctitis.

Endoscopic Management

Endoscopic therapy can play an important role in the treatment of chronic radiation-induced bowel injury. Argon plasma coagulation (APC) is currently the treatment of choice for bleeding, before considering the use of formalin therapy. APC has been found to stop bleeding in 80% to 90% of cases and is a safe approach because it coagulates at a superficial depth (Fig. 3). Some studies also demonstrate improvement of bowel function after APC. However, like formalin therapy, patients may require multiple APC treatments. It is important when performing APC to avoid the dentate line because contact may result in anorectal pain. Potential complications for APC include anorectal pain and abdominal cramping. Although



FIG. 3 Argon plasma coagulation of rectal ulcer. *(From Araujo IK, Muñoz-Guglielmetti D, Mollà M. Radiation-induced damage in the lower gastrointestinal tract: Clinical presentation, diagnostic tests and treatment options. Best Pract Res Clin Gastroenterol. 2020; 48–49:101707.)*

neodymium-doped yttrium aluminum garnet (Nd:YAG) laser therapy, radiofrequency ablation, and cryotherapy are alternative endoscopic treatments that can be performed to treat bleeding, they are now rarely performed due to the effectiveness of APC.

Surgical Management

More than 30% of patients with chronic radiation-induced bowel injury will require surgical intervention. Surgery is indicated for patients whose symptoms are unable to be managed medically or endoscopically, as well as for patients with complications including perforations, fistulae, strictures, obstruction, intractable pain, and incontinence. Surgery for patients with radiation-induced bowel injury is fraught with technical challenges and a high potential for complications. Morbidity and mortality rates after surgical intervention can range from 30% to 65% and 6.7% to 25%, respectively. The irradiated abdomen can contribute to a hostile operative environment with friable tissue, extensive adhesions, and high risk for bowel injury and poor healing. Careful preoperative planning based on individual patient factors in a multidisciplinary/specialized setting and a structured approach to operative intervention is therefore critical to achieving safe and effective surgery. It is important to also appreciate the risk of recurrence or de novo malignancy in the irradiated bowel segment during preoperative planning. Once the decision to proceed with surgery is made, effort must be made to correct modifiable factors and optimize the patient preoperatively. This may entail correcting electrolyte derangements and providing enteral nutrition for severely malnourished patients. Surgical options for radiation-induced bowel injury include limited bowel resection, bypass/exclusion procedures, stricturoplasty, and fecal diversion.

The choice of surgical incision for patients with chronic radiation injury should be carefully considered because patients who undergo radiation therapy have impaired wound healing. Some surgeons may prefer a low transverse incision inferior to the umbilicus to avoid the irradiated area. Others may prefer a lower midline incision to allow for adequate exposure and in case further interventions are needed

in the future. A Pfannenstiel incision may be considered for thin female patients. The role of minimally invasive surgery for radiation-induced bowel injury is controversial. A diagnostic laparoscopy with abdominal entry via open Hasson technique would determine whether a minimally invasive approach is feasible, with dense adhesions or pelvic fibrosis serving as contraindications. Once the abdomen is entered and the severity of disease is assessed, dissection should begin proximally, where radiation-induced damage is less severe, and move distally. Gentle handling and extreme care of tissue via sharp dissection using Metzenbaum scissors is recommended to prevent bowel injury. Blunt dissection can be associated with a high risk of enterotomy and should be avoided.

For patients with extensive, dense adhesions, limited adhesiolysis should be performed only in the area of interest and only if the bowel is resectable because there is increased risk for fistula formation and bowel injury. Patients with pelvic adhesions generally have small bowel segments adherent in the pelvis; bowel adherent to the sacrum may be extracted from the pelvis with careful dissection, although it is important to avoid damage to the presacral veins and to be able to deal with any ensuing hemorrhage that could occur. Enterotomies would commit the surgeon to extracting the bowel from the pelvis. If a bowel segment were fibrosed to the sacrum, it may be safer to leave this segment attached while applying diathermy to the mucosal surface. Hydrodissection via saline injection into dense interloop adhesions can prevent serosal injuries.

Limited bowel resection of the involved segment is generally preferred over other surgical alternatives such as bypass/exclusion because it is associated with decreased rates of reoperation and increased survival. During bowel resection, careful consideration is necessary when selecting the two pieces of bowel to be used for bowel anastomosis. Grossly irradiated bowel can appear pale, mottled, yellowish/gray, or telangiectatic with features of vascular insufficiency (Fig. 4). However, irradiated bowel can also appear indistinguishable from normal bowel. Anastomotic leak rates between two pieces of irradiated bowel can be as high as 50%; as such, anastomosis between nonirradiated bowel is recommended when possible. If an anastomosis is necessary, the cecum and terminal ileum should be avoided as these segments often experience severe radiation injury. Hand-sewn anastomosis is favored when possible to avoid staple-line ischemia. Because radiation can lead to friable, thickened, and foreshortened mesentery, it is also recommended to over-sew the mesentery with an interlocking heavy #1 chromic suture between clamps rather than simply ligating the mesentery with vessel sealers or a clamp, cut, tie technique.



FIG. 4 Intraoperative comparison of radiation-damaged small bowel *(left)* with healthy bowel *(right)*. *(From Hogan NM, Kerin MJ, Joyce MR. Gastrointestinal complications of pelvic radiotherapy: medical and surgical management strategies. Curr Probl Surg. 2013; 50[9]:395–407.)*

Although bowel resection is preferred, bypass/exclusion can be considered in patients with extensive adhesions and/or pelvic fixation in which resection is not possible. Bypass is associated with a decreased risk of bowel or mesenteric injury and lower anastomotic leak rate compared with bowel resection; however, it increases the risk of blind loop syndrome and fistula formation from the affected segment left behind, which can contribute to further complications. In select cases, stricturoplasty may be considered as an intestine-preserving alternative to more extensive bowel resection or bypass techniques to reduce risk of short gut syndrome and avoid total parenteral nutrition (TPN) dependence.

The management of postradiation enteric and pelvic fistulae are similar to those employed for other types of fistulae, including sepsis management, nutritional optimization, and fistula maturation/output optimization. Higher pelvic fistulae (rectovaginal, rectourethral) can be treated with proctectomy and anastomosis of colon to distal nonradiated rectum or anus. Hand-sewn coloanal anastomosis should only be considered in younger patients with intact sensation, function, and control. Interposition of well-vascularized tissue (omentum or rectus pedicle flap) between the affected organ and anastomosis is highly recommended. Lower pelvic fistulae can be managed similarly or via a perineal (Kraske) or transsphincteric (York-Mason) approach. Flap reconstruction (gracilis, omentum, rectus, bulbocavernosus, or Martius) should be considered for better healing. In severe circumstances, it may be necessary to perform a pelvic exenteration.

Fecal diversion has been found to be effective in the management of pain, tenesmus, incontinence, obstruction, and sepsis and for patients who are not optimal surgical candidates. Because dissection can be difficult in an irradiated pelvis with greater risk for bowel injury, loop ileostomies and transverse/descending colostomies may be safer to perform than sigmoid colostomies.

PREVENTION

The risk of radiation-induced bowel injury can be minimized with careful attention to radiotherapy planning and radiation delivery methods. Recent advances in radiation therapy techniques have sought to maximize radiation dose to the tumor while minimizing radiation to adjacent normal tissues. One method for doing so is 3D conformal radiation therapy (3DCRT), which utilizes 3D planning via CT and computer technology to plan and deliver radiation treatment that matches the shape of the tumor, thereby allowing for higher dose of radiation delivery to the tumor with less effect on normal tissue. Intensity-modulated radiation therapy (IMRT) is another technology in which varying intensities of radiation are delivered in a planned field with clear identification of malignant vs. normal tissue. Brachytherapy is another method that can be used alone or in conjunction with EBRT to reduce normal tissue injury. Proton therapy is also a new technology being used by certain tertiary centers as an option to minimize the amount of radiation to structures and organs surrounding the target anatomy.

Other strategies to reduce radiation injury include prone positioning, protective belly boards, and ensuring that the bladder is full during radiation delivery. Amifostine, a prodrug that metabolizes into a thiol metabolite that functions as a free radical scavenger, has demonstrated benefit in some studies to prevent symptoms of acute radiation proctitis, though these findings have largely been reported in small, single center studies. Operative maneuvers including the use of omental slings and tissue expanders to fill the pelvis can be considered if radiation were to be administered postoperatively.

Suggested Readings

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Preoperative Bowel Preparation: Is It Necessary?

Anna Chudnovets, MD, and Sandy Hwang Fang, MD

Patients who undergo colorectal surgery for cancer and inflammatory bowel disease often have associated risk factors that impair wound healing, such as chemoradiation therapy, steroid therapy, and malnutrition. Additional complicating factors include case complexity, perineal wounds, and combined multispecialty cases. Due to the nature of the colon and rectum yielding high bacterial inoculum and these contributing factors, the risk of postoperative infections after surgery is significant, with an incidence approaching 40%.

The overall objective for the use of bowel preparation in colorectal surgery is to reduce postoperative complications:

1. Decrease the rate of surgical site infections (SSIs)
2. Decrease anastomotic leak rates
3. Alter gut microbiome

A bowel preparation accomplishes these goals via two mechanisms: the evacuation of fecal material from the colon and the eradication of stool bacterial load. In addition, a bowel preparation should not alter the histologic appearance of the mucosa.

Historically, bowel preparations have created a harsh physiologic response to the human body. Newer bowel preparation formulations are smaller in volume, ingested in a short period of time with effective evacuation of stool, while also decreasing gastrointestinal discomfort and side effects, such as nausea and emesis. In addition, these newer drugs produce no fluid shifts, electrolyte imbalances, or dehydration, which optimizes the patient, leading into the operative stage of colorectal surgery with goal-directed fluid therapy (GDFT) as part of the enhanced recovery pathway or enhanced recovery after surgery (ERP or ERAS).

This chapter discusses the bowel preparation types, the efficacy of mechanical bowel preparations (MBP) versus oral antibiotics (OA) versus no bowel preparation, colorectal disease pathology and indications for bowel preparation, and its role in ERAS.

TYPES OF BOWEL PREPARATION

There are two types of bowel preparation: mechanical bowel preparation and oral antibiotics. MBPs are oral cathartics that clear feculent material from the colon. OA decrease intraluminal bacterial load.

Mechanical Bowel Preparation

Two types of MBPs exist: hyperosmotic versus isosmotic (Table 1). Hyperosmotic MBPs (e.g., magnesium citrate, sodium phosphate) exert an osmotic effect, drawing fluid into the bowel lumen, as a mechanism of flushing out colonic contents. Although patients are able to tolerate ingestion of these lower volume formulations, they cause electrolyte and fluid imbalances and dehydration. Patients subsequently become orthostatic and may develop acute kidney injury. Contraindications to hyperosmotic solutions include renal failure, acute coronary syndrome, congestive heart failure, bowel obstruction, ileus, intestinal malabsorption, and ascites. The use of hyperosmotic MBP solutions is not recommended in current consensus guidelines for ERPs.

ERAS consensus guidelines recommend the utilization of isosmotic MBPs, which consist of osmotically balanced, nonabsorbable solutions that do not produce significant fluid or electrolyte shifts. Isosmotic bowel preparations are deemed safe in patients with the comorbidities of hepatic disease, congestive heart failure, and renal failure.

Large volume polyethylene glycol (PEG) preparations include GoLYTELY, Colyte, NuLytely, and TriLyte. Patients have difficulty tolerating these large-volume solutions as they are not palatable and cause nausea and emesis in 4% to 17% of patients. New low-volume PEG (1–2 L) preparations combined with other agents have been developed and include MiraLAX, HalfLytely, MoviPrep, and BiPeglyte.

There are multiple studies/clinical trials and meta-analyses that show conflicting results for the effectiveness of MBPs in regard to surgical outcomes. In a Cochrane review in 2011, 18 randomized controlled trials were reviewed that included 5805 participants; 2906 patients were administered MBP while 2899 received no bowel preparation before elective colorectal surgery. There was no statistically significant difference between the MBP and non-MBP groups in regard to anastomotic leak for colonic resections and low anterior resection. These results are similar to a recent meta-analysis, published in 2018, evaluating eight studies with 1065 patients. However, both studies have reported that evidence quality is low due to the variation in bowel preparations. Because of this, MBP alone is generally not recommended for elective colorectal surgery.

Oral Antibiotics

First-line antibiotics include a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole (Table 2). The most common side effects are nausea and emesis. Multiple randomized controlled trials have reported a significant improvement in SSIs with the use of OA. Two large studies from American College of Surgeons National Surgical Quality Improvement Program (NSQIP) (>300,000 patients) and one large meta-analysis of prospective studies (69,000 patients) have confirmed that many medical centers are using OA alone for their bowel preparations before colorectal surgery. These studies suggest that OA alone is associated with similar SSI rates to OA plus MBP and lower SSI rates as compared with both MBP alone and no bowel preparation.

TABLE 1 Mechanical Bowel Preparations

Adjuncts to Mechanical Preparation	Agent	Volume/Dose	Mechanism	Use
PEG (electrolyte lavage)	Colyte* GoLYTELY*	3785 mL 4000 mL	No solid food for at least 2 hours before ingestion of the solution; 240 mL (8 oz) every 10 minutes until rectal output is clear or 4 L are consumed	Divided dose regimens (3 L the night before procedure, 1 L morning of procedure) may improve patient tolerance. PEG is considered safer than osmotic laxatives/NaP for patients with electrolyte/fluid imbalances, renal or liver insufficiency, CHF, or renal or liver failure.
Sulfate-free PEG (improved smell/taste, more palatable for patients)	NuLYTELY* TriLyte*	4000 mL 4000 mL	No solid food for at least 2 hours before taking the solution; 240 mL (8 oz) every 10 minutes until rectal output is clear or 4 L are consumed	Similar efficacy to PEG
Low-volume PEG and bisacodyl tablets (decrease volume-related discomfort [e.g., bloating, cramping])	HalfLytely and bisacodyl tablet bowel prep MiraLAX	2000 mL 255 g in 2000 mL	Only clear liquids on the day of the preparation. Dosage is four bisacodyl delayed-release tablets (5 mg) at noon. Wait for bowel movement or maximum of 6 hours; 240 mL (8 oz) low-volume PEG (i.e., HalfLytely) or 240 mL (8 oz) of clear liquid containing one capful of MiraLAX or other PEG-3350 regimen every 10 minutes until 2 L are consumed.	Equally effective as 4 L solutions; additional studies needed regarding safety
Aqueous NaP solutions	Fleet	90 mL with 48 oz additional liquid	Only clear liquids can be consumed on the day of preparation. Two doses of 30–45 mL (2–3 tbsp.) of oral solution are given at least 10–12 hours apart. Each dose is taken with at least 8 oz of liquid followed by an additional minimum of at least 16 oz of liquid. The second dose must be taken at least 3 hours before the procedure.	May cause significant fluid shifts. Not for use in pediatric or elderly patients or those with bowel obstruction, gut dysmotility, other structural intestinal disorders, renal or liver failure, or congestive heart failure. NaP may cause ulceration or mucosal abnormalities; do not use in patients with inflammatory bowel disease. Patients with compromised renal function or those taking ACE inhibitors or ARBs are at risk for phosphate nephropathy. In 2006, the FDA issued an alert regarding the risk for acute phosphate nephropathy, a type of acute renal failure, with use of oral sodium phosphate solution or tablets.
Oral sodium phosphate (tablet)	Visicol (discontinued)	32–40 tablets with 48 oz clear liquid	Dosage is 32–40 tablets: 20 tablets on the evening before the procedure and 12–20 tablets the day of the procedure (3–5 hours before). The 20 tablets are taken as 4 tablets every 15 minutes with 8 oz of clear liquid. Bisacodyl is prescribed by some physicians as an adjunct.	Early tablet composition included higher concentration of microcrystalline cellulose per tablet, which left residue obscuring the mucosal surface. Later tablet composition decreased microcrystalline cellulose concentration. Overall, tablet NaP is not associated with significantly improved patient tolerance when compared with aqueous NaP.

TABLE 1 Mechanical Bowel Preparations—cont'd

Adjuncts to Mechanical Preparation	Agent	Volume/Dose	Mechanism	Use
Enemas	Tap water Soap suds Fleet enema Fleet bisacodyl Enema Fleet mineral oil	500–1000 mL 500–1000 mL 135 mL 10 mg 1.25 oz 37.5 mL 480 mL	Distention and lavage of rectum and distal colon	Routine addition of enemas to oral preparation does not improve the quality of bowel cleansing but does increase patient discomfort. Use enemas in patients presenting for endoscopy with poor distal colon preparation and in patients with defunctionalized distal colon (e.g., Hartmann's).
Bisacodyl	Bisacodyl	5-mg tablet	Poorly absorbed diphenylmethane that stimulates colonic peristalsis, used as adjunct for NaP or PEG preparations	Has been found to decrease the volume of PEG preparation required
Saline laxatives	Magnesium citrate (liquid) Picolax (sodium picosulfate/ magnesium citrate)	250–300 mL	Hyperosmotic saline laxatives that increase motility by increased intraluminal volume	Addition of magnesium citrate to PEG allows for lower volume preparation. Use with extreme caution in patients with renal insufficiency or renal failure because of exclusive renal excretion of magnesium.
Senna	Senna Senokot X-Prep Syrup (8 mg/5 mL)		Anthraquinone derivatives (glycosides and sennosides) are activated by colonic bacteria and directly increase the rate of colonic motility, with a subsequent increase in colonic transit and reduced water and electrolyte secretion.	Senna with PEG may improve the quality of preparation and reduce volume required.
Simethicone	Gas-X Mylicon Mylanta Generic formulations (80 mg)		Antiflatulent, often used to prevent foam formation after PEG preparation. Mechanism of action is unclear.	May improve lumen visualization and patient toleration of bowel prep
Metoclopramide	Reglan Generic formulations also available	5 mg	Dopamine antagonist gastro-prokinetic, increasing the amplitude of gastric contraction, with increased peristalsis in duodenum and jejunum but without change in colonic motility	May reduce nausea, bloating; does not improve colonic cleansing
Carbohydrate-electrolyte solutions	Gatorade E-Lyte Generic formulations	20 oz	Used with PEG and/or NaP solution to improve flavor and prevent NaP-related fluid and electrolyte shifts	Carbohydrate-based solutions more palatable for patients; however, associates with a theoretical risk of cautery-induced explosion if these carbohydrates are metabolized by colonic bacteria into explosive gases.

*Flavored options are available.

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CHF,* congestive heart failure; *FDA,* US Food and Drug Administration; *NaP,* sodium phosphate; *PEG,* polyethylene glycol.

Modified from Wexner SD, Beck DE, Baron TH, et al. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). *Dis Colon Rectum.* 2006;49:792–809.

Currently, there is a prospective randomized controlled trial using the Rethinking Clinical Trials (REaCT) platform and NSQIP to compare no bowel preparation versus preoperative OA alone to evaluate SSI rate in elective colorectal surgery. Results are pending at this time. A similar multicenter randomized controlled trial was performed in Spain (ORALEV) in which 536 patients were randomized to no OA versus OA. The incidence of SSI in the no OA group (30/269, 11%) was significantly higher than in the OA

TABLE 2 Oral Antibiotic Regimens

Oral Antibiotic Prophylactic Regimen*	Use in Prior Literature
Neomycin + erythromycin	Coppa, 1988; Kaiser, 1983; Khubchandani, 1989; Lau, 1988; Nichols, 1973; Stellato, 1983
Metronidazole + neomycin	Epsin-Basany, 005; Hanel, 1980; Lewis, 2002; Nohr, 1990 (included bacitracin); Reynolds, 1989
Metronidazole + kanamycin	Lazorthes, 1982; Monrozies, 1983; Takesue, 2000
Tinidazole + neomycin	Peruzzo, 1987
Kanamycin + erythromycin	Ishida, 2001; Kobayashi, 2007

*Each of these oral antibiotics was combined with a range of intravenous antibiotics in the studies listed.
Modified from Bellows CF, Mills KT, Kelly TN, Gagliardi G. Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone in the prevention of surgical site infections after colorectal surgery: a meta-analysis of randomized controlled trials. *Tech Coloproctol.*2011;15:385–395.

group (13/267, 5%) (χ^2 test, p = 0.013). The no OA group had more complications (76/269, 28%) compared with the OA group (51/267) (P = 0.017).

MECHANICAL BOWEL PREP VS ORAL ANTIBIOTICS VS NO BOWEL PREPARATION

The combination of MBP and OA was described as early as 1973 when the Nichols-Condon bowel prep (a combination of MBP and OA) reported a decrease in the SSI rate from 43% to 9%. In 2012, a retrospective study utilizing the Veterans Affairs Surgical Quality Improvement Program preoperative risk and SSI outcome data evaluated no bowel preparation versus MBP alone versus OA alone versus MBP + OA. Those receiving no bowel preparation had similar SSI rates to those who had MBP only (18.1% vs 20%). Patients receiving OA alone had a SSI rate of 8.3%, and those receiving OA + MBP had an SSI rate of 9.2%. In adjusted analysis, the use of OA alone was associated with a 67% decrease in SSI rate (OR = 0.33, 95% CI 0.21–0.50). OA + MBP was associated with a 57% decrease in SSI rate (OR = 0.43, 95% CI 0.34–0.55). A retrospective analysis of the NSQIP colectomy cohort from 2011 to 2012 subsequently showed that the use of OA alone decreased SSI rates, consequently decreasing postoperative length of stay (LOS) and readmission rates.

The rate of antibiotic resistance or *Clostridium difficile* infection is similar in the OA alone, no bowel preparation, and OA + MBP groups.

OUTCOMES OF SURGERY DEPENDENT ON TYPE OF SURGERY

Studies have demonstrated that right colon bacterial concentrations range from 10^6 to 10^7 bacteria/g of stool content, whereas these numbers rise to 10^{11} to 10^{12} bacteria/g in the rectosigmoid. Several studies have demonstrated a lower risk of SSIs after right colectomies versus left colectomies or rectal resections. Studies evaluating patients undergoing right-sided versus left-sided colectomies/proctectomies show a preventative function of OAs in left-sided colectomies/proctectomies with an overall incidence SSIs as 7.01% vs 15.89% (p= 0.004) and superficial SSIs as 2.34% vs 7.01% (p= 0.03).

TABLE 3 Our Protocol at Johns Hopkins Hospital

	Medication	Comments
Mechanical bowel preparation	MiraLAX (238 g) Bisacodyl (four 5-mg tablets)	MiraLAX (238 g) mixed in a clear liquid and started at noon the day before surgery and completed after hourly administrations. Bisacodyl tablets taken as an adjunct to MiraLAX.
Oral antibiotics	Neomycin (six 500-mg tablets) Metronidazole (six 500-mg tablets)	Taken in three doses the day before surgery

Clear liquid diet initiated the day before surgery up until 2 hours before surgery.

BOWEL PREPARATION IN ERAS

ERAS guidelines recommend the routine use of combined isosmotic MBP with OA before elective colorectal surgery (Table 3). With the addition of oral carbohydrate loading to MBP, in addition to the emphasis on intake of clear liquids up to 2 hours before surgery as denoted by American Society of Anesthesiologists (ASA) Fasting Guidelines, patients undergoing elective colorectal surgery better tolerate adverse side effects of MBP while also requiring less fluid administration intraoperatively.

CONCLUSION

The use of isosmotic MBP + OA as part of the ERAS pathway prevents postoperative complications, such as SSIs, and reduces hospital LOS, costs, and readmission rates. Although evidence shows that MBP alone has not shown benefit, evidence is lacking for the use of OA alone. Future studies, such as an ongoing prospective randomized controlled trial using the REaCT platform and NSQIP will help to inform the perioperative benefits of OA alone.

SUGGESTED READINGS

Holubar SD, Hedrick T, Gupta R, et al. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on prevention of postoperative infection within an enhanced recovery pathway for elective colorectal surgery. *Perioperative Medicine*. 2017;6(1):1–18.

Khangura SD, La Fleur P, Argáez C, Adcock L. Bowel preparation for elective colorectal procedures: a review of clinical effectiveness, cost-effectiveness, and guidelines. *Canadian Agency for Drugs and Technologies in Health*. 2018 Jul 13. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537801/.

Management of Diverticular Disease of the Colon

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INTRODUCTION

Diverticular disease of the colon is common and a progressively increasing burden on both patients and the healthcare system. This term includes both asymptomatic diverticulosis as well as complications arising from diverticulosis that require further medical evaluation and treatment. Approximately 50% of Americans older than 60 years of age are diagnosed with diverticulosis; however, hospital admission rates resulting from complications of the disease, such as diverticulitis and diverticular bleeding, are specifically increasing in patients younger than 45 years of age. Underestimation of the prevalence of this disease in the young often leads to misdiagnosis of diseases causing similar symptoms, such as appendicitis. Inpatient treatment rates for diverticulitis have risen in young adults and show geographic variation caused by dietary habits and environmental factors.

Colonic diverticula are typically not true diverticula as they do not involve all layers of the bowel wall, but only consist of mucosa and submucosa protruding through the muscularis propria. Intraluminal pressure is thought to cause this herniation of mucosa through weak points of the muscle layer, where intramural branches of the vasa recta penetrate to deliver blood to the luminal layers of the colonic wall. Contributing factors that cause increased intraluminal pressure include a low-fiber diet with small-caliber stools and constipation as well as consumption of red meat. Other risk factors for developing diverticular disease are overweight and obesity, physical inactivity, smoking, use of nonsteroidal antiinflammatory drugs (NSAIDs), and a positive family history. In Western countries, diverticula usually occur in the sigmoid colon, whereas in Asia, right-sided location is common.

Diverticular disease usually remains asymptomatic, but 4% to 15% of affected individuals may develop diverticulitis during their lifetime, and another 5% to 15% develop diverticular bleeding. Diverticulitis refers to inflammation of the diverticulum resulting from a combination of poorly understood factors including bacterial stasis, the presence of a fecalith, an altered microbiome, impaired mucosal barrier function, and a subsequent inflammatory cascade. Although its pathogenesis is not completely understood, clinical and histopathologic findings in patients with diverticulitis show some similarities to those found in ulcerative colitis. Certain types of diverticulitis, such as segmental colitis associated with diverticulosis (SCAD), is considered to be an inflammatory bowel disease, suggesting an autoimmune etiology. Recent studies suggest that genetic predispositions involving immunomodulatory genes may also play a role.

Diverticular bleeding is typically painless and usually occurs in the absence of colonic inflammation. It originates from ruptured vasa recta at either the dome or neck of the diverticulum and is arterial. Repeated microtrauma involving mechanical and chemical stress within the diverticular lumen leads to thinning of the mucosal layer and subsequent rupture of arterial branches. Diverticular bleeding is more likely to occur in right-sided diverticular disease. This is because diverticula of the right colon typically have a wider lumen, exposing a larger mucosal surface area to luminal stress, along with a thinner colonic wall.

This chapter will focus on evaluation and management of patients with diverticulitis. A brief section about the evaluation and treatment of patients with diverticular bleeding is included as this topic will also be covered in the chapter devoted to gastrointestinal bleeding.

MANAGEMENT OF DIVERTICULITIS

Clinical Presentation and Diagnosis

Uncomplicated acute diverticulitis is typically located in the sigmoid colon and characterized by the symptom triad of left lower quadrant pain, fever, and leukocytosis. A mobile sigmoid colon or atypical manifestation in other segments of the colon can lead to abdominal pain in locations other than the left lower quadrant, such as the suprapubic region or even the right-side of the abdomen.

Severe complications occur in approximately 25% of cases and can complicate the diagnosis of underlying diverticulitis. Complications involve abscesses that occur in 30% of cases, fistula in 14%, and free perforation with peritonitis in 1% to 2% of patients. Colonic stricture with subsequent bowel obstruction is uncommon. For patients with complicated diverticulitis, medical treatment may be ineffective, and the majority require surgical intervention. Complications can be highly variable, and differential diagnoses must be excluded; therefore findings on physical examination and on blood and urine analyses should be further evaluated with diagnostic imaging. Computed tomography (CT) is the mainstay imaging modality in the assessment of acute diverticulitis and accompanying complications. A CT of the abdomen and pelvis with intravenous and oral contrast is used to evaluate the severity of inflammation and the presence of bowel strictures, obstruction, and local or distant complications such as abscesses and fistulas. In patients with contrast allergy, a noncontrast study or an alternative approach may be performed (e.g., magnetic resonance imaging or ultrasonography), particularly in the pregnant patient. Ultrasonography may identify a hypoechoic colonic wall with a fecalith obstructing the diverticulum, an adjacent bowel wall, and mesenteric edema, which may indicate abscess formation. The diagnostic accuracy of ultrasound is, however, dependent on the examiner's skill and experience.

Classification of diverticulitis is essential to follow a standardized treatment algorithm that provides the highest success rates for disease management. The Hinchey classification, originally published in 1978, is used as a basis to provide evidence-based management strategies for patients with diverticular disease. The modification by Wasvary et al. is widely used and is based on CT findings concerning abscess formation and peritonitis (Table 1). Both imaging and clinical evaluation are required for a complete patient assessment.

Management of the Patient with Acute Diverticular Disease

Uncomplicated Diverticular Disease

The inflammatory processes in uncomplicated diverticulitis (Stage 0 or Ia) are restricted to the colon only, while complicated diverticulitis shows signs of inflammation beyond the colon, involving the peritoneum and pericolic structures. Although antibiotic therapy for acute uncomplicated diverticulitis has been the traditional treatment recommendation for many years, there have now been several large prospective randomized clinical trials showing that uncomplicated diverticulitis can be treated *without* antibiotics (Table 2). It will take clinical practice a long time to follow this evidence. Much of this is the result of established practice patterns and patient expectations. In the event that symptoms limit oral intake or are severe enough to warrant hospital admission, fluid resuscitation and bowel rest will result in improvement while gradually advancing to a low-residue diet. If antibiotics are used for diverticulitis, they should cover both gram-negative and anaerobic bacteria, which is provided by either ciprofloxacin plus metronidazole or levofloxacin plus metronidazole.

TABLE 1 "Staging" or Grading of Diverticulitis Severity*

Hinchey Classification		Modified Hinchey Classification by Wasvary	
		0	Mild clinical diverticulitis
I	Pericolic abscess/phlegmon	Ia Ib	Colonic wall thickening/confined pericolic inflammation Confined pericolic or mesocolic abscess (<5 cm)
II	Pelvic, distant intraabdominal or retroperitoneal abscess	II	Pelvic, distant intraabdominal or retroperitoneal abscess
III	Generalized purulent peritonitis	III	Generalized purulent peritonitis
IV	Generalized fecal peritonitis	IV	Generalized fecal peritonitis

*Based on the Hinchey classification and modified Hinchey classification by Wasvary to reflect computed tomographic findings.

TABLE 2 Overview of Selected Multicenter Randomized Controlled Trials

Study	Acronym	Investigation	Main Findings
DIverticulitis: **A**nti**B**iotics **O**r c**L**ose **O**bservation?)	DIAB-OLO	Cost-effectiveness of conservative treatment (hospital admission plus antibiotics) versus liberal treatment (no antibiotics and no strict need for hospital admission); primary endpoint: time-to-full recovery	In patients with uncomplicated diverticulitis, observational treatment without antibiotics shortens hospital stay and does not prolong recovery
Antibiotika **V**id **O**komplicerad **D**ivertikulit (Swedish for "antibiotics in uncomplicated diverticulitis")	AVOD	Treatment of uncomplicated diverticulitis with antibiotics versus without antibiotics; primary endpoint: complications and emergency surgery during hospital stay	No differences in diverticulitis recurrence, diverticulitis complications, or emergency surgery rates (sigmoid resection) in the long-term; antibiotic treatment had no favorable outcome
Outpatient versus Hospitalization Management for Uncomplicated Diverticulitis	DIVER	Hospitalization versus outpatient treatment in patients with uncomplicated diverticulitis; primary endpoint: treatment failure rate of outpatient protocol, need for hospital admission	Outpatient antibiotic treatment and diet is effective and safe, cost-saving, and associated with a similar quality of life compared with hospitalization with intravenous antibiotic treatment
Perforated **DIV**erticulitis: sigmoid resection with or without **A**nastomosis	DIVA (LADIES trial)	Sigmoidectomy with primary anastomosis versus Hartmann's procedure in purulent perforated diverticulitis; primary endpoint: 12-month stoma-free survival rate	Primary anastomosis leads to increased stoma-free survival and is more cost-effective compared with the Hartmann's procedure
Lapar**O**scopic **LA**vage trial	LOLA (LADIES trial)	Laparoscopic lavage and drainage versus Hartmann's procedure versus sigmoidectomy with primary anastomosis; primary endpoint: major morbidity and mortality	Premature end of the LOLA group: higher rate of in-hospital major morbidity, mortality, and reintervention rate in the laparoscopic lavage arm
SCANdinavian **DIV**erticulitis trial	SCANDIV	Laparoscopic lavage versus primary resection in patients with perforated diverticulitis; primary endpoint: severe postoperative complications within 90 days	Laparoscopic lavage does not reduce severe postoperative complications, increases the reoperation rate, and leads to a higher risk of missing associated colon carcinomas
DIverticulitis–**LA**paroscopic **La**vage trial	DILALA	Laparoscopic lavage versus Hartmann's procedure in patients with purulent perforated diverticulitis; primary endpoint: number of reoperations within 12 months	Patients undergoing lavage have fewer reoperations and equal hospital readmission and mortality rates.

Because of an increasing prevalence of *Escherichia coli* resistance to fluoroquinolones worldwide, amoxicillin-clavulanate monotherapy or trimethoprim-sulfamethoxazole plus metronidazole can be used as an alternative.

Two randomized controlled trials showed no difference in patient outcome comparing treatment with antibiotics versus fluid resuscitation only. The most recent trial from the Dutch Diverticular Disease Collaborative Study Group (DIAB-OLO) demonstrated that no difference concerning mild or serious adverse events could be found between groups, but a significantly higher rate of adverse events were associated with antibiotic treatment. Long-term follow-up data, 11 years after The Swedish Antibiotic Therapy of Acute Uncomplicated Colonic Diverticulitis (AVOD) trial, showed no difference in recurrence rates, complications, surgical treatment rates for the disease, and quality of life between the patient groups. Based on these data, otherwise healthy patients with uncomplicated diverticulitis can be treated without antibiotics. Evidence from randomized controlled trials has also shown that a 4-day course of intravenous

antibiotics was as effective as a 7-day course, while clinical outcomes of inpatient and outpatient antibiotic treatment in otherwise healthy patients tolerating oral intake did not differ (DIVER trial). If a patient's clinical status does not improve after 5 days of treatment with persistent fever, leukocytosis, and elevated acute-phase proteins (C-reactive protein), further CT evaluation for an abscess should be considered.

Patients who present with uncomplicated diverticulitis have a low incidence (<2%) of occult colonic malignancy in contrast with those with complicated diverticulitis, in whom the incidence is 8% to 11 %. Colonoscopy is typically performed 6 weeks *after* symptom resolution, especially in those of screening age and family history. In case of recurrent episodes affecting quality of life, smoldering disease, or immunocompromise, elective colon resection may be indicated.

Diverticular Disease with Pericolic Abscess

Complicated diverticulitis that is accompanied by either a mesocolonic (stage Ib) or more distant abscess formation (stage II) occurs in 15% to 40% of acute diverticulitis patients. It can be treated nonoperatively with antibiotics in an outpatient setting in stable patients with abscesses ≤3 cm in size. Abscesses >3 cm or patients who do not respond to antibiotic treatment alone require percutaneous drainage, typically via a transabdominal approach (Fig. 1). Alternative approaches are transgluteal for pelvic abscesses (even though they are associated with greater patient discomfort and a higher risk of drain dislocation) and transvaginal or transrectal approaches. Conservative treatment strategies are typically effective with small abscesses, with an overall success rate in 80% of patients presenting such abscesses. There is a failure rate of up to 34% with nonoperative treatment of abscesses >3 cm in size.

If the patient is in stable condition with nonoperative treatment, the diet is gradually advanced to a low-residue diet. If a CT-guided drain is placed, decreasing white blood cell and drain output to <30 mL/day indicate when the drain can be considered for removal. In many cases, a drain contrast study will show the size of the residual abscess cavity and whether there is a communication to the colon. The rate of recurrent abscesses after conservative treatment is high, although it is considerably lower after percutaneous drainage (25%–60% vs. 15%–25%). The overall failure rate of these nonoperative approaches is 15% to 32%. In case of failure, surgery is indicated, with urgent abscess drainage and colectomy, typically with primary anastomosis and proximal diversion.

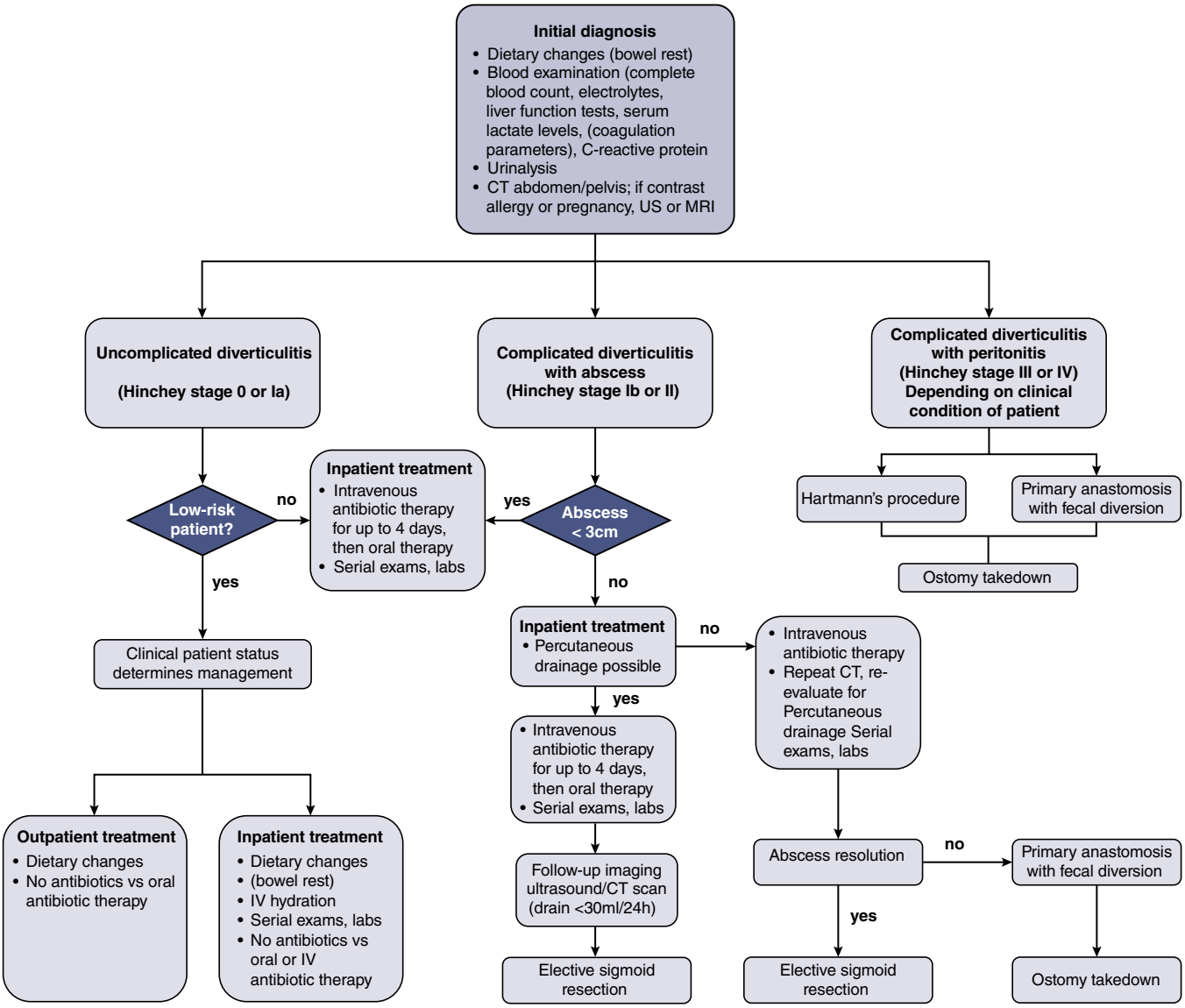


FIG. 1 Management of acute diverticulitis. This evidence-based algorithm should be individualized and modified based on the patient's clinical course.

Diverticular Disease with Perforation/Peritonitis

Purulent peritonitis (Hinchey III) and feculent peritonitis (Hinchey IV) cannot be distinguished from one another clinically. Emergency surgery with abdominal exploration is necessary for diagnosis. Hinchey III is defined by an occult colonic diverticular perforation with abscess formation and subsequent abscess rupture. Hinchey IV denotes a free perforation of a diverticulum with peritoneal fecal contamination.

Emergency surgery is required in 15% to 32% of patients who are hospitalized for acute diverticulitis. Acutely ill patients with diverticulitis and peritonitis should undergo expedited intravenous antibiotic therapy, fluid resuscitation, and emergency surgery. Abdominal exploration, resection of the acutely inflamed colon containing the area of perforation, and thorough peritoneal lavage should be performed. Overall, 30-day hospital mortality after emergency colectomy as reported by a retrospective National Surgical Quality Improvement Program (NSQIP) study in 2013 was 5.1%. Significantly higher mortality rates up to 53% were found in patients with two or more of the following risk factors: age >80 years, ASA class 4 or 5, elevated serum creatinine (>1.2 mg/dL), and hypoalbuminemia (<2.5 g/dL).

Two types of colectomy can be performed: (1) resection with primary anastomosis with or without proximal diversion (loop-ileostomy) or (2) resection with discontinuity and a Hartmann rectal stump and proximal end colostomy. Although discontinuity with a Hartmann stump was once the standard in an emergency setting, several randomized controlled trials and meta-analyses have demonstrated that primary anastomosis with or without proximal diversion yields favorable outcomes. In 2019, the DIVA arm of the LADIES trial showed a significantly higher 12-month stoma-free survival rate in patients receiving primary anastomosis with or without a defunctioning ileostomy compared with patients undergoing Hartmann procedures in perforated diverticulitis (95% vs. 72%). There were no significant differences in terms of morbidity and mortality between groups (see Table 2).

Bowel reconstruction with closure of an end colostomy after a Hartmann procedure is associated with higher morbidity compared with closure of a loop ileostomy after primary anastomosis with proximal diversion because of the extent of the actual disease and procedure. For this reason, high-risk patients who are at substantial risk of anastomotic leakage and major complications often never undergo the second operation of colostomy closure and Hartmann takedown. It is estimated that there are more than 5-fold the number of Hartmann procedures performed than the number of Hartmann reversals, and most of these colostomies can be considered permanent. The decision on whether bowel continuity should be restored after resection in patients with Hinchey III or IV diverticulitis should consider patient factors (presence of shock, hemodynamic stability, immunosuppression, age) and intraoperative findings (quality of tissue, presence of pan-abdominal inflammatory changes). The experience of the respective surgeon should determine the most appropriate procedure in these high-risk settings.

An alternative to bowel resection in case of perforated diverticulitis is laparoscopic lavage with drain placement. This procedure is not recommended with feculent perforation (Hinchey IV). It can be considered in select patients with purulent peritonitis (Hinchey III); however, colectomy is generally preferred as the need for secondary interventions is higher with laparoscopic lavage. Three randomized controlled trials investigated laparoscopic lavage in Hinchey III disease: the LOLA trial, SCANDIV trial, and DILALA trial (see Table 2). These studies were heterogeneously designed and focused on different techniques and endpoints. Several meta-analyses have tried to make sense of this heterogeneity. Overall, laparoscopic lavage was associated with a higher rate of surgical reintervention (20% vs. 7%, LALA trial) and a high rate of subsequent abscess formation requiring drainage (20% vs. 0%, LALA trial). An acute or elective surgical intervention was necessary in 48% of cases following laparoscopic lavage (LALA trial). Deep surgical site infection (32% vs. 13%) and unplanned reoperation rates (27% vs. 10%) were also higher in the lavage group (SCANDIV trial). The DILALA trial, however, showed that the lavage group had a 45% reduced risk of undergoing reoperations 2 years after the initial procedure.

Laparoscopic lavage is, however, an appealing approach because of its shorter operative time and lower risk for cardiac complications, wound infection, and stoma formation. This procedure may have a limited role in select young patients with a low ASA score and high BMI to reduce the risk of a stoma in the acute setting, allowing for a future elective resection. The lack of homogenous supporting evidence does not, however, allow for a general recommendation for this procedure.

Treatment of Sequelae of Complicated Diverticulitis

Diverticular Stricture

Strictures of the colon can result from chronic inflammation in patients with smoldering or recurrent diverticular disease. In the case of a diverticular stricture, underlying malignancy must always be suspected, and an oncologic resection of the diseased colonic segment with lymph node clearance should be performed if colonoscopy cannot be performed preoperatively to confirm the diagnosis.

Diverticular Fistula

Fistulas can develop in up to 2% of patients with diverticular disease, with colovesical fistulas representing half of all fistulas. Other types of fistulas include colocutaneous fistulae following interventional drain placement for abscess drainage, colovaginal fistulas, which almost always occur in women who have undergone prior hysterectomy, or rarely coloenteric or colouterine fistulas. Fistulas can also occur in the presence of Crohn's disease or cancer, and colonoscopy should be performed to clarify their etiology. In patients with fistulas, sepsis and clinical instability are uncommon. Patients can often be evaluated and monitored in the outpatient setting until the time of elective surgery.

Surgical Treatment

Route of Access

Surgical approaches for colectomy in patients with diverticular disease include open surgery with laparotomy or minimally invasive surgery with either a laparoscopic or robotic approach. Regardless of route of access, surgical management of diverticular disease follows the same principles. A minimally invasive approach is preferred if expertise is available, as this has been associated with superior outcomes in terms of reduced postoperative morbidity and reduced hospital stay. The robotic approach has been associated with decreased conversion rates because of improved optics and instrument maneuverability and is especially useful when dealing with inflammatory disease adherent to the pelvic side wall. Compared with the laparoscopic approach, robotic access has been associated with reduced rates of ileus and postoperative complications and a shorter length of hospital stay, but significantly increased hospital charges and longer operative times.

Clinical factors, such as hemodynamic stability, patient comorbidities, the presence of coexisting bowel obstruction, and prior abdominal procedures causing adhesions determine whether minimally invasive surgery is feasible or open surgery should be performed. Several studies have shown that a minimally invasive approach can be performed in the emergency setting with improved morbidity. Clinical factors in the high-risk patient and longer operative times of laparoscopic procedures can, however, influence the decision regarding choice of approach.

In the acute situation, it is important to mark the patient for a possible stoma site in the sitting position and to avoid skin folds and creases. In obese individuals, the upper abdomen may provide a thinner abdominal wall, with easier stoma creation. Marking several possible stoma sites is never wrong. Remember, the patient may have the stoma a long time, and a well-placed stoma is essential.

Open access is performed via midline laparotomy. For laparoscopic access, four port incisions are required, followed by a subsequent suprapubic incision to remove the resected specimen. A large periumbilical camera port and two 5-mm ports in the right upper quadrant

and left lower quadrant are placed. The port in the right lower quadrant should be of larger size because access to an endoscopic stapler should be provided. Robotic access incisions are dependent on the robotic system used. The Si robot incisions are similar to those of laparoscopic access, with modified placement of the large camera port to the right of the umbilicus. The Xi robot requires ports oriented along a straight diagonal line from the lower right abdomen medial to the anterior superior iliac spine upward toward the patient's left, with an additional 5-mm assistant port in the right lower quadrant.

Common Surgical Themes Among All Routes of Access

1. **Work from normal to abnormal.** Beginning to work in a phlegmon can be challenging.
   Open: Begin dissection proximally, freeing up retroperitoneal structures superiorly and slowly working toward the area of inflammation
   Minimally invasive: Lateral-to-medial: same as for open
   Minimally invasive: Medial-to-lateral: essentially begins in "normal" retroperitoneal plane proceeding laterally toward inflammation
2. **Visualize the left ureter.** If technical difficulties are anticipated, ureteral stents are useful. See https://youtu.be/pVaFId9UuC4 for use of indocyanine green in ureteral stents for easy intraoperative visualization.
3. If not performing an anastomosis, resect the area of perforation. There is **no need to go down lower to the rectum itself** because this will make the subsequent surgery more difficult.
4. If performing an anastomosis, **the distal part of the colorectal anastomosis should lie within the upper rectum.** This is most easily located as the area where the colonic tenia confluence. If an anastomosis is made in the sigmoid colon, there is an up to 25% recurrence rate.
5. If extra colonic length is needed, **the splenic flexure may need to be mobilized and the inferior mesenteric vein and/or artery may need to be divided.**
6. The **proximal line of transection should be in soft pliable bowel.** All of the diverticula-bearing colon does not need to be removed.
7. If there is a **dense inflammatory scar around the rectum, the rectum may need to be mobilized to allow a circular stapler to pass.**

In case of bowel reconstruction with primary anastomosis, an end-to-end circular stapler is used to create a double-stapled or triple-stapled anastomosis. If there is a lot of edema or an inability to pass a stapler transanally, a hand-sewn colorectal anastomosis is an option. In cases in which fecal diversion is appropriate, either a protective loop-ileostomy (primary anastomosis and proximal diversion) or an end colostomy (Hartmann procedure with rectal stump and discontinuity) is created. Placement of a drain is generally not required if the dissection is above the level of the peritoneal reflection. In the case of a colovesical fistula, a drain is typically placed near the bladder repair.

Most Common Surgical Errors

1. No preoperative stoma marking
2. Anastomosis performed in the distal sigmoid colon
3. Attempt to resect all colonic diverticula
4. Very low Hartmann procedure performed, making subsequent closure more difficult

MANAGEMENT OF DIVERTICULAR BLEEDING

Clinical Presentation and Diagnosis

Three to five percent of patients with diverticular disease develop diverticular bleeding, presenting as either bright red blood per rectum, hematochezia, or melena. Risk factors include the use of NSAIDs, thrombocyte aggregation inhibitors, and anticoagulants, which is common among the elderly. Although diverticular bleeding can cause severe blood loss, it will stop spontaneously in approximately 80% of cases. The overall mortality rate is 2% to 4%. Recurrent bleeding is common and occurs in up to 38% of patients.

Diverticular disease is the underlying cause of more than 40% of cases of lower gastrointestinal bleeding. Typically, patients present with painless hematochezia. Initial standard management includes establishing large-gauge peripheral intravenous access at two different sites, cardiopulmonary monitoring, and supplemental oxygen. Initial laboratory analyses should include complete blood count, electrolytes, liver parameters, lactate levels, and coagulation parameters if the patient is on anticoagulant therapy. Hemoglobin levels are serially reevaluated, and blood transfusion is considered according to the patient's clinical status and the dynamics of changing hemoglobin levels. A hemoglobin level of 6 g/dL absolutely indicates the need for a blood transfusion in the acute setting. Patients with a history of cardiovascular disease should receive blood at an Hb level of 8 g/dL, and a level of 10 g/dL should be maintained.

Recommendations for withholding anticoagulants or antiplatelet drugs in patients with acute diverticular bleeding are based on moderate to low quality evidence. The type of drug, the history of the patient determining their individual thrombotic risk, and their clinical status should all be considered. Aspirin as a primary prophylaxis for cardiovascular events generally can be continued, even perioperatively in the case of emergent surgical treatment. In patients with a low thrombotic risk and unstable gastrointestinal hemorrhage under warfarin therapy, anticoagulation can be immediately reversed using prothrombin complex and vitamin K. Once the bleeding has stopped, warfarin therapy should be restarted after an interval of 7 days. In case of high thrombotic risk (mechanical heart valve, atrial fibrillation with a prosthetic heart valve or mitral stenosis, recent venous thromboembolic event [within prior 3 months]), however, the pausing of warfarin therapy has to be evaluated carefully. Anticoagulant therapy with heparin can be considered as a transitional solution in an emergency setting. With heparin therapy, monitoring the partial thromboplastin time (PTT) every 6 hours is essential. Dosing should be carefully adjusted according to PTT levels and body weight.

The two main diagnostic approaches to distinguish diverticular bleeding from other etiologies of lower gastrointestinal bleeding are colonoscopy and computed tomography angiography (CT-A).

Endoscopic Strategies for Diverticular Bleeding

Colonoscopy is performed to identify the endoluminal source of bleeding, while also providing an opportunity for hemostatic intervention. Ideally, the clinically stable patient with lower gastrointestinal bleeding receives colonoscopy within 24 hours of hospital admission, following a bowel preparation. Endoscopic treatment includes epinephrine injection (1:10,000, 1–2 mL aliquots), bipolar cautery, endoclipping, band ligation, or application of topical hemostatic agents (e.g., Hemospray).

Radiologic Strategies for Diverticular Bleeding

Following unsuccessful endoscopic evaluation, recurrent bleeding, or clinical instability of a patient that does not allow for colonoscopy, CT-A of the abdomen and pelvis is considered. CT-A sensitivity is relatively low (85%), but the technique is sensitive enough to detect bleeding rates of 0.3 to 0.5 mL/min. Only active bleeding sources can be detected, which can be critical because of the intermittent dynamic of diverticular bleeding. Minimally invasive interventional treatment using selective angioembolization can be performed via vasopressin infusion or coil embolization. Once the bleeding source is identified, success rates of embolization are up to 85%.

Surgical Strategies for Diverticular Bleeding

Surgery in patients with diverticular bleeding is indicated in emergency settings with persistent or recurrent bleeding that cannot be

managed via either endoscopic or angiographic approaches. Indications are transfusion of 6 units of blood within 24 hours to maintain a hemoglobin level, persistent bleeding for 72 hours, or bleeding recurrence after initial treatment.

If the source of bleeding cannot be identified preoperatively, a subtotal colectomy with end ileostomy should be considered. Even in cases of successful preoperative localization, a targeted segmental colectomy is associated with a rebleeding rate in 14% of cases. The mortality rate for colectomy for diverticular bleeding in an emergency setting is 25%. Overall rebleeding rates 1 year after hospital discharge range from 4% to 42%. Therefore, a prophylactic elective resection after initial bleeding in patients at high-risk for rebleeding episodes can be considered.

Clinically stable patients who tolerate longer operative times should receive colectomy via a laparoscopic approach. Hemodynamic instability and cardiovascular comorbidities indicate an open approach.

In case of subtotal colectomy, after mobilization of the distal ileum beyond the ligament of Treves, the entire colonic mesentery is taken down. An end ileostomy with a rectal stump is created in the event of hemodynamic instability. In select stable patients undergoing elective surgery for diverticular bleeding, an ileorectal anastomosis can be considered.

CONCLUSION

In summary, management of diverticular disease has a significant role in everyday clinical practice, and the therapeutic algorithm is largely based on the patient's clinical status and on diagnostic imaging and endoscopy to exclude the presence of complications such as abscesses/fistula or cancer. Antibiotic therapy is a therapeutic standard in complicated diverticulitis; however, several randomized prospective studies have shown that they are not necessary in the treatment of uncomplicated diverticulitis. Although patients with recurrent disease generally benefit from clinical improvement and elective surgery in a symptom-free interval, patients with perforated diverticulitis require emergency surgical treatment. Once a Hartmann procedure is performed, reconstruction of fecal continuity is challenging and, in the end, often not successful. Recent studies show that primary anastomosis with or without a protective ileostomy can prevent many patients from having a lifelong stoma without excess morbidity. Stronger evidence, however, is required before including these strategies in the treatment algorithm.

Bleeding of the lower gastrointestinal tract often originates from diverticula, and treatment can be challenging in the acute setting because of the use of anticoagulants or antiplatelet medication, particularly in the elderly. Endoscopic control of bleeding and interventional angioembolization show high success rates. A laparoscopic approach is an option in hemodynamically stable patients with recurrent bleeding undergoing resection. In case of hemodynamic instability, a laparotomy with resection of the respective bowel segment up to a subtotal colectomy in cases of an unknown bleeding source must be considered.

Careful clinical examination of the patient accompanied by established diagnostic algorithms lead the way in treating the complications associated with diverticular disease.

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MANAGEMENT OF CHRONIC ULCERATIVE COLITIS

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder (IBD) characterized by inflammation in the rectum (proctitis) that may extend proximally to include the colon (proctocolitis). Unlike Crohn's disease, which can affect anywhere in the gastrointestinal (GI) tract from the mouth to the anus, UC only affects the mucosa and submucosa of the colon and rectum. In general, UC is continuous, starting in the rectum (proctitis) and, in many patients, extending more proximally into the colon, first the sigmoid or descending colon (left-sided or distal colitis) and, in more severe cases, proximal to the splenic flexure (extensive or pancolitis). Patients exhibit a range of symptoms including frequent, small-volume, bloody diarrhea, urgency, hematochezia, proctalgia, and colicky abdominal pain. Associated hematochezia varies in frequency but is usually small volume and typically does not cause rapid drops in hemoglobin. In severe cases, patients can have significant weight loss, anorexia, and fatigue. With rectal inflammation, patients can develop rectal pain,

spasm, and difficulty evacuating. In general, UC is a chronic disease, but patients may experience acute exacerbations or periods of remission, particularly those undergoing medical therapy.

EXTRACOLONIC MANIFESTATIONS OF UC

Extracolonic manifestations of UC include arthritis, eye disease (uveitis, episcleritis, iritis, conjunctivitis), oral aphthous ulcers, hepatobiliary disorders (asymptomatic transaminitis and primary sclerosing cholangitis [PSC]), erythema nodosum, and pyoderma gangrenosum (pretibial area and peristomal). Many extracolonic manifestations improve after proctocolectomy, but surgery does not improve outcomes in PSC, ankylosing spondylitis, or sacroiliitis.

In patients with UC and PSC, the liver symptoms usually occur in the setting of significant colonic symptoms and, in general, persist even after proctocolectomy. Therefore, it is important that management be collaborative with gastroenterology, hepatology and/or liver transplant surgery, and colorectal surgery. Patients with UC and PSC are at higher risk for dysplasia and colorectal cancer and should undergo annual colonoscopic surveillance beginning when PSC is diagnosed.

RISK FACTORS

The etiology of UC is poorly understood, but it is multifactorial with genetic, microbial, and environmental contributing factors. The microbiome, GI infections (bacterial, viral, and parasitic), food allergies, antibiotic exposure, dietary habits such as high sugar intake, or toxins have all been implicated in animal models and/or population-based studies. Cigarette smoking, of note, has been shown to be protective against UC, even though it is a risk factor for Crohn's disease. The relationship and data regarding cigarette smoking are complex, and the overall health benefits of smoking cessation outweigh the theoretical disease control benefits in UC, therefore all patients should be encouraged to cease smoking.

DIAGNOSIS

Patients are usually evaluated by a gastroenterologist in the outpatient setting or, in the case of acute severe ulcerative colitis (ASUC), the inpatient setting. By the time of surgical evaluation, the diagnosis has generally been made. Endoscopy (sigmoidoscopy and/or colonoscopy) with biopsy is the gold standard for making the diagnosis of UC. Examination of the terminal ileum can help avoid misdiagnosis of Crohn's disease, and a complete examination can help rule out malignancy. The endoscopist should grade the mucosa using the Mayo endoscopic subscore (Table 1) and include photographs in the report. The mucosa in UC is erythematous, friable, edematous, and in severe cases can present with large ulcerations. Although pseudopolyps or even strictures can be seen in a UC postinflammatory state, the presence of strictures or fibrotic disease should raise suspicion for Crohn's colitis or malignancy. Biopsies should be taken from inflamed areas to confirm both chronic and active colitis, and to rule out viropathic effects seen with cytomegalovirus (CMV).

TABLE 1 Mayo Endoscopic Subscore

Score	Disease Activity	Endoscopic Feature
0	Normal or inactive	None
1	Mild	Decreased vascular pattern, erythema, mild friability
2	Moderate	Absent vascular pattern, marked erythema, friability, erosions
3	Severe	Spontaneous bleeding, ulceration

Supplemental tests include laboratory testing, stool testing, and imaging. In addition to complete blood count and complete metabolic panel, the inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often associated with disease activity. Stool testing should be obtained to rule out *Clostridioides difficile (C. diff)* and other common bacterial, viral, and parasitic pathogens. Fecal calprotectin is a noninvasive fecal marker commonly used to differentiate between inflammatory versus noninflammatory diarrhea in the outpatient setting and correlates well with disease activity in many patients. CT scan is frequently used in the acute setting to rule out toxic megacolon or perforation but has limited utility for evaluating the small intestine. CT enterography and MR enterography delineate the bowel better and, importantly, can identify any small bowel disease that might suggest the patient's diagnosis is in fact Crohn's disease and not UC.

MEDICAL THERAPY

Medical therapy for UC aims to both improve symptoms and heal the colon mucosa. Treatment is tailored for *induction* of remission followed by *maintenance* of remission. Agents for induction and maintenance for mild to moderate UC include aminosalicylates (mesalamine or diazo-bonded 5-ASA) given orally and/or topically by suppository or enema. Oral prednisone, rectal steroids, or oral or rectal budesonide multimatrix (MMX) can also be used to aid in achieving remission.

Medical therapy for moderate to severe disease requires biologics (monoclonal antibodies) with or without an immunomodulator (e.g., azathioprine) or small molecules. Except for steroids, medications used for induction of remission for moderate to severe UC are continued for maintenance. Nonresponse or loss of response among individuals on biologic agents is managed by dose-intensification or switching to a different biologic agent or small molecule.

For patients with ASUC requiring hospitalization, management includes bowel rest, intravenous hydration, venous thromboembolism prophylaxis, minimizing narcotics, and cessation of antidiarrheal agents to avoid toxic megacolon. *C. diff* should be ruled out, and flexible sigmoidoscopy aids in both risk-stratification and to rule out superimposed CMV colitis. Medical management involves intravenous steroids and biologic agents. Surgical consultation for patients with acute colitis can be helpful to discuss possible surgery earlier in the hospital course. As described later, in the setting of ASUC, surgery results in an end ileostomy. Allowing patients to be partners in this decision and, if time permits, affording them the opportunity to talk to an enterostomal nurse and to patients who have previously undergone surgery for UC can improve the experience.

SURGERY AND ULCERATIVE COLITIS

Overview

The 10-year cumulative risk of colectomy for patients with UC is 10% to 15%, and the rate appears to be decreasing in the era of biologics. Despite evolving medical therapies, patients come to surgery for three main reasons: (1) failure of medical management to control either the intestinal or extraintestinal manifestations of UC, (2) dysplasia and colorectal cancer, or (3) toxic megacolon.

The first is far and away the most common indication for surgery. A patient with UC is cured of colitis by removing the entire colon and rectum (from the terminal ileum to the anorectal junction). This stands in contrast to Crohn's disease where surgery is used to address immediate symptoms, but there is always the risk of the disease returning in a new area.

Patients with UC are at higher risk of colorectal cancer and require routine endoscopic surveillance beginning 8 to 10 years after disease onset or sometimes sooner. Colonoscopy should occur every 1 to 3 years depending on risk factors such as PSC, a family history of colorectal cancer, and whether active inflammation is present. In the past, patients with dysplasia were encouraged to undergo surgery due a high rate of colorectal cancer even with immediate colectomy. Now with

improved endoscopic techniques, patients with visible and resectable dysplasia can be safely followed with close colonoscopic surveillance by experienced gastroenterologists using dye spray or virtual chromoendoscopy and high-definition endoscopes. In the event of persistent invisible multifocal or high-grade dysplasia, unresectable dysplasia, or colorectal cancer on biopsy, patients should undergo proctocolectomy.

Patients with advanced disease despite maximal medical therapy may also progress to toxic megacolon, characterized by colonic dilation, fevers, tachycardia, leukocytosis, and abdominal distension. This requires urgent surgical intervention to prevent perforation.

While the surgical concepts are the same for all UC patients, the approach should be tailored to each patient's indications, urgency, comorbidities, and severity (corticosteroids, biologics, nutritional status) as well as long-term goals of care with regards to life with an ostomy versus bowel frequency. Shared decision making and a team-based approach with the patient, family, gastroenterologist, and surgeon should be embraced to ensure that the patient is knowledgeable and prepared for the operation(s) and long-term impact on lifestyle.

Total Abdominal Colectomy with End Ileostomy

For urgent indications (toxic megacolon, severe medically refractory disease, refractory ASUC, perforation), total abdominal colectomy with end ileostomy is the best course of action. It is a relatively short operation (2–3 hours) that removes a good amount of diseased bowel (colon) and diverts the fecal stream away from the rectum, allowing the mucosa to partially heal. The rectum is left in place during this operation to reduce the risk of complications associated with pelvic dissection in the setting of severe inflammation and to allow for restoration of fecal continence via an ileal pouch later. Before surgery, if time allows, the patient should have a visit with an enterostomal therapist and the site for the end ileostomy should be selected. It is usually in the right lower quadrant, but it is important that it is tailored to the patient's body habitus. A poorly placed ileostomy (in a skin fold or scar, belt line, etc.) can be very challenging to manage, time consuming, and lifestyle limiting for the patient and family.

The approach should be laparoscopic if the surgeon has experience and the patient is hemodynamically stable. A fully laparoscopic, hand-assisted laparoscopic, or robotic approach have all been described. In general, after the pneumoperitoneum is established, the colon is mobilized, either with a medial to lateral approach with ligation of the vessels first (ileocolic, middle colic, and inferior mesenteric) or lateral to medial approach with ligation of the vessels second. High ligation is not needed unless there is concern for dysplasia or malignancy, and it is generally safest to stay close to the colon when dividing the mesentery.

In a medial to lateral approach, the dissection begins on the left by the sigmoid colon, which is retracted anteriorly to identify the inferior mesenteric artery pedicle. A window is created to isolate the pedicle, and before ligation it is important to identify and preserve the left ureter and gonadal vessels. After ligation, the dissection then proceeds superiorly separating the colon from Gerota's fascia up to the splenic flexure. The lateral attachments are taken next, following the white line of Toldt to free the descending colon from the retroperitoneum. Division of the rectosigmoid junction with a stapler is performed next, followed by ligation of mesenteric vessels. Attention is then turned to the right colon with identification and ligation of the ileocolic artery. The medial dissection proceeds superiorly toward the hepatic flexure, followed by a lateral dissection releasing the peritoneal attachments. After dividing the hepatic flexure, all remaining attachments along the transverse colon are divided. The colectomy is completed with division of the terminal ileum. Of note, based on surgeon preference, the dissection either proceeds from left to right (as described) or right to left.

There are a few key considerations when selecting the proximal and distal resection sites. The rectosigmoid junction should be divided either intracorporeally or extracorporeally (via Pfannenstiel or lower midline incision). If the rectosigmoid bowel is thick and edematous, it is possible that the staples will not hold. If there is concern, the selected division point should allow for the rectosigmoid area to be matured to the skin as a mucous fistula. Other strategies for managing a challenging rectal stump include oversewing the staple line and decompressing the rectum with a rectal tube. Delayed intraabdominal breakdown of the rectal stump results in sepsis and usually needs to be managed with reoperation. The proximal division should be in the very distal terminal ileum so that sufficient small bowel remains for an ileal pouch if the patient desires.

After the colectomy specimen is removed, the ileostomy should be brought out through the previously marked area and everted or "Brooked." By having the ileostomy above the skin, it will allow for a well-fitting ileostomy appliance and reduce risk of skin breakdown, pain, and discomfort. When bringing the ileostomy through the abdominal wall, it is also important to ensure that the mesentery of the small bowel is not twisted as this can lead to obstruction and/or ischemia requiring reoperation.

For most patients, the total abdominal colectomy will restore appetite, weight, energy, and overall quality of life. There will be some bloody mucus drainage from the rectum, but if patients are warned to expect this it is usually quite manageable.

Completion Proctectomy/Total Proctocolectomy

For patients undergoing surgery for dysplasia, cancer, or chronic medically refractory disease (not hospitalized, not on high dose steroids, and without signs of malnutrition), the best approach is to remove the colon and rectum (total proctocolectomy) in one operation. In this case, the patient and surgeon should plan to either proceed with ileal pouch anal anastomosis (IPAA) with a temporary diverting loop ileostomy or simply remove the rectum and remain with a permanent end ileostomy. If the plan is to complete the proctocolectomy in one operation, the colectomy is completed as described before and the rectum is removed as described later.

Proctectomy can be completed laparoscopic, hand-assisted laparoscopic, robotic, or open. The rectum is identified, and the inferior mesenteric artery is noted coursing along the retroperitoneum. The peritoneum is incised, and the left ureter is identified. The inferior mesenteric artery and vein are ligated. The dissection is then carried into the pelvis posteriorly by developing the plane between the mesorectum and the fascia propria of the rectum. The superior hypogastric plexus should be identified and preserved. Once the pelvic floor is reached, the anterior dissection should be initiated by developing the plane between the rectum and prostate or vagina. Care should be taken to err on the side of the rectum and, in men, avoid entering Denonvilliers' fascia as nerves controlling sexual function course around the pelvic brim and are at risk of injury. The lateral stalks of the rectum should be divided on the right and left, and the rectum should now be free circumferentially to the pelvic floor. This can be confirmed by placing a finger in the anus. If the patient is not to have an ileal pouch constructed, the rectum and anus will be completely removed by completing the dissection from the anus. This dissection is initiated with a self-retaining retractor effacing the anus. It is generally a simple dissection conducted from the perineum in the intersphincteric (between the internal and external anal sphincter) groove. This is usually bloodless and leaves the external sphincter in place to help with perineal wound healing and prevent herniation later.

The perineum is closed in multiple layers approximating the muscle layers using Vicryl or other absorbable suture, followed by skin closure. Surgical closed suction drains are typically left in the presacral space to protect the perineal wound from seroma formation and reduce the risk of infection and dehiscence.

Creation of Ileal Pouch Anal Anastomosis

Most patients will desire ileal pouch creation; IPAA is the most common operation done for UC in the United States. Although it is associated with more risks (short and long term) than end ileostomy, for many patients restoring intestinal continuity is important to their

quality of life. For most patients with an IPAA, it is reasonable to expect 6 to 10 bowel movements per day. The stool will be looser, although consistency may improve with time as the small bowel adapts to absorb some water. A significant number of patients will experience urgency and even some fecal incontinence, but for the most part the pain associated with bowel movements is gone.

It is important to recognize scenarios where IPAA is not appropriate. These include patients with a history of fecal incontinence or sphincter injury, history of anorectal disease (anal fistula), uncertainty related to the diagnosis of UC versus Crohn's disease (indeterminate colitis or IBD unclassified), and those who are frail and would not be able to tolerate the complications associated with IPAA (pelvic sepsis). IPAA should not be undertaken in patients with Crohn's disease except by expert surgeons in specific situations as it is associated with a much higher rate of postoperative complications and pouch failure.

If the plan is to create an ileal pouch, when the rectal dissection is at the level of the pelvic floor, the rectum is transected with a stapler, approximately 1 cm above the anal sphincters. After the rectum is removed, the ileal pouch is created. If the colectomy was done in a prior operation, the terminal ileum is freed up from the ileostomy site. The distal terminal ileum is identified as is the superior mesenteric artery. The "tip" of the small bowel is located—the area of the small bowel that will reach the furthest into the pelvis. This is usually 10 to 15 cm proximal from the distal end. If this "tip" can touch the pubic bone, it will likely reach the anus. The two limbs of the ileal pouch are aligned, and a linear stapler is used to fashion the pouch (Fig. 1). Usually, two loads of the linear stapler are needed as the goal is to have the pouch 10 to 12 cm in length. The pouch to anus anastomosis is created with a circular stapler (Fig. 2). The anvil is placed in the pouch, secured with purse-string suture, and the handle is placed in the anus. The anastomosis is fashioned by firing the stapler. It is essential that there is excellent visibility in the pelvis when creating the anastomosis to ensure that the small bowel, bladder, vagina, etc. do not fall into the staple lines. There should be two complete "donuts" on the stapler, and the pouch should be inspected for bleeding by sigmoidoscopy and for air tightness by inflating air into the

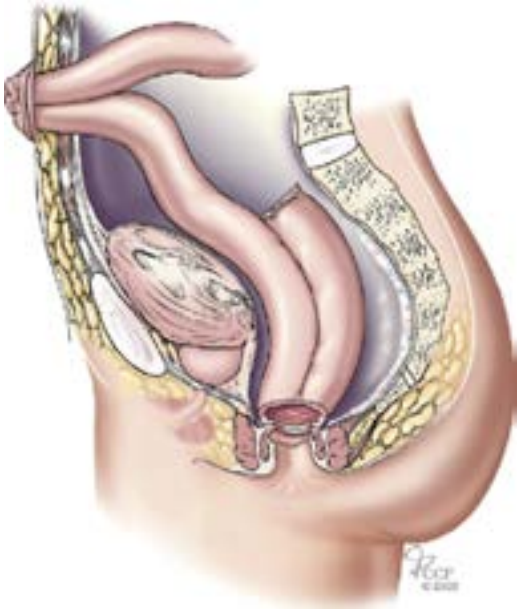


FIG. 1 Ileal pouch anal anastomosis in place with diverting loop ileostomy. *(From Hasan T. Kirat, Feza H. Remzi. Ileal Pouch-Anal Anastomosis: Indications and Technique. Seminars in Colon and Rectal Surgery. 2009; 20[2]:82–87.)*

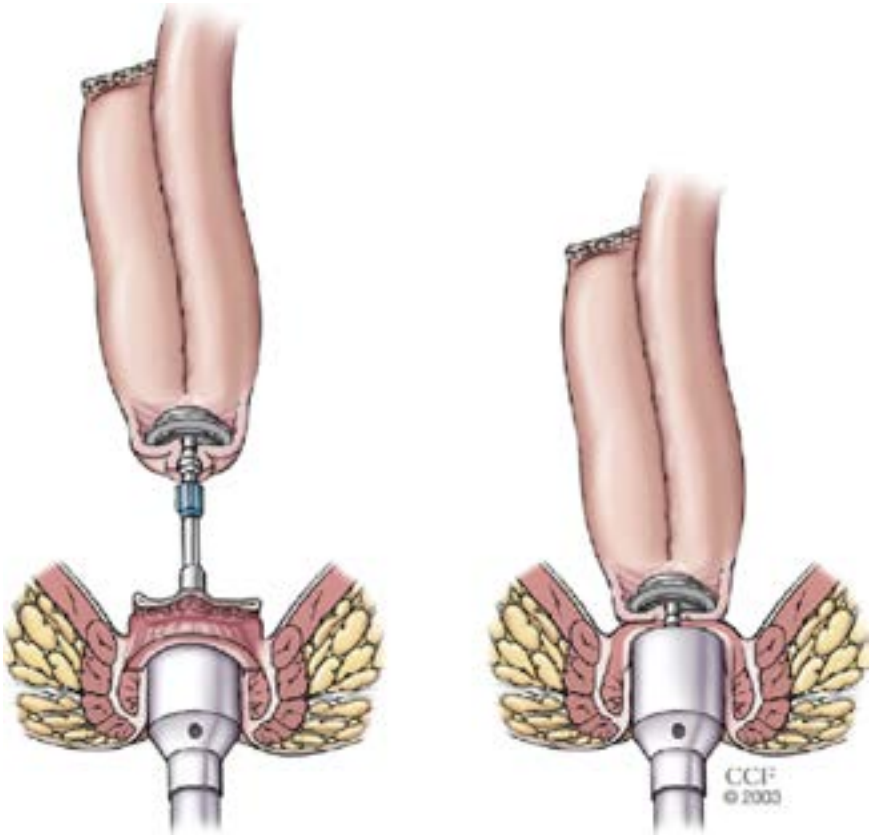


FIG. 2 Ileal pouch anal anastomosis creation using a circular stapler. *(From Hasan T. Kirat, Feza H. Remzi. Ileal Pouch-Anal Anastomosis: Indications and Technique. Seminars in Colon and Rectal Surgery. 2009; 20[2].)*

pouch and looking for air bubbles in the pelvis (saline irrigation is used to submerge the pouch from the abdominal side).

Most surgeons, when creating an IPAA, protect the pouch with a diverting loop ileostomy, created using more proximal small bowel brought up as a loop in the right lower quadrant. Although this does not prevent postoperative pelvic sepsis, it mitigates the severity as the fecal stream is diverted. The diverting loop ileostomy is closed in a separate operation about 3 months later. In most cases, this can simply be done with an incision around the ileostomy site, and the hospital stay is 1 to 2 nights. Rarely, more extensive dissection is needed, and a laparotomy is required. Before the ileostomy closure operation, the ileal pouch is interrogated with a Gastrografin enema to check for leaks at the staple lines and sometimes a flexible sigmoidoscopy to dilate the anus and inspect the mucosa.

PERIOPERATIVE AND POSTOPERATIVE CONSIDERATIONS

Perioperative Management

Enhanced recovery protocols beginning in the days leading up to surgery and continuing through postoperative management should be used. Pain medication regimens should limit opioids and maximize nonopioid analgesia including regional analgesia as appropriate. For patients on high-dose, long-term steroids, a short course of steroid taper should be used to avoid manifestations of adrenal insufficiency. Surgical site infection prevention bundles including presurgery bathing with chlorhexidine, mechanical bowel preparation with oral antibiotics (elective surgery), preincisional prophylactic antibiotics (cefazolin and Flagyl, or as determined by the hospital), alcohol-based skin preparation in the operating room, and appropriate attention to sterile technique using a closing set when suturing on the fascia and skin should be employed. Early ambulation with deep venous thrombosis prophylaxis is essential to reduce the risk of clot formation as this patient population is at significantly increased risk. Catheter-associated urinary tract infection bundles should also be employed comprising of careful insertion by a trained provider and prewash with antiseptic soap; early removal either at the end of the surgical case or the following morning should also be integrated into the care.

Ileal Pouch Complications

Complications can be divided into immediate perioperative complications associated with pelvic surgery and longer-term complications more specific to the ileal pouch. Surgical risks include injury to surrounding structures, especially nerves associated with sexual and urinary function, infection related to leaking at staple lines leading to pelvic abscess and sepsis, bleeding and ileus, or early postoperative small bowel obstruction. Overall, the short-term complication rates are in the range of 10% to 15%. Postoperative management should also include monitoring for persistent frank blood in the stool consistent with intraluminal bleeding (although some bleeding is expected in the first few days), which may require endoscopy with inspection of the staple line. Hemodynamically unstable patients should be taken to the operating room. Early anastomotic leak will present with fever, tachycardia, leukocytosis, and pelvic abscess on cross-sectional imaging and is usually treated with a percutaneous drain, but sometimes it is very low in the pelvis and needs to be drained transanally in the operating room.

Pouch-specific issues include acute, recurrent, or chronic inflammation in the ileal pouch, termed pouchitis. This can occur in about half of patients and is generally treated with antibiotics, mesalamine, topical steroids, budesonide, or biologic agents. A small subset of patients may develop de novo Crohn's disease after IPAA. Medically refractory pouchitis, especially secondary to de novo Crohn's disease, may lead to pouch failure and necessitate end ileostomy and/or pouchectomy. Patients with inactive UC and no prior pelvic surgery have similar infertility rates to the general population. However, women should be counseled that IPAA has been reported to increase the infertility rate compared with medically managed patients, although laparoscopic approaches may preserve fertility.

SUMMARY

Patients with UC are best cared for by a patient-centered transdisciplinary team that includes an experienced surgeon, gastroenterologist, enterostomal therapist, and, if needed, hepatologist and dermatologist. Surgical approaches should be tailored to the patient's goals of care, and patients who have previously undergone surgery for UC can serve as an important resource for future patients.

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Management of Toxic Megacolon

Jonathan E. Efron, MD

Toxic megacolon was first described in 1933 at Massachusetts General Hospital as a case report but became more widely known in the 1950s. It is an infrequent, potentially life-threatening condition that results from any inflammatory condition of the colon. It is most commonly seen as a complication of inflammatory bowel disease (IBD), more commonly ulcerative colitis (UC) than Crohn's disease (CD) and some infectious colitides, most commonly with *Clostridium difficile*–associated (pseudomembranous) disease (CDAD). In cases of IBD, toxic megacolon results as a progression from fulminant colitis. Although fulminant colitis is not precisely defined, this term generally refers to severe inflammation of the colon with associated systemic toxicity with or without colonic dilatation. According to the diagnostic criteria of Truelove and Witts for the disease activity in UC, fulminant colitis is diagnosed by the presence of bloody diarrhea more than 10 times, heart rate

higher than 90 beats/min, temperature above 37.5°C, requirement of blood transfusion, erythrocyte sedimentation rate (ESR) more than 30 mm/hr, with the presence of abdominal distension and tenderness on clinical examination, and dilated colon on x-ray. In the context of CDAD, according to the Dallal classification of CDAD severity, fulminant colitis is diagnosed by the presence of a heart rate above 120 beats/min, leukocytosis with more than 30% bands, severe oliguria, and requirement of mechanical ventilator and vasopressors. Toxic megacolon is defined as segmental or total colonic distension of 6 cm or more in the presence of acute colitis with systemic toxicity. Radiologically, it typically exhibits dilatation of the proximal colon with thickened inflamed distal colon and associated pneumatosis. Unlike colonic obstruction, in which cecal dilation with perforation is a concern, the transverse colon is the most common area of dilatation in toxic megacolon.

Given the other conditions that cause colonic distention, such as colonic pseudo-obstruction and Hirschsprung's disease, toxic megacolon is distinguished from these conditions by its systemic manifestations of toxicity. Early diagnosis and aggressive medical management are pivotal to prevent progression to the associated high morbidity and mortality. Moreover, prompt recognition of disease progression and severity and timely surgical intervention may be lifesaving. The mortality rate for patients with toxic colitis significantly increases when the disease progresses to perforation—2% for those patients without perforation or 40% to 50% for those patients with perforation; therefore, close observation and surgical intervention before perforation is essential.

CAUSE, INCIDENCE, AND PATHOGENESIS

Any inflammatory condition of the colon can result in toxic megacolon. These include IBD, infectious causes including pseudomembranous colitis caused by *C. difficile* or other bacteria, such as *Salmonella, Shigella, Campylobacter,* or *Entamoeba,* and ischemic colitis (Box 1).

The incidence of toxic megacolon varies by the underlying cause. In patients with UC, it is estimated to be 5%, and the risk is higher early on in the disease. Historically, the reported incidence of CDAD ranged between 0.4% and 3%. However, with the changes in the epidemiology of *C. difficile* infections and emergence of new strains, there has been a 23% annual increase in the rate of hospitalizations resulting from CDAD in the United States.

The pathogenesis of the toxic dilatation of the colon is not fully understood. However, it is thought to be a result of severe inflammation of the colon associated with release of inflammatory mediators that induce colonic smooth muscle relaxation and inhibit colon motility. The acute severe mucosal inflammation becomes transmural and extends into the smooth muscle layer, resulting in loss of motor tone and paralysis. The severely inflamed smooth muscle produces nitric oxide, which is released into the colonic wall and further inhibits smooth muscle tone and causes dysmotility and atony. This generally causes dilatation of the colon proximal to the colonic segment that is severely inflamed. The toxic systemic response results from bacterial translocation and subsequent bacteremia.

Several other factors such as hypokalemia, hypomagnesemia, opiates, anticholinergic or antimotility agents, antidepressants, barium enemas, and colonoscopy may affect adversely colonic motility and exacerbate colon dilatation.

BOX 1 Causes of Toxic Megacolon

Most Common

Ulcerative colitis
Clostridium difficile–associated colitis

Less Common

Crohn's disease
Salmonella
Shigella
Campylobacter
Yersinia
Cytomegalovirus
Entamoeba histolytica
Cryptosporidium
Ischemia colitis
Chemotherapy
Colonoscopy
Barium enema
Drugs that slow colonic motility (narcotics, antidiarrheal drugs, anticholinergic drugs)

DIAGNOSIS

The diagnosis of toxic megacolon is based on both clinical and radiologic findings. Therefore, a thorough history and physical examination are crucial. The diagnosis must be suspected in patients who have diarrhea, abdominal distension, and signs of systemic toxicity.

The patient's history typically reveals symptoms of severe colitis that preceded the acute onset of colonic dilatation. These include severe diarrhea (usually bloody), abdominal pain, fever, chills, and tachycardia. Obtaining a history about a previous diagnosis of IBD with the extent of colonic involvement and medical therapy and recent use of antibiotic or other medications such as steroid, antimotility, and chemotherapeutic agents will help in determining the underlying cause.

Physical examination reveals significant localized or generalized abdominal tenderness and reduced bowel sounds accompanied with signs of systemic toxicity, such as fever, tachycardia, and hypotension. Presence of signs of peritonitis may indicate colonic perforation. However, it is not uncommon that peritoneal signs maybe masked by high dose steroid treatment typically used in IBD patients with fulminant colitis.

The best acceptable clinical criteria for the diagnosis of toxic megacolon were described by Jalan et al. in 1969. The presence of three of the following criteria is required for the clinical diagnosis: fever higher than 101.5°F (38.6°C), heart rate higher than 120 beats/min, white blood cell count above 10.5 ($\times 10^9$/L), or anemia. In addition, patients should have one of the following criteria: dehydration, mental changes, electrolyte disturbances, or hypotension.

A plain abdominal x-ray is useful in confirming the diagnosis of toxic megacolon as it identifies the proximal colonic distention and may be used to follow the disease course and the rate of colon expansion. It typically shows dilatation of the ascending and transverse colon that varies from 6 cm up to 15 cm. Once the transverse colon is dilated past 8 cm, there should be great concern for pending perforation. Other radiologic features include presence of air fluid levels and the loss of normal haustral pattern in the colon with thickening and edema of colonic wall. Small bowel and gastric distension may be seen as well, and they have been shown to be significant predictors of toxic megacolon and progression to multisystem organ dysfunction in UC.

Computed tomography (CT) scan of the abdomen and pelvis is useful in confirming the diagnosis, excluding other causes of colonic dilatation, such as obstructing colonic cancer or diverticular stricture, and helping to exclude other abdominal complications, such as colonic perforation and ascending pyelophlebitis. Presence of colonic wall thickening, submucosal edema, pericolic stranding, and thickened haustra are indicative of severe colitis. As with plain abdominal x-rays, the presence of dilatation of the transverse colon (greater than 6–8 cm) confirms the diagnosis of toxic megacolon (Fig. 1).

Laboratory tests are not specific and show the findings of systemic inflammatory response with leukocytosis, anemia, elevated ESR or serum C-reactive protein, and electrolyte abnormalities with hypokalemia, hypomagnesemia, and hypoalbuminemia. These findings, if not corrected, may exacerbate the condition.

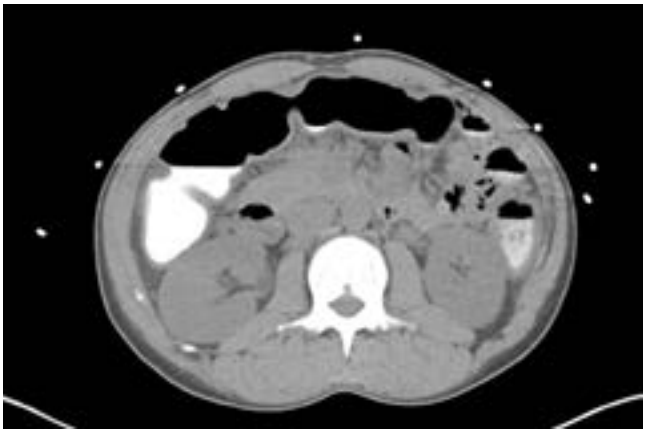


FIG. 1 Computed tomography scan of the abdomen showing dilated and thickened wall of the colon.

TABLE 1 Laboratory Tests for the Diagnosis of *Clostridium difficile* Infection

Test	Sensitivity	Specificity
Cell cytotoxicity assays	60%–100%	96%–99%
Cell culture neutralization assay	67%–86%	97%–100%
Enzymatic detection of glutamate dehydrogenase	71%–91%	76%–98%
Enzyme immunoassay tests for toxins A and B	39%–76%	84%–100%
Nucleic acid amplification test for toxins A and B	84%–100%	94%–100%

Stool sample for culture, sensitivity, and *C. difficile* toxin assay should be sent as well as blood culture because bacteremia occurs in up to 25% of patients with toxic megacolon. Several tests to detect *C. difficile* are available. Sensitivity and specificity of each test vary; therefore, it is recommended to perform a two-stage test approach to improve the diagnosis accuracy. Stool culture is highly sensitive; however, it does not differentiate between the presence of *Clostridium* bacteria and active infection. It generally is used in conjunction with other diagnostic tests (Table 1). The commonly used two-stage test approach includes initial screening with glutamate dehydrogenase assay followed by confirmation of a positive test with cell cytotoxicity assay. Some centers use toxin B gene PCR testing with nucleic acid amplification test as a single test to diagnose *C. difficile*.

Limited endoscopy, proctoscopy, or sigmoidoscopy may be considered to determine the cause of toxic megacolon in patients who are not known to have IBD. It can differentiate between the infectious causes of toxic megacolon because the finding of pseudomembranes is suggestive of CDAD, whereas the presence of inclusion bodies in the biopsies indicates cytomegalovirus (CMV) colitis as an underlying cause, which may occur in patients with IBD. It should be performed with extreme caution, without bowel preparation, and with minimal air insufflation; the endoscope should be advanced only as far as necessary to make a diagnosis. Complete colonoscopy should not be performed because of the high risk of perforation.

THERAPY

Management of toxic megacolon requires coordination between medical and surgical services with aggressive attempts of medical therapy and early surgical intervention in the absence of improvement, development of complications, or deterioration.

Medical Therapy

Regardless of the underlying cause of toxic megacolon, immediate aggressive supportive management in an intensive care unit must be initiated.

There is no evidence to support the use of nasogastric tube decompression because it does not decompress the colon. Frequent patient repositioning has been described as a method of colon decompression based on the observation that gas tends to accumulate in the transverse colon if the patient remains in the prone position and may be redistributed to the distal colon and rectum with frequent repositioning. There is no strong evidence to support use of this technique; however, it is simple and may be attempted.

Complete bowel rest with adequate intravenous fluid replacement is required. Electrolyte abnormalities, especially hypokalemia, dehydration, and anemia can exacerbate colonic dysmotility and must be corrected aggressively. Any medications that affect colonic motility such as opiates, antimotility agents, and anticholinergics should be discontinued immediately. Prophylaxis for deep venous thrombosis and gastric ulcer should be administered. Broad-spectrum antibiotics were found to reduce the mortality from septic complications that result from associated bacteremia or colonic perforation and should be initiated, whereas any agent that may have led to *C. difficile* overgrowth should be discontinued. Frequent clinical assessment and close monitoring with physical examination, serial complete blood counts, electrolyte monitoring, and abdominal x-rays must be performed (Fig. 2).

Management of Patients with Inflammatory Bowel Disease

High-dose intravenous steroid (hydrocortisone 100 mg every 6 hours) should be administered immediately to patients known to have IBD who have symptoms of fulminant colitis to prevent progression to toxic megacolon. There is no evidence that steroid therapy increases the risk of perforation; however, it may mask the signs of colonic perforation, so again close surveillance is required.

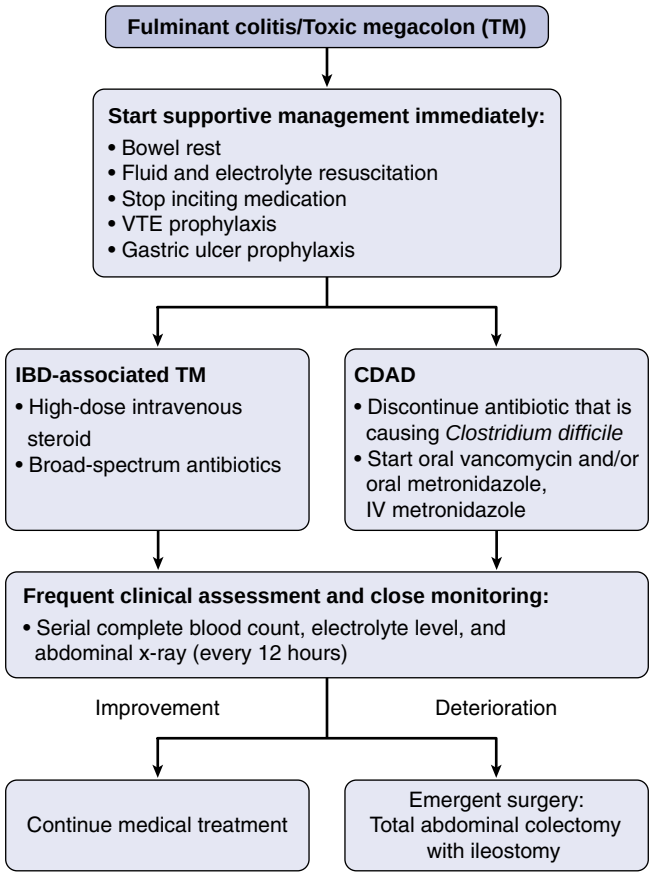


FIG. 2 Management algorithm for toxic megacolon.

Aminosalicylic acid products are used in mild to moderate cases of UC; however, there are no data to support their benefit in treating toxic megacolon. Similarly, cyclosporine and antitumor necrosis factor-alpha (TNF-α) are immunosuppressant medications used in severe cases of UC. Both medications are initiated if there is no response to high-dose intravenous steroids within 3 days. Although generally not started for patients with acute toxic megacolon, as mentioned these drugs are often given to patients with fulminant colitis who are not responding to steroid therapy and so are often seen in patients who progress to surgery. Some data suggests that cyclosporin may have an initial effect in 80% of patients with severe fulminant colitis bordering on toxic megacolon and therefore may reduce the need for emergent surgery. The medical management is the same regardless of the defined IBD: UC, CD, or indeterminant colitis.

Management of Patients with Clostridium difficile*–Associated Disease*

If toxic megacolon is thought to be caused by CDAD, the antibiotics thought to have initiated the *C. difficile* infection should be withdrawn immediately, and treatment with oral vancomycin (125–500 mg four times a day) and/or oral metronidazole (200–500 mg four times a day, or 500 –750 mg three times a day) is initiated. Intravenous metronidazole is also acceptable. If a patient cannot tolerate oral vancomycin because of severe ileus, it may be administered via an enema or nasogastric tube. There have been reports of successful treatment of severe *C. difficile* colitis with colonoscopy and intracolonic vancomycin lavage. We would advise against this in patients suspected of having toxic megacolon due to the risk of perforation, which significantly increases the mortality rate of the patient.

Surgical Therapy

Timing of surgical intervention is paramount in decreasing the morbidity and mortality of toxic megacolon and improving the patient's overall outcome. Medical management has been reported to be effective and successful in 50% to 70% of patients with toxic megacolon. However, delay in surgical intervention carries a risk of developing abdominal complications such as colonic perforation and abdominal compartment syndrome, which increases the mortality rate from 2% to 50%.

The possible need for surgical intervention and the nature of surgery must be discussed with patients and their families on admission. All patients must be evaluated and marked by an enterostomal therapist who should mark the best site for an end ileostomy.

Surgery is absolutely indicated in the presence of progressive colonic dilatation, uncontrolled hemorrhage, development of complications such as free perforation, and with general clinical deterioration. This includes progressive sepsis with continued tachycardia, hypotension, or the need for presser agents to maintain blood pressure. Lack of improvement within 48 hours is also a relative indication for surgical intervention. It is better to proceed to the operating room sooner as opposed to later, and any of the previously mentioned findings should push the surgeon to operate.

Mechanical bowel preparation is contraindicated, and the surgery typically is performed through an open approach for two reasons. The significant colon dilatation and friability of the colonic wall do not allow for a workable space or graspable tissue and therefore preclude a laparoscopic approach. The patient is often unstable and needs significant resuscitation from sepsis, requiring a quick efficient operation. Patients with fulminant colitis who have not progressed to toxic megacolon are often managed with a laparoscopic total colectomy and end ileostomy. If the surgeon feels the colonic distention will not interfere with laparoscopic visibility, the patient is hemodynamically stable and not on any pressor medications, and colonic wall does not appear significantly thinned or necrotic, an attempt at a laparoscopic total colectomy is feasible.

The current surgical standard of care for patients with toxic megacolon who require surgery is total colectomy with end ileostomy. This removes the diseased colon and allows restoration of intestinal continuity after the patient has recovered. The rectum should not be resected at the time of this emergent operation despite how inflamed it may appear. The bowel is often fragile with a high likelihood of intraoperative perforation with manipulation resulting from the significant dilatation and inflammatory process, and thus it should be handled with extra care. During hepatic and splenic flexures mobilization, the colonic mesentery is divided close to the bowel wall to avoid damage to retroperitoneal structures.

The rectal stump is often just as severely inflamed and, therefore, difficult to manage. If the rectosigmoid junction appears too inflamed to hold staples or sutures, then the surgeon should leave a short segment of sigmoid colon to form a mucous fistula to decompress the remaining colon and rectum. In obese patients, the rectal stump may be brought through the inferior aspect of the midline fascial incision and left buried in the subcutaneous space. This will be removed at time of stoma reversal, and if the stump blows out, it allows for decompression through the wound as opposed to in the peritoneal cavity. If a rectal stump is left in the peritoneal cavity, it should be decompressed in the operating room with a rectal tube that is left in place to allow for further postoperative decompression and possible vancomycin enemas. Drains should be left on top of the stump. A rectal stump leak typically occurs 5 to 10 days after surgery; therefore, if a patient manifests signs of peritonitis 5 to 7 days after surgery after initially recovering well, the surgeon should have a high suspicion for rectal leak. Emergent return to the operating room with washout and drainage is necessary.

Postoperative care requires transferring the patient to an intensive care unit where all supportive measures are continued as needed. Preoperative antibiotics are discontinued within 24 hours, and intravenous steroids are tapered to a maintenance dose (equivalent of 10–20 mg of prednisone per day). On restoration of gastrointestinal motility, enteral feeding is given. The rectal tube is removed on the fifth to seventh postoperative day.

An alternative, less invasive, colon-preserving surgical approach for the treatment of CDAD is the formation of a loop ileostomy with antegrade vancomycin irrigation of the colon. In a case-controlled study, Neal et al. treated 42 patients with creation of a loop ileostomy after visual assessment of colon viability. Intraoperatively, colonic lavage with 8 L of warmed polyethylene glycol 3350/electrolyte solution was performed via the ileostomy and drained via rectal tube. Postoperatively, patients received antegrade vancomycin enema (500 mg in 500 mL of lactated Ringer's every 8 hours for 10 days) via the efferent limb of the ileostomy. All patients received intravenous metronidazole (500 mg every 8 hour for 10 days). These patients were compared with matching historical controls treated with total colectomy and end ileostomy. In the study cohort, 35 (83%) cases were performed laparoscopically. The colon was preserved in 39 (93%) patients, and subsequent colectomy was required for continued sepsis in one patient and for abdominal compartment syndrome in two patients. When compared with a historical population, mortality was reduced from 50% to 19%.

Although this novel surgical approach may represent a less-invasive surgical treatment with promising outcomes, the results of this study are limited by the retrospective nature and lack of randomization that introduce a selection bias. Furthermore, there are no clear criteria to suggest which patient may benefit from this approach. Finally, the results were never reproduced by other investigators. There has been little written recently, but the technique may still be considered for those patients who are less severe. The 2015 practice parameters of the American Society of Colon and Rectal Surgeons for the management of *C. difficile* infection considered that the evidence for loop ileostomy formation in the management of toxic megacolon from *C. difficile* to be weak and strongly recommend the standard surgical approach in managing these patients, which is subtotal colectomy with end ileostomy. Loop ileostomy with antegrade colonic vancomycin lavage should not be considered in the severely septic patient requiring significant (presser or ventilatory) support.

OUTCOMES

The mortality rates from IBD-associated toxic megacolon have changed dramatically over the years. In an early review (1976) of 604 patients, the overall mortality was 19%, and it was higher in medically managed patients when compared with patients who were treated with early surgery (27% vs. 19.5%). The presence of perforation increased the mortality to 41.5% compared with 8.8% in the absence of perforation. In more recent reports, mortality rate after colectomy is 2% to 5%. Older age and multiple comorbidities are associated with a higher mortality rate. The mortality rate after colectomy for CDAD remains high. In a systematic review (2009) of 1433 patients, it was found to be 41.3%. Preoperative intubation, acute renal failure, multiorgan failure, and requirement of vasopressors were found to be predictors of postoperative mortality.

SUMMARY

Toxic megacolon can complicate inflammatory or infectious colitis. It is a life-threatening emergency characterized by severe colonic distension and systemic toxicity. Early recognition, a multidisciplinary management approach, and the time of surgical intervention are crucial to improving outcomes.

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Surgical Management of Crohn's Colitis

Hanjoo Lee, MD, Alessandro Fichera, MD, and James W. Fleshman Jr., MD

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract first described by Burrill Crohn, Leon Ginzburg, and Gordon Oppenheimer in 1932. The disease was thought to be limited to the small intestine and was referred to as "regional enteritis." Subsequent observations confirmed that CD may not only affect any segment of the gastrointestinal tract but also involve a slew of extraintestinal organs including the bronchopulmonary, integumentary, ocular, and joint systems. Currently, 3 million patients are affected by the disease in the United States with an incidence of 3 to 20 cases per 100,000 people. Interestingly, the past five decades have seen a gradual increase in incidence. Populations with Northern European and Jewish heritage exhibit the highest incidence of CD. However, an increasing trend amongst Asian and Hispanic populations has also been noted in recent years. The disease onset shows bimodal peaks around ages 20 and 50, although diagnosis in children is not uncommon. Few pathologies involving the gastrointestinal tract have puzzled the medical community as much as CD. The pathophysiology of the disease is exceedingly difficult to characterize due to the complex interplay between multiple environmental and genetic factors involved. The environmental factors include gastrointestinal infection, chronic use of nonsteroidal antiinflammatory medications, and exposure to antibiotics to name a few. Generally, a disruption in the integrity of the intestinal mucosa and natural gut flora are thought to be involved. Perhaps the most remarkable known risk factor is smoking. Active and passive smoking as well as previous history of smoking are all shown to increase the risk of development and worsening disease severity. Several genetic risk factors have been identified including mutations in *MLH1,* a DNA mismatch repair gene, and in *CARD15*, a nuclear factor-kappa B transcription factor. Increased incidence in identical twins and first-degree members of Crohn's patients also points to hereditary contribution of disease development. Clinical presentation of CD is multifaceted. It may range from minimal symptoms to fulminant colitis or debilitating perianal disease. As mentioned before, CD can affect the entire gastrointestinal tract. In 20% to 30% of cases, the disease presents as isolated Crohn's colitis (CC). When CC is suspected, it is extremely important to differentiate this diagnosis from ulcerative colitis (UC). Although there is a symptom overlap between CC and UC, the goal of surgical treatment is different. A prudent practitioner must be aware of several key differences between these two entities. Skip lesions, rectal sparing, longitudinal ulcers, intestinal and perianal fistulizing disease, and mucosal cobblestoning are all notable characteristics pointing toward CC rather than UC (Fig. 1). Abdominal pain, fever, and diarrhea are common initial symptoms of CC, and occasionally a palpable abdominal mass can be present. Unlike UC, rectal bleeding is uncommon in CC. Development of carcinoma of the colon is well described in patients with CC based on the extent of involvement and duration of the disease, and it is not dissimilar to the risk in UC.

The presentation of CC as a solely perianal disease is rare (<6%), but almost 20% of patients with CC will develop perianal disease over their lifetime. History and physical exam alone can be useful in establishing the diagnosis of CC. Laboratory workup should include C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and albumin levels in addition to the standard complete blood count and basic metabolic panel. These values can also be used to assess disease progression. Plain x-rays of the abdomen are helpful initial radiographic tools to identify free perforation and evaluate severity of colonic dilation. Barium enema can show several characteristic findings of CC including longitudinal or transverse ulcers, deep fissuring of the bowel wall, coarse mucosa cobblestoning, or longitudinal intramural fistulas. Single or double contrast barium enemas are rarely used due to the excellent tomographic techniques available that can provide enterography with no heavy contrast or risk of perforation. Computed tomography (CT) with enterography is useful in evaluating bowel wall thickness, stricturing, intraabdominal abscess, internal hernias, and/or extraintestinal involvement. If previous surgical history is unclear, CT can help clarify the anatomy. Endoscopic examination of the colon with biopsy is crucial for diagnosis and grading of disease intensity. Proctosigmoidoscopy may be sufficient in diagnosing

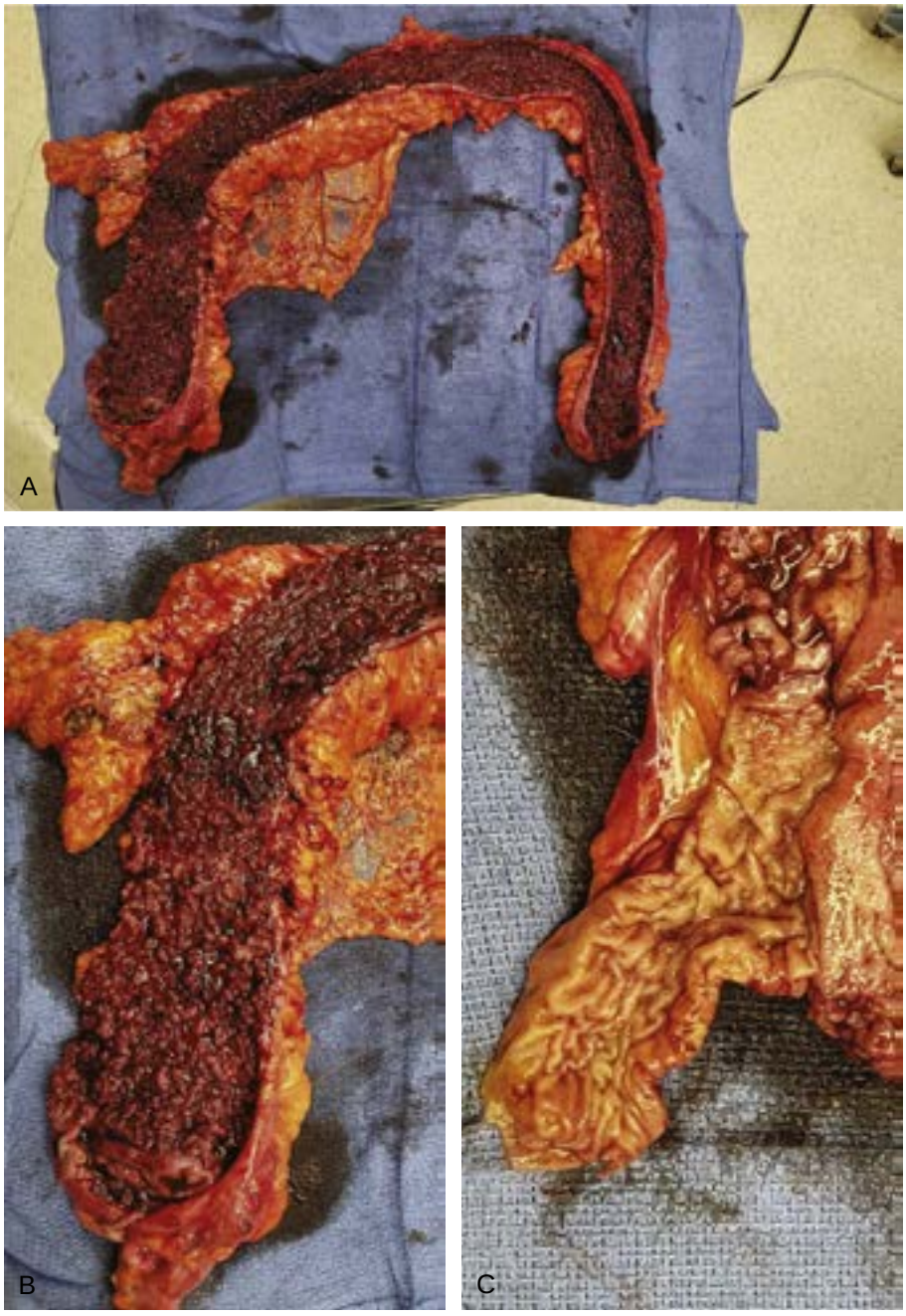


FIG. 1 Mucosal appearance of CC. **(A)** Entire colon is involved on a TAC specimen. **(B)** Extensive mucosal cobblestoning is present. **(C)** Normal-appearing terminal ileum.

CC, but most practitioners prefer full colonoscopy, especially in the preoperative setting. This is because 40% of CD spares the rectum regardless of perianal involvement. If UC is suspected, biopsy of the rectum, even if normal appearing on visual inspection, is helpful to rule out pathologic inflammatory changes. In 10% to 15% of cases, differentiation between UC and CC may truly not be possible even under pathologic examination. These cases are categorized as inflammatory bowel disease unclassified (IBDU) and called indeterminate colitis. In the absence of definitive microscopic findings (i.e., noncaseating granulomas), pathologists often refer to clinical information to arrive at their definitive diagnosis.

MEDICAL MANAGEMENT

Similar to UC, initial management of CC should be supportive care with bowel rest, intravenous hydration, and antibiotics. Placement of a nasogastric tube may alleviate symptoms if the stomach and small bowel are dilated. Intravenous glucocorticoids should be initiated early in the course of management. Serial abdominal exam, plain radiographic films, and serologic markers described previously can be used to monitor disease progression. If symptoms do not improve in 72 hours, use of an anti-TNF antibody (infliximab) should be considered. Generally, response to anti-TNF should occur within 5 to 7 days.

INDICATION FOR SURGICAL INTERVENTION

Despite the remarkable advances in medical therapies in the past two decades, surgery still plays an important role in the management of CD. In fact, lifetime risk of needing a resection ranges between 50% to 80%, and this rate remained relatively stable in the postbiologics era. Therefore, discussion with patients about indication for surgery should occur early in the disease process so that a fully informed decision can be made when the need for surgery arises. The indications for surgical intervention can be categorized into emergent, urgent, and elective (Table 1). Acute abdomen with diffuse peritonitis, severe bleeding, and hemodynamic instability undoubtedly warrant emergent exploration. Toxic megacolon, acute large bowel obstruction unresponsive to medical management, and intraabdominal abscess without successful control of sepsis by percutaneous drainage often require urgent exploration within the same hospitalization. Elective surgery is appropriate in cases where disease continues to progress despite extensive medical therapy, partial obstruction with fecalization of the small bowel, persistent intraabdominal abscess despite percutaneous drainage and antibiotics, presence of high-grade dysplasia or malignancy, and failure to thrive in children. Every effort should be made to transition urgent surgery to an elective surgery setting to gain invaluable time needed to optimize the patient and reduce the risk of postoperative complications.

PREOPERATIVE OPTIMIZATION

Colonic resection for CC, regardless of the specific indication, is associated with significant morbidity. Postoperative outcomes are intimately associated with preoperative optimization. Multidisciplinary management including gastroenterology, infectious disease, enterostomal nursing, nutrition, surgery, and interventional radiology is critical. Since inflammatory bowel disease management has numerous nuances, it is best managed in a facility that cares for tertiary and quaternary level patients and provides optimal resources for the high-risk complex gastrointestinal procedures. Patients referred for surgery are typically immunocompromised and malnourished. Dose-dependent operative morbidity with steroid therapy is well documented. In contrast, no clear association has been established between use of immunomodulators such as azathioprine, 6-mercaptutopurine, and methotrexate and postoperative morbidity. Safety of preoperative exposure to biologic agents is a highly controversial subject due to a number of large-scale studies that showed conflicting results. Given the lack of conclusive data, urgent surgery generally should not be delayed based on recent exposure to biologic agents alone, and fecal diversion should be individualized based on the overall clinical picture.

Nutritional status is a significant preoperative factor to consider not only in CD but in any complex surgical case. Malabsorption of nutrients and change in dietary habits are inherently associated with CD before resection. Therefore, nutritional optimization is of critical importance. Notably, weight loss >10% is associated with postoperative intraabdominal septic complication. Nutritional supplementation can be administered via either elemental enteral alimentation (EEA) or total parenteral nutrition (TPN). EEA is preferred over TPN due to maintenance of the physiologic route of nutrient absorption and avoidance of complications associated with TPN and central line placement. Preoperative EEA supplementation, for 3 months when feasible, has been shown to reduce the rate of postoperative septic complications. If intraabdominal sepsis is present, medical management should be initiated immediately, and it should include intravenous hydration and initiation of antibiotics to cover enteric flora. The antibiotic regiment can then be tailored according to culture results. Any intraabdominal collection >3 cm should be managed with percutaneous drainage with interventional radiology whenever possible. These measures may lead to a definitive resolution with medical therapy or serve as a bridge to surgery. If an enterocutaneous fistula is present, early involvement of a wound and ostomy nurse is critical. The reduction of the surrounding secondary inflammatory response to an area of severe disease or local perforation should be a primary goal of preoperative optimization.

The tissue handling characteristics of a "phlegmon" will often result in secondary injury of secondarily involved normal intestine and a wider resection of intestine than actually required to manage the disease. The risk of short bowel syndrome is thus increased. Patience on the part of the surgeon and patient will soften the tissue to allow sharp, atraumatic dissection in normal tissue planes. Patients with CD are at increased risk of developing venous thromboembolism (VTE) due to several associated factors including hypercoagulability in a proinflammatory state, malnutrition, anemia, thrombocytosis, prolonged hospital stay with limited mobility, and use of steroids. Venous thromboprophylaxis should be initiated during the optimization period and carried through the operation unless significant bleeding risk is present. The risk of VTE continues to be elevated at least 30 days after an operation, and VTE prophylaxis should be continued postoperatively. Judicious use of postdischarge VTE prophylaxis should be considered, especially if other risk factors are involved such as smoking, obesity, prolonged pelvic surgery, immobilization, and malignancy.

TABLE 1 Indications for Surgical Intervention for Colonic Crohn's Disease

Emergent	• Acute abdomen with diffuse peritonitis • Severe bleeding • Hemodynamic instability
Urgent	• Toxic megacolon • Acute large bowel obstruction unresponsive to medical management • Intraabdominal abscess without successful control of sepsis by percutaneous drainage
Elective	• Continued disease progression despite extensive medical therapy • Partial large bowel obstruction with fecalization of the small bowel • Persistent intraabdominal abscess despite percutaneous drainage and antibiotics • Presence of high-grade dysplasia or malignancy • Failure to thrive in children

SURGICAL MANAGEMENT

Surgical options for CC are segmental colectomy, total abdominal colectomy (TAC) with or without ileorectal anastomosis, total proctocolectomy (TPC) with a permanent end ileostomy, and restorative proctocolectomy with ilea-anal pouch anastomosis in a selected patient population (Table 2). While minimally invasive surgery for CD disease has been found to be associated with better short-term outcomes, the approach should be tailored to the clinical presentation and surgeon's skills and expertise. The critical principles of small bowel preservation apply to CC. This is especially important if the patient has already lost a significant amount of small bowel. The absorptive capacity of the colon that is not diseased can reduce diarrhea and possible "short bowel syndrome" secondary to operative treatment of ileocolonic CD. If <20 cm colon is affected, especially in the proximal colon, segmental resection with primary anastomosis should be considered. Leaving behind a segment of colon does put the patient at increased risk of recurrence, up to 62% at 5.5 years. This risk should be clearly discussed with the patient before surgery. Typical surgical considerations and principles apply to segmental colectomies for CC.

TABLE 2 Surgical Options for Colonic Crohn's Disease

Segmental colectomy	• Previous multiple small bowel resections • <20 cm involved segment in the proximal colon, segmental resection with or without primary anastomosis should be considered
Total abdominal colectomy (TAC)	• More than two segments of colon are involved with rectal sparing and anastomosis is deemed unsafe • Patient is in extremis with pancolitis and a total proctocolectomy is not indicated • Definitive diagnosis is not established, and indeterminate colitis is considered
Total proctocolectomy (TPC)	• Involvement of two or more segments of colon especially with perianal fistulizing disease • Visible dysplasia not amenable for complete endoscopic removal • Multifocal dysplasia, dysplasia in the surrounding flat mucosa • Carcinoma in the setting of pancolitis
Ileal pouch-anal anastomosis (IPAA)	• Absence of small bowel or perianal involvement with a definitive preoperative diagnosis of CC

Total Abdominal Colectomy

In a patient without free perforation, the preferred methods for TAC are laparoscopic mobilization of the abdominal colon and transection of the terminal ileum and rectosigmoid junction through a Pfannenstiel incision or intracorporeal transection at the rectosigmoid junction and extraction through the ileostomy site incision. There are several indications for TAC: (1) when more than two segments of colon are involved, with rectal sparing, and anastomosis is deemed unsafe; (2) when a patient presents in extremis with pancolitis, but a TPC is not indicated; and (3) when definitive diagnosis is not established, and indeterminate colitis is considered. The dissection for laparoscopic TAC begins with transection of the ileocolic pedicle and mobilizing the cecum away from the right iliac vessels at the right pelvic brim in a medial to lateral fashion and continues in a clockwise rotation to the hepatic flexure taking care to avoid injuring the duodenum. The gastrocolic ligament and any ligamentous attachments to the liver, spleen, and pancreas are divided to mobilize the transverse colon. The lateral attachments of the right colon to the lateral abdominal sidewall are divided last to finally release the right colon to the midline. The authors prefer to divide the omentum distal to the gastroepiploic arcade and remove it with the specimen. Many surgeons would try to preserve the omentum, but the difficulty in releasing the omentum from an inflamed transverse colon is likely to result in a colotomy and fecal spillage.

The splenic flexure is mobilized in an antegrade fashion from the right to the left, when feasible. When severely inflamed or in obese patients, it may be necessary to return to the splenic flexure in the retrograde fashion after partial mobilization of the left colon. Care must be taken to divide the base of the mesentery of the splenic flexure with sealing energy in case the arc of Riolan is a significant vessel and the branches of the inferior mesenteric vein (IMV) persist. All ligamentous attachments of the splenic flexure should then be dissected close to the colon to avoid injury to the splenic capsule. The left colon is mobilized by dividing the lateral attachments and freeing it off of the retroperitoneum starting at the left pelvic brim and dissecting medially, taking care to avoid injury to the left ureter. Ureteral stents placed at the induction of anesthesia can facilitate identification and protection of the ureters in a patient with severe inflammation in the descending colon and sigmoid regions. A medial approach to releasing the left colon and rectosigmoid junction allows avoidance of inflammatory attachments of the sigmoid and left colon to the critical structures at the pelvic brim. Working from soft normal dissection planes toward the diseased areas gives a better chance to complete the dissection and avoid injury to diseased and normal structures. Unlike TAC for malignancy, ligation of the vascular supply to the colon does not need to occur close to its origin in CC, and the mesentery can be ligated closer to the colon.

To date, the benefit of extended mesenteric resection for CD in reducing recurrence rate is not clearly established. However, the mesentery near the diseased bowel is often inflamed and thickened, so the soft, normal embryologic plane at the base of the mesentery may be the preferred dissection plane. Care must be taken to avoid significant bleeding from the thickened, friable mesentery during the transection of the vessels and at the point of transection of the colon. The rectum is identified at the distal sigmoid colon where the tenia coli "splay" out onto the anterior surface of the rectum. The peritoneal reflection is incised around the pelvic sidewalls and the proximal rectum is mobilized using the areolar tissue plane posterior to the rectum at the sacral promontory. The terminal ileum and the rectosigmoid junction are transected with a linear cutter stapler to control spillage after dividing the mesentery up to the bowel wall, either intracorporeally or through a small Pfannenstiel incision. The rectosigmoid junction is the preferred level of distal transection. This provides adequate rectal length for ileorectal anastomosis or creation of a mucus fistula and removes all colonic mucosa. Depending on the clinical scenario either an end ileostomy or ileorectal anastomosis is performed using either hand-sewn or stapled technique.

Patients who are restored to intestinal continuity with an ileorectal anastomosis often experience a period of rapid return of bowel function followed by a sudden decrease in bowel function, marked abdominal distension, and vomiting. This phenomenon, sometimes described as "ileorectal syndrome", is caused by exposure of the terminal ileum to a high back pressure from the rectal vault. Drainage of rectal contents and relief of build-up of pressure in the ileum using an in-dwelling large catheter (24–34F) in the rectum can alleviate this ileal response to perceived obstruction caused by normal rectal pressures withholding stool from evacuations until a steady bowel function returns.

There are certain factors that need to be considered when deciding between ileorectal anastomosis and end ileostomy. The rectum and the perianal region must be examined carefully to make sure they are free of stricturing or fistulizing disease before committing to ileorectal anastomosis. Adequate sphincter resting tone and maximal squeeze pressures are required to prevent incontinence of liquid stool. The presence of fistulotomy or episiotomy scars should raise concern for postoperative inadequate control of liquid stool. The patient's general condition such as nutritional status, weight loss, usage and dosage of steroidal agents, and smoking status should be reviewed to determine the feasibility of anastomosis. Opting for an end ileostomy confers a lower rate of recurrence of CD, especially in active smokers and patients with penetrating disease. The ileostomy and Hartmann stump of the rectum allows the surgeon to appreciate the natural history of the patient's disease to determine whether an ileorectal anastomosis is possible in the future. A Brook ileostomy should be performed in the acute setting, in cases of indeterminate colitis, and when the rectum is involved. Management of the rectal stump remains controversial. It is the authors' preferences to drain the stump with a rectal tube and leave a drain by the staple line for the duration of the hospital stay. The transected Hartmann rectal stump of an inflamed rectum is at risk for dehiscence of the upper staple line due to active disease and tissue friability. Other surgeons bring the stump to the incision and either suture it to the fascia or

open it as a formal mucus fistula. These two options require a longer stump that may not be feasible with sigmoid involvement or in the obese patient.

Total Proctocolectomy

If two or more segments of colon are involved, and if associated perianal fistulizing disease is present, TPC with end ileostomy should be performed. Any presence of visible dysplasia not amenable for complete endoscopic removal, multifocal dysplasia, dysplasia in the surrounding flat mucosa, or carcinoma in the setting of pancolitis should also warrant TPC and end ileostomy. This is based on the observation that more than a third of patients who undergo colectomy for dysplasia are found to have multifocal dysplasia. In addition, 14% to 40% of patients who undergo colectomy for carcinoma in CC eventually develop metachronous cancer. The proctectomy portion of TPC proceeds after the abdominal portion as described earlier. Typically, the pelvic dissection follows the total mesorectal excision (TME) plane performed for rectal cancer surgery. This plane allows for decreased blood loss especially in the presence of inflamed mesorectum. Using electrocautery, the loose avascular areolar tissue of the retrorectal space is dissected to mobilize the rectum with the mesorectum intact. Once the posterior dissection is complete to the levator ani, the lateral attachments and the anterior Denonvilliers' fascia/rectovaginal septum are dissected to the levator ani to completely mobilize the mesorectum. Extra care must be taken not to mistake the pelvic parietal fascia for the fascia propria of the rectum because the loose avascular areolar tissue between presacral fascia and pelvic parietal fascia can look identical to the one present in the retrorectal space. Surgeons often realize this mistake mid-dissection and, in an attempt to return to the correct retrorectal space, transect the hypogastric nerve embedded within the pelvic parietal fascia. A helpful hint is that if median sacral vessels running on the sacral periosteum are visualized, the dissection plane is already in a posterior plane deep to the desired plane anterior to the pelvic parietal fascia. One technique to reduce potential pelvic nerve injuries is to perform close rectal dissection (CRD). In this technique, the dissection is performed close to the rectal muscle wall within the mesorectum. This minimizes the risk of injury to the hypogastric nerves, the pelvic splanchnic nerves, and the inferior hypogastric plexus.

When ileal pouch-anal anastomosis (IPAA) for benign disease was randomized to CRD and TME, the CRD group suffered significantly fewer severe complications and improved quality of life. However, dissection through the mesorectal tissue often results in bleeding and is understandably associated with longer operating time (approximately 30 minutes). Once the rectum is completely mobilized intraabdominally as close to the anal canal as possible, the transperineal portion of the procedure is begun. Intersphincteric dissection for the completion proctectomy is preferred, whenever possible. The dissection is begun at the anal verge in the palpable intersphincteric groove with a circumferential incision into the space between the internal and external sphincters. The autonomic internal sphincter circular fibers do not twitch when touched with electrocautery. The somatic external sphincter fibers that encircle the internal sphincter fibers do twitch. The longitudinal rectal muscle fibers run at right angles to the circular fibers in the intersphincteric space and guide the dissection cephalad to the level of the puborectalis muscle. Preserving the well-vascularized external sphincter reduces the size of the perineal wound, allows better pelvic closure and healing, and reduces the risk of injury to the vagina/prostate and neurovascular bundle. Notwithstanding, extra care must be taken during anterior dissection to avoid injury to the vagina or the prostatic capsule. Frequent palpation of the posterior vaginal wall or the bladder catheter in the perineal and prostatic urethra helps to maintain orientation in the correct dissection plane. The dissection progresses circumferentially in a cephalad direction, and the levator ani muscles are finally separated from the rectum at the puborectalis sling to join with the dissection plane from the intraabdominal portion of the procedure. Once the rectum is removed, a drain is left in place in the pelvis through the abdominal wall or perineum. The levator ani, the external sphincter, and the ischiorectal fat are approximated in layers across the midline, but the subcutaneous tissue and skin are left open. This serves the purpose of draining the wound as well as leaving an opening that cosmetically resembles an anal orifice. The drain is typically removed in two weeks if drainage is minimal.

Restorative Proctocolectomy with Ileal Pouch Anal Anastomosis

There is a rare, select patient group with isolated CC without small bowel or perianal involvement who may be candidates for IPAA. If the diagnosis of CD is made before IPAA, pouch failure rate is 15%. If the patient is able to keep the pouch, functional outcomes and quality of life are similar between IPAA for CD and UC.

Minimally Invasive Surgery

Adaptation of laparoscopic surgery for CD has been rather unhurried in the surgical community compared with other arenas of abdominopelvic surgery. This is because the disease involves chronically inflamed bowel with friable and thickened mesentery that makes laparoscopic surgery particularly challenging. The initial randomized and observational studies comparing the outcomes of laparoscopic colectomy to open surgery have been promising. Similar to comparative studies for other colorectal disorders, laparoscopic colectomy showed decreased morbidity, decreased blood loss, faster return of bowel function, shorter hospital stays, and, in some cases, decreased costs. Furthermore, laparoscopic surgery allows specimen extraction through a Pfannenstiel incision, which affords decreased incisional hernia rate and pain (Fig. 2). Fistulizing disease warrants a special mention as it adds another layer of complexity. So far, comparative observational studies have shown that although operating time, conversion rate to open surgery, and rate of stoma creation are all increased, overall morbidity rate remains the same between laparoscopic surgeries for fistulizing and nonfistulizing disease. Individual surgeon's skill and comfort level should dictate if laparoscopic surgery is feasible in these cases. The use of hand-assisted laparoscopic surgery is an intermediate step between open operation and totally laparoscopic operations. The experienced hand, inserted through an airtight seal in the Pfannenstiel incision, can facilitate dissection by finding planes, identifying structures, encircling vessels bluntly, and guiding the incision by feel to speed the operation, thus reducing stress and risk and achieving the same outcomes as a pure laparoscopic procedure.

Robotic Surgery

Advantages of robotic surgery including intracorporeal anastomosis, smaller incision, and minimal manipulation of the bowel generally apply to CD. Robotic surgery is associated with a median of 2-day shorter length of stay and lower 30-day complication rate compared with open surgery. When robotic TAC for CC was compared with laparoscopy, no differences were noted including complications. Evidence in favor of robotic surgery in the management of CD is still in development.

SURGICAL PEARLS

- Utilize transversus abdominis plane (TAP) block and enhanced recovery after surgery (ERAS) pathway to improve outcomes.
- If proceeding with laparoscopy, have predetermined criteria for conversion to open operation. This can be based on operative findings, inability to make progress, or hemodynamic instability.
- Position with memory foams and chest straps in obese patients to avoid brachial plexus injury caused by shoulder brace and sliding of the patient on the table.

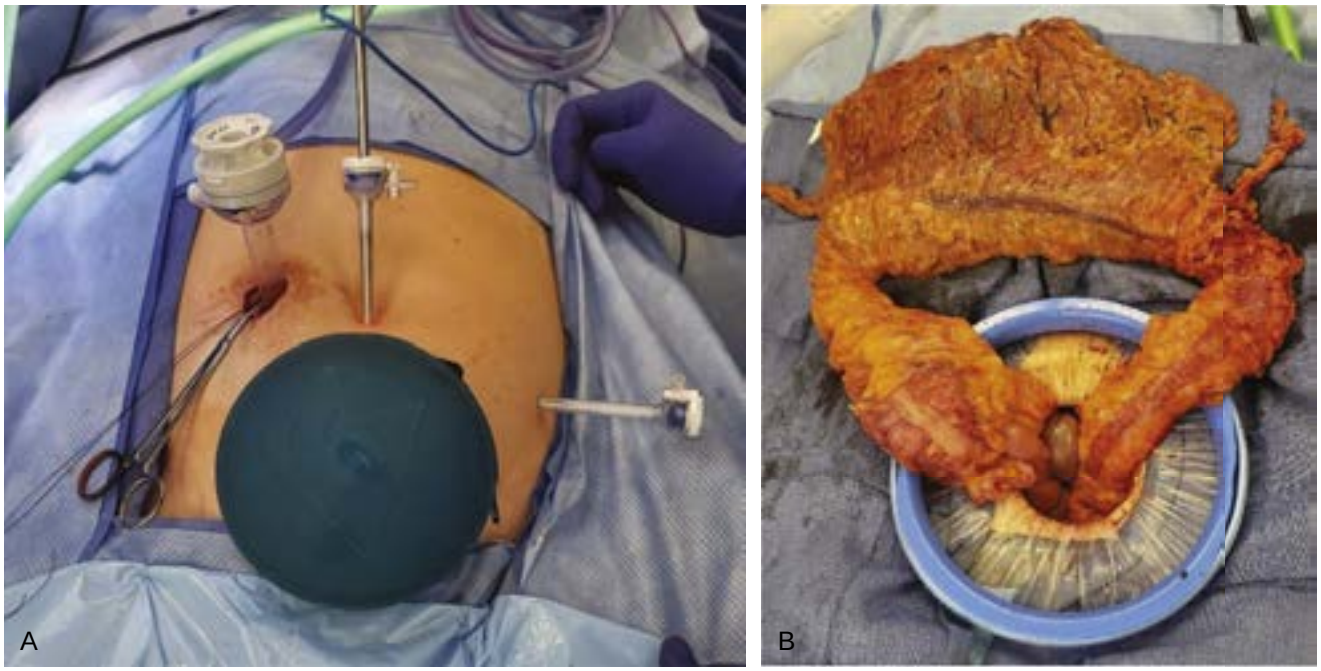


FIG. 2 Hand-assisted laparoscopic TAC. **(A)** 5-mm umbilical laparoscope port for the camera, 12-mm right working port at the site of the future stoma (this is also the entry site), 5-mm left lateral assistant port, Pfannenstiel incision for hand assist and specimen extraction. **(B)** The entire colon is externalized through the Pfannenstiel incision.

- Tilt operating table at appropriate angles to improve visualization with gravity movement of abdominal contents.
- Set up stirrups to keep legs no more than 10 degrees flexed at hips to allow adequate motion of instruments.
- Foley catheter should be in place before trocars are inserted.
- Keep insufflation pressure below 15 mm Hg if possible.
- Insert trocars under direct vision with camera.
- Insert instruments with camera guidance if at all possible.
- Lift tissue without grasping whenever possible.
- Start dissection at the base of the mesentery at the vascular bundle to make bloodless dissection possible.
- Ensure no twist in the mesentery of the small bowel for ileostomy. This may require reinsufflation of abdomen for laparoscopic view of cut edge of mesentery without twist.
- Know the protocol for air embolism: Trendelenburg and left lateral decubitus positioning to move the air into the right atrium to be aspirated.

POSTOPERATIVE MANAGEMENT

To date, there is no validated scoring system to stratify risk factors for postoperative recurrences. However, some of the known risk factors include penetrating disease, two or more previous CD surgeries, history of extensive small bowel resection of >10 cm, age <30 at diagnosis, an interval <10 years between diagnosis and surgery, and presence of perianal disease. Finally, smoking is an important modifiable risk factor that portends higher risk of recurrence. The number of risk factors involved can help categorize patients into low, moderate, and high risk of recurrence. Patients with no risk factor are considered low risk. These patients may stay off of medical therapy after surgery unless recurrence is noted at 6-month surveillance colonoscopy. Presence of several risk factors put the patient at moderate risk of recurrence. These patients should be aggressively managed with medical therapies including anti-TNF therapy in combination with immunomodulator. Alternatively fecal calprotectin monitoring 3 months after surgery can serve as an early indication for endoscopic examination.

CONCLUSION

Despite a century of advances in medical and surgical therapy, CD remains a clinical challenge for the treatment team and a chronic malady for patients. The complexity of the disease process and multifaceted phenotypic presentations demand multidisciplinary management. To date, the majority of patients suffering from CD ultimately will require surgery, and therefore surgeons are an integral part of this multidisciplinary team. A thorough preoperative workup is imperative to establish a clear diagnosis of CC and to adequately optimize nutritional status. A number of surgical techniques are available as minimally invasive options enter the fray. Each technique should be tailored to the patient's condition and the surgeon's skill and clinical judgment.

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Ischemic Colitis

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DEFINITION AND EPIDEMIOLOGY

Ischemic colitis (IC) is a condition that occurs when the blood supply to colonocytes does not meet metabolic demands. It is the most common cause of gastrointestinal (GI) ischemia. Injury can occur in one of two ways: at the initial incident of decrease in blood flow phase and/or after reperfusion. If the injury occurred only at the mucosa, it can be reversible. However, a transmural injury can present as a life-threatening condition that can lead to stricture formation, perforation, sepsis, and death. The incidence of IC ranges from 4.5 to 44 cases per 100,000 persons per year. Patients generally present after the age of 60, and there is a higher prevalence in women. The incidence of IC is expected to rise given the growing proportion of elderly patients. It most commonly occurs after aortic or cardiac surgeries. The severity of the disease dictates specific management strategies. About 20% of patients diagnosed with IC will require operative intervention, typically in an emergent setting.

ETIOLOGY

To understand the pathophysiology behind IC, we must consider the arterial anatomy of the colon. As shown in Figure 1, the colon is supplied by the superior mesenteric artery (SMA), inferior mesenteric artery (IMA), and branches of the superior rectal artery. In addition to these primary arterial branches, there is a rich collateral circulation. Griffith's point, at the splenic flexure, and Sudek's point, at the rectosigmoid junction, are particularly prone to ischemia, cumulatively compromising 80% of IC cases. These high-risk, or "watershed," areas identify the regions in the colon between two major arteries; the splenic flexure is the area between the SMA and the IMA arterial supply, and the rectosigmoid junction is the region between the IMA and the superior rectal artery supply. The former area is mostly supplied by the marginal artery; however, in 50% of the population, this artery is poorly developed. During aortic surgery, when intraperitoneal, efforts should be made to ensure that the left colon has adequate blood supply if the IMA is acutely sacrificed.

IC is classified according to the mechanism of decreased blood flow to the colon. This is most commonly nonocclusive, as in cases of shock, drugs, and colon obstruction. Less commonly, IC occurs after a vascular insult, which could be due to an arterial thrombosis, embolism, or even a venous occlusion. A special entity is the postoperative IC that can occur after cardiac and vascular surgeries, in which there is an intraoperative temporary cessation of blood flow to the colon. For example, following abdominal aortic aneurysm repair or bypass, if the IMA was sacrificed or if there was prolonged cross clamp time, IC can occur.

During periods of hypotension, blood flow is redirected to the brain at the expense of the splanchnic circulation. At a histologic level, the initial ischemic changes are always in the mucosa on the antimesenteric side. These changes will eventually spread through the colon wall to the serosa if the insult continues. Mucosal injury will develop in 20 minutes to 1 hour of decreased blood flow, whereas transmural infarction occurs within 8 to 16 hours. Additional insult occurs when blood flow is reestablished, causing reperfusion injury. Reperfusion injury is associated with the release of reactive oxygen species, which causes lipid peroxidation within cell membranes and leads to cell necrosis.

Risk factors for IC include advanced age, female gender, peripheral artery occlusive disease, coronary artery disease, heart failure, chronic obstructive pulmonary disease, and inflammatory bowel disease (IBD). Postoperative IC occurs most commonly after aortic surgery or after cardiac surgery with temporary GI vascular

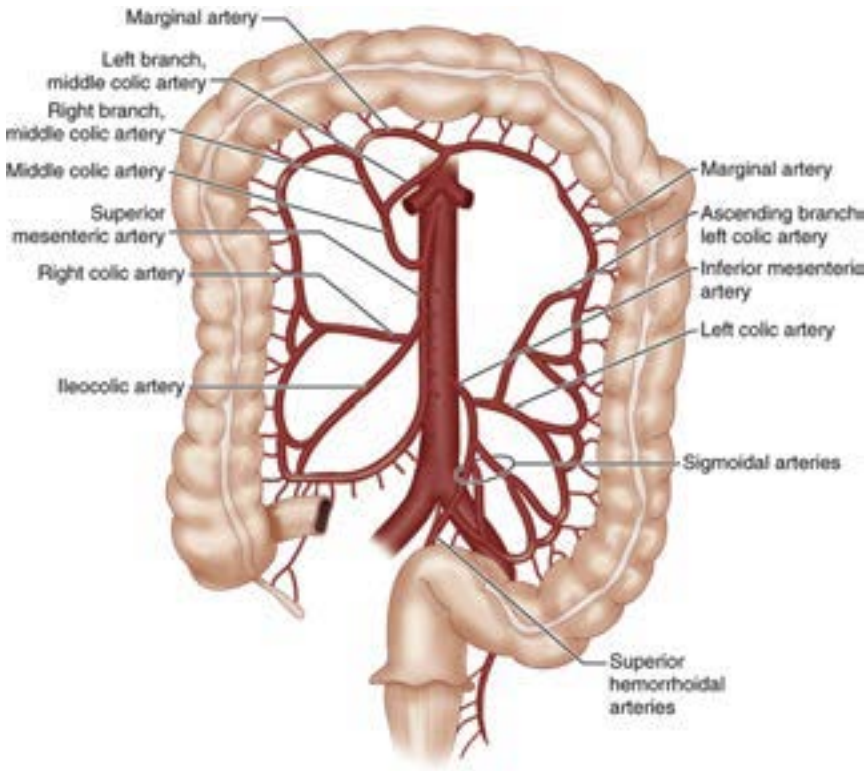


FIG. 1 Colon blood supply. *(From Araghizadeh F, Abdelnaby A, Colorectal surgery. In Anatomy and Physiology. Elsevier; 2013.)*

exclusion. In addition, the odds of developing IC are higher in cigarette smokers, both current and former (relative to never smokers). The use of cardiovascular medications such as diuretics or digoxin and psychotropic medications within the past month of presentation is also significantly associated with IC.

CLASSIFICATION

One can classify IC into mucosal vs. transmural types with further classification by severity as mild, moderate, and severe IC. Severe IC often involves transmural infarcts of the colon wall, which leads to peritonitis, sepsis, perforation, and death. Another way to look at different types of IC is by anatomic location or distribution: segmental colitis or sidedness. A special entity is isolated right-sided colon ischemia (IRCI) as it is associated with poor outcomes. IRCI has 30-day mortality rate of 20.3% compared with 9.0% in those with non-IRCI, higher frequency of severe cases requiring surgical intervention (40.9% of patients compared with 10.3% in those with non-IRCI), and is associated with acute mesenteric ischemia. Pancolitis and IRCI may be seen frequently in patients with sepsis, and IRCI is associated more frequently in patients with coronary artery disease and chronic kidney disease on hemodialysis. 61% of episodes of IC that required surgical intervention had either IRCI or bilateral (pancolonic) patterns of ischemia.

PRESENTATION

The presentation of IC is often vague, and the diagnosis is often delayed while other differential diagnoses are ruled out. The most common symptoms of IC are acute onset abdominal pain, hematochezia, and an urgent desire to defecate. Gangrenous colitis is characterized by increasing abdominal tenderness, guarding, rebound tenderness, rising temperature, and paralytic ileus. The sudden onset of a toxic colitis with signs of peritonitis and a rapidly progressive course are typical of universal fulminant colitis, a rare variant of IC. Rectal bleeding is found more frequently in non-IRCI (69.9%) compared with IRCI (39.4%). One must have a high index of suspicion when patients present with severe acute abdominal pain without bleeding, especially if they have the common risk factors associated with IRCI. A timely diagnosis of IRCI is important for patient survival.

DIAGNOSIS

After a thorough history and physical examination looking for specific risk factors for IC, laboratory studies, imaging, and endoscopy might be used to reach the correct diagnosis.

Routine laboratory studies are unhelpful in reaching a diagnosis of IC but are important for prognostication and assessing severity. Leukocytosis is a frequent finding. Elevated lactate, urea, and creatinine are sometimes found. Some patients may present with metabolic acidosis and a base deficit in cases of severe ischemia, gangrene, and sepsis. Decreased hemoglobin levels, low serum albumin, and the presence of metabolic acidosis can be used to predict severity of IC.

Imaging usually involves a CT scan, but sometimes in entertaining other differential diagnoses, an abdominal x-ray is ordered. Classic findings on an x-ray include thumbprinting, which indicates mucosal edema. In cases of bowel perforation, an x-ray is a quick way to see free air under the diaphragm. The use of contrast enemas had previously been the diagnostic modality of choice, but has been replaced, for the most part, by CT imaging and colonoscopy.

CT is the most helpful modality in the initial assessment of the patient with abdominal pain. It can exclude other causes of abdominal pain, suggest a location and source of ischemia, and identify complications associated with more advanced disease (Figs. 2 and 3). CT will frequently show bowel wall thickening, thumbprinting, and pericolonic stranding with or without ascites. After reperfusion, there may be evidence of submucosal edema or hemorrhage. Emboli or thrombi causing complete arterial occlusion are occasionally seen with corresponding thin, unenhancing colonic wall due to complete lack of reperfusion. CT findings of colonic pneumatosis and



FIG. 2 Contrast enhanced axial CT image demonstrating foci of gas in the portal veins *(arrow)*. Peripherally branching air on CT helps differentiating portal venous gas from pneumobilia, which typically is more central. Significant bowel distention is also noted.

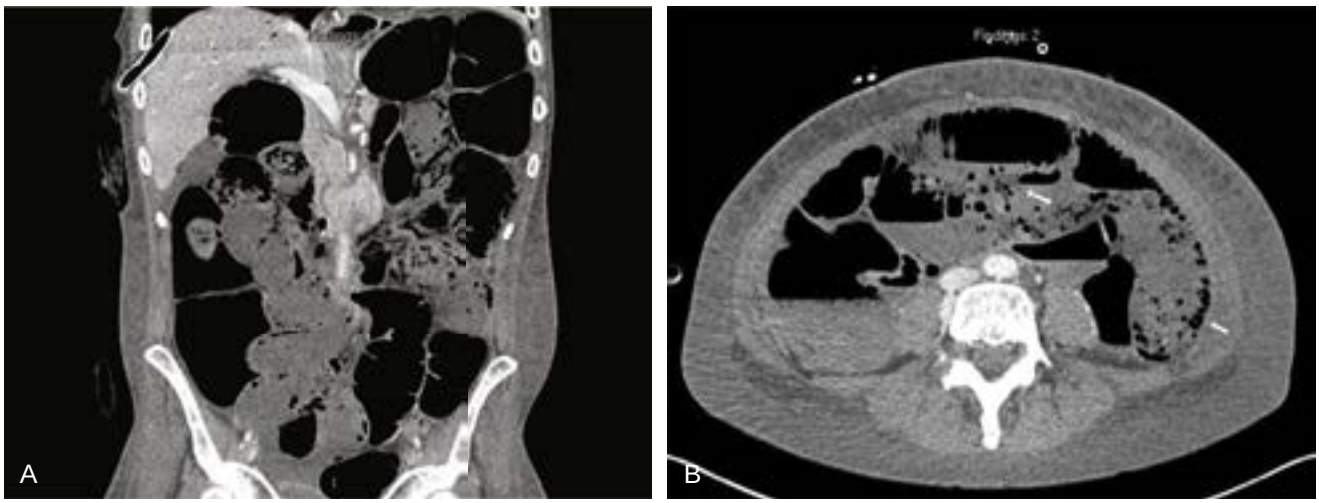


FIG. 3 **A** and **B**, Contrast enhanced axial CT image showing extensive dilatation and pneumatosis *(arrow)* of the small bowel. Pneumatosis was also seen in the cecum, corresponding to the superior mesenteric artery vascular tract. Mesenteric venous gas is noted as well *(arrow with *)*.

portomesenteric venous gas can be used to predict the presence of transmural colonic infarction but can also be present with other conditions like chronic obstructive pulmonary disease and infectious colitis. CT can also be diagnostic in severe cases, showing bowel perforation and free air in the peritoneal cavity. Of course this should be suspected on physical examination. In a patient in whom the presentation of IC may be a heralding sign of acute mesenteric ischemia (e.g., IRCI, severe pain without bleeding, and atrial fibrillation) and the multiphasic CT is negative for vascular occlusive disease, traditional splanchnic angiography should be considered for further assessment. Angiography is otherwise rarely helpful in diagnosing IC as most cases are caused by transient hypoperfusion.

The gold standard for confirming diagnosis of IC is endoscopy, where ischemic mucosa can be identified and biopsied for confirmation. Thus, early colonoscopy (within 48 h of presentation) should be performed in suspected IC cases to confirm the diagnosis. Typical findings of IC include segmental erythema, edema, mucosal ulceration, submucosal hemorrhagic nodules, and involvement of watershed areas. Occasionally, pseudomembranes related to mucosal sloughing are observed. The colonic single stripe sign, a single linear ulcer running longitudinally along the antimesenteric colonic wall, is associated with IC (Fig. 4). After 48 hours, sloughing occurs, the purple submucosal hemorrhages dissipate, and ulcerations develop. In more severe ischemia with transmural infarction, the mucosa may appear gray-green or even black (Fig. 5).

Endoscopy will also allow biopsies to be taken to further confirm diagnosis. On histologic examination, signs of IC include mucosa of normal architecture with necrosis and sloughing of the surface epithelium, loss of epithelium in the superficial aspects of the crypts (with or without ghosts of crypts), mucin depletion and reactive changes in the residual crypt epithelium with nuclear hyperchromasia and increased mitoses, paucity or complete absence of acute inflammatory cells, and the presence of hyalinosis in the lamina propria (Fig. 6).

SEVERITY

IC is classified into three categories: mild, moderate, and severe. Most cases of IC are mild or moderate, and about 20% are severe at initial presentation.

The classification is based on clinical, laboratory, imaging, and endoscopic criteria. Management is driven accordingly. For mild and moderate disease, treatment is supportive care, which includes bowel rest, intravenous fluids, optimizing cardiac output, avoiding medications that could worsen colonic ischemia like vasopressors, correction of electrolytes and nasogastric tube decompression for ileus. For confirmed IC, intravenous antibiotics are used to treat bacterial translocation that occurs when the mucosal barrier is damaged. The antibiotic(s) selected should include both aerobic and anaerobic pathogens. You should not expect to cover highly resistant pathogens. The duration of antibiotic therapy needed has yet to be studied and determined, although some authors have recommended 2 weeks. However, a period covering the time of mucosal injury when translocation is theoretically occurring seems reasonable.

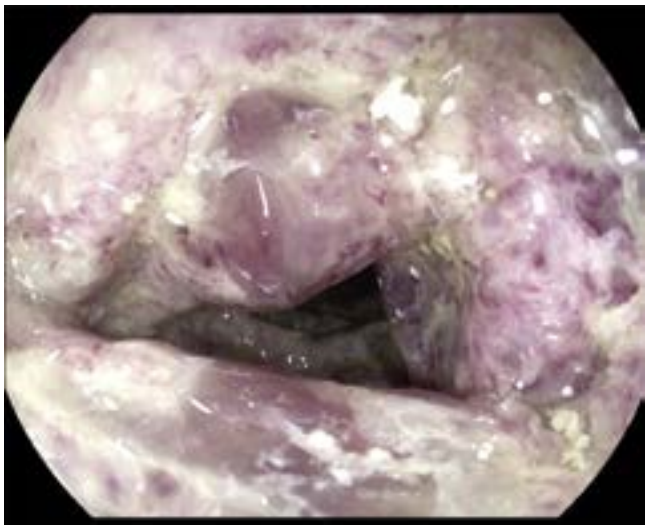


FIG. 5 Colonoscopic image showing cyanotic/black mucosal nodules with deep ulcerations until mucosal necrosis. *(From Maimone A, De Ceglie A, Siersema PD, et al. Colon ischemia: A comprehensive review. Clin Res Hepatol Gastroenterol. 2021;45(6):101592.)*

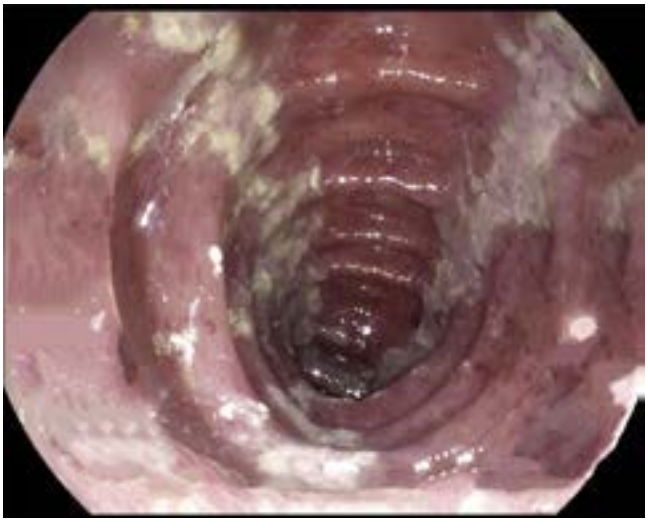


FIG. 4 Colonoscopic image of linear ulcerations placed along the longitudinal axis of the colon. *(From, Maimone A, De Ceglie A, Siersema PD, et al. Colon ischemia: A comprehensive review. Clin Res Hepatol Gastroenterol. 2021;45(6):101592.)*

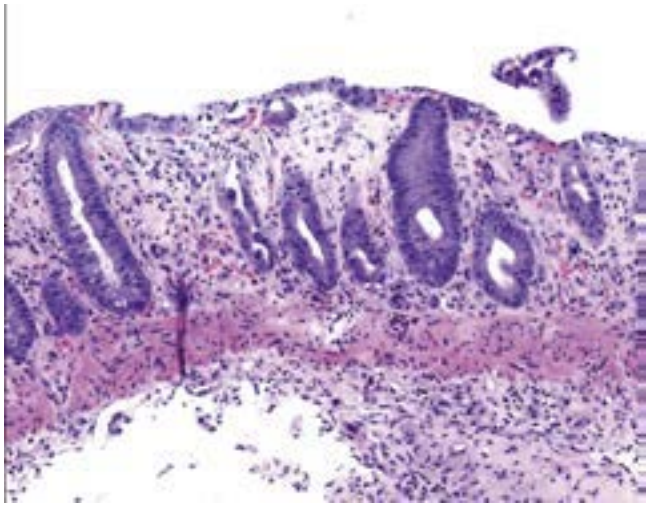


FIG. 6 Ischemic colitis, H&E, 100×. This image shows characteristic features of ischemic colitis, including superficial epithelial injury, crypts with atypia including nuclear hyperchromasia, and hyalinized lamina propria. The crypts appear closer together due to lamina propria collapse. *(Image courtesy Jacqueline Birkness-Gartman, MD.)*

A heart rate of >100 beats per min and systolic blood pressure of <90 mm Hg at the time of diagnosis are associated with the need for surgical intervention and/or mortality as are Hgb <12 mg/dL, hyponatremia (Na <136 mEq/L), LDH >450 U/L, and blood urea nitrogen (>28 mg/dL). A pancolonic distribution of disease and IRCI also portend a poor outcome.

Patients who meet criteria for severe disease need a surgical evaluation and most often will require operative intervention. This was the initial management in 53.6% of those with IRCI versus 14.5% in those with non-IRCI.

Surgical intervention should be considered in the presence of IC accompanied by hypotension, tachycardia, and abdominal pain without rectal bleeding; for IRCI and pancolonic IC; and in the presence of gangrene.

SURGICAL APPROACH

Operative management of patients with IC is either in the acute setting or for treatment of the sequelae of colon ischemia. In the acute setting, operative indications include peritonitis on examination, massive bleeding, fulminant colitis, portal venous gas or pneumatosis on imaging with clinical picture of IC, or worsening clinical condition on medical management alone.

The general principle of surgery is to remove all segments of the colon that are grossly ischemic (Fig. 7). Surgery is usually approached with a midline laparotomy; however, in certain circumstances, a diagnostic laparoscopy may be warranted. However, it can be difficult to determine the extent of resection as the serosa can be misleading as it will appear normal until transmural necrosis occurs. Therefore, a preoperative CT scan or endoscopic evaluation of the colon is important to establish the extent of bowel involvement. Intraoperatively, one may use Doppler ultrasonography, endoscopy, or photoplethysmography to assess mucosal viability or colonic blood flow. After adequate resection has occurred, in patients where there is concern for ongoing ischemia, it is not uncommon to leave the fascia open and bowel in discontinuity and take the patient to the intensive care unit for continued resuscitation for a planned second-look laparotomy and closure in 12 to 48 hours to make sure all necrotic tissue has been removed.

The decision to construct an anastomosis versus an ostomy depends on many factors. The main concern is anastomotic leak or nonhealing anastomosis. A primary anastomosis can be done safely in uncomplicated isolated right colon ischemia when the rest of the bowel appears very well perfused. However, for left-sided IC, published opinion advocates for an end colostomy and rectal stump (Hartmann procedure), which can be reversed later (i.e., no sooner than 6–8 weeks postsurgery). In selected cases, it may be reasonable even with left-sided disease to perform a primary anastomosis with or without a protective diverting loop ileostomy. With additional experience with preoperative localization of the extent of ischemia, less invasive surgical approaches may become more attractive.



FIG. 7 Portion of intestine with ischemia (cecum, *top right of image*). Compare with normal pink-tan mucosa *(bottom right of image).*
(Image courtesy Arianna Rubinetti, MS, PA [ASCP] and Kevan Salimian, MD, PhD.)

POSTOPERATIVE COURSE

Overall, the postoperative course of patients undergoing surgery for acute IC is associated with high rates of morbidity and mortality. Two-thirds of patients with severe IC requiring surgery develop medical complications such as pneumonia, urinary tract infections, atrial fibrillation, postoperative myocardial infarction, acute renal failure, or the need for hemodialysis. There is a 37% in-hospital mortality rate for severe IC.

Independent risk factors of mortality after emergent colectomy for IC include elderly age, poor functional status, multiple comorbidities, low output heart failure (e.g., cardiac ejection fraction <20% on echocardiogram), preoperative septic shock, preoperative blood transfusions, preoperative acute renal failure, and delay from hospital admission to surgery. Postoperative death is associated with the peak preoperative lactate level (if above 2.5 mmol/L), amount of intraoperative blood loss, pre- and intraoperative catecholamine administration, subtotal or total colectomy, need for dialysis postoperatively, and an American Society of Anesthesiologists (ASA) class 4.

Operative intervention is sometimes required for sequelae of IC such as symptomatic colonic strictures or for ostomy reversal. Studies showed high rates of complications after ostomy reversal (i.e., longer length of stay, anastomotic leaks, and mortality). Other indications for a second operation include facial dehiscence and wound complications. Patients with nongangrenous IC sometimes present with abdominal pain, bloating, and obstructive symptoms weeks after their initial episode. If a stricture is suspected, either a colonoscopy or a contrast enema can identify it; the latter is helpful to describe the length and location of the stricture. In 10% of the cases, strictures develop as the colon heals. If clinically significant, causing obstruction or severe abdominal pain, strictures need operative intervention by elective resection and primary anastomosis. Alternatively, there are nonoperative methods to temporize symptoms when surgery is not feasible, such as balloon dilation, and in some instances, stenting.

CONCLUSION

The incidence of IC has increased during the last few decades. Acute IC continues to represent a very deadly disease associated with high rates of morbidity and mortality. IC in the community typically presents in older patients with multiple comorbidities. Patients who survive their initial episode may require additional intervention, and around 7% of patients will have another episode within 5 years. IC is challenging to diagnose due to its nonspecific presentation, but efforts should be directed to early consideration of this diagnosis when risk factors and clinical conditions warrant.

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Management of Clostridioides Difficile Colitis

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Clostridioides (formerly *Clostridium*) *difficile* infection (CDI) is an important cause of community and nosocomial acquired diarrhea. It is associated with significant morbidity and mortality, especially amongst the immunosuppressed and elderly. This chapter will review the clinical presentation and treatment options for patients with CDI.

BACKGROUND

While *C. difficile* was first described as an important cause of antibiotic-associated colitis in 1978, it was not until the early 2000s that CDI was experienced as a threatening nosocomial problem due to an increase in disease frequency, severity, and mortality. This change was attributed in part to the emergence of hypervirulent strains, including NAP1/BI/027. Antibiotic stewardship programs and strict infection control measures allowed for early case identification and treatment, leading to a dampening of CDI incidence. Nonetheless, CDI remains an important cause of nosocomial acquired infection and an increasingly recognized cause of community acquired disease and transmission.

C. difficile is an anaerobic toxin-producing gram-positive bacillus that can exist in spore form (outside the colon) or vegetative forms. The bacteria produce two exotoxins (toxin A and toxin B) responsible for the colitis and diarrhea. Hypervirulent strains have been associated with significantly increased toxin production and subsequently a more severe clinical course. Ingestion of spores of *C. difficile* via a fecal-oral route is a common cause of transmissibility, and transmission is higher in patients with active disease compared with asymptomatic carriers.

Clinical Risk Factors for CDI

Several risk factors for contracting CDI have been identified. The most widely recognized and modifiable risk factor for CDI is antibiotic use; CDI can occur up to 3 months after antibiotic discontinuation. Antibiotics result in a disruption of the balanced normal colonic microbiota allowing pathogenic *C. difficile* bacteria to multiply and cause disease. While clindamycin was the first antibiotic to be associated with CDI, many other antibiotics have since been implicated. Antibiotic resistance patterns of *C. difficile* have also been found to be correlated to virulence. Another important risk factor for CDI is advanced age. Furthermore, immunosuppression, inflammatory bowel disease (IBD), gastrointestinal surgery, and length of hospitalization have all been associated with increased risk of CDI. Special attention needs to be paid to patients with IBD, as disease exacerbation can mimic *C. difficile* colitis. Although some epidemiologic studies have implicated gastric acid suppression as a risk factor, this association was not consistently found after adjusting for confounding factors and is most likely to be the result of patient illness and hospital length of stay.

CLINICAL PRESENTATION

Although some patients can be asymptomatic carriers of *C. difficile*, CDI usually has clinical manifestations that can range from mild colitis to fulminant severe disease with toxic megacolon. Patient factors and pathogen characteristics have been implicated in the severity of the clinical course. Increasing age, immunosuppression, and comorbidities are amongst the most reported predictors of severe disease presentation.

Different CDI severity classification systems exist; however, there is no universally accepted system. This limitation is likely because of the inability of one scoring system to accurately predict the clinical course, be simple enough to allow widespread point-of-care use, and allow for time-dependent variables to be adjusted as the patient's clinical course evolves. In general, the existing CDI severity classifications include a combination of factors associated with increased morbidity and mortality. These factors include physical examination findings, signs of shock, and laboratory data. A useful disease classification system was published in 2017 by the Infectious Disease Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) and is summarized in Table 1. Thus, the evaluation of patients with CDI should include a history, physical examination including vitals, urine output, fluid requirements, as well as laboratory tests including complete blood count (with significant leukocytosis being a hallmark, but not a pathognomonic feature, of CDI), renal function tests, albumin, and lactate as a marker of end-organ perfusion.

DIAGNOSIS

Testing is recommended for patients with unexplained new onset diarrhea (3 stools/day) especially in the presence of risk factors for CDI. Patients should be placed on preemptive isolation while awaiting results. Hand hygiene with soap and water is superior to alcohol-based hand-hygiene products for elimination of *C. difficile* spores and is recommended in addition to contact precautions including gloves and gowns.

TABLE 1 Disease Severity and Recommended Treatment

Disease Severity	Clinical Characteristics	Recommended Treatment
Nonsevere disease	Leukocytosis, WBC ≤15,000 or serum creatinine <1.5 mg/dL	Vancomycin 125 mg PO QID × 10d OR fidaxomicin 200 mg PO BID × 10d Use metronidazole 500 mg PO TID if none of the above available
Severe disease	Leukocytosis WBC ≥15,000 or serum creatinine >1.5 mg/dL	Vancomycin 125 mg PO QID × 10d OR fidaxomicin 200 mg PO BID × 10d
Fulminant disease	Hypotension/shock, ileus, or megacolon	Vancomycin 500 mg QID PO/PT (consider adding rectal vancomycin if ileus) + IV metronidazole (500 mg q8h)
Recurrent disease		Pulse-tapered vancomycin regimen or fidaxomicin regimen is recommended. Fidaxomicin, vancomycin with or without rifaximin, and fecal microbiota transplant (FMT) are used for second or subsequent recurrences. With recurrences presenting with fulminant disease, in addition to the antibiotic regimen administered, some advocate for the addition of FMT.

TABLE 2 Diagnostic Tests for *C. difficile*

Test	Details	Sensitivity	Specificity	Substance Detected
Selective anaerobic culture	Rarely used Takes a long time to finalize Can be useful in patient with ileus (rectal swab)	High	Low	*C. difficile* vegetative cells or spores
Cell culture cytotoxicity assay	Resource intensive and time consuming, not routinely done Has been used as a gold standard test	High	High	Free toxins
Nucleic acid amplification tests (NAAT)	Detects one or more genes specific to toxigenic strains Capable of detecting asymptomatic carriers	High	Low/ Moderate	*C. difficile* nucleic acid (toxic genes)
Enzyme immunoassay *C. difficile* glutamate dehydrogenase (GDH)	GDH antigen is an essential enzyme produced by all *C. difficile* isolates, but cannot differentiate between toxigenic and nontoxigenic strains	High	Low	*C. difficile* common antigen
Enzyme immunoassay for *C. difficile* toxins A and B	Most strains produce toxins A and B although some strains produce toxin B only, but CDI due to strains producing toxin A alone has not been reported	Low	Moderate	Free toxins

A variety of laboratory tests for *C. difficile* exist. They can detect either the organism itself or the toxins in the stools. To avoid false positive results, laboratory protocols recommend that only liquid or loose stool samples be tested. Stool toxin tests are often used as a multistep algorithm either with glutamate dehydrogenase (GDH) assay or nucleic acid amplification tests (NAAT) assay followed by toxin-recognition to help differentiate between asymptomatic carriers and patients with the disease. A summary of the commonly used tests is presented in Table 2.

Endoscopy

Pseudomembranes are a characteristic endoscopic feature of CDI that appear as raised white and yellow plaques and consist of toxin-induced ulcers with inflammatory cells and mucous (Fig. 1). Confirmatory endoscopy with flexible or rigid sigmoidoscopy is not necessary; however, it is often performed to exclude other causes of colitis such as cytomegalovirus infection, graft-versus-host disease, IBD exacerbation, or ischemic colitis. Endoscopic confirmation has also been used in cases where a decision on surgical management needs to be expediently made and the situation does not allow waiting for confirmatory laboratory testing.

Imaging

Abdominal imaging can aid in the diagnosis of colitis and identify complications requiring operative intervention. Rarely, complications such as free air may also be seen. Classically, plain films were used to assess for "thumb printing" secondary to submucosal edema or toxic megacolon with colonic distention. Nowadays, an infused computed tomography (CT) scan of the abdomen and pelvis is the preferred imaging modality to assess the degree, extent, and complications of the colitis. Typical findings in severe or fulminant disease include pancolitis with significant colonic thickening and ascites (Fig. 2A). If gastrointestinal contrast is given, it can be seen trapped between the edematous haustral folds (accordion sign) (Fig. 2B). Evidence of complications such as bowel perforation, toxic megacolon, and ischemia can also be seen on CT.

MEDICAL TREATMENT

Given the role of antibiotics in the development of CDI and its potential recurrence, it is recommended to stop the inciting antibiotics as soon as possible. Early treatment for CDI while awaiting confirmatory tests should be initiated, especially in patients with severe or fulminant disease. Although probiotics can decrease the occurrence of



FIG. 1 Endoscopic appearance of pseudomembranes. *(From Iseman DT, Hamza SH, Eloubeidi MA. Pseudomembranous [Clostridium difficile] colitis. Gastrointest Endosc. 2002;56[6]:907.)*

CDI, they have no role in the treatment of the disease. Metronidazole was commonly used for treatment; however, vancomycin or fidaxomicin have been found to be superior to metronidazole and have largely replaced it. The recommended treatment regimen with these agents is based on disease severity and is outlined in Table 2. For the first recurrence, a pulse-tapered vancomycin regimen or fidaxomicin regimen is recommended. Fidaxomicin, vancomycin with or without rifaximin, and fecal microbiota transplant (FMT) are used for second or subsequent recurrences.

With recurrences presenting with fulminant disease, in addition to the antibiotic regimen administered as outlined in Table 2, some advocate for the addition of FMT.

Patients with severe colitis require special attention. They should have large bore intravenous access and accurate measurements of intake and output to guide aggressive fluid resuscitation

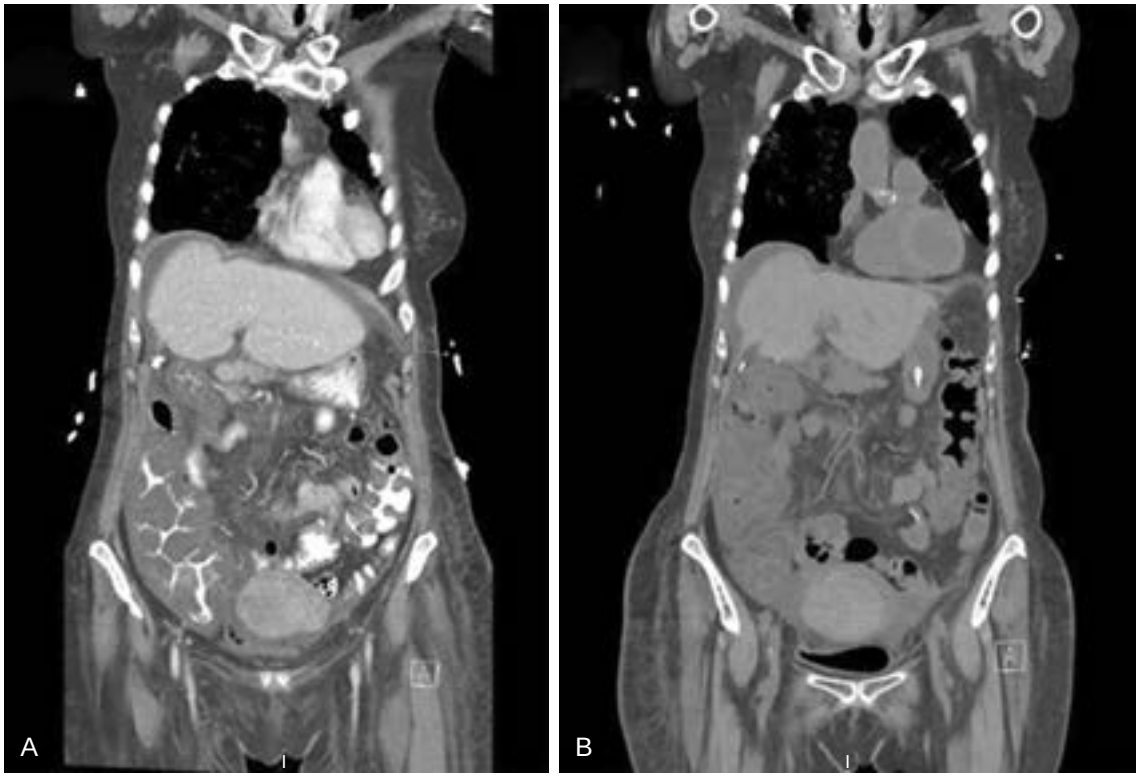


FIG. 2 Computed tomography scan showing fulminant *Clostridioides difficile infection,* with (**A**) and without (**B**) contrast.

with crystalloids. Acute kidney injury is a common complication of severe colitis and resuscitation is generally the initial approach. Patients should be kept fasting with complete bowel rest until their symptoms improve. We recommend serial clinical examinations of patients with severe disease including vital signs, abdominal examination, and laboratory investigations as the clinical course can evolve rapidly. Prompt recognition of complications associated with the colitis will allow early management and improve outcomes. A multidisciplinary approach including surgeons, intensive care and infectious disease specialists, may aid in the care of these patients.

SURGICAL MANAGEMENT

Although rare (0.3%–6.2% depending on the epidemic status), surgical management is reserved for patients with fulminant disease who fail to respond to medical management, worsen on treatment, or in whom complications related to the colitis arise including hemodynamic compromise, abdominal compartment syndrome, or colonic perforation (Box 1).

BOX 1 Indications for Surgical Management

- Colonic perforation
- Full-thickness ischemia
- Peritonitis, worsening abdominal exam despite adequate medical treatment
- Abdominal compartment syndrome
- Hemodynamic instability with ongoing or increasing need for vasopressor support
- Need for intubation and mechanical ventilation
- Worsening end-organ failure (especially renal failure)

In the absence of absolute indications for surgery, no clear guidelines exist to define failure of medical management or the optimal timing to intervene with surgery. Despite the morbidity associated with emergency surgery in critically ill patients, evidence from retrospective studies suggests that earlier time to surgical intervention with fulminant disease improves survival compared with continued medical management alone.

Total Abdominal Colectomy with End Ileostomy

An open total abdominal colectomy (TAC) with an end ileostomy remains the gold standard operation for patients with fulminant *C. difficile* colitis (FCDC) requiring surgery and is the operation to which all others are compared. Outcomes after segmental colectomies for the treatment of FCDC have been shown to be inferior to TAC, and thus segmental colectomy is not recommended even if the colitis appears to be limited to a part of the colon on CT imaging. Upon entry into the abdominal cavity, usually profuse ascites is encountered. The colon usually appears dilated and edematous but otherwise has a normal serosal surface, as this is a mucosal disease. The distal extent of the resection is at the rectosigmoid junction, where the rectum is transected and stapled; however, if the rectosigmoid appears too friable and there is heightened concern for rectal stump blowout, the surgeon can consider a more proximal transection to allow delivery of a distal stapled end of more proximal sigmoid as a mucous fistula. It is our preference to place a Malecot rectal catheter in the rectal stump for the first few postoperative days to allow decompression while healing. Postoperatively, patients should remain in a monitored setting until their vital functions are stable without the supportive measures offered in the intensive care unit and until their systemic inflammatory response syndrome (SIRS) starts improving. Postoperative length of stay is often prolonged by the patient's comorbidities, and rapid recovery is limited by the severity of the multiorgan system involvement. After recovery, ileorectal anastomosis can be

performed if the patient has returned to a functional baseline. This usually occurs starting at 3 to 6 months postoperatively. Given the significant postoperative morbidity associated with a colectomy for severe CDI, many patients do not reach a level of fitness suitable to endure another extensive operation for restoration of gastrointestinal continuity with an ileorectal anastomosis. In the literature, most patients who undergo a TAC do not eventually have restoration of gastrointestinal continuity.

Colonic Lavage and Diverting Loop Ileostomy

The creation of a diverting loop ileostomy (DLI) with colonic lavage has been advocated as a less-invasive alternative to TAC in this critically ill-patient population. In 2011, Neil et al. described this approach, which consists of the creation of a DLI with colonic lavage with warm polyethylene glycol solution and postoperative antegrade installation of vancomycin flashes by the ileostomy (Fig. 3). In their single-institution, single-surgeon series, the authors compared 42 patients who underwent surgery for FCDC with 42 historical patients who had undergone TAC. The authors observed a decreased 30-day postoperative mortality for patients who underwent a DLI compared with TAC. In addition to the survival benefit, the authors demonstrated increased ileostomy closure rates at six months. A minority of patients in the DLI group required conversion to a TAC either due to the development of abdominal compartment syndrome or for failure of improvement. Since the first description of this novel procedure, few studies have compared it to TAC. There remains a lack of high-quality prospective data comparing these two operations given the difficulty in conducting such studies in the setting of a disease associated with high mortality in the emergency setting. A recent meta-analysis of 733 patients with DLI and 2950 patients with TAC found no difference in postoperative morbidity or mortality but found higher gastrointestinal restoration rates for patients with DLI.

Thus, while no recommendations can be made on which patients would best benefit from DLI vs. TAC, we believe patients with severe disease early in their disease course, who do not have any complications associated with their colitis necessitating a TAC (perforation, ischemia, or toxic megacolon), can be offered a DLI with colonic lavage. However, one must be cautious that patients need close follow-up as the diseased colon is still in situ, and thus there is a longer time to resolution of SIRS. Typically, patients may take up to a few days to a week in this SIRS state before improving. Tables 3 and 4 summarize the current evidence and the advantages and disadvantages of each operation.

Theoretically, the creation of a DLI is relatively simple; however, there are a few technical challenges associated with fulminant disease state and with performing the colonic lavage. We summarized the steps of the operation in Box 2 and at the following link https://www.youtube.com/watch?v=1VMQrEI6jro&t=26s. Furthermore, comorbidities such as elevated BMI may be challenging and may be overcome with the creation of an end loop ileostomy.

SPECIAL POPULATION: PATIENTS WITH INFLAMMATORY BOWEL DISEASE

IBD, particularly ulcerative colitis, is a risk factor for the development of CDI. Patients with IBD are also more likely to need surgical intervention and have longer length of stay and increased mortality with CDI.

TABLE 3 Comparison Between Total Abdominal Colectomy and Diverting Loop Ileostomy and Colonic Lavage

	Pros	Cons
Diverting loop ileostomy	Less invasive operation and minimally invasive option Higher gastrointestinal restoration rates Improved postoperative morbidity compared with total abdominal colectomy (TAC)	Limited data supporting its use Optimal patient population not defined Patients may require reoperation in the event of failure Slower resolve of systemic inflammatory response
Total abdominal colectomy	Definitive management Faster resolution of the systemic inflammatory response	High morbidity and mortality Low gastrointestinal restoration rates

TABLE 4 Summary of Published Papers Mortality Following Total Abdominal Colectomy and Diverting Loop Ileostomy

	Study Design and Location	Study Interval	Patient Population (n)	30-Day Postoperative Mortality
Neal et al. (2011)	Prospective cohort, single center	2009–2011	DLI: 42 TAC: 42	DLI 19% vs. TAC 50% ($P = 0.006$)
Fashandi et al. (2017)	Retrospective, single center	2011–2015	DLI: 10 TAC: 13	DLI 30% vs. 23% 50%, ($P = 1$)
Ferrada et al. (2017)	Retrospective, multicentric	2010–2014	DLI: 21 TAC: 77	DLI 17.2% vs. TAC 39.7% ($P = 0.002$)
Hall et al. (2018)	Retrospective review of prospectively maintained database (ACS-NSQIP)	2011–2016	DLI: 47 TAC: 410	DLI 36% vs. TAC 31% ($P = 0.451$)
Juo et al. (2019)	Retrospective review of administrative database (NIS database)	2011–2015	DLI: 613 TAC: 2408	DLI 26.0% vs. TAC 31.1% ($P = 0.28$) *In-hospital mortality

ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; *DLI*, diverting loop ileostomy; *NIS*, Nationwide Inpatient Sample; *TAC*, Total abdominal colectomy.



FIG. 3 Example of set-up for diverting loop ileostomy and colonic lavage. **(A)** Foley catheter inserted into distal limb of the ileostomy, sutured to the rod. **(B)** Feeding access tubing used to administer vancomycin flushes.

BOX 2 Technical Details and Tips

- Exploratory laparotomy or diagnostic laparoscopy confirming diagnosis and ruling out contraindications to DLI (laparoscopy is preferable if patient is a candidate and the surgeon is comfortable with this approach).
- Creation of a diverting loop ileostomy 20 cm from the ileocecal valve in a typical fashion (Brooke proximal limb, flush distal limb; Fig. 3A).
- Inserting a catheter, typically 18F Foley urinary catheter into the distal limb of the ileostomy, ideally positioned in the cecum (Fig. 3B).
- Lavage of the colon is performed with 8L of polyethylene glycol (PEG) solution warmed to 37°C.
- Foley catheter connected to the bag containing the PEG solution using urologic connection tubing (used in cystoscopy), allowing flow control of the PEG solution to the diseased colon.
- PEG solution administered in increments, ensuring that effluent drainage is collected in the rectal tube.
- If the procedure is performed laparoscopically, pneumoperitoneum can be maintained at 7–10 mm Hg during lavage. Laparoscopic bowel graspers may be used to aid in pushing the fluid along the colon.
- If performed by a laparotomy, the abdomen is kept open, and the surgeon can manually aid the movement of the fluid through the colon.
- If trouble is encountered getting fluid through the colon, the patient may be moved into the Trendelenburg/reverse Trendelenburg positions as well as left side up/down and right side up/down to move the fluid along the colon.
- Rarely, flexure mobilization may be necessary.
- Due to fluid sequestration in the diseased and atonic colon, an abdominal compartment syndrome (ACS) may occur during or after the operation and the surgeon should be aware of this possibility.
- Abdominal drain can be left to remove excess ascites and potentially reduce the risk of ACS
- Postoperatively, vancomycin flushes (500 mg in 500 mL of lactated Ringer's) are delivered to the diseased colon through the Foley catheter that was left in the efferent limb of the ileostomy. The first vancomycin flush is given after completion of the PEG flushes, and administration should be continued every 8 h for 10 days or until the patient has clinically recovered (Fig. 3A and B).

Given that CDI can mimic IBD flares, it should be considered in patients with worsening, smoldering, or relapsing IBD. While the treatment for CDI in patients with IBD is identical to patients without IBD, given the increased morbidity and mortality in this population, they should be monitored closely and have a lower threshold for early surgical intervention. It remains important to note that while CDI enteritis is a very rare event, it can occur after TAC with end ileostomy or following ileal pouch anal anastomosis, as a rare cause of pouchitis, and should be excluded in the event of a high-output ileostomy with SIRS.

CONCLUSION

CDI is a common cause of colitis especially in the surgical population. Most patients respond well to treatment with medical management alone. A small proportion of patients need intensive care unit admission to support the multisystem organ failure that can arise. Surgery may be required for the treatment of fulminant disease or to treat complications of the colitis needing urgent surgical attention. Although TAC is the standard operation, DLI and lavage has recently emerged as an alternative in select patients early in their disease.

Acknowledgments

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Management of Large Bowel Obstruction

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Large bowel obstruction has traditionally been managed with urgent if not emergent surgery resulting inevitably in a laparotomy and stoma. However, in the past two decades with increasing use of endoscopy and experience with minimally invasive techniques, management can be more specifically tailored to the severity of obstruction and etiology. Nonetheless the management of large bowel obstruction requires prompt evaluation and diagnosis.

ETIOLOGY

The cause of large bowel obstruction can be categorized broadly as either mechanical or functional. Mechanical obstruction is more common than functional and often results from a neoplastic process. Mechanical obstructions can result from intrinsic or extrinsic processes, such as colorectal and ovarian cancer, respectively. Colorectal carcinoma is the most common etiology and accounts for nearly half of mechanical large bowel obstructions. Up to one-third of patients with colorectal cancer have a near or complete mechanical obstruction because of tumor burden, often representing an advanced stage.

Diverticular disease is the second most common cause of mechanical large bowel obstruction. Chronic inflammation in the sigmoid can cause a stricture in up to 17% of patients. This often results in a more chronic presentation of a large bowel obstruction. However, complicated diverticulitis with significant inflammation can also present as a large bowel obstruction due to the inflammatory stricture, phlegmon, or abscess. The third most common cause of large bowel obstruction is volvulus, and this occurs in 5% to 10% of all large bowel obstructions. Volvulus is a result of a long redundant segment of colon that has developed an axial rotation about its colonic mesentery. Because the blockage is not only of the colon lumen but also involves the mesentery, the risk of strangulation and ischemia is significantly higher that other causes of large bowel obstruction. The most common location for volvulus is the sigmoid colon (60%–70%), followed by the cecum (25%–40%), and very rarely the transverse colon (1%–4%).

Functional causes of large bowel obstruction are less common than mechanical obstructions. These include colonic pseudo-obstruction (Ogilvie's syndrome), narcotic-induced adynamic ileus, and adynamic ileus due to systemic illness such as toxic megacolon from *Clostridium difficile* infection. Treating the underlying cause in functional large bowel obstruction often improves the symptoms.

CLINICAL PRESENTATION

Large bowel obstruction symptoms vary based on the acuity of the obstruction, resulting in a wide range of symptoms. Typically, patients will present with crampy abdominal pain, distension, and obstipation. Patients with an incompetent ileocecal valve will eventually present with nausea and emesis. Often, acute large bowel obstruction is associated with signs of hypovolemia and electrolyte imbalances secondary to fluid sequestration in the intestines as well as oral intolerance. Symptoms from chronic obstruction are typically mild and often associated with change in bowel habits, bloating, narrow caliber stools, and unintentional weight loss. This constellation of findings should raise suspicion for malignancy.

DIAGNOSIS

History and Physical Examination

Prompt evaluation and diagnosis beginning with a focused history and physical examination should occur in patients presenting with signs and symptoms of a large bowel obstruction. Obtaining a careful history of the development of symptoms can often cue surgeons to the most likely diagnosis. Patients may report a rapid or slow progression of their symptoms depending on the etiology. Recent orthopedic or gynecologic procedures are commonly associated with the development of colonic pseudo-obstruction. A family or personal history of colonic neoplasms, diverticular disease, or inflammatory bowel disease, as well as findings on previous colonoscopy (if performed) should be ascertained as this helps narrow the diagnosis. A review of current medications may indicate prescription medication-induced constipation but equally importantly can provide an overview of the patient's overall underlying health status and comorbid conditions.

The physical examination classically reveals a tympanitic and distended abdomen. On occasion, a mass can be palpated through the abdominal wall in thin patients. Focal tenderness on examination may suggest ischemia or localized perforation, whereas diffuse tenderness is concerning for peritonitis. A digital rectal examination is an important part of the exam and should be performed on all patients to rule out fecal impaction, foreign body, or anorectal malignancy as the cause. In elderly patients and/or those with severe comorbid medical problems, it is important to ascertain goals of care, especially when advanced malignancy is suspected.

Imaging

Because of ease in accessibility, upright and supine abdominal radiographs are often the first images obtained. For the diagnosis of large bowel obstruction, plain films have a sensitivity and specificity of 84% and 72%, respectively. Importantly, they can help rule out an abdominal disaster such as pneumatosis coli or pneumoperitoneum, which in the right clinical context may obviate additional imaging. Cecal distension of 9 to 12 cm on plain abdominal film is concerning for impending perforation. In the setting of an incompetent ileocecal valve, reflux of contents back into the small intestine may reflect as air-fluid levels of the small bowel with distension. When colonic volvulus is the cause of large bowel obstruction, plain films can confirm the diagnosis. The classic findings of a sigmoid volvulus are seen in about two-thirds of patients and are commonly described as the "bent inner tube" sign or an "omega loop." In the case of cecal volvulus, this classically presents as the "coffee bean" sign; however, it is only seen radiographically in less than 20% of the patients.

Contrast enemas (CEs) were once the gold standard in the diagnosis of large bowel obstruction. However, because these tests are labor intensive and require additional time, CEs are not readily accessible and are underutilized. CEs have a 96% sensitivity and a 98% specificity for diagnosing large bowel obstruction, compared to the 84% and 72%, respectively, of plain abdominal films. Classic finding is a "bird's beak" deformity at the site of a volvulus or an "apple core lesion" at the site of an obstructing cancer. CE can also provide additional details such as the length, width, and tortuosity of the narrowing that may be helpful when intraluminal stents are being considered. In cases of colonic pseudo-obstruction, contrast will freely flow without evidence of transition point. Additionally, in the setting of fecal impaction, contrast may be therapeutic.

Computed tomography (CT) has become the preferred imaging modality in the evaluation of a patient with signs and symptoms of a large bowel obstruction. CT is much more readily accessible than CE and has largely supplanted CE as the diagnostic modality of choice. CT confirms the diagnosis of large bowel obstruction with almost 100% sensitivity and 90% specificity; it also allows multiplanar reconstruction that further facilitates the definitive etiology of large bowel obstruction. Finally, CT may have a substantial impact on the clinical management of a large bowel obstruction by demonstrating signs of intestinal ischemia, early pneumatosis, or pneumoperitoneum leading to earlier interventions.

TREATMENT

Initial Management

In concert with the initial history and physical, laboratory assessment should include serum chemistry and electrolytes, complete blood count, and lactate level. Hypovolemia and electrolyte imbalances are common and should prompt aggressive resuscitation with accurate monitoring of intake and output with a urinary catheter. Decompression with a nasogastric tube should be performed early. If surgery is a consideration, preoperative antibiotics and stoma marking should occur as an ostomy is frequently required.

Surgical Management

The optimal surgical management and approach, either laparoscopic or open, will vary according to the degree of obstruction, the underlying etiology of large bowel obstruction, as well as the clinical condition of the patient. Broadly, the surgical management of large bowel obstructions can be guided by the urgency of decompression, emergent or nonemergent.

Emergent Surgical Management

Patients who present with impending perforation on imaging, pneumoperitoneum (evidence of existing perforation), peritonitis, and/or with clinical signs of sepsis require emergent intervention. The best approach in this setting is a midline laparotomy that allows for decompression of the bowel, prompt identification of the lesion, and adequate exposure for a variety of procedures. Laparoscopic intervention may be difficult secondary to colonic distension and/or clinical instability. The primary goal of surgery in this setting is to decompress the large bowel as expeditiously as possible to prevent ischemia or perforation, if it has not already occurred. Ideally, this would entail treating the underlying etiology of the obstruction. When the obstructing lesion is resectable, the next decision is whether to restore intestinal continuity following resection. In general, under emergent setting where the patient is unstable or with gross intraabdominal contamination, primary anastomosis is contraindicated. For these patients, segmental resection with an end stoma is the safest choice.

For lesions on the right side, proximal to the splenic flexure, a *right hemicolectomy with end ileostomy* is recommended. For left-sided lesions, a *Hartmann procedure* should be performed. Introduced in 1923 by Henri Hartmann specifically for the management of large bowel obstruction, the Hartmann procedure involves resection of the distal obstruction and the formation of an end colostomy. To perform a Hartmann procedure, the patient should be placed in the lithotomy position, which greatly enhances pelvic dissection and allows for access to the rectum if necessary. After resection of the lesion, decompression of the colon is best achieved with an end colostomy. In a review of 35 studies by van de Wall and colleagues, of the 6249 patients who underwent a Hartmann procedure, only 44% underwent reversal with a mean time to reversal of 7.5 months. Morbidity rate was 3% to 50% (mean, 16.3%) and mortality rate from 0% to 7.1% (mean, 1%).

It is important to inspect the entire colon proximally to rule out any injury due to distension or synchronous pathology and, when feasible, to exteriorize the distal colon conduit as a mucus fistula or in the subcutaneous tissue at the inferior midline incision or the stoma site to facilitate reversal in the future. Given the emergent nature of the procedure, distinguishing between malignancy and inflammation can be difficult; however, attempts should be made to provide an oncologic resection when feasible.

Conversion from segmental resection to *subtotal colectomy* is rarely needed and determined by the integrity of the colon proximal to the obstruction. A subtotal colectomy is indicated when perforation, large serosal injuries, or synchronous lesions are found at the time of exploration. When performing a subtotal colectomy in the emergent setting, creation of an end ileostomy is often necessary.

Less commonly, there are circumstances in which addressing the underlying cause is not feasible. In instances of unresectable malignancy, diffuse carcinomatosis, severe inflammation, or in patients who are extremely unstable, a *diverting loop colostomy* proximal to the obstruction is indicated. A loop colostomy is preferred over an end colostomy as the blind end that is left in the abdomen may perforate. A colostomy relieves patients of their symptoms and limits subsequent concerns for an anastomotic leak.

However, colostomies can be associated with significant morbidity, including high rates of parastomal hernia (50%), decreased quality of life, and low rates of stoma closure.

Nonemergent Surgical Management

In the absence of generalized peritonitis, perforation, or sepsis, the nonemergent management of a stable patient allows for more surgical treatment options. The surgical technique will depend on the skill of the surgeon as well as available hospital resources.

In patients with a right-sided obstruction and the point of obstruction is proximal to the splenic flexure, urgent *right hemicolectomy with primary anastomosis* should be considered and can often be performed laparoscopically in a stable patient with limited bowel distension. This procedure is associated with low anastomotic leak rates (<5%) in a hemodynamically stable patient who has not undergone a bowel preparation. An alternative is performing a *right hemicolectomy with primary anastomosis and proximal diverting loop ileostomy*. This can be considered in patients who may have associated small bowel dilation or who are immunosuppressed, on steroids, or malnourished from chronic obstruction where concern for anastomotic leak is higher or where a leak would preclude or delay further treatment such as chemotherapy in the setting of cancer. Additionally, reversal of a loop ileostomy is a less morbid surgery than reversal of an end ileostomy.

There is more debate regarding the preferred surgical procedure for an obstructing lesion arising in the descending sigmoid colon, rectum, or anus. Traditionally, primary anastomosis at the initial procedure was avoided because of the higher rates of anastomotic leak (20%). Currently, *segmental resection with primary anastomosis* is a good option for carefully selected patients if the proximal colon is not dilated significantly. Retrospective reviews have shown similar rates of operative mortality and anastomotic leak in carefully selected patients undergoing left-sided colectomy compared with right-sided colectomy. Furthermore, quality of life is improved. A good option for a high-risk patient is *segmental colectomy, anastomosis, and a diverting loop ileostomy*. This still allows for diversion of the fecal stream, and in the event of an anastomotic leak, intraabdominal sepsis is contained and can usually be managed nonoperatively with percutaneous drainage and antibiotics. Loop ileostomy reversal is a less invasive operation and patients will more likely undergo this procedure to have their intestinal continuity restored as compared to reversing a Hartmann's procedure. The disadvantage is that ileostomy management in some patients (particularly the elderly) may be challenging with fluid and electrolyte shifts.

Colonic Lavage

In select patients, the use of an on-table colonic lavage may permit a single-stage surgery in the setting of a left-sided large bowel obstruction. Following resection of the lesion, the colon should be fully mobilized at both hepatic and splenic flexures to facilitate irrigation and allow descending colon to extend beyond the abdominal cavity. Next, an appendectomy is performed, and a catheter is passed into the cecum and secured with a purse-string suture. This catheter is attached to a large bag of warmed saline and elevated on a pole. If the cecum is thinned, an alternative is to insert the catheter into the terminal ileum and secure with a purse-string suture. The staple line at the distal segment of colon is opened and a generous length of sterile corrugated tubing is placed into the lumen of the descending colon. The tubing is secured in place with umbilical tape or a purse string and then draped off the table into a basin. Three to six liters of warmed saline is then flushed through the colon. This is continued until the effluent clears (Fig. 1). The catheter and tubing are removed, and the site of the appendectomy is closed. Before the anastomosis, the colon is inspected for injuries that may have occurred during the lavage. The anastomosis is then performed in the standard fashion, either end-to-end or side-to-side if there is a large bowel size discrepancy. A modified version of this method uses a Y-shaped connector (Fig. 2). One limb allows for retrograde infusion of saline through the descending colon and the other is attached to drainage tubing. This modification is appealing as it obviates the need for the appendectomy or cecostomy. In a study by Jung and colleagues, 171 patients with an obstructing left-sided lesion received intraoperative colonic lavage with primary anastomosis. Compared with elective, nonobstructed patients during the same interval, anastomotic leakage and wound infection were not significantly different.

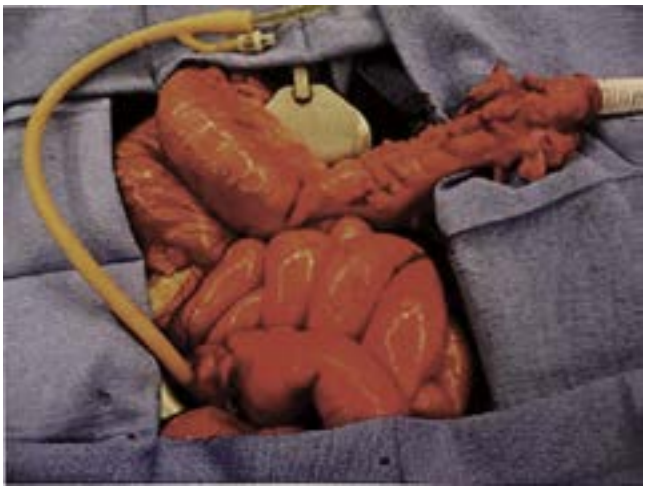


FIG. 1 On-table colonic lavage.

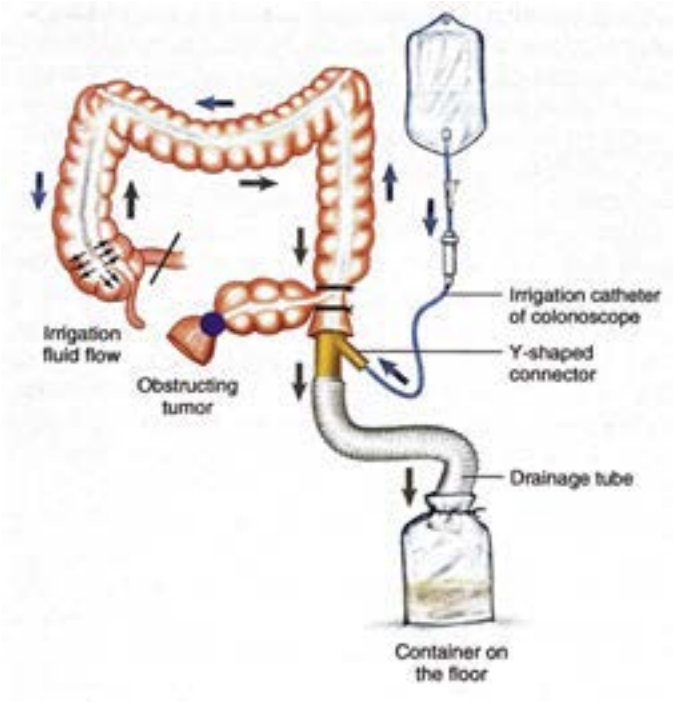


FIG. 2 Alternative colonic lavage using a Y-shaped connector.

Endoscopic Stenting

In the past decade, endoscopic management of obstructing large bowel lesions has gained significant attention. Much of the literature is on stenting of obstructing left-side lesions, and although reports of right-sided lesions exist, the indication is less clear. In the appropriately selected patient, endoscopic stents can be tremendously beneficial. Indications for stent placement include palliation of an

inoperable obstructing lesion (e.g., stage IV colorectal cancer) and as a temporizing "bridge" to definitive therapy in a patient with a curable or potentially curable lesion. The ability to stent a curable or potentially curable lesion affords time for colonic decompression, medical optimization, endoscopic evaluation for synchronous lesions, and increases the likelihood of a single-stage operation. Contraindications to stent placement include any of the previously discussed indications for emergent surgery, an abscess/infection closely associated with the lesion, short and tethered colon, and a lesion less than 5 cm from the anal verge.

Perioperative antibiotic coverage is unnecessary for stent placement. Gentle tap water enemas should be used to evacuate stool distal to the lesion. If an oral bowel preparation is desired, it may be attempted only if the obstruction is partial and the patient is closely monitored for the development of new or worsening symptoms. Colonoscopic evaluation of the lesion must be done with the utmost care; forceful attempts to traverse beyond the lesion are strictly avoided. Perforation is the most feared complication of stent placement. To mitigate the procedural risk of perforation, insufflation with carbon dioxide is preferred over room air because of the dramatically faster clearance time. The most common stents used in the United States are uncovered, self-expanding metal stents (SEM). Through-the-scope (TTS) and over-the-wire, also referred to as non-TTS, are the two conventional approaches to stent placement. TTS is usually the first-line approach (Fig. 3). The TTS system requires a colonoscope equipped with a working channel to pass the guidewire and stent. The scope is advanced and parked in an area immediately distal to the lesion. Contrast is administered and the lesion assessed with fluoroscopy. The guidewire is then advanced safely beyond the lesion followed by the stent (Seldinger's technique). Endoscopy and fluoroscopy confirm the correct location of the wire and the stent. Most TTS systems encourage a proximal and distal stent overlap of 2 cm. For longer lesions, additional stents can be placed in series. If assessment of the lesion shows anatomy unfavorable for TTS (e.g., available size of the stents), the procedure is converted to over-the-wire.

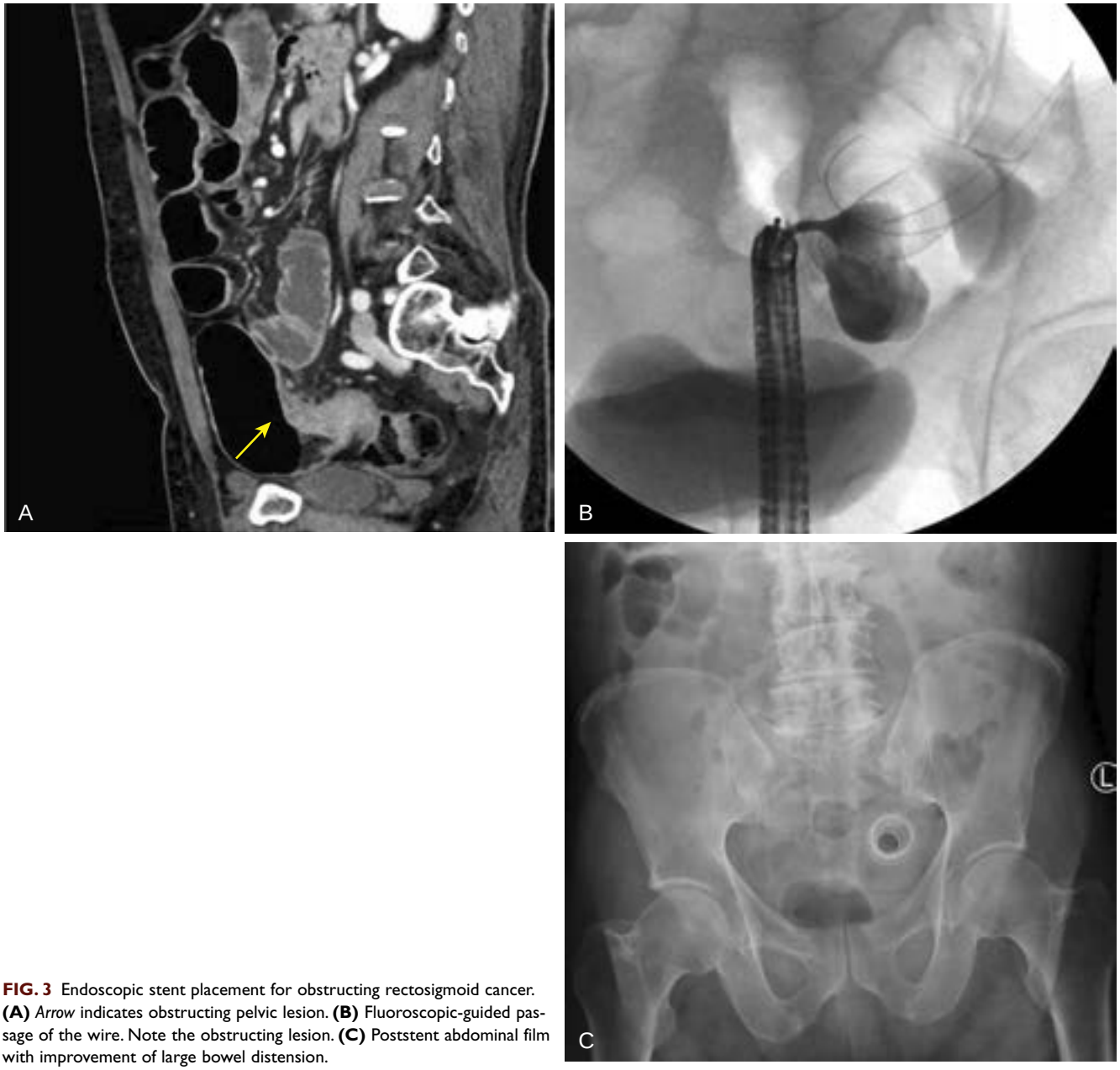


FIG. 3 Endoscopic stent placement for obstructing rectosigmoid cancer. **(A)** *Arrow* indicates obstructing pelvic lesion. **(B)** Fluoroscopic-guided passage of the wire. Note the obstructing lesion. **(C)** Poststent abdominal film with improvement of large bowel distension.

With the guidewire fixed, the colonoscope is withdrawn entirely. The appropriate stent is selected and passed directly over the wire into position using fluoroscopy. Fluoroscopic or postprocedural abdominal films are obtained to confirm the typical stent appearance of a narrowed or waisted midportion with proximal and distal flaring. The flaring represents adequate overlap into normal, low-resistance lumen. To reduce development of rapid restenosis, the intraluminal diameter at the midportion of the stent should be at least 24 mm. Balloon dilation should not be attempted because of significant risk of perforation. If imaging does not demonstrate flaring at one or both ends of the stent, additional stenting is likely necessary and typically done in an end-to-end fashion. Patients should expect gradual improvement of symptoms over 3 to 5 days as the stents reach maximal expansion and the colon decompresses. For descending colon and beyond, patients are advised to consume a low-residue, low-fiber diet along with daily laxatives (e.g., polyethylene glycol) to promote soft stools that are unlikely to become impacted at the stent. It is important that if definitive therapy is planned, it should be done within 7 to 14 days following placement of the stent. Patients who receive stenting for palliation and the anticipated duration greater than 2 weeks have a significantly increased risk of stent complications, primarily perforation. Multidisciplinary discussion should weigh the possibility of surgical palliation in this high-risk population. Current literature reports successful stent placement for acute large bowel obstruction between 70% and 90%. In a pooled analysis by Sebastian et al., 25% of the 1198 patients who underwent stent placement for obstruction developed a complication. Most common complications include stent migration, reobstruction, and perforation. The most serious complication is perforation and occurs in 4% to 5% of patients. Intrinsic factors that may increase the risk of stent-related perforation include longer segment of obstruction (median length of 64 mm), benign etiology, and extraluminal origin.

SPECIFIC SITUATIONS

Sigmoid Volvulus

Volvulus, from the Latin, *volvere*, means to roll. The classic patient with a sigmoid volvulus presents with colicky lower abdominal pain and obstipation. The demographic profile most affected by sigmoid volvulus is a black male older than 70 years with significant comorbidities. The two primary goals for management of sigmoid volvulus are to relieve the obstruction and prevent recurrence. The gold standard in the management of uncomplicated sigmoid volvulus is endoscopic detorsion, gross inspection to ensure viability of the colon, and placement of a drainage catheter (successful in up to 70%–90% of patients). Endoscopic reduction converts an emergency situation into an elective one and allows preparation of bowel and patient prior to definitive surgery. Failure of endoscopic reduction and/or presence of bowel ischemia is an indication for emergent resection. Primary anastomosis in this setting is an ongoing controversy and dependent of clinical picture of the patient. When endoscopic reduction is successful, definitive elective operation is recommended based on the high rate of recurrence; most studies cite a rate in the 50% to 80% range. Atamanalp and colleagues published data from a single-center review of 686 patients. They found morbidity and mortality of 35% and 16% for emergent surgery for recurrent sigmoid volvulus and 12.5% and 0% for elective surgery, respectively. Some suggest performing the definitive surgery as early as the index admission. Regardless of timing, the approach can be either open or minimally invasive. The redundant colon and narrowed mesentery leading to sigmoid volvulus results in an anatomical configuration that facilitates sigmoid resection with minimal difficulty. The gold standard is resection with primary anastomosis. For isolated sigmoid volvulus and the elective sigmoid colectomy, the recurrence rates are very low.

Cecal Volvulus or Bascule

The second most common site of colonic volvulus is the cecum (Fig. 4). In patients with cecal volvulus, there is a female predominance, and typically patients are in the second and third decade of life, younger than those presenting with sigmoid volvulus. Presentation is similar to small bowel obstruction with abdominal distension, nausea, and vomiting; however, this can vary. There are three types of cecal volvulus:

1. Axial cecal volvulus: A twist of the intestines in which the affected cecum remains in the right lower quadrant.
2. Loop cecal volvulus: The cecum and terminal ileum are twisted in the axial plane and the affected cecum typically lies in the left upper quadrant.
3. Cecal bascule: A redundant cecum folds in the sagittal plane onto itself and the proximal ascending colon leaving the affected cecum within the right upper quadrant.

All three types necessitate either an acquired or congenital hypermobile cecum and ascending colon. Types 1 and 2 are the most common, accounting for roughly 80% of cecal volvuli. Unlike types 1 and 2, type 3 does not exhibit torsion. Patients who present

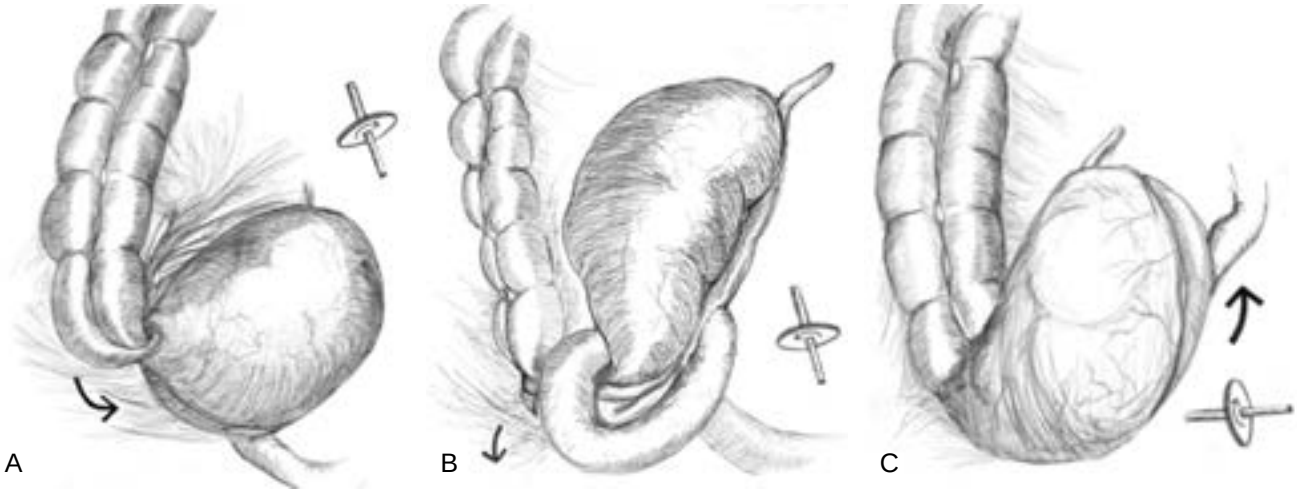


FIG. 4 Types of cecal volvulus. **(A)** Type 1, axial cecal volvulus. **(B)** Type 2, loop cecal volvulus. **(C)** Type 3, cecal bascule. *(Courtesy Matthew P. Kelley, MD.)*

with type 3 typically have a much more insidious presentation. Endoscopic management is not recommended for cecal volvulus or bascule because of a low rate of successful detorsion, and colonic ischemia can be missed in up to 25% of patients. For the patient presenting with a high probability of cecal volvulus, the operation of choice is an exploratory laparotomy. Severe ischemia, necrosis, or perforation occurs in up to 44% of patients with cecal volvulus; if present, mortality rates are equally as high. Management of the patient with nonviable cecum is resection and creation of end ileostomy, with consideration for mucous fistula. If the cecum is viable or with patchy ischemia, there is less consensus on the appropriate management. Nonresectional options include detorsion with cecopexy and cecostomy. Widely variable rates of recurrence, morbidity, and mortality have been demonstrated, although there is a paucity of recent data that compares these options and with respect to viable versus nonviable bowel. Distillation of the current data favors ileocecectomy with primary anastomosis for patients with acute cecal volvulus, even when bowel appears viable. Laparoscopic approach is an acceptable option in stable patients with limited bowel distension if performed by an experienced surgeon.

Acute Colonic Pseudo-Obstruction

Acute colonic pseudo-obstruction (ACPO) is also referred to as Ogilvie's syndrome in homage to British surgeon Sir Heneage Ogilvie who in 1948 identified two patients who presented with large bowel distension without an identifiable lesion. This syndrome is most encountered in the hospitalized, elderly male patient. Hospitalization is notably unrelated to the presenting symptoms rather for unrelated surgical procedure (most commonly involving pelvic dissection) or traumatic bony injury. Additional predisposing factors include severe electrolyte disturbances, certain medications, and acute deconditioning. Presentation is consistent with other etiologies of large bowel obstruction, including nausea, vomiting, and persistent abdominal pain. A significant portion of these patients will continue to pass loose stool. Focal peritonitis confined to the right lower quadrant may be a warning sign of impending perforation because of the profound cecal distension. These findings should encourage expeditious intervention. Perforation at the time of presentation occurs in about 15% of patients and often is associated with abdominal tenderness, cecal diameter greater than 12 cm, fever, and leukocytosis. Abdominal plain films are the best initial imaging study, although findings are nonspecific. Second-line imaging has traditionally been with water-soluble CE. Unfamiliarity with the technique coupled with the risk of perforation makes this option less favorable. The gold standard imaging modality is CT; findings include diffuse colonic distension, possible transition point near splenic flexure, and, importantly, no evidence of a mechanical obstruction. Nonoperative management of ACPO is successful in more than two-thirds of patients. This consists of aggressive fluid resuscitation, repletion of serum electrolytes as necessary, cessation of possible offending medications (e.g., opioids, anticholinergics), and bowel rest. The use of nasogastric and rectal tubes for decompression may also encourage the passage of flatus. These principles of nonoperative management are continued for up to 72 hours. During this period, it is essential to monitor the patient with the use of serial imaging and physical examination.

Failure to improve over this period necessitates the next step in the algorithm, neostigmine. Neostigmine increases the availability of acetylcholine through its antiacetylcholinesterase mechanism. In the colon, additional acetylcholine results in improved contractility and generalized motility. Before administration, the patient should be transferred to a unit with continuous cardiopulmonary monitoring and the ability to administer atropine, glycopyrrolate, or both. Neostigmine is contraindicated in patients in whom there is suspicion for ischemia or perforation, severe acute bronchospasm, poorly controlled cardiac dysrhythmia, or pregnancy. With the patient connected to continuous monitoring, the first dose of neostigmine of 2 to 5 mg is given intravenously over 1 to 5 minutes. Success is achieved with passage of flatus, stool, or decreased abdominal distension. Patients are observed over the next 80 minutes. Atropine and glycopyrrolate should be readily available if there is development of bradycardia or bronchospasm, respectively. Neostigmine is successful at treating ACPO in more than 90% of cases. For patients who are partial responders or nonresponders after one dose, a second can be administered with high rates of success. For those who fail to respond to neostigmine, the next step in management is endoscopic decompression. Geller et al. reviewed 50 patients with ACPO treated with colonoscopic decompression and found clinical success in 95% following a single intervention, 18% needed at least one additional colonoscopy; for patients who did not receive a decompression tube at the time of the procedure, clinical success was only achieved in 25%. Regarding technical considerations, insufflation should be minimized and preferably with carbon dioxide. The scope should be advanced into the right colon. A decompression tube is strongly recommended and should originate from the right colon; however, randomized controlled trial data are lacking to support the use of decompression tubes. Evidence does, however, support the use of polyethylene glycol solution after endoscopy and neostigmine to lower recurrence rate. The endoscopist should remove as much gas as possible during withdrawal of the scope. If endoscopic decompression is not possible or unsuccessful, percutaneous cecostomy can be used with variable success. When all these interventions have been unsuccessful, operative management is indicated. The surgery is dictated by the intraoperative findings. A minilaparotomy may be enough to assess the viability of the colon. If there is no evidence of perforation or ischemia, a tube cecostomy or surgical cecostomy may be sufficient. When ischemia is identified, the affected region should be resected, including subtotal colectomy if indicated. Primary anastomosis is not recommended but rather the creation of end colostomy with or without mucous fistula.

SUMMARY

Large bowel obstruction is a serious disorder that often necessitates surgical intervention. Rapid evaluation is essential to providing appropriate management. The approach and type of surgery will be largely dependent on the clinical condition of the patient and surgeon comfort. Emergent laparotomy should be performed in unstable patients with peritonitis and/or signs of symptoms of ischemia. Segmental resection with primary anastomosis should be considered in patients who are stable and have minimal barriers to healing. Endoscopic stenting can be considered as a bridge to surgery or as palliation in select patients.

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Enteral Stents in the Treatment of Colonic Obstruction

Shruti Mony, MBBS, Clement Wu, MBBS, and Mouen Khashab, MD

INTRODUCTION

Large bowel obstruction is frequently encountered by surgeons and gastroenterologists. Although up to 30% of cases are caused by malignant obstruction from colon cancer, benign causes such as ischemia, radiation injury, volvulus, and diverticular or inflammatory bowel disease are other etiologies. Malignant large bowel obstruction is a surgical emergency, with operative management carrying a high morbidity and mortality of 15% to 34% and 32% to 54%, respectively.

Since the experimental use of uncovered self-expandable metal stents (SEMS) by Spinelli et al. in the early 1990s, colonic stents have significantly evolved. In the past, their primary indication was for palliation of inoperable colorectal malignancy avoiding the need for surgical diversion and stoma formation. The indications of colonic stenting have now expanded beyond palliation to include treatment of benign and malignant colonic obstructive disease as well as a bridge to surgery (BTS) for malignant disease.

The advantages of colonic stenting include converting emergency surgery to elective surgery and minimizing the risks associated with emergency surgery. Elective surgery is preferred as it is cost-effective and allows time to optimize the patient's nutritional status, restore bowel function, and increase the chance of primary anastomosis. From an oncologic perspective, it enables completion of cancer staging and administration of neoadjuvant therapy. However, concerns regarding complications and long-term oncologic outcomes necessitate multidisciplinary discussion in certain instances. This chapter focuses on the indications, contraindications, techniques, and outcomes of colonic stenting.

INITIAL EVALUATION

It is imperative to understand the underlying etiology of a colonic obstruction as well as accurately define the stricture location before any intervention. A thorough physical examination and radiographic imaging should be performed to exclude a surgical abdomen and luminal perforation. The therapeutic approach differs for benign disease versus malignancy. Inflammatory, ischemic, or anastomotic colon strictures can often be managed with endoscopic balloon dilation. Malignant colonic strictures will not respond to endoscopic balloon dilation, which also carries a non-trivial risk of perforation in these patients. Alternative management strategies such as placement of a SEMS or surgical intervention is often required.

INDICATIONS FOR STENT PLACEMENT

Malignant Colonic Obstruction

Malignant colonic obstruction (MCO) is primarily caused by left-sided colorectal cancer (Fig. 1). Right-sided (proximal) colon cancer presents less frequently with colonic obstruction and is often managed with one-stage surgery without the need for bowel preparation or permanent stoma formation. The outcomes of SEMS deployment in this group are conflicting, and prospective trials are warranted. On the contrary, left-sided MCO benefits from SEMS and surgical decompression. There are three main indications for SEMS placement in patients with MCO: (1) bridging to elective surgery, (2) palliation in nonoperative candidates, and (3) overcoming extrinsic compression from extracolonic tumors.

International guidelines provide limited and contrasting information on the management of MCO and lack standardization, specifically for surgically resectable colorectal cancer presenting with frank obstruction. A recent review of the international guidelines by Webster et al. showed that there is a lack of high-quality evidence to define the best management strategy in terms of morbidity, mortality, and long-term oncologic outcomes. Clinical practice guidelines are more consistent in the setting of disease palliation. Colonic stenting is recommended as the treatment of choice in such cases.

Bridge to Elective Surgery

The advantages of preoperative colonic SEMS placement as a bridge to future definitive surgical intervention include the following:

1. Restoration of bowel function with a one-stage operation and avoiding the need for an ostomy, thus also improving quality of life (QoL)
2. Conversion of an emergency surgery to an elective surgery

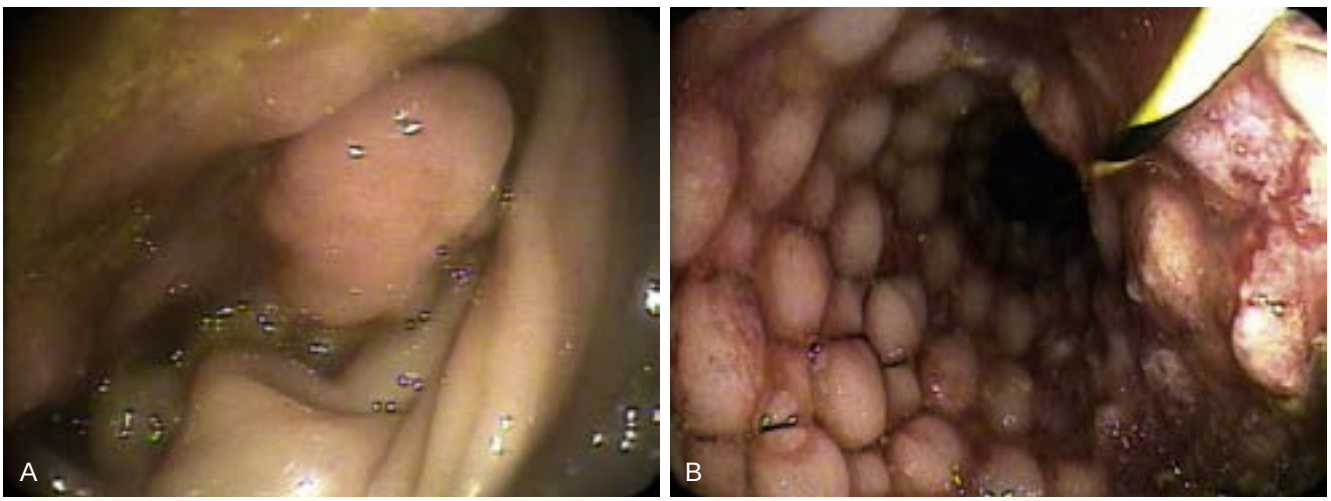


FIG. 1 **(A)** Endoscopic view of obstructing proximal rectosigmoid adenocarcinoma. (**B**) Endoscopic view of obstructing rectosigmoid adenocarcinoma followed by immediate poststent deployment. Endoscopic view with decompression of the luminal obstruction.

3. Nutritional optimization
4. Improvement of surgical outcomes, including reduction of complication rates, shortening hospital stays, and increasing rates of primary anastomosis
5. Assessment and optimization of underlying comorbid medical illnesses
6. Reduction of morbidity and mortality associated with surgery
7. Increasing time for optimal staging workup and administration of neoadjuvant therapy

Initial results for the use of SEMS as a BTS for left-sided MCO were promising. Prior meta-analyses showed that BTS stenting was associated with lower complication rates, higher primary anastomosis rate, and lower permanent stoma rates compared with emergency surgery. However, subsequent randomized clinical trials (RCTs) comparing preoperative SEMS to emergency surgery showed conflicting results in terms of adverse events and oncologic safety. The hypothesis was that placement of SEMS may cause microperforations that result in peritoneal seeding and increase the risk of metastatic spread.

Despite superior short-term outcomes, data from nonrandomized and retrospective studies raised concerns of long-term oncologic outcomes in patients with potentially curable disease who underwent BTS stenting. There was thus a shift in the guideline recommendations, with many advising against stenting between 2014 and 2016 including the European Society of Gastrointestinal Endoscopy (ESGE). However, several more recent studies have reported that stenting does not compromise oncologic outcomes. The results from the recent multicenter randomized controlled trial by Arezzo et al. (ESCO trial, 2020) allowed better analysis of the long-term outcomes from BTS stenting. This was a multicenter RCT in which patients with left-sided malignant large bowel obstruction were randomized to receive either BTS stenting or emergency surgery. The median follow-up was approximately 3 years, and no significant differences were observed in the BTS stenting group compared with the emergency surgery group in terms of overall survival, time to progression, and disease-free survival. The authors postulated that previously reported high rates of stent-associated perforation were caused by variation in operator experience.

A more robust meta-analysis by Foo et al. (2019) included seven RCTs comparing the safety of preoperative colonic stents versus emergency surgery among 448 patients with acute left-sided MCO. Notably, three of the seven RCTs were prematurely terminated. Two RCTs were terminated because of a high perforation rate in the BTS stenting arm, and one RCT was terminated because of a high anastomotic leakage rate in the emergency surgery arm. The overall complications were significantly lower in the SEMS group (RR = 0.605; $P = 0.032$). The overall 30-day mortality rate was similar in both groups (RR = 0.963; $P = 0.918$); however, the overall recurrence rate was significantly higher in the SEMS group (37.0% vs. 25.9%; RR = 1.425; $P = 0.049$). Specifically, the systemic recurrence in the SEMS group was 25.3% versus 15%, while the locoregional recurrence was not statistically significant between the groups. There was also no difference in 3-year disease-free survival or 3-year overall survival between the groups. The findings by Foo et al. were in line with the results of a meta-analysis by Spannenburg et al (2020), which showed that SEMS as a BTS had significant advantages in terms of short-term surgical outcomes but no significant difference in long-term outcomes in 3- and 5-year disease-free survival and overall survival. Additionally, SEMS placement was found to have a lower 30-day mortality rate, lower overall complication rate, less cumulative blood loss, and a higher chance of receiving a primary anastomosis, avoiding the need for a stoma with a shorter length of hospital stay.

The previous lack of high-quality evidence has limited the ability of clinicians to elucidate the best management strategy in terms of morbidity, mortality, and long-term oncologic outcomes. Recent guidelines have again begun advocating stenting as a BTS including the updated 2020 ESGE guidelines that now recommend colonic stenting as a BTS to be discussed, within a shared decision-making process, as a treatment option in patients with potentially curable left-sided obstructing colon cancer as an alternative to emergency resection. This is also supported by the American Society of Gastrointestinal Endoscopy (ASGE) guidelines. Among the surgical societal guidelines, the National Institute for Health and Clinical Excellence (NICE) and the World Society of Emergency Surgery (WSES) have advocated the use of SEMS in acute left-sided MCO, especially in centers with considerable expertise. The Eastern Association for the Surgery of Trauma (EAST) conditionally recommends SEMS in comparison with open surgery, when available, as it has shown to decrease mortality and decrease emergency procedures.

Although more long-term data are necessary to confirm the safety of SEMS as a BTS, it is important to understand that stenting should only be considered at specialized centers after multidisciplinary discussions among the endoscopy, surgical, and oncology teams.

Palliative Stenting

Patients with unresectable neoplasia carry a poor prognosis and are considered high risk for surgery given their comorbidities and poor functional status. Thus, the goal for treating these patients is to prolong survival and improve QoL by avoiding the need for permanent colostomy. SEMS placement helps achieve this goal. In the palliative setting, the surgical and gastroenterology guidelines are more consistent, recommending stenting as the preferred alternative to decompressive surgery.

Abelson et al (2017) conducted a large database cohort study among 345 patients and found no differences in the rates of post-procedure complications between patients with palliative stenting and those with a stoma. Palliative stenting was associated with a shorter length of stay, lower rates of discharge to a rehabilitation or nursing facility, and reduced hospital costs. A recent systematic review and meta-analysis of RCTs by Ribeiro et al. (2018) comparing the use of SEMS to emergency surgery solely for palliative intent reported similar 30-day mortality, mean survival, length of ICU stay, and rate of early complications between both groups. Although surgery was associated with a higher clinical success, SEMS resulted in a shorter hospital stay and lower rates of permanent colostomy (14.3% vs. 86.1%). Early complications of SEMS (perforation, migration, and obstruction) were observed in 36.5% of patients, while surgical complications (nonfunctioning ostomy, suture dehiscence, and intestinal volvulus) were observed in 24.1% of patients.

A multidisciplinary approach regarding the risks and benefits of palliative SEMS placement is paramount and should be undertaken in the context of a patient's overall outlook, goals of care, and expected subsequent oncologic therapy. Patient selection should be dictated by a multidisciplinary consultation or tumor board meeting. Palliative SEMS placement can complement new chemotherapies to improve survival and QoL of patients with unresectable colorectal neoplasia. Lastly, prophylactic colonic stent placement is not recommended in patients who are not yet symptomatic.

Extrinsic Malignancy

The majority of colonic obstructions are caused by intraluminal cancer. Rarely, extracolonic malignancy may result in extrinsic compression of the colonic lumen and result in obstruction. The most common causes include gynecologic (ovarian and uterine) malignancies, bladder cancer, advanced gastric cancer, or metastatic lesions to the pelvis.

Most often, these patients have limited surgical options because of their advanced disease with reduced life expectancy. Management is challenging as a result of several factors: (1) Tumors are multifocal, compressing a long segment of large bowel, and often associated with peritoneal carcinomatosis, and (2) most patients have an extensive surgical history with dense pelvic adhesions or have had prior

exposure to radiotherapy. The technical and clinical successes of stenting are lower when compared with primary colorectal tumors. Proper patient and family counseling is key in setting a realistic expectation and preparing the patient for the potential need for surgical intervention in case of an immediate technical failure or long-term clinical failure.

Benign Colonic Disease

Benign colonic strictures resulting in clinically significant obstruction can be caused by factors related to diverticulitis, inflammatory bowel disease, ischemia, radiation, postoperative anastomotic strictures, or complex colorectal fistulas including colovesical and colovaginal fistulas. Anastomotic strictures are known to be the most common complication following colonic surgery, seen in up to 30% of cases. The bulk of scientific literature on the management of benign colonic strictures stems from Crohn's disease strictures, which are usually found at the ileocecal valve or at the surgical anastomoses. The available data on management of strictures from other etiologies, such as diverticular disease, colonic ischemia, and radiation injury, are limited.

The morphology of benign strictures differs from malignant ones in that they are associated with increased fibrosis and scarring; thus, therapy is more challenging. Some of the endoscopic therapies include endoscopic balloon dilation (EBD), intralesional steroid injections, SEMS placement, endoscopic incisional therapies, and more recently, placement of a lumen-apposing metal stent (LAMS). Graded EBD is the recommended initial treatment for benign strictures and should be considered before alternative endoscopic or surgical therapies. On one hand, balloon dilation has a high clinical success exceeding 88% (Fig. 2), but on the other hand it has a high recurrence rate of 30% to 88%, often requiring redilations. Strictures remain refractory in >20% of cases and may eventually require surgical revision. Patients with complex anastomoses or multiple strictures are less likely to have favorable treatment outcomes compared with those with a short (<4 cm) focal stricture in a straight colonic segment. In patients with Crohn's disease, it is preferable to avoid dilation in the setting of poor prognostic factors for response to dilation, such as active inflammation, presence of large ulcers within a stricture, or smoking. Intralesional steroid injection is a known adjunct that can enhance the effectiveness of balloon dilation, reducing the time to redilation, and should be considered, especially in cases of acute inflammatory strictures.

On the basis of paucity of data and heterogeneous studies, SEMS should not be used as first-line therapy for benign strictures. Uncovered colonic SEMS are typically not removable and may predispose patients to long-term complications. The use of fully covered self-expandable metal stents (FCSEMS) in benign colonic strictures is not FDA approved; however, off-label use of FCSEMS could be considered in refractory or recurrent benign colonic strictures. Some of their drawbacks include patient intolerance, iatrogenic stricture formation, and a high rate of early stent migration of up to 40%, which may reduce long-term clinical success. Recently, endoscopic suturing of FCSEMS to overcome migration has been used, but

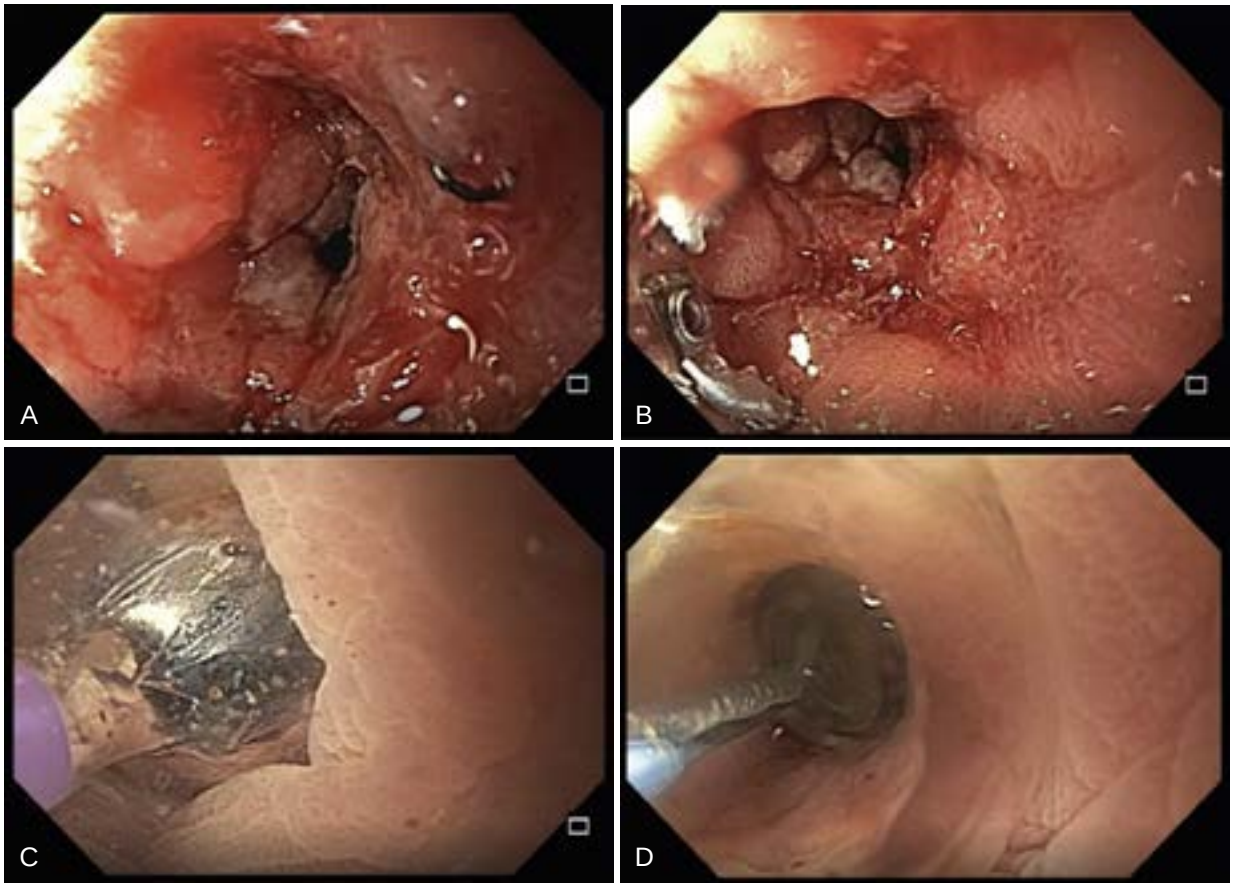


FIG. 2 Endoscopic balloon therapy for benign strictures. **(A)** History of colonic diverticulitis status after sigmoid colectomy and colostomy followed by takedown complicated by stricture at left-sided colorectal anastomosis with erythema and edema. **(B)** The stricture was approximately 3 mm in width (compared with opened biopsy forceps). **(C)** A long 0.035-inch guidewire was passed across the stricture, and a through-the-scope dilating balloon was used to dilate the stricture to 11 mm. **(D)** Water was infused, and the balloon was pulled close to the scope lens to enable visualization of the lumen of the stricture during dilation. *(From Copland AP, Wang AW. Clinical Gastrointestinal Endoscopy (3rd ed.). Chapter 40: Colonic Strictures.)*

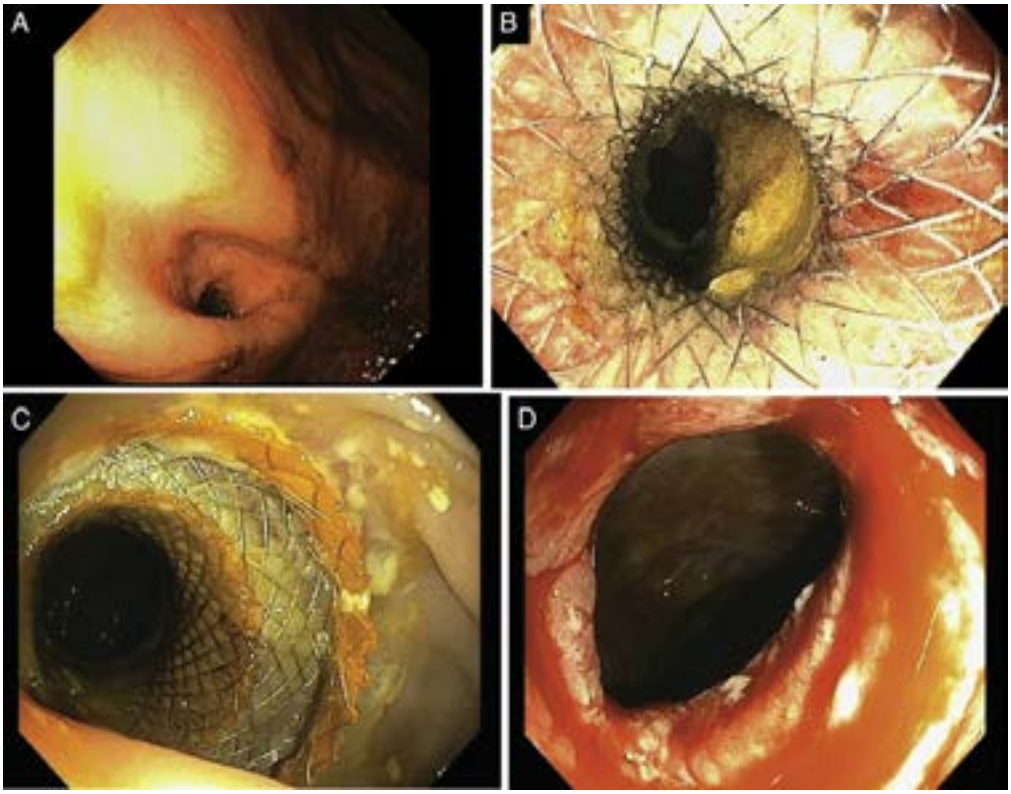


FIG. 3 Lumen-apposing metal stent for benign colonic stricture from Crohn's disease. **(A)** Crohn's disease–related high-grade stricture. (**B** and **C**) Endoscopic view of fully covered lumen-apposing, self-expanding metal stent (AXIOS; Boston Scientific). **(D)** Stricture following removal of lumen-apposing metal stent showing significant improvement. *(From Clinical Gastroenterology and Hepatology Image of the Month: Treatment of Crohn's Disease Anastomotic Stricture with a Lumen-Apposing Metal Stent. Jordan E. Axelrad, Simon Lichtiger, Amrita Sethi. Published May 18, 2017. Figures A, B, and D: doi.org/10.1016/j.cgh.2017.05.016.)*

this procedure is expensive and technically difficult and should be performed by experienced endoscopists. Caruso et al. (2015) performed a retrospective analysis of 16 patients who had postsurgical anastomotic colorectal strictures that were refractory to endoscopic dilation and underwent stent therapy, and they reported a 100% technical and early clinical success with median follow-up of 21 months. Prolonged clinical success was achieved in 9/16 (56%) cases. There were no major complications, including perforation and bleeding. Stent migration occurred in 3 (19%) cases, and a larger median stent diameter was significantly associated with a more successful clinical outcome (26 mm vs. 20 mm, $P = 0.006$). In certain clinical situations, covered esophageal stents have also been used in an off-label manner to treat benign colonic strictures. Unfortunately, most covered esophageal stents come on a stiff introducer (ranging from 16Fr to 24Fr in size) and within short catheters and must be passed over a guidewire, not through the scope channel (TTS), thus limiting their use to left-sided colonic strictures. However, one commercially available covered esophageal stent in the United States made by Taewoong Medical (Niti-S Esophageal TTS, Gyeonggi-do, South Korea) comes on a 10.5Fr flexible catheter that can be deployed through the channel of a therapeutic gastroscope, which might enable successful covered metal stenting of difficult to reach or angulated colonic strictures.

Endoscopic incisional therapies using a sphincterotome or a needle-knife to perform strictureplasty allows for controlled radial mucosal incisions along the circumference of the stricture. Whereas there is evidence that this may be a viable approach in select cases, such procedures should only be performed by interventional endoscopists with considerable expertise and in settings with the appropriate radiologic and surgical backup.

Lastly, the use of a LAMS for benign gastrointestinal strictures has emerged as an alternative to other traditional endoscopic therapies. The unique design, short length, saddle shape, and wide flange at each end are design features that facilitate stent retention, which improves patient tolerance and makes them less prone to migration (Fig. 3). Their safety and long-term efficacy data are lacking; however, they might be an alluring prospect for benign strictures. With an increasing interest in endoscopic intraluminal surgery, newer technologies will undoubtedly become available in the future. The management of colonic obstruction is summarized in Figure 4.

CONTRAINDICATIONS TO COLONIC STENTS

The absolute contraindications to stent placement include the presence of colonic perforation or severe colonic ischemia with impending necrosis, which can be assessed with a thorough physical examination and radiologic imaging. Other contraindications are summarized in Table 1.

Technical Considerations

Types of Colonic Stents

Currently all commercially available SEMS for MCO are uncovered because of the high rate of migration associated with covered SEMS. Most commercially available SEMS work with the same mechanism; the main features to consider include stent dimensions, material, design, and delivery system. The various types of colonic stents are summarized in Table 2.

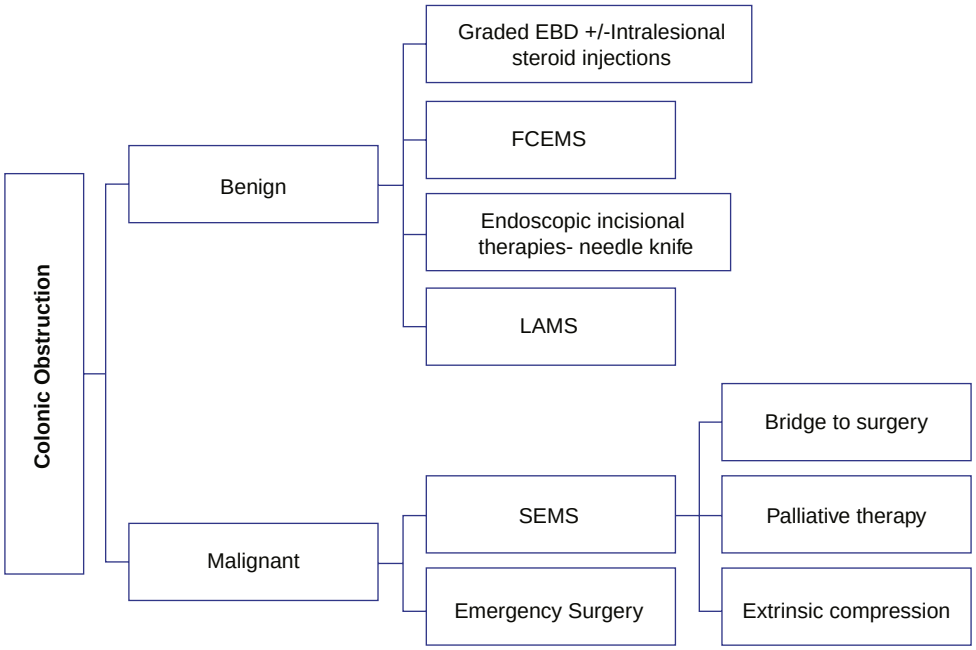


FIG. 4 Summary of management of colonic obstruction/stricture.

TABLE 1 Contraindications to SEMS Placement

Contraindication	
Absolute	• Colonic perforation or severe colonic ischemia with impending necrosis
Relative	• Distal rectal lesions with 5 cm from the dentate line (stents crossing the anal verge can induce severe pain, tenesmus, bleeding, and risk of migration) • Presence of diffuse peritoneal carcinomatosis (higher failure rate) • Persistent severe coagulopathy (risk of bleeding) • Patients on chemotherapy with antiangiogenic drugs (such as bevacizumab) • Tumors close to the anal verge (<5 cm)
Special considerations	• Lesions in tortuous or angulated portions of the colon, such as the splenic flexure (technically challenging and may have a higher failure rate) • The use of prophylactic stents in patients with metastatic disease to prevent potential obstruction is not recommended. • Right-sided or proximal colonic lesions are better managed with surgical resection with primary anastomosis or stoma creation. Although SEMS placement is performed in some palliative cases, it is not recommended given the technical challenges and non-inferiority to surgery.

SEMS, Self-expandable metal stent

TABLE 2 Various Types of Colonic Stents

Manufacturer	Model Name	Stent Covering	Delivery System	Material	Body Diameter/Flange Diameter (mm)	Length (mm)
Boston Scientific	WallFlex colonic*	Uncovered	TTS, 10F	Nitinol	22, 25/27, 30	60, 90, 120
	Ultraflex precision colonic*	Uncovered	Non-TTS, OTW, 16F	Nitinol	25/30 (proximal flange)	57, 87, 117
	Wallstent colonic and duodenal endoprosthesis*	Uncovered	TTS, 10F	Stainless steel	20, 22/Minimal, no flare	60, 90, 120
Taewoong Medical	Niti-S enteral colonic D type*	Uncovered	TTS, 10F	Nitinol	18, 20, 22, 24, 26, 28/, no flare	60, 80, 100, 120
	Niti-S Enteral Colonic S-type*	Partially covered	TTS, 10F	Nitinol	20, 22/28, 30	60, 80, 100,120
		Partially covered	NON-TTS	Nitinol	22, 24, 26, 28/30, 32, 34	60, 80, 100, 120

Continued

TABLE 2 Various Types of Colonic Stents—cont'd

Manufacturer	Model Name	Stent Covering	Delivery System	Material	Body Diameter/Flange Diameter (mm)	Length (mm)
Cook Endoscopy	Evolution colonic*	Uncovered	TTS	Nitinol	25/30	60, 80,100
M.I. Tech	Hanarostent colon/rectum*	Uncovered and fully covered	TTS: 10.2F, 10.5F; NON-TTS 24F	Nitinol	20, 22, 24/26, 28, 30	60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160
	Choostent colon/rectum (CCC)	Fully covered	NON-TTS	Nitinol	22, 24/30, 32, both ends flanged; available symmetric and asymmetric	100, 180
EndoChoice	Bonastent	Uncovered/partially covered	TTS, 10F and 12F	Nitinol	22, 24, 26	60, 80, 100
ELLA-CS	SX-ELLA colorectal (Enterella)	Uncovered and covered	Non-TTS, 15F (uncovered), 18F (covered)	Nitinol	20, 22, 25	82, 90, 113, 135
S & G Biotech	EGIS colorectal	Covered single or double	TTS, 10F	Nitinol	20, 22	60, 80, 100, 120
	Hercules SP colorectal stent dual type	Inner uncovered, outer partially covered Composed of two separate stents sequentially deployed	Non-TTS	Nitinol	28 outer, 18 inner	110, 130, 150, 170, 190 (outer)
Leufen Medizintechnik OHG	Ecostent	Uncovered	Non-TTS	Nitinol	30/36 both ends flared	8, 10
MICRO-TECH Europe (Dusseldorf, Germany)	MICRO-TECH colon and rectum stent	Uncovered and partially covered	TTS, non-TTS	Nitinol	30/36 25/30 (covered)	8, 10, 12

*FDA approved

Stent Dimensions

The uncovered stents in the United States come in sizes that fall between 5.7 and 12 cm in length and mid-body diameters of 20 to 30 mm (with variably flanged ends that are wider than the width of the stent body) after deployment. They come within a 10Fr catheter that fits through the accessory channel of an adult colonoscope or a therapeutic gastroscope (with a channel diameter of at least 3.7 mm), which allows for the stent to be placed using both endoscopic and fluoroscopic visualization.

Stent Material

SEMS are composed of a radiopaque, woven, metal mesh with a cylindrical shape that exerts self-expansion forces. In their unexpanded form, they fit through the channel of an endoscope. Following deployment to the desired location, they expand to oppose the luminal surface of interest. Although the basic delivery system and deployment mechanism are identical, stents are classified based on their coating and manufacture material.

Stents are made from stainless steel or other alloys such as Nitinol (comprising nickel and titanium) or Elgiloy (comprising cobalt, chromium, and nickel). Nitinol is the most widely used metal alloy. Its main advantage over other stent materials is its malleability at low temperatures and strong radial forces at body temperature without losing its flexibility (Fig. 5). Stainless steel stents are relatively stiff and may affect the quality of imaging studies such as MRI. Stents made of Elgiloy are thinner, more elastic, and more flexible, and they are MRI-compatible with less imaging artifact.

Covered versus Uncovered Stents

Uncovered stents have bare wires, while covered stents have a silicone membrane over the bare wires. Covered stents can be subdivided into fully and partially covered stents. Although covered stents reduce the risk of tumor ingrowth and can be used to seal fistulas, fully covered stents have less anchoring power and an increased risk of migration compared with uncovered stents. Partially covered stents with flared uncovered segments at both ends were developed to overcome migration risk. Patency rates between uncovered and covered SEMS are thought to be similar, however more data are required to validate these findings. In a systemic review and meta-analysis by Mashar et al. (1 RCT and 9 observational studies including 753 patients) comparing covered and uncovered stents in management of MBO, uncovered stents were associated with a lower risk of complications (RR 0.57, 95% CI 0.44–0.74, $P < 0.0001$), tumor overgrowth (RR 0.29, 95% CI 0.09–0.93, $P = 0.04$), and stent migration (RR 0.29, 95% CI 0.17–0.48, $P < 0.00001$); longer duration of patency (MD 18.47, 95% CI 10.46–26.48, $P < 0.00001$); lower need for stent reinsertion (RR 0.38, 95% CI 0.17–0.86, $P = 0.02$); and higher risk of tumor ingrowth (RR 4.53, 95% CI 1.92–10.69, $P = 0.0008$). Rates of technical success (RR 1.02, 95% CI 0.99–1.04, $P = 0.21$), clinical success (RR 1.03, 95% CI 0.98–1.08, $P = 0.32$), perforation (RD 0.01, 95% CI 0.03–0.02, $p = 0.65$), bleeding (RD 0.00, 95% CI 0.03–0.03, $P = 0.98$), stool impaction (RR 0.56, 95% CI 0.12–2.04, $P = 0.38$), and stent obstruction (RR 2.23, 95% CI 0.94–5.34, $P = 0.97$) were similar. These results concluded that uncovered stents were superior in the management of MBO. It is worth mentioning that only uncovered colonic SEMS are available in the United States.

Technical Aspects of Stent Deployment (Box 1)

Pre-stent placement

Before performing colonic SEMS placement, one should assess the location and morphology of the stricture (Fig. 6). The imaging modalities commonly used include a retrograde water-soluble contrast enema (barium enema or Gastrografin) (Bracco Diagnostics Inc., Monroe



FIG. 5 Various types of self-expandable uncovered metal colonic stents. *(From Baron TH, Wong Kee Song LM, Repici A. Role of self-expandable stents for patients with colon cancer (with videos). Gastrointest Endosc. 2012;75:653–662.)*

Township, NJ) or cross-sectional imaging (CT scan). These imaging modalities can help delineate the anatomy (number, length, location, and degree of stricturing) and in some cases reveal synchronous proximal lesions and rule out the presence of a leak or perforation. CT scans can also assist with defining the surrounding soft tissue, lymph nodes, and more distant organs, which can be critical in cases of mass lesions, as well as in inflammatory bowel disease, which can be further complicated by fistulas or abscesses. Patients are usually given one or two cleansing enemas to prepare the distal colon. Oral bowel prep should be avoided as it may worsen the symptoms of obstruction. In some cases, a diagnostic colonoscopy is warranted in determining the etiology of a stricture as it can help obtain sampling for pathologic diagnosis.

In patients with complete obstruction and dilated colon proximally, prophylactic intravenous antibiotic therapy is recommended by the surgical societies. It is postulated that during insufflation for stent deployment, the increase of wall tension and intestinal barrier damage may cause microperforations resulting in bacterial translocation. However, several studies report a negligible risk of infection within 48 hours post-stenting. Likewise, Kim et al. performed a propensity score-matched analysis of prophylactic antibiotics for colonic stenting that did not show significant differences in infectious complications (such as fever, bacteremia, and systemic inflammatory response syndrome) between patients who received antibiotic prophylaxis and those who did not. The ESGE and ASGE do not recommend the routine use of antibiotic prophylaxis.

Stent Deployment Process

The procedure is usually carried out in the endoscopy suite or operating room depending on the physician performing the procedure.

BOX 1 Technical Aspects of Stent Placement

Prerequisites

Thorough history and physical examination; rule out perforation
Assess location and morphology of stricture with contrasted imaging:
Retrograde barium/Gastrografin enema or CT with contrast
Avoid oral mechanical bowel prep; consider enemas
Diagnostic colonoscopy (some cases)

Intraprocedural

Endoscopy suite or operating room
General anesthesia preferred
Left lateral position
Therapeutic gastroscope or colonoscope (depending on location)
CO_2 insufflation

Stent Deployment

Combined endoscopy and fluoroscopy technique
TTS stent deployment with guidewire

Post-stent care

Confirm large bowel decompression on endoscopy
Post-procedure imaging (x-ray or CT)
Repeat x-ray in 2 days to confirm stent expansion and position

TTS, Through the scope.



FIG. 6 Morphology of colonic stricture with apple core lesion, pathognomic for colonic adenocarcinoma. **(A)** Barium enema showing morphology of colonic stricture. **(B)** CT abdomen and pelvis (sagittal view) with intravenous and intraluminal contrast showing a colonic stricture *(arrow).* *(From Copland AP, Wang AW.* Clinical Gastrointestinal Endoscopy *3rd ed. Chapter 40: Colonic Strictures.)*

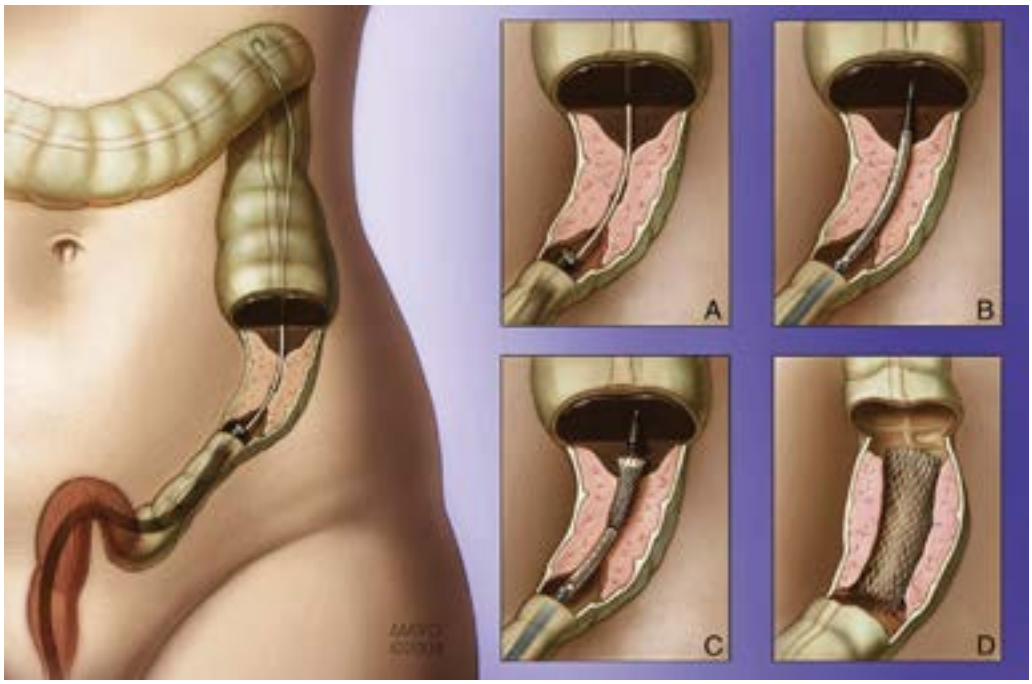


FIG. 7 Through-the-scope (TTS) colonic self-expandable metal stent placement process. The endoscope is passed to the lesion, and a guidewire is advanced across the obstruction *(far left).* **(A)** The catheter is advanced across the lesion. **(B)** The predeployed stent is advanced through the endoscope channel and across the lesion. **(C)** The restraining sheath is withdrawn. **(D)** The stent is fully deployed. *(From Baron TH, Wong Kee Song LM, Repici A. Role of self-expandable stents for patients with colon cancer (with videos). Gastrointest Endosc. 2012;75:653–662.)*

Anesthesia choice is based on physician preference, but intubation is recommended in cases of acute colonic obstruction given the risk of aspiration during the procedure. Patients are placed in the left lateral position to facilitate passage of the endoscope. For left-sided colonic strictures, a therapeutic gastroscope is often the instrument of choice, but for more proximal or right-sided strictures, an adult colonoscope may be required. CO_2 insufflation is preferred over air as CO_2 is more rapidly absorbed and leads to reduced abdominal discomfort and may decrease the risk of perforation.

A SEMS can be loaded using two different delivery systems: through-the-scope (TTS) stents or over-the-wire (OTW) stents. TTS stents are traditionally loaded into 10Fr catheters, introduced over the guidewire, and placed across the stricture under endoscopic and fluoroscopic guidance. OTW stents are passed over the guidewire and placed under fluoroscopic visualization. The use of simultaneous side-by-side endoscopy with a small-caliber endoscope is recommended in some cases but not mandatory. This technique is preferred in case of rectal or sigmoid strictures, acute angulations, or other conditions with poor endoscopic visualization. Both fluoroscopic and endoscopic guidance is preferred as fluoroscopy not only assists in defining the stricture but also adjunctively guides stent placement. TTS colonic SEMS placement is illustrated in Figure 7 and Video 1.

TABLE 3 Technical Tips for Stent Deployment and Guidewire Passage

Instrument	Technical Tip
Triple-lumen biliary occlusion (stone retrieval) catheter	Method 1: Catheter with the balloon inflated to 12–15 mm and positioned just distal to or impacted at the obstruction site followed by stricturogram Method 2: Biliary stone retrieval balloon passed beyond the stricture and then inflated to a large-diameter 12–15 mm, and balloon is withdrawn until it abuts the proximal shelf of the stricture meeting resistance. The endoscopist then holds the catheter at the biopsy port. The balloon is deflated and withdrawn while keeping the finger position on the catheter. When the balloon is seen endoscopically on the distal aspect of the stricture, the distance from the endoscopist's fingers to the biopsy port corresponds to the length of the stricture.
Guidewires	Using hydrophilic biliary guidewires (e.g., Glidewire; Boston Scientific)
Cap, sphincterotome	For lesions at flexures or corners, a clear cap to obtain a more en face view and a sphincterotome, preferably a rotatable sphincterotome (e.g., Autotome RX; Boston Scientific), are used to orient the catheter in the direction of the lumen.
Stent deployment	SEMS should be of suitable length to bridge the stricture and extend at least 2 cm on each side of the obstruction. Keep in mind the degree of SEMS shortening during deployment and stent migration away from the endoscope.

On reaching the stricture, a guidewire with a hydrophilic soft/floppy tip (typically a 0.035-inch-diameter guidewire for added stiffness) is passed across the stricture. Careful guidewire passage and measuring the appropriate stricture length are key steps to technical success of the stent deployment process. A few additional technical tips are described in Table 3.

Deployment of TTS uncovered or covered metal stents follows similar principles and involves an assistant deploying the stent while the endoscopist pulls back on the restraining catheter until the stent is released. The stent is then deployed by withdrawing the constraining sheath or unraveling string (depending on the device). Most colonic SEMSs deploy from a proximal (oral) to distal (rectal) fashion. Although there is no validated rule for stent deployment, it is recommended that the SEMS should be of suitable length to bridge the stricture and extend at least 2 cm on each side of the obstruction once the stent is deployed. One must also account for the degree of shortening that occurs during deployment and stent migration away from the endoscope. If stent coverage is inadequate, an additional stent can be deployed overlapping the existing stent. It is important to keep the wire in place across the lesion until the final position of the stent is assessed radiographically because passing a wire through a newly deployed stent can be technically challenging. In patients who present with complete colonic obstruction, consideration should be given to leaving the guidewire in place after stent deployment to pass a colonic decompression tube through the stent and into the proximal bowel if immediate passage of stool does not occur after stent placement. For right-sided colonic obstruction, stents can also be successfully placed proximally, although the lesions typically require a TTS SEMS placed via an adult colonoscope.

After stent deployment, additional balloon dilation is not recommended because it is associated with a high risk of perforation. Because of the nature of the self-expansion, stents are allowed to slowly expand over time. The peristaltic movements of the colon after decompression may facilitate full expansion. Immediately after stent placement, the enema examination can be repeated to document post-stenting patency and correct positioning, although this is not always needed.

FOLLOW-UP CARE

Immediately following stent placement, large bowel decompression, confirmed on endoscopy, is suggestive of successful deployment of a stent. If a nasogastric tube is present, it can often be removed the following day. A postprocedural abdominal radiograph or CT is obtained immediately after stent placement to confirm position and exclude free air (Fig. 8). An abdominal x-ray is repeated within 24 to 48 hours when full expansion of the stent is expected. A liquid diet can typically be initiated within 24 to 48 hours of stent placement in most patients. Several days are needed for complete decompression to a normal-sized colon.



FIG. 8 Postprocedural abdominal radiograph demonstrating a well-positioned transverse colon stent across a malignant stricture.

OUTCOMES AND ADVERSE EVENTS

The mortality rate of colonic stenting is roughly 1.5% to 3%. Technical success (immediate or short-term success) is defined

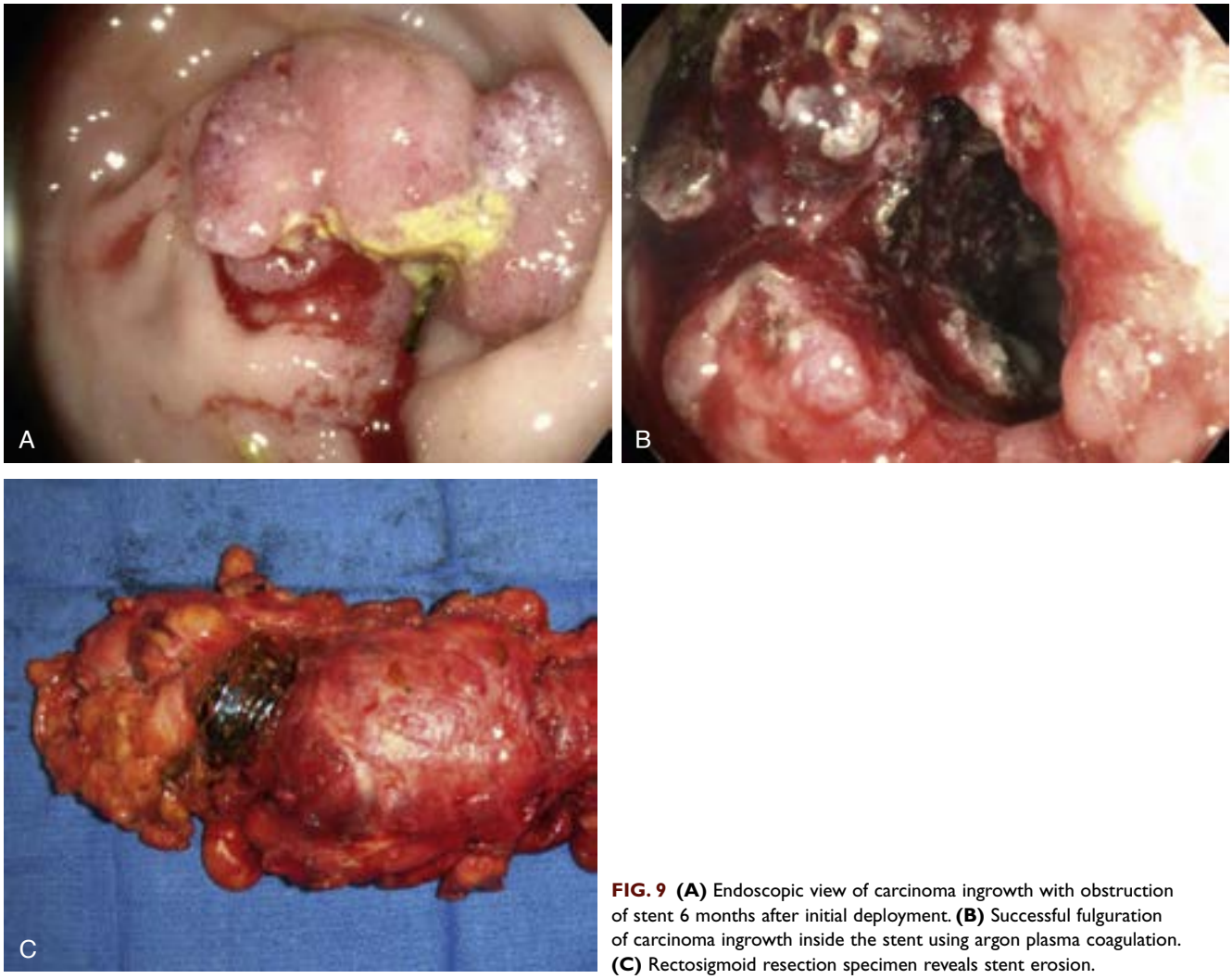


FIG. 9 **(A)** Endoscopic view of carcinoma ingrowth with obstruction of stent 6 months after initial deployment. **(B)** Successful fulguration of carcinoma ingrowth inside the stent using argon plasma coagulation. **(C)** Rectosigmoid resection specimen reveals stent erosion.

as the ability to safely deploy and properly position the stent across the stricture without any immediate complication. Clinical success (long-term success) is defined as the ability to achieve long-term decompression without the need for operative intervention to treat long-term failure of the stent or related complications. Colonic stenting has a high technical success of 80% to 100% and clinical success of 70% to 100%. The rates of complications are variable across studies but can be broadly divided into early (<2 weeks) and late (>2 weeks) complications, with an overall complication rate of 10% to 15%.

Early Complications

Perforation

The most feared complication is perforation. The rate of perforation in malignant obstruction is 6% across various studies, while that of silent or microperforations is up to 14%. Angiogenesis inhibitors (e.g., bevacizumab) are independent risk factors of perforation, even in the absence of stenting, and are known to increase the rate of perforation to 12.8%. The ESGE does not recommend the combination therapy of stent with antiangiogenic drugs (Fig. 9). Perforation rates are highest in colonic SEMS deployment for benign strictures (18%). When large perforations occur, they are best managed operatively. Microperforations may be managed with bowel rest and intravenous antibiotics.

Stent Migration and Failure

Failure of the stent to resolve the obstruction and early stent migration (seen in 4%–11.7%) should raise suspicion for stent malposition (inadequate stricture coverage), incomplete expansion, or undetected synchronous tumors. Stent migration rates are determined by the type of stent deployed, the degree of stenosis, the proximal and distal clearance, and the flare diameter. Short stents, smaller-diameter stents (<25 mm), and covered stents have higher rates of migration. SEMS migration can typically be managed endoscopically by removing the migrated stent with the goal of either placing a larger stent or a different type of stent that might be less prone to migration. Other alternatives to replacing a migrated SEMS include observation (particularly if the stricture has become more patent following stenting) or more definitive surgical intervention.

Abdominal/Rectal Pain and Incontinence

Abdominal/rectal pain and incontinence may occur if stents are placed within 5 cm of the anal verge. Pain is also commonly caused by mucosal irritation from the stent itself. Bleeding may occur in up to 5% of patients. This is usually mild to moderate in severity, however endoscopic interventions are recommended before surgery.

Late Complications

Late stent migration can be seen in cases following chemotherapy or radiotherapy with subsequent tumor shrinkage.

Occlusion by Fecal Impaction and/or Tumor Ingrowth

Tumor ingrowth has been reported in 15% of patients. Although most patients currently treated with palliative stents succumb to their

disease before obstructing, the impact of newer chemotherapeutic agents on long-term survival may affect the rate of this long-term complication. Tumor ingrowth and fecal impaction of the stent can be managed endoscopically by placing another stent through the occluded stent.

CONCLUSION

Colonic SEMS are an important part of the treatment armamentarium of managing obstructing colorectal cancer. It is a relatively safe and effective procedure that is used for palliation of obstruction and as a bridge to a safer, less morbid surgery. As newer technologies and medical therapies continue to evolve, surgeons and gastroenterologists must work in close collaboration to appropriately select patients who would most benefit from these interventions.

Suggested Readings

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Management of Acute Colonic Pseudo-Obstruction (Ogilvie's Syndrome)

Marshall S. Bedine, MD

Acute colonic pseudo-obstruction (ACPO), often known as Ogilvie's syndrome, is a condition of sudden onset associated with an acute dilation of the colon with no evidence of mechanical obstruction. The syndrome was first reported by William Ogilvie in 1948.

Pathogenesis of ACPO has been thought to be related to impairment of the autonomic nervous system leading to an atonic distal colon and functional obstruction. When this occurs, colonic diameter increases with a rise in tension on the colonic wall. This, in turn, increases the risk of colonic ischemia and perforation as the colon dilates and cecal diameter exceeds 10 to 12 cm. Ischemia with or without perforation increases rapidly as the colon dilates, particularly if the duration of distention exceeds 6 days.

ACPO most often occurs in hospitalized or institutionalized patients usually with severe comorbid illness. Associated conditions include infection, cardiac disease, and inoperative trauma as well as orthopedic procedures including hip and spine surgery or after pelvic surgery. In one study, 92% of postpartum cases of ACPO were in patients following cesarean section after complicated pregnancies. The incidence of ACPO is approximately 1:1000 of hospitalized patients. If colonic ischemic or perforation occur, the mortality may be as high as 50%.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations of ACPO may occur gradually or rapidly with abdominal pain occurring in 80% of patients associated with distention. Nausea and vomiting are frequent, and constipation or even diarrhea has been reported in 40% to 50%.

Physical examination reveals a protuberant abdomen that is tympanic to percussion and associated with bowel sounds in up to 90% of patients. Fever, abdominal tenderness, and peritoneal signs are worrisome and suggest colonic ischemia or impending perforation.

The diagnosis of ACPO is made on imaging studies. CT of the abdomen and pelvis typically demonstrate proximal colon dilation with an intermediate transition zone near the splenic flexure (Fig. 1). Occasional dilation may extend to the rectum. This will exclude a mechanical obstruction. Plain abdominal films can be used to monitor interval changes of colonic dilation (Fig. 2). Contrast enemas can be hazardous and may increase the risk of perforation. Stool cultures and stool evaluation for *Clostridioides difficile* toxin should be obtained. Hypokalemia, hypocalcemia, and hypomagnesemia are common and should be corrected. The differential diagnoses include acute mechanical obstruction, toxic megacolon, and chronic intestinal pseudo-obstruction.

MANAGEMENT

Initial management of ACPO should include keeping the patient NPO, attempting decompression with nasogastric and rectal tube suction, and avoiding inciting medications such as opioids, anticholinergics, antipsychotics, cytotoxic drugs, calcium channel blockers, and clonidine (Fig. 3). Fluid and electrolyte imbalance should be corrected. Mobilizing the patient, if possible, should be considered. Positioning the patient in a prone position with hips elevated can be helpful in allowing the patient to pass gas for relief of distention. These maneuvers should be considered for 24 to 48 hours as long as the patient is undergoing frequent physical examinations and abdominal films at 12-hour intervals. The response to conservative management may vary between 20% and 92%. A surgical consultation should be obtained as soon as a diagnosis has been made to guarantee optimal care (Box 1).

When conservative management is ineffective, pharmacologic agents should be considered. The primary pharmacologic treatment of ACPO

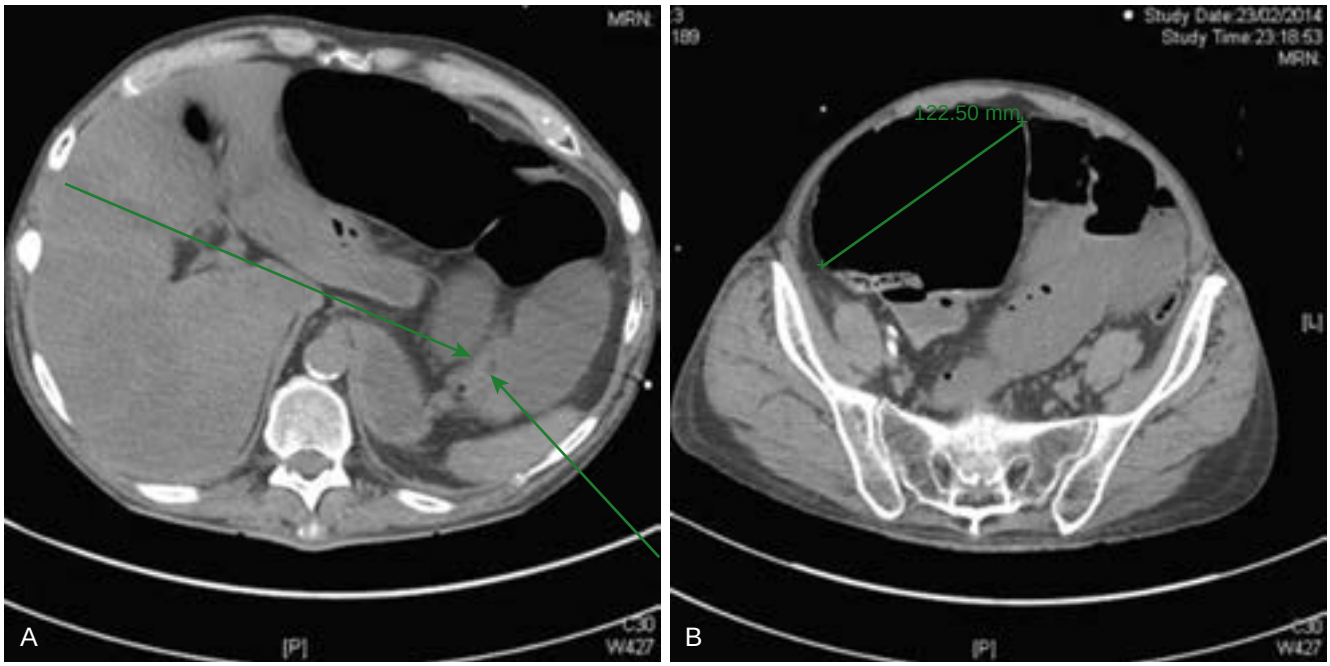


FIG. 1 CT images of colonic dilation, with arrows denoting transition point in the absence of mechanical obstruction **(A)**, consistent with Ogilvie's syndrome, and a ruler demonstrating cecal diameter at the typical threshold of concern for perforation (12 cm) **(B)**. *(From Pereira et al. Ogilvie's syndrome—acute colonic pseudo-obstruction.* J Visceral Surg. *2015;152:99–105.)*

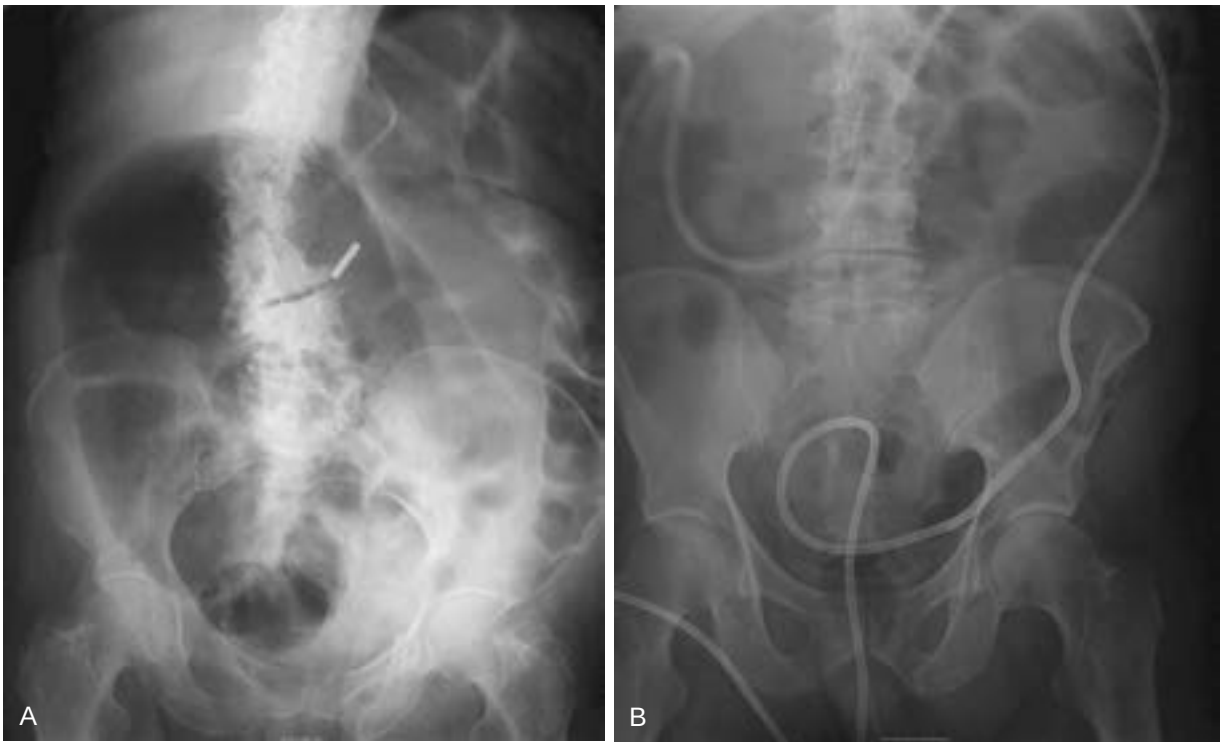


FIG. 2 Upright abdominal plain films demonstrating acute colonic pseudo-obstruction before **(A)** and after **(B)** placement of a decompression tube. *(From Saunders MD. Acute colonic pseudo-obstruction.* Best Pract Res Clin Gastroenterol. *2007;21:671–687.)*

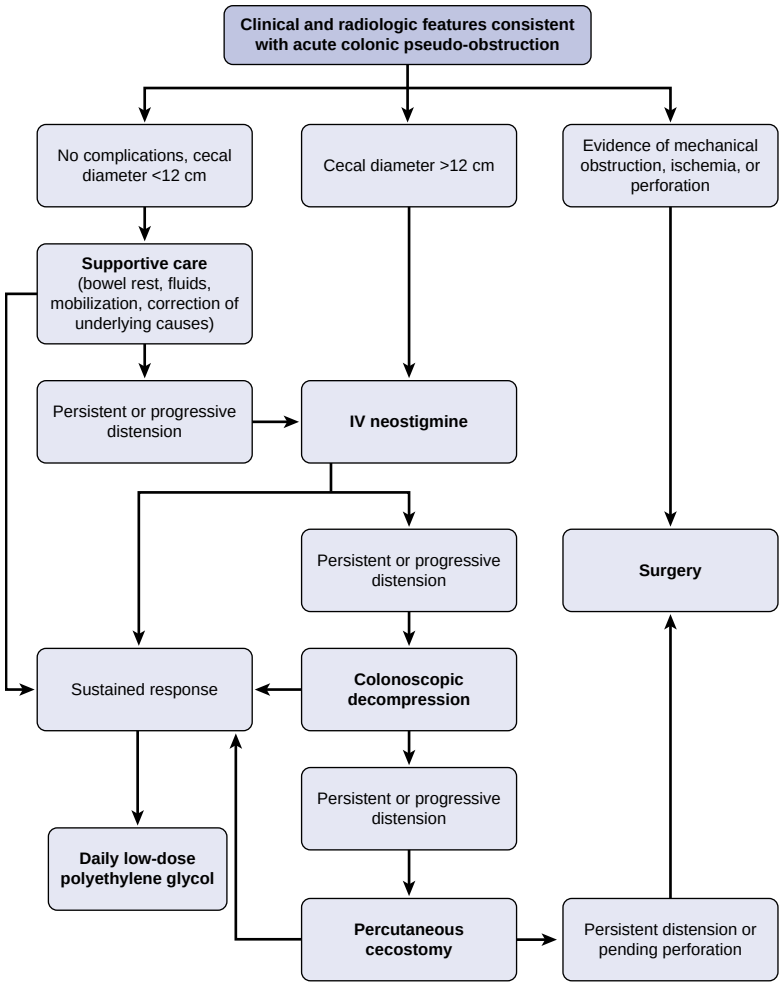


FIG. 3 Algorithmic approach to stepwise therapy in acute colonic pseudo-obstruction.

BOX 1 Conservative Management

1. Correct metabolic abnormalities
2. Follow CBC, electrolytes, serum lactate
3. Check stool for *Clostridioides difficile*
4. Decompression with nasogastric and rectal tubes
5. NPO with intravenous hydration
6. Serial imaging and physical examinations
7. Avoid opiates, anticholinergics, calcium channel blockers, and antipsychotics

is the use of neostigmine, an anticholinesterase parasympathomimetic agent. This is indicated in patients with ACPO with a cecal diameter of 12 cm who have failed conservative management. Neostigmine (2 mg) is given intravenously over a 5-minute period with constant monitoring of vital signs and electrocardiography. Patients should be supine on a bedpan as they may respond quickly with passage of gas and stool. A response will generally occur within 30 minutes. Glycopyrrolate should be available to treat bradycardia. Response to neostigmine will occur in up to 94% with the initial dose. There is a recurrence rate of about 31%. A second dose can be given no sooner than 8 hours but up to 24 hours later, which may lead to a further response of 40% to 100%. Three placebo-controlled, double-blind, randomized trials have demonstrated the effectiveness of neostigmine (Box 2).

Risk factors for neostigmine failure include male gender, younger age, electrolyte imbalance, and postsurgical status. It is recommended that regular administration of polyethylene glycol via nasogastric tube may also increase the effectiveness of treatment with neostigmine.

Neostigmine has most often been administered intravenously in a bolus, but studies have shown success with subcutaneous neostigmine or continuous infusion of 0.4 mg/h in saline over 24 hours. Subcutaneous neostigmine has been shown to result in passage of stool within a median of 29 hours. Continuous infusion of neostigmine was associated with greater bowel diameter reduction in 24 hours, and adverse events may also be diminished by continuous infusion. In one study, subcutaneous neostigmine was found to be safe and effective. Response to a bolus infusion is more rapid.

Bradyarrhythmias may occur in 5% to 10% of patients with other potential side effects being bronchoconstriction, hypotension, agitation, abdominal cramps, nausea and vomiting, salivation, and diaphoresis. Glycopyrrolate 0.4 mg may attenuate some of these side effects. Mechanical intestinal obstruction, urinary tract obstruction, or peritonitis are absolute contraindications. Particular care must be taken in patients with heart rates of <60 beats per minute, systolic blood pressure of <90 mm Hg, reactive airway disease, recent myocardial infarction, and concomitant β-blocker use. The usage of neostigmine in the setting of pregnancy has not been studied.

BOX 2 Neostigmine Therapy

1. 2 mg intravenously over 5 minutes with available glycopyrrolate or atropine
2. Consider 0.4 mg/h IV continuous infusion
3. Monitor EKG, oxygen saturation, and blood pressure
4. Adjust for renal failure if:
   - Creatinine clearance less than 50 mL/min 50%
   - Creatinine clearance of less than 10 mL/hr 75%
5. Avoid if:
   - Mechanical, intestinal, or urinary tract obstruction
   - Bradycardia less than 60 bpm or systolic blood pressure less than 90 mm Hg
   - Recent myocardial infarction
   - Peritonitis
   - β-Blocker use

Other pharmacologic agents have been used with varied response. Anecdotal reports have recommended the use of erythromycin, metoclopramide, and cisapride (not available in the United States). These drugs have yielded inconsistent results. Oral pyridostigmine, a long-acting acetylcholinesterase inhibitor, has been successful in treating some patients refractory to neostigmine. In one report, a patient was treated with methylnaltrexone, a μ-opioid-receptor antagonist. This is an option for treatment of patients who have been on opioid treatment. Prucalopride has also been reported to be successful. These drugs will require further studies before routine use can be considered.

COLONOSCOPIC DECOMPRESSION

When patients do not improve with either conservative management or infusion of neostigmine, endoscopic colonic decompression should be considered. The procedure should be done without prior preparation to decrease the risk of perforation. The risks of colonoscopic decompression include a perforation rate of 2% and mortality of 1%. The procedure can be performed without air insufflation preferably using small amounts of CO_2. Air and liquid stool can be aspirated through a large-bore suction channel. The ascending colon and cecum may not be well perfused and appear ischemic. Adequate decompression can be obtained when the colonoscope is passed to the proximal transverse colon under fluoroscopic guidance. Decompression may be effective in 50% by suction of air and liquid. Most endoscopists will pass a guidewire through the accessory channel of the colonoscope and slowly withdraw the scope under fluoroscopic guidance. A decompression tube can then be passed over the guidewire followed by low intermittent suction with saline flushes every 4 to 6 hours to decrease obstruction of the decompression tube. Repeat colonoscopy is often required due to a recurrence rate of 40%. Randomized controlled trials are not available supporting the use of decompression tubes. The use of polyethylene glycol after endoscopic decompression is recommended. There is limited data suggesting that colonoscopic decompression is superior to neostigmine infusion. Other studies suggest that both modalities are equivalent (Box 3).

PERCUTANEOUS CECOSTOMY

Among patients who are at high perioperative risk and have failed conservative, pharmacologic, and endoscopic decompression, percutaneous cecostomy (PECcecum) may be considered for colon decompression. PEC-cecum tubes can be placed endoscopically or through interventional radiology techniques with an excellent response rate. However, this is an invasive procedure with serious adverse events that include wound infection, bleeding, perforation, granuloma, and buried bumper necrosis. Such procedures should be managed by experts in interventional radiology and therapeutic endoscopy. Adequate studies of these procedures are lacking.

BOX 3 Endoscopic Decompression

1. Failure to respond to conservative management and trial of neostigmine
2. Persistent ACPO
3. Colonoscope passed to hepatic flexure or cecum
   - Avoid air-limited CO_2 infusion
   - Large bore suction of air in stool
   - Guidewire placement through accessory channel under fluoroscopy
   - Decompression tube placed over guidewire
4. Low intermittent suction
5. Flush tube with saline every 4–6 hours
6. 72-hour limit then remove tube
7. Avoid with ischemic mucosa, perforation, or peritonitis

SURGICAL THERAPY

When the previous management options are unsuccessful, surgery should be considered. These patients have a high morbidity and mortality rate with mortality in the range of 30% to 60%. Surgery may include the placement of a cecostomy tube or subtotal colectomy and stoma formation. High mortality rates are associated with those patients with ischemic disease or perforation.

SUMMARY

ACPO presents with signs and symptoms of mechanical colonic obstruction without evidence of structural lesions. It is a motility disorder that occurs primarily in hospitalized patients with comorbid medical illness or recent surgery or trauma. Diagnosis is made by performance of cross-sectional imaging. There is a high rate of complications from ischemia and perforation. Close monitoring should be done with serial imaging, bowel rest, intravenous fluids, and frequent imaging studies. If colonic distention persists or progresses, pharmacologic treatment with neostigmine should be considered followed by endoscopic colonic decompression with guided intraluminal tube placement. Further treatment may necessitate percutaneous cecostomy by experienced experts followed by either laparoscopic or open surgery. Surgery for refractory ACPO carries a high mortality rate.

Suggested Readings

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Management of Colonic Volvulus

Jose G. Guillem, MD, and Jonathan M. Stem, MD

INTRODUCTION

Colonic volvulus, or a twisting of the colon on its tethered mesenteric axis, is a rare condition that accounts for less than 5% of bowel obstructions in the United States. In other regions of the world, colonic volvulus is more prevalent, accounting for up to 50% of intestinal obstructions. It most commonly occurs in the sigmoid colon, followed by the cecum. The transverse colon and splenic flexure are additional rare sites of occurrence.

SIGMOID VOLVULUS

Sigmoid volvulus is the most common form of colonic volvulus accounting for 50% to 90% of all cases. It is associated with significant morbidity and mortality, with mortality rates approaching 10%. There is a 2:1 male predominance as well as an association with increasing age. Patients typically present in the seventh decade of life or beyond. In addition to advancing age, many factors including diet, race, diabetes, pregnancy, and constipation/dysmotility increase one's risk for sigmoid volvulus. Institutionalized patients as well as those with psychiatric and neurologic disorders are at a greater risk secondary to gastrointestinal dysmotility resulting from behavioral and pharmacologic factors.

Presentation is analogous to that of any large bowel obstruction: obstipation, abdominal distention, pain, and cramping. Early in the patient's course, there is often a lack of systemic manifestations. Tachycardia, hypotension, and oliguria occur with progressive disease. In more advanced cases, characterized by ischemia and perforation, patients may present with peritonitis and sepsis. Diagnosis relies upon radiographic findings such as a "bent inner tube" or "omega loop," which are noted on plain films in 60% to 75% of patients (Fig. 1). If plain films are nondiagnostic, computed tomography (CT) will provide additional diagnostic information by demonstrating a mesenteric whirl and paucity of rectal gas (see Fig. 1). CT provides a near 100% accuracy in the diagnosis of sigmoid volvulus.

Once the diagnosis of sigmoid volvulus has been made, initial treatment may be operative or nonoperative depending upon the stability and examination of the patient. Initial management strategies aim to relieve the large bowel obstruction with either reduction of the volvulus or resection of the affected colon. Further definitive treatment is directed at the prevention of recurrence.

The initial decision point in the management of the patient with sigmoid volvulus is dictated by hemodynamic stability and physical findings. Patients who are stable, with no evidence of colonic ischemia, including fever or peritonitis, should proceed with an attempt at endoscopic detorsion. This can be accomplished by the use of a rigid proctoscope or a flexible endoscope. Rigid proctoscopy should be performed only in the setting of a lack of access to standard flexible endoscopy, as it carries a higher risk of perforation and does not afford the ability to visually inspect colonic mucosa. Upon insertion of the endoscope, a classic "pinwheel" appearance is noted at the point of torsion of the colonic mucosa (Fig. 2). With gentle pressure and insufflation, the scope should be passed through the torsed segment. The remaining colon should be endoscopically decompressed, ultimately allowing for detorsion of the colon. Rates of successful endoscopic detorsion are variable, ranging from 55% to 94%. After detorsion, we prefer to leave a soft red-rubber catheter in the colon to allow for continued decompression and prevention of a short-term recurrence of the volvulus.

After successful detorsion of the sigmoid volvulus, the focus moves to prevention of recurrence, which can occur in up to 85% to 90% of cases. Measures aimed to prevent recurrence of sigmoid volvuli historically consisted of two main strategies: colonic fixation and resection. There have been numerous methods of colonic fixation described; however, these are typically not recommended as many carry a significant risk of recurrence. In spite of this, there may be a role for their use in highly selected cases.

The current gold standard approach for the prevention of recurrent sigmoid volvulus is sigmoid colon resection with primary anastomosis. Because morality rates are as high as one in three with recurrent volvulus, it is recommended that elective resection be

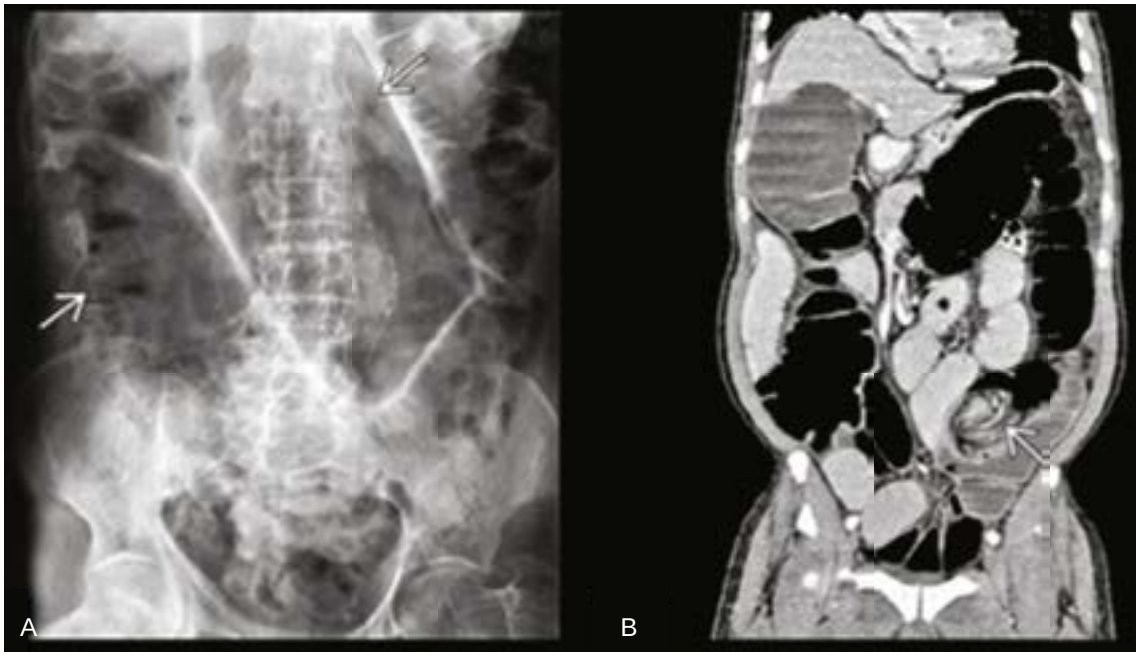


FIG. 1 (A) Plain film abdominal radiograph demonstrating the classic "bent inner tube" sign of sigmoid volvulus directed towards the right upper quadrant. **(B)** Coronal CT image displaying a mesenteric whirl characteristic of sigmoid volvulus. *(From Federle M, Lau, J. Sigmoid Volvulus. In:* Imaging in Abdominal Surgery. *Elsevier; 2018, 282.)*

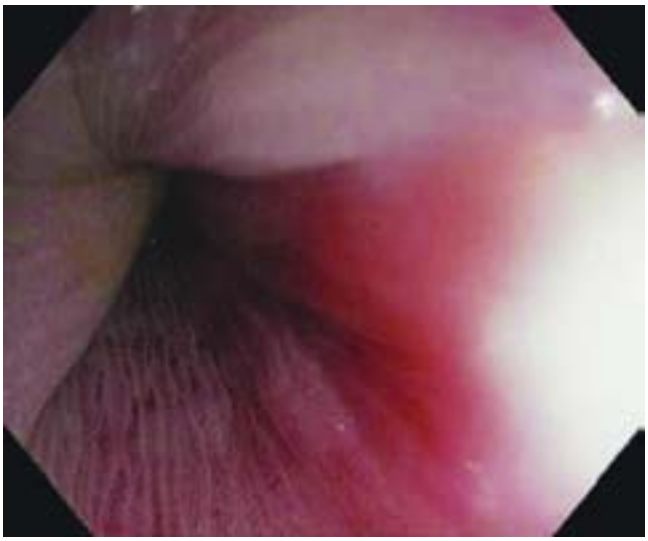


FIG. 2 Classic pinwheel appearance of colonic mucosa visualized during endoscopic decompression of sigmoid volvulus. *(From Tang S-J, Wu R. Endoscopic decompression, detorsion, and reduction of sigmoid volvulus. Video J Encyclopedia GI Endos. 2014;2:22.)*

performed during the index hospitalization. Both open and minimally invasive laparoscopic or robotic techniques are acceptable. When performing an open resection, a lower midline laparotomy or Pfannenstiel incision will typically suffice. Resection with end colostomy and Hartmann's pouch, as well as primary anastomosis with diverting loop ileostomy, are additional acceptable options that may be used when severe colonic edema is encountered. In all cases of sigmoid resection, a nononcologic resection is performed, ligating the sigmoid mesentery close to the bowel. Recurrence after sigmoidectomy for volvulus is extremely rare. One specific setting in which recurrence rates remain high after sigmoidectomy, however, is in patients presenting with megacolon. Recurrence rates after sigmoidectomy in megacolon are greater than 80%. In this circumstance, consideration may be given to subtotal colectomy. One caveat is that the patient's ability to tolerate such an operation must be thoroughly considered.

In contrast to clinically stable patients, those presenting with signs of ischemia, perforation, sepsis, or evidence of shock should proceed with emergent surgical intervention as should those that fail attempted endoscopic detorsion. After initial resuscitation and administration of broad-spectrum antibiotics, a midline laparotomy should be performed with resection of the ischemic or perforated segment of bowel. Compromised bowel should not undergo detorsion before resection. In the setting of perforation, copious irrigation of the abdomen with saline is performed. After resection of the specimen, two options may be considered at the time of initial operation: primary anastomosis versus end colostomy with a Hartmann's pouch. The decision to restore gastrointestinal continuity is dependent upon intraoperative findings and patient-specific factors. Proximal bowel dilatation, fecal contamination, and the presence of ongoing hemodynamic abnormalities must be weighed when deciding upon restoration of continuity. Additional patient factors such as nutritional, functional, and frailty status must be taken into account. Surgical resection in the emergent setting is associated with higher rates of mortality. This should be addressed with patients and family at the time of initial presentation.

CECAL VOLVULUS

The second most frequent type of colonic volvulus is the cecal volvulus, which accounts for 10% to 40% of colonic volvulus cases. In general there are two types of volvuli that can occur in the cecum. The most common is characterized by an axial twisting of the cecum and accounts for up to 90% of cases. In this type, the cecum rotates around its long axis forming a clockwise twist, leaving the cecum in the right lower quadrant. The less common type is not a true volvulus but rather a folding of the cecum upon itself directed toward the hepatic flexure, known as a *bascule.* Overall this accounts for only 10% of reported cases.

Although a mobile cecum predisposes one to volvulus, factors and conditions often noted in patients presenting with cecal volvulus include chronic constipation, psychiatric illness, high fiber



FIG. 3 **(A)** Plain film abdominal radiograph demonstrating the classic "coffee bean" sign of cecal volvulus, with the axis directed toward the left upper quadrant. **(B)** Coronal CT image revealing distended, upside-down, backward cecum with the ileocecal valve pointed lateral. *(From Federle M, Lau J. Cecal Volvulus. In:* Imaging in Abdominal Surgery. *Elsevier; 2018, 283.)*

diet, chronic laxative use, pregnancy, and prior abdominal surgeries. Cecal volvulus has a slight female predominance of 1.4:1.

The presentation of cecal volvulus is variable and nonspecific. Patients may present in a chronic or acute manner. Symptoms may be mild and intermittent including dull, crampy abdominal pain and constipation. Other common signs and symptoms are obstipation, severe pain, and nausea/vomiting. Radiographic workup is essential in all suspected volvulus patients. In very few cases, plain film abdominal x-rays will be diagnostic. Plain film radiographs diagnostic of cecal volvulus will reveal a large, dilated loop of colon with a classic "coffee bean" sign pointing to the left upper quadrant (Fig. 3). Most often there will be an associated paucity of rectal gas. CT scan provides the added benefit of assessing bowel for ischemia or signs of impending ischemia. Intestinal thickening, hypoenhancement of the bowel wall, pneumatosis, and abdominal free fluid should prompt more urgent operative intervention.

Similar to sigmoid volvulus, patients presenting with signs of cecal ischemia, perforation, or shock should immediately undergo aggressive fluid resuscitation, administration of broad-spectrum antibiotics, and proceed to the operating room for emergent intervention. Surgical intervention in the emergent setting consists of an ileocolic resection or right hemicolectomy, ensuring resection of the compromised segment. Primary anastomosis at the time of the initial operation will be dependent on many patient-specific factors including hemodynamics, comorbidities, fecal contamination, and local inflammatory changes.

For patients who present without signs of acute shock or perforation, surgical intervention, although not emergent, remains urgent in nature. Unlike sigmoid volvulus, endoscopic reduction is not recommend because attempts are unlikely to be successful (approximately 30% success rate) and may lead to perforation. Initial operative management consists of assessment of bowel viability. This should be done via laparotomy. Minimally invasive techniques are hindered by the gross distension of the cecum and proximal small bowel. Upon laparotomy and inspection of the abdomen, necrosis of the cecum is a common finding necessitating resection with consideration of primary anastomosis. If no necrosis is detected, a right hemicolectomy or ileocolic resection with a side-to-side stapled anastomosis is typically performed.

In the absence of necrosis, nonresection techniques such as detorsion with or without cecostomy and cecopexy have been described in the literature. These techniques are not recommended, however, due to their high recurrence rates as well as high morbidity and mortality. Both cecostomy and cecopexy are reserved for patients who are poor resection candidates due to their underlying comorbid conditions or physiologic status. It is important to assess the quality of the bowel wall when considering these strategies. The fragile or edematous tissue typically associated with cecal volvulus is a poor candidate for holding suture. This can ultimately lead to complications such as leak and failure of apposition to the abdominal wall or retroperitoneum.

Rare Types of Volvulus

Sigmoid and cecal volvuli account for the majority of colonic volvulus with other types of volvuli occurring in rare instances. Transverse colon and splenic flexure volvuli account for 2% to 5% of all colonic volvulus cases. Typically, these occur in a younger patient population with an increased incidence in women. Similar to other forms of volvulus, predisposition to transverse colon and splenic flexure volvuli is due to conditions that elongate the colon and its mesentery. These include high fiber diet, chronic constipation, and colonic obstruction. Additionally, the loss of the traditional attachments of the colon due to abdominal surgery is associated with increased rates of splenic flexure volvulus.

Patients will present in a similar manner to other types of volvulus, with either acute symptoms of large bowel obstruction or more chronic and intermittent symptoms. Diagnosis is rarely made by using plain films alone. Splenic flexure volvulus is characterized by a "coffee bean" sign in the left upper quadrant on abdominal x-ray. Conversely, volvulus of the transverse colon can be characterized by an "inverted coffee bean" sign. Additionally, two distended loops of colon and a paucity of rectal gas may be visualized. CT imaging provides improved diagnostic capability and will reveal a mesenteric whirl. Oftentimes, laparotomy is required to determine the location of the whirl and volvulus. Due to the rarity of the condition, diagnosis is delayed in many instances, leading to high mortality rates.

Treatment of these rare types of volvulus is similar to that of cecal volvulus. Endoscopic decompression should not be attempted because recurrence rates are high. The initial step in treatment is laparotomy with assessment of bowel viability. Noncompromised bowel may be detorsed before resection. The extent of the resection depends upon the location of the volvulus. Options for resection consist of extended right hemicolectomy or a segmental resection.

Determination of primary anastomosis versus end colostomy will depend upon patient-specific factors and operative findings.

One other form of volvulus is ileosigmoid knotting, which is exceedingly rare in Western society. This occurs when a loop of ileum becomes entangled with the sigmoid colon leading to obstruction. There are three major types of ileosigmoid knotting. Type 1, accounting for approximately 50% to 60% of cases, occurs when a portion of ileum encircles the sigmoid colon. Type 2 accounts for approximately 20% of cases and is characterized by wrapping of the sigmoid colon around a loop of ileum. In both type 1 and type 2, wrapping can occur in a clockwise or counterclockwise fashion. Type 3, a rare entity, consists of the ileocecal segment wrapping around the sigmoid colon. The remaining cases are of indeterminate anatomy.

Most commonly, ileosigmoid knotting occurs in males (approximately 80%) in the late third or fourth decade of life. The true incidence is unknown, and the majority of case reports are from Asia, Africa, and the Middle East. Clinical presentation consists of abdominal pain and tenderness with associated symptoms of small bowel obstruction such as distention, nausea, and emesis.

Diagnosis can be challenging as radiographic imaging will reveal dilated loops of small bowel accompanied by a distended sigmoid loop. Abdominal plain films alone are rarely diagnostic. In addition to bowel dilatation, CT imaging will reveal whirling of the ileal and sigmoid mesentery with associated medial deviation of the cecum and left colon. Ileosigmoid knotting may be confused for sigmoid volvulus on imaging prompting attempted endoscopic decompression. In these cases, endoscopic decompression will fail due to the wrapping of the mesentery, further raising the suspicion for ileosigmoid knotting.

After initial resuscitation, emergent laparotomy is indicated because clinical deterioration is often rapid due to the quick progression of knotted bowel segments to ischemia. In fact, upon operative exploration, gangrenous bowel is discovered in more than 70% of cases. Operative management will vary depending on the nature of the ileosigmoid knot as well as the stability and condition of the patient. As the majority of cases present with gangrene, resection is typically performed. In many cases, multiple resections are necessary. In the event that a viable sigmoid colon is encountered, resection is recommended to prevent further recurrence. The decision to perform primary anastomosis versus enteric diversion will depend upon many factors.

SUMMARY

Colonic volvulus is a rare entity in the United States, accounting for <5% of all intestinal obstructions. In spite of this, a high index of suspicion must be present as prompt surgical evaluation is a necessity. Clinical presentation is quite variable, ranging from chronic mild symptomatology to acute obstruction and shock. Only in the case of sigmoid volvulus is initial endoscopic decompression appropriate. Definitive treatment consists of operative intervention. Although techniques without resection are described in rare specific circumstances, colonic resection is considered the gold standard to alleviate obstruction and prevent future recurrence. Operative decision making regarding performance of primary anastomosis must be decided on an individualized basis and is impacted by many patient-specific factors as well as surgeon experience and comfort.

Suggested Readings

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Management of Rectal Prolapse

Shannon N. Radomski, MD, and Alodia Gabre-Kidan, MD, MPH

ETIOLOGY

Rectal prolapse is defined as a prolapse of either the full or partial thickness rectal wall through the anus beyond the anal verge. Prolapse that does not go beyond the anal verge—internal prolapse or intussusception—is managed differently and will not be discussed in this chapter.

Rectal prolapse is far more common in women than in men and has a peak incidence in the sixth or seventh decade of life. In these patients, rectal prolapse can coincide with prolapse or dysfunction of other pelvic floor organs indicating an underlying etiology of pelvic floor weakness, which in women is often from multiparity. However, rectal prolapse can also occur in men and nulliparous women suggesting a different etiology related to constipation and/or straining due to disordered defecation.

Although rectal prolapse relies on surgical correction as the mainstay of treatment, it is important to recognize that the causative factors for each patient may differ, and adjunctive treatments such as pelvic floor physical therapy, consultation with urogynecologists, and bowel modifications should be employed to optimize the success of any surgical repair.

PRESENTATION

Patients with rectal prolapse can present with a number of different symptoms. Most commonly patients describe prolapse of tissue that spontaneously reduces or has to be manually reduced, rectal pressure or discomfort, bleeding, mucus drainage, constipation or inability to fully evacuate, fecal urgency, or fecal incontinence. Prolapse can be a significant source of stress for patients, and many describe limiting their activities to be near a bathroom or planning their days to accommodate for bowel habits.

Constipation can be both a cause of the rectal prolapse and a result of it. Disordered defecation/pelvic floor dyssynergia leads to increased straining, which can result in a prolapse, especially in patients who do not have risk factors for pelvic floor weakness. Once the prolapse becomes recurrent, it can act as a mechanical obstruction making evacuation even more difficult and lead to an increase in the behaviors (straining, increased toilet time) that will worsen the prolapse. This is a point of debate as many feel that it is not the mechanical obstruction of the prolapse but the ongoing, unaddressed

pelvic floor issues that worsen the prolapse. With chronic prolapse, fecal incontinence can also occur from the rectal prolapse stenting open the sphincter complex and allowing feces to leak. Over time, however, chronic stretch of the sphincter complex by the prolapsed segment of rectum can lead to irreversible impairment in continence. It is important to discuss this with patients before repair in order to appropriately set expectations. Surgical repair of the prolapse will address the mechanical issue but may not result in a return to their functional baseline.

EVALUATION

Any patients presenting with rectal prolapse should have a thorough pelvic floor history and physical examination. It is important to obtain a detailed history including onset of symptoms, bowel habits, prior obstetrical history, prior anorectal surgery, associated pelvic organ symptoms (urinary incontinence, frequency, prolapse, rectocele, etc.), and colonoscopy history. Physical examination for rectal prolapse can occur in the left lateral or prone jack-knife position. External visual examination can yield important information such as presence of fecal smearing, mucus drainage, skin irritation or breakdown from moisture, a patulous anus, and presence of any prolapsed tissue at rest. The patient is then asked to bear down. If the prolapse cannot be elicited with Valsalva in the left lateral or prone jack-knife positions, the patients should be asked to Valsalva in a seated position on the commode. If the prolapse still cannot be elicited, photographs of the prolapse as it occurs at home can be helpful and/or further testing such as defecography can be pursued. Hemorrhoidal prolapse is far more common than true rectal prolapse and patients often cannot distinguish between the two; thus it is important for the surgeon to visualize the prolapsed tissue themselves. Full thickness rectal prolapse appears as concentric rings/circles as the rectum telescopes out of the anus while hemorrhoidal prolapse creates radial lines from the center of the anus as the hemorrhoidal columns prolapse out. Partial thickness, or mucosal, prolapse can also occur and appears as a shorter segment of prolapsed rectum lacking the radial lines of hemorrhoidal prolapse. The treatment of mucosal prolapse differs from full thickness prolapse, thus distinguishing between the two is important to guide future interventions. It is also important to document anal sphincter tone during the examination as well as presence or absence of any associated vaginal prolapse. For patients with multicompartmental prolapse, a combined approach with a urogynecologist is favored to address all potential issues during one surgery as opposed to requiring the patient to undergo multiple surgeries.

MANAGEMENT/SURGICAL APPROACH

When considering repair of a rectal prolapse, there are several decision points that can aid in the ultimate choice of approach. First and foremost, acutely incarcerated prolapse must be recognized because this constitutes a surgical emergency. Similar to an incarcerated hernia, the prolapsed bowel can become ischemic if not reduced in a timely fashion. Temporizing measures such as applying sugar to the mucosa of the prolapsed segment of rectum can be used in cases where the bowel is edematous but not ischemic. If the bowel still will not reduce after application of sugar, then urgent surgical repair must be considered. In the setting of acute incarceration that cannot be reduced, a perineal rectosigmoidectomy is most prudent as it ensures that all compromised rectum is excised. Abdominal approaches can be used if ischemia is not present and the rectum reduces with induction of anesthesia and relaxation of the sphincter complex. Fortunately, acute incarceration is relatively rare owing to the stretch of the sphincter over time. As the sphincter is stretched by chronic prolapse, the likelihood that it will be constricting and not allow the rectum to be reduced is lowered.

Putting emergent indications aside, the majority of rectal prolapse repairs will occur in the elective setting. The approach to repair will need to take the degree of prolapse (full thickness vs. partial thickness), patient factors (comorbidities, prior surgery), and associated pelvic floor pathology into account. There are six widely used approaches to prolapse outlined in Figure 1, not taking into account the choice of open, laparoscopic, or robotic approaches to abdominal procedures. Thiersch wire procedures will not be discussed as they are largely of historical interest with high rates of complications.

PARTIAL THICKNESS PROLAPSE

Mucosal Sleeve Resection

The first decision point is whether the patient is experiencing a partial or full thickness prolapse. Partial thickness prolapse is repaired with a perineal approach using a Delorme procedure. This is a mucosal sleeve resection, which excises the redundant mucosa and sutures it back to the anal transition zone just proximal to the dentate line (Fig. 2). Of note, this procedure can also be used in short segment (<5 cm) full thickness prolapse. After the patient is positioned, the rectum is retracted out to reproduce the maximum amount of prolapse. A solution of saline mixed with epinephrine is injected into the submucosal layer both to lift it off of the underlying muscular layers but also to aid with hemostasis. A circular incision is created just proximal to the dentate line with electrocautery and carried down to this submucosal layer. In a patient with full thickness prolapse, plicating sutures would then be placed through the muscularis to accordion the rectum back to the anal canal. These are typically placed in four quadrants to offset the sutures to account for the mesorectum. The redundant mucosa is then amputated, and the remaining mucosa is sutured back to the proximal resection point.

FULL THICKNESS PROLAPSE

The options for repair of full thickness prolapse are separated into abdominal or perineal approaches (see Fig. 1). Traditionally we recommend a perineal approach to elderly or frail individuals as it avoids the physiologic stress associated with a major abdominal surgery and, in patients who are unfit for general anesthesia, can be done under regional anesthesia. In fact, Altemeier was not the first person to describe this technique, but his paper in 1952 described his experience using this approach in elderly, high-risk patients and was the beginning of the association of age and comorbidities with a perineal approach. However, this dogma is challenged by the evolution of better anesthetic techniques and the use of minimally invasive surgical techniques with relatively low rates of complications and faster recovery. Still, however, for some patients with full thickness prolapse who may be unacceptably high risk for an abdominal approach or have had multiple prior abdominal surgeries, a perineal approach is a good option.

Perineal Rectosigmoidectomy

Unlike a Delorme procedure, a perineal rectosigmoidectomy, or Altemeier procedure, is a full thickness resection and coloanal anastomosis. Once the patient is in position, the rectum is again prolapsed out to its maximum amount and a full thickness incision is made through the rectal wall about 1 to 2 cm proximal to the dentate line. This is carried around circumferentially and the pelvis is typically entered anteriorly between the rectum and vagina/prostate by dividing the peritoneal attachments to enter the pouch of Douglas. The lateral ligaments are similarly divided using an energy device to ensure hemostasis. The rectum and sigmoid colon are then prolapsed out by taking posterior attachments and vessels of the mesorectum and mesocolon until the colon cannot be prolapsed any further. The full thickness colon wall is then divided making sure to take the mesocolon at this level so as to not devascularize the segment that will become part of the anastomosis. It is important to place anchoring, full thickness sutures through the colon wall as it is circumferentially divided as it can retract back into the abdomen without

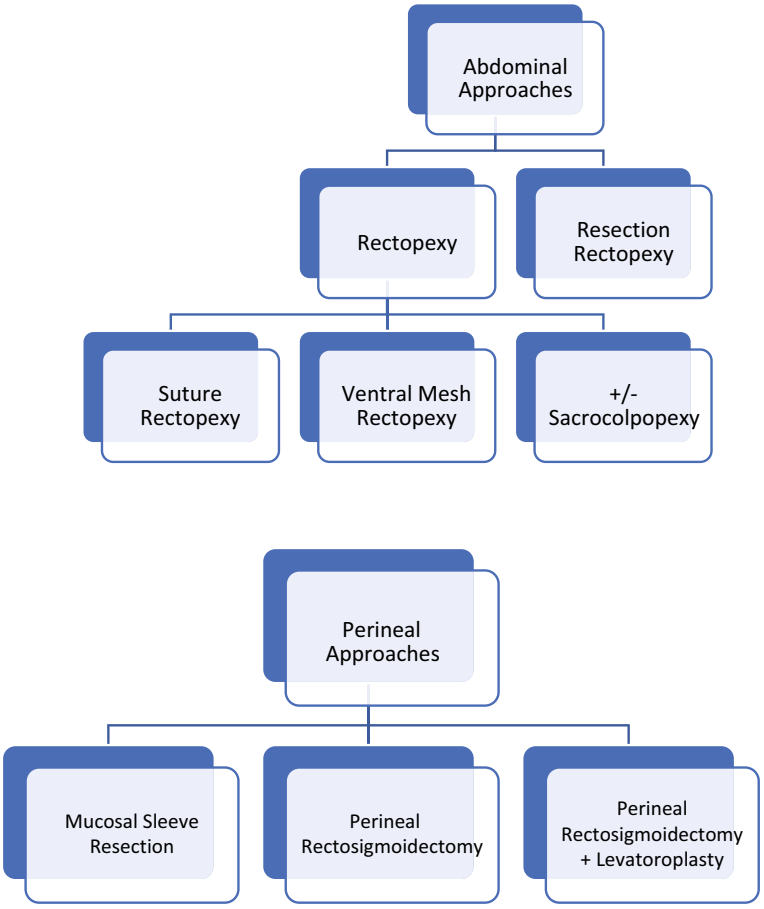


FIG. 1 Approaches to rectal prolapse.

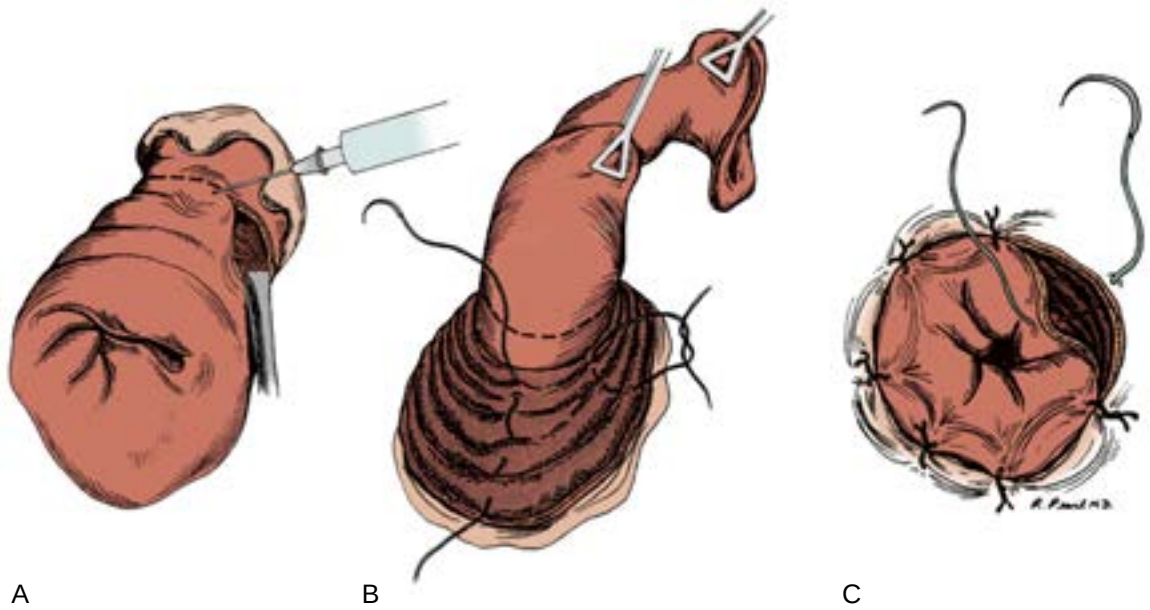


FIG. 2 Mucosal sleeve resection. **(A)** Injection of saline mixed with epinephrine to life submucosal layer. **(B)** Plication of muscularis and division of redundant mucosa. **(C)** Handsewn anastomosis. *(From Doane S, Yeo C. Shackelford's* Surgery of the Alimentary Tract, *Vol. 2. 2019:1097–1112.)*

them. At this point, if the patient had preoperative incontinence and has a wide levator hiatus, a posterior levatorplasty can be performed with interrupted sutures to narrow the levators. This can also be performed anteriorly for very wide defects, but care must be taken not to incorporate the anterior structures or make the opening too narrow. The coloanal anastomosis can be performed in a handsewn or stapled fashion depending on preference. For a stapled approach, the anvil of the stapler is placed in the proximal colon and a purse

string is sewn around the anal canal through which the stapler would be placed. Some surgeons advocate for the creation of a small colonic J-pouch to act as a reservoir, but a straight coloanal anastomosis with levatorplasty is an option as well to help with incontinence as a result of chronic stretch of the sphincter complex.

Abdominal Approaches

There are two main abdominal procedures for rectal prolapse: rectopexy or resection rectopexy. These can be accomplished via open, laparoscopic, or robotic approaches, and in a resection rectopexy the surgeon would perform a sigmoid colectomy in conjunction with their chosen rectopexy technique. Centered around this decision point is the debate as to whether resection rectopexy offers an advantage over rectopexy alone. Advocates of resection rectopexy argue that a redundant sigmoid colon contributes to constipation, which then leads to the prolapse. Advocates of a rectopexy alone argue that segmental resection is not an adequate operation for constipation and adding a resection increases the potential for complications, especially in frail patients. This was studied as one arm of the PROlapse Surgery PErineal or Rectopexy (PROSPER) trial that is still, to date, the largest randomized trial comparing approaches to rectal prolapse. In this study, there was no significant difference in recurrence between patients undergoing a resection rectopexy versus suture rectopexy alone, although the main limitation was inadequate sample size to power all comparisons.

The next decision point is in the technique used for the rectopexy. The most common technique is a suture rectopexy, but ventral mesh rectopexy is gaining in popularity for a number of reasons that will be discussed.

Suture Rectopexy

The goal of suture rectopexy is to fully mobilize the rectum down to the levator muscles and restore its anatomic position by suturing it to the sacral promontory to allow further scarring and fibrosis to occur to fix the rectum back in place. Whether this is accomplished in an open, laparoscopic, or robotic approach depends on surgeon experience. The rectum is fully mobilized by incising the peritoneum at the sacral promontory, and this dissection is carried down to the levator muscles posteriorly. It is important to note that the surgeon should not divide lateral stalks of the rectum close to the rectal wall but rather leave peritoneal "wings" to suture back to the sacral promontory. Care must be taken to avoid injury to the hypogastric nerves when performing this posterior dissection. Once the rectum is fully mobilized, the lateral stalks are placed on tension to bring the rectum back to its anatomic position and suture it to the sacral promontory on both sides with nonabsorbable suture or tacks if using a minimally invasive approach. The sutures should be placed lateral to the hypogastric nerves and medial to the ureter and, once they are tied down, should not narrow the rectum or place it at a sharp angle, which will make evacuation difficult postoperatively. Potential areas for concern postoperatively include increased constipation due to division of lateral stalks and compromise of nervous innervation running within them as well as potential for sexual dysfunction in men due to the extensive posterior mobilization with increased risk of nerve damage. Many surgeons advocate for a perineal approach to full thickness prolapse in men to avoid these areas of potential nerve damage altogether.

Ventral Mesh Rectopexy

There have been many approaches to rectal prolapse that involve the use of mesh either as a material to fix the rectum to or as a sling/wrap to return the rectum to its usual position in the pelvis. A ventral mesh rectopexy avoids the posterior dissection and division of the lateral stalks that are worrisome in a suture rectopexy and relies on an anterior fixation. Similar to a suture rectopexy, the peritoneum is incised over the sacral promontory taking care to avoid the hypogastric nerves and iliac bifurcation. This is only performed on one side of the rectum, typically the right side. This dissection is carried down laterally and into the rectovaginal septum with a complete dissection anteriorly to the pelvic floor (Fig. 3). A strip of mesh is cut and placed into the space between the rectum and

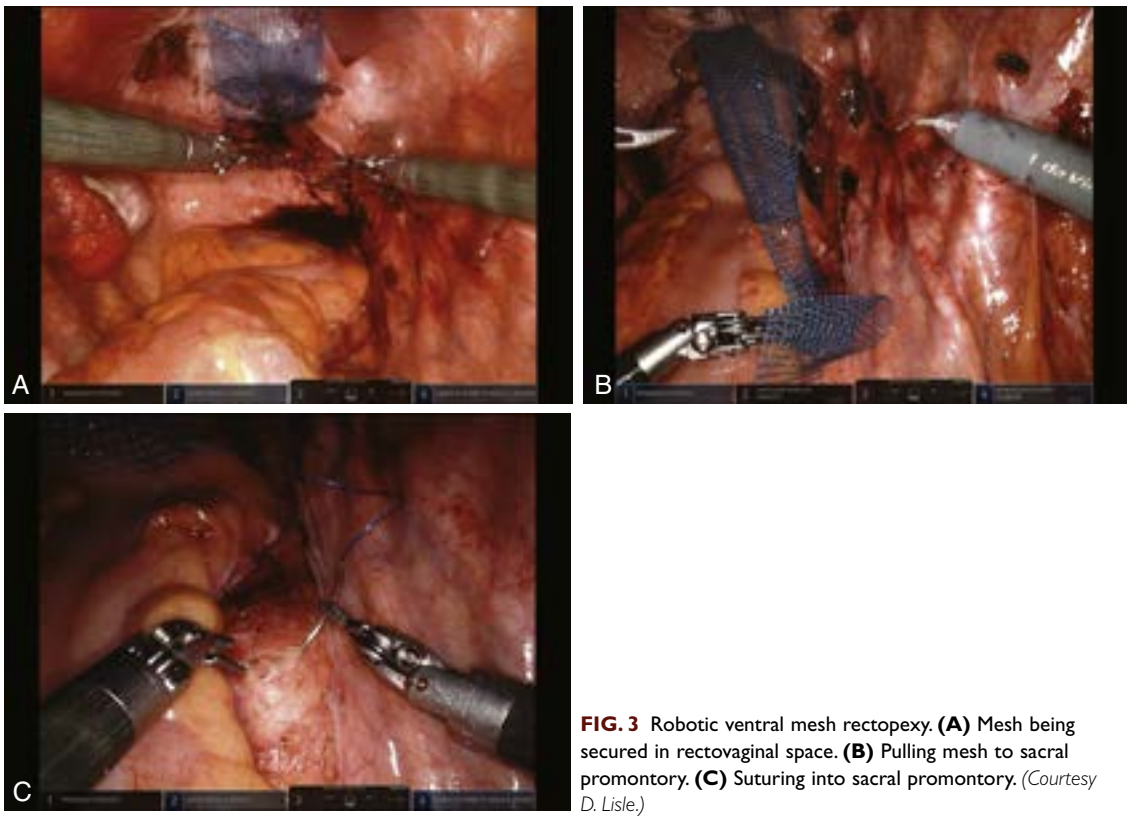


FIG. 3 Robotic ventral mesh rectopexy. **(A)** Mesh being secured in rectovaginal space. **(B)** Pulling mesh to sacral promontory. **(C)** Suturing into sacral promontory. *(Courtesy D. Lisle.)*

vagina and sutured to the anterolateral rectal wall on either side of the rectum also incorporating a small amount of pelvic floor musculature into sutures. The mesh is then stretched to the sacral promontory and tacked or sutured to the right side of the promontory after it has been adequately cleared. The peritoneum that has been incised laterally is usually then sutured back to itself to cover the mesh if possible.

Advantages to ventral mesh rectopexy include lack of a posterior mobilization and potential autonomic nerve injury, as well as the ability to address multicompartmental prolapse in a combined approach with our female pelvic medicine and reconstructive surgery (FPMRS) colleagues. Potential complications include mesh erosion and/or infection, which has motivated some surgeons to use biologic mesh instead of synthetic mesh. Regardless, rates of erosion even with synthetic mesh are quite low and reported to be anywhere between 2% to 4%. There have not been many studies to determine if there is a difference between recurrence rates using biologic versus synthetic mesh, but in a recent meta-analysis by Lobb et al. of suture rectopexy versus ventral mesh rectopexy, there was no statistically significant difference in recurrence between the two groups.

Recurrent Prolapse

The complication that is an inherent risk of any rectal prolapse repair is recurrence. Data in the literature vary widely depending on the degree of prolapse present preoperatively, the approach, and patient factors. The widely accepted dogma that perineal approaches lead to higher rates of recurrence has been challenged with the results of the PROSPER trial showing that there was no statistically significant difference in recurrence between perineal and abdominal approaches. However, this trial also showed recurrence rates between 13% and 31%. This is much higher than the averages reported in the literature, which are typically below 10% to 15% and are likely a reflection of specialization of surgeons and a multidisciplinary approach to pelvic floor dysfunction.

The most important factor to consider in the approach to a recurrent rectal prolapse is the type of repair the patient underwent previously. Every effort should be made to obtain previous operative records. The biggest mistake that can be made is to inadvertently leave behind a segment of devascularized colon. This can only happen in patients who had a previous resection via a resection rectopexy or perineal rectosigmoidectomy. In these patients, the safest approach is a rectopexy as it does not involve any further resection and potential for vascular compromise. In patients who had a previous perineal rectosigmoidectomy, a repeat perineal rectosigmoidectomy can be performed provided that their previous anastomosis is fully resected.

CONCLUSION

Rectal prolapse is a debilitating disease that can be successfully treated with a thoughtful surgical approach. Many factors including presenting symptoms, patient comorbidities, bowel function, and degree of prolapse must be considered as there is no single superior approach that will be successful for every patient. However, with the right surgical approach and technique, patients can experience a drastic improvement in their quality of life and often even a return to their preoperative functional baseline.

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Surgical Management of Constipation

Nathalie Mantilla, MD, and Jose R. Cintron, MD

Healthy bowel habits are those considered regular, soft formed consistency, and without the need for excessive straining. However, they may vary in frequency and consistency from one person to another and still be considered normal. Constipation is a common condition defined by fewer than three bowel movements per week, hard stools requiring excessive straining to pass, and/or sensation of incomplete emptying after defecation. Chronic constipation is classified as functional (primary) or secondary. Functional constipation subtypes are based on the etiology: slow-transit constipation (colonic dysmotility), normal transit constipation, and/or obstructed defecation syndrome (pelvic floor dysfunction, rectal hyposensitivity, organ prolapse, internal intussusception). Secondary chronic constipation may be related to medications and/or medical conditions (neurologic or endocrine problems, irritable bowel syndrome, etc.).

Constipation affects approximately 15% of the population worldwide and is a common cause of visits to gastroenterologists and colorectal surgeons. Despite its benign nature, it can be quite debilitating and can significantly impact the quality of life of those who suffer from it.

ANATOMY AND PHYSIOLOGY

Normal defecation is a multistep physiologic process that involves various organs. Colonic mucosa and musculature play an important role in stool formation through a proper balance between water absorption and bowel motility. Coordination of the pelvic floor and abdominal muscles is required in the final steps of stool elimination. Colonic peristalsis helps advance the stool bolus distally as it thickens inside the bowel lumen. Once feces reach the rectum, distention of the rectal wall and feedback from specialized cells in the proximal anal canal will aid distinguishing between gas, solid or liquid stools, and facilitates evacuation when socially acceptable. This process requires coordination between autonomic and somatic nervous system functions.

DIAGNOSIS

Clinical Assessment

A thorough evaluation is required for patients with suspected constipation, including an in-depth interview discussing associated symptoms (such as rectal bleeding, weight loss, changes in stool caliber, etc.) medical, surgical, and family history medications, diet, toilet habits, and so on. Characteristics of the stools should be discussed, including consistency (Bristol stool form scale, Fig. 1), caliber, and frequency. It is also crucial to know the onset and duration of symptoms. Reported symptoms are useful to distinguish the type of constipation. Infrequent hard stools refer more to cases of colonic dysmotility, whereas patients with pelvic floor dysfunction and obstructed defecation syndrome complain more of incomplete evacuation and straining. Abdominal pain that alleviates after defecations may indicate irritable bowel syndrome (Box 1). Evaluation of events occurring at the onset of symptoms may identify causes or contributing factors such as new diagnoses or medications. For example, hypercalcemia, hypothyroidism, neurologic problems, psychosocial issues, the use of opioids, antidepressants, anticholinergics, calcium channel blockers, and calcium supplements are among some common conditions and medications to look for when taking the history. Unfortunately, in many cases of constipation, no cause is identified. A focused abdominal and pelvic physical examination is critical, which should include external inspection followed by digital rectal examination, including evaluation of anal tone, presence of stools, and puborectalis muscle. In women, vaginal examination may be necessary when rectocele is being ruled out. Rome criteria are used to identify constipation and its subtypes but do not assess severity of the condition (Box 2). Complementing the clinical evaluation with validated instruments may help to distinguish the type of constipation, impact on quality of life, and the need to pursue additional diagnostic testing. Multiple questionnaires have been made available to assess the severity of constipation and to follow up on the response to treatment.

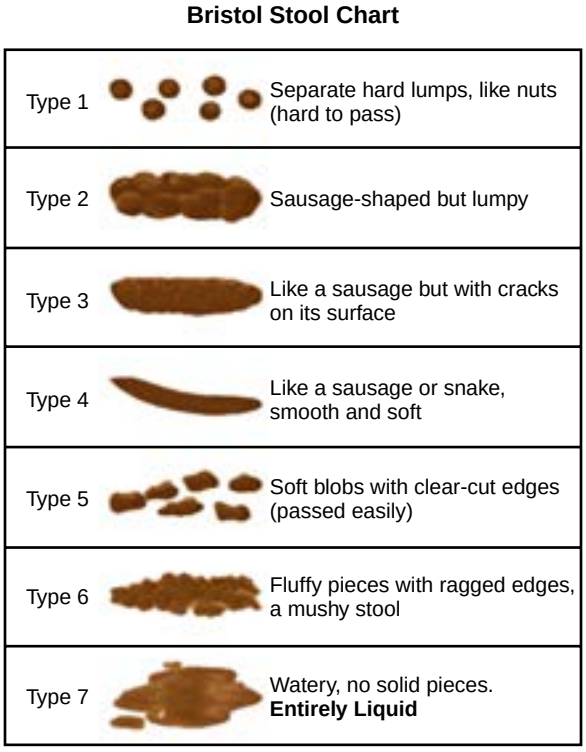


FIG. 1 Bristol stool form scale. *(From Lewis SJ, Heaton KW. Stool Form Scale as a Useful Guide to Intestinal Transit Time. Scand J Gastroenterol. 1997;32[9]:920–924.)*

BOX 1 Rome IV Criteria for IBS-C

Recurrent abdominal pain, on average, at least 1 day per week in the past 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis
- Patient reports that abnormal bowel movements are usually constipation (such as type 1 or 2 Bristol stool form scale)

IBS-C, Irritable bowel syndrome with predominant constipation.
From Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150(6):1393–1407.

BOX 2 Rome IV Criteria for Functional Constipation

Requires two or more of the following:

- Straining with more than 25% of defecations
- Lumpy or hard stools (Bristol stool form scale 1 or 2) more than 25% of defecations
- Sensation of incomplete evacuation more than 25% of defecations
- Sensation of anorectal obstruction/blockage more than 25% of defecations
- Manual maneuvers to facilitate more than 25% of defecations (such as digital evacuation or support of the pelvic floor)
- Fewer than three spontaneous bowel movements per week

Plus:

- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

From Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150(6):1393–1407.

Following screening recommendations or the presence of alarming symptoms, a colonoscopic evaluation should be included to rule out intraluminal lesions, strictures, or any other underlying conditions. Adjunct blood tests to rule out endocrine disorders should be included when clinically indicated (thyroid and parathyroid function, diabetes, etc.).

Radiologic Testing

Sitz Marker Study (Radiopaque Marker Study)

In cases where colonic transit requires further investigation, radiopaque markers, scintigraphy, or wireless motility capsules can be used. The sitz marker study is simple, inexpensive, and easily available because it only requires swallowing the capsule containing the ring-shaped markers and abdominal plain films on the day of ingestion of radiopaque markers by the patient and on day 5 after the ingestion. A normal test is considered if, on day 5, at least 80% of the markers have passed. In cases when more than 20% of the markers are still observed in the colon, the study is considered abnormal. Slow-transit constipation is suggested in cases when the markers are distributed throughout the colon (Fig. 2), whereas retained markers in the rectosigmoid colon are suggestive of obstructed defecation.

Defecography

Defecography is a dynamic test that can be performed using fluoroscopy (cinedefecography), magnetic resonance (MRI

defecography), or ultrasound equipment (ecodefecography) and uses radiologic contrast or ultrasound gel to opacify the rectum and capture images during the evacuation process for further analysis (Fig. 3). It is used to rule out associated pathologies such as rectoceles or intussusceptions and nonrelaxing puborectalis as the cause of obstructive defecation. Each technique offers valuable information, but they all have advantages and limitations.

Anorectal Physiology Testing

In selected cases when pelvic floor dysfunction is suspected, anorectal physiology testing might be useful, such as anorectal manometry (ARM) measuring resting and squeeze pressures, rectal volume sensation, rectoanal inhibitory reflex, and balloon expulsion (Fig. 4). Additionally, electromyography (EMG) is useful in evaluating proper puborectalis contraction and relaxation.



FIG. 2 Sitz marker study. Radiopaque marker study 5 days after ingestion of the Sitz marker capsule. Retention of markers present throughout the colon, suggesting colonic dysmotility. *(From Kapadia M, Varma M. Evaluation of Constipation and Treatment of Abdominal Constipation. In Steele S, et al.* The ASCRS Textbook of Colon and Rectal Surgery. *Springer; 2016.)*

MANAGEMENT

Medical Management

The first line of treatment for constipation is usually nonoperative and includes patient education about diet modifications to increase fiber and water intake. Fiber-rich foods and fiber supplements are both acceptable options and are recommended before beginning laxatives and/or enemas. Behavioral education regarding toilet habits is a critical part of the education and treatment (straining, time spent sitting on the toilet, etc.).

Osmotic laxatives (polyethylene glycol, magnesium hydroxide, and lactulose) are safe options that have been demonstrated to be very effective in most cases of constipation. Short-term use of stimulant laxatives (bisacodyl) is recommended. Newer alternatives such as lubiprostone and linaclotide should be reserved for cases when fiber and water intake is adequate and osmotic and stimulant laxatives have failed.

Noninvasive Techniques

Biofeedback therapy is a useful therapy in cases of constipation due to pelvic floor dyssynergia. It has shown to improve the number of spontaneous bowel movements by correcting pelvic muscle dysfunction, mirrored by improved quality of life.

Surgical Management

Refractory cases are those that fail to improve symptoms consistently after appropriate medical treatment and in which surgery provides the only option to restore quality of life. Figure 5 shows the algorithm for management of constipation.

Colonic Slow-Transit Constipation

For patients with confirmed colonic dysmotility as the cause of constipation in whom nonoperative measures have failed, total abdominal colectomy with creation of an ileorectal anastomosis (TAC-IRA) has shown excellent results and is the procedure of choice (overall success rates are approximately 86%). Segmental colectomies are not recommended in these cases because failure rates are as high as 100%. Upper gastrointestinal dysmotility problems must be ruled out before proceeding to perform a colectomy to decrease chances of recurrent constipation. It is imperative to have a thorough conversation with the patient, setting clear expectations about outcomes and possible complications. TAC-IRA can be performed open or

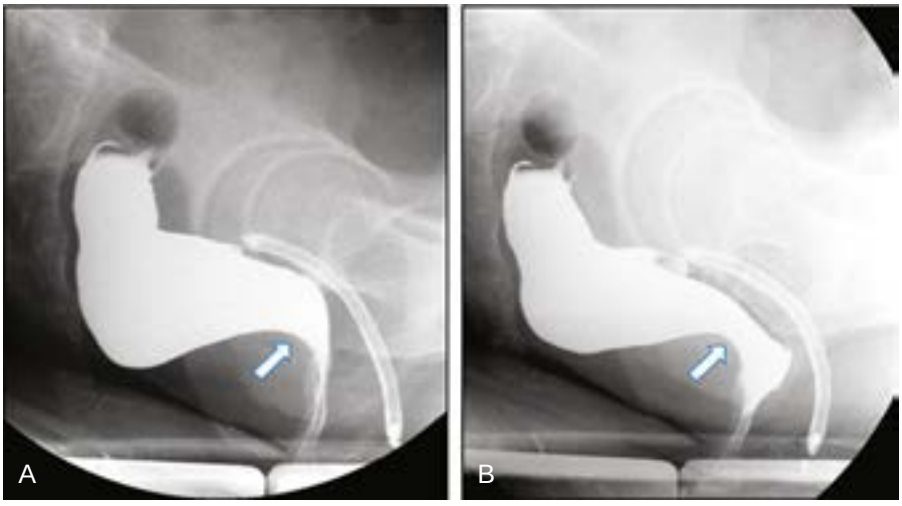


FIG. 3 Defecography. Dyskinetic puborectalis muscle syndrome. Note abnormally deep puborectalis impression *(arrow)* at rest **(A)** and at evacuation phase **(B)**. During the evacuation phase, there is lack of pelvic floor descent. *(From Ah Young Kim. How to Interpret a Functional or Motility Test - Defecography.* J Neurogastroenterol Motil. *2011;17[4]:416-420.)*

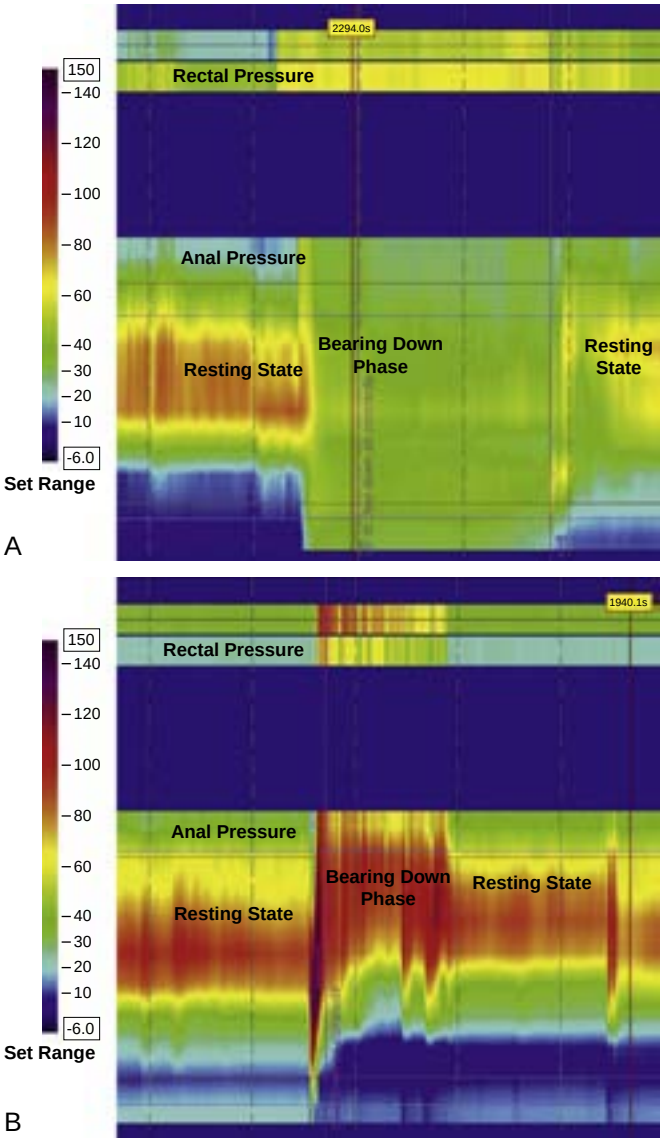


FIG. 4 Anorectal manometry. **(A)** Normal manometry. Green = 20 mm Hg pressure. **(B)** Dyssynergic defecation. Red = 100 mm Hg pressure. *(From Rao SS, Meduri K. What is necessary to diagnose constipation?* Best Pract Res Clin Gastroenterol. *2011;25[1]:127–140.)*

using a minimally invasive approach (laparoscopic or robotic) with good outcomes and low morbidity. The approach will depend on the surgeon's preference and patients' preexisting conditions (e.g., prior abdominal surgeries). Anastomotic leak has been reported between 1% to 11%, bowel obstruction up to 33%, and postoperative ileus up to 24%. Special attention must be paid to proper orientation of the small bowel to avoid torsion of the mesentery, which could carry devastating consequences. Evaluation of the anal sphincter is imperative, including ARM testing when physical exam triggers concern such as low sphincter tone or poor squeeze effort. The rationale behind this is the incidence of diarrhea and fecal incontinence after this type of surgical procedure, which can be as high as 46% and 47%, respectively.

In some patients with colonic slow-transit constipation, ARM testing may identify an additional component of pelvic floor dysfunction. This group should be treated with biofeedback before subtotal colectomy (TAC-IRA), because higher rates of recurrent constipation are common. Similarly, if rectal intussusception or a rectocele/enterocele is identified on defecography, repair of the outlet obstruction may be necessary before or at the same time of TAC-IRA. Details about surgical repair of rectoceles are described in the outlet obstruction constipation section.

Total Abdominal Colectomy with Ileorectal Anastomosis

The approach (open, laparoscopic, or robotic) will depend on the patient's preexisting conditions, abdominal surgical history, and surgeon's preference and expertise. The authors prefer and recommend a minimally invasive approach whenever feasible due to the benefits of less postoperative pain, fewer wound infections (particularly in obese patients), and faster bowel recovery. A detailed description of the laparoscopic technique will be discussed in the following sections.

Preoperative. A mechanical bowel preparation with polyethylene glycol or sodium phosphate in addition to a Nichols and Condon prep is used preoperatively. Patients should undergo education and marking of potential stoma sites in case it is necessary, as well as become enrolled in the enhanced recovery after surgery (ERAS) protocol per each institution.

Intraoperative. The procedure is performed under general anesthesia, and patients should be placed on an antislip pad and well secured to the operating table to eliminate unwanted sliding during intraoperative changes in position, while also protecting the skin and nerves at pressure points. A modified lithotomy position with the legs slightly abducted and arms tucked to the sides provides access to the anorectal area. Sequential compression devices (SCD) should be placed on both legs unless otherwise contraindicated before anesthetic induction. Surgical prophylactic antibiotics should be administered within one hour of the skin incision to reduce surgical site infections. Antibiotic selection will vary based on institutional resistance patterns and availability, as well as the patient's allergies. The authors prefer ceftriaxone and metronidazole in the absence of contraindications. All patients should undergo a venous thromboembolism (VTE) risk assessment perioperatively and be managed accordingly. A Foley catheter should be inserted under sterile conditions and the rectum irrigated with a mixture of Betadine and warm sterile water solution. An orogastric tube should be inserted to decompress the stomach but removed postoperatively. Pneumoperitoneum can be established using a Veress needle or a Hasson's technique depending on the patient's body habitus and prior surgeries, as well as the surgeon's preference. Traditionally, a 12-mm trocar is placed in the umbilical region to introduce a 10-mm 30-degree laparoscope. An abdominal pressure of 15 mm Hg is achieved, and upon entering the abdominal cavity, visceral injuries caused by the entry instrument should be ruled out. Initially, four additional ports are placed under direct laparoscopic vision: we use 5-mm ports, one on each flank, one in the suprapubic position, and one in the subxiphoid region. Eventually, one of the 5-mm ports will be replaced by a 12-mm trocar to introduce the laparoscopic linear stapler. Depending on the body habitus of the patient, a 12-mm trocar can be placed in the right lower quadrant at the beginning of the surgery. When using a hand-assisted technique, a Gelport (Applied Medical; Rancho Santa Margarita, CA) is placed in the lower abdomen through a Pfannenstiel incision. Figure 6 shows a suggested port placement for laparoscopic cases. Dissection of the colon can be performed using different approaches (top-down, bottom-up, medial to lateral, or lateral to medial). The authors prefer the medial to lateral approach, therefore this will be the technique described next.

Colonic mobilization can be initiated on the left or right side instinctively, keeping in mind that leaving the dissection of the flexures for later facilitates self-retraction of the colon, otherwise it will be floppy, compromising the exposure. Depending on which side of the colon is being mobilized, adjustment of the patient's position will improve exposure. Retraction of the omentum

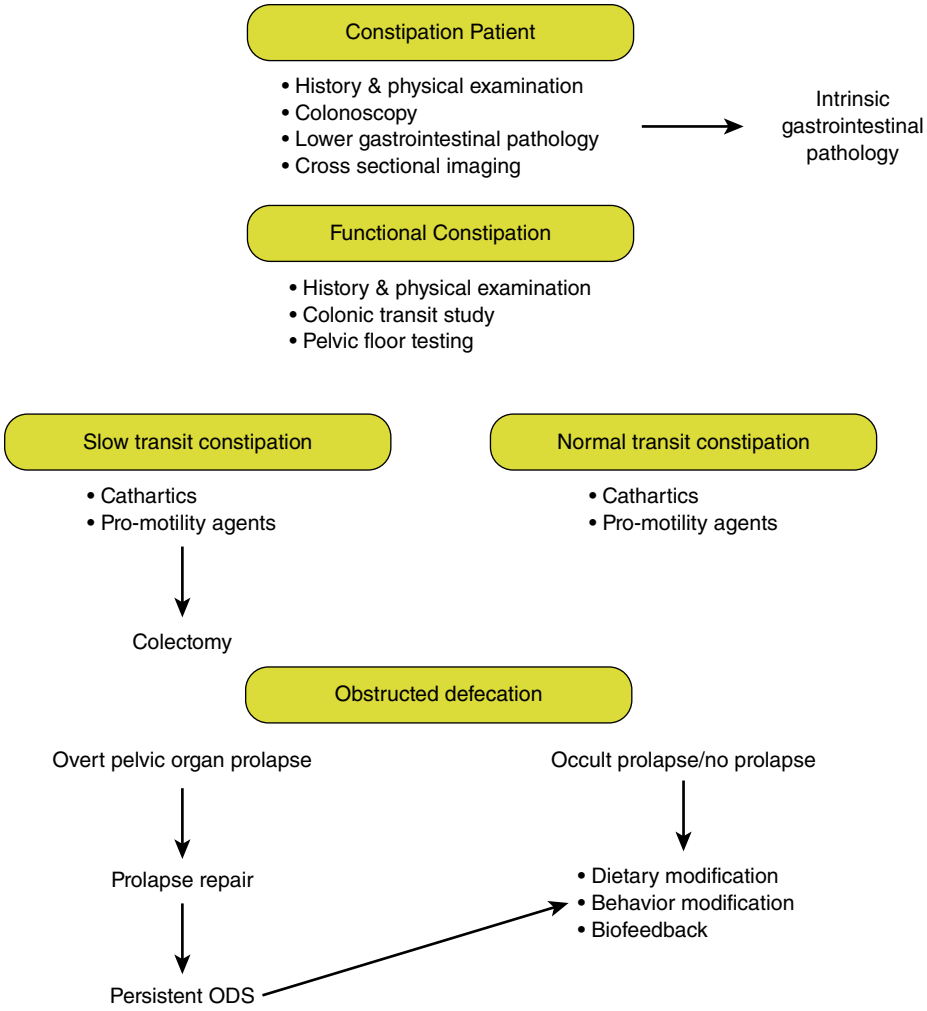


FIG. 5 Algorithm of the management of constipation. *(From McNevin MS. Obstructed Defecation. In Steele S, et al.* The ASCRS Textbook of Colon and Rectal Surgery. *Springer; 2016.)*

and transverse colon into a cephalad position over the liver and stomach is one of the first steps in either right or left colectomies. Ligation of named vessels does not need to be at their origin, but rather an intramesenteric dissection is acceptable. Energy devices, clips, and staplers are some of the available options to ligate vessels depending on the anatomy and diameter of the vessel and surgeons' preferences. During right colectomies, dissection and identification of the ileocolic vessels is a main step, in addition to identification and preservation of critical structures such as the duodenum and right ureter. During left colectomies, identification of the inferior mesenteric artery (IMA) is aided by palpation of the promontory either by hand during hand-assisted procedures or using a grasper during straight laparoscopy. The inferior mesenteric vein (IMV) is identified lateral to the duodenum at the ligament of Treitz, caudal to the inferior border of the pancreas. Its ligation usually facilitates the identification of the plane of dissection between the left mesocolon and the retroperitoneal structures. Careful manipulation of the IMV is crucial, as an inadvertent tear or avulsion can result in retraction of the proximal end underneath the pancreas, producing significant bleeding that can be hard to control. Mobilization of the flexures requires preservation of the spleen and tail of the pancreas on the left side and gallbladder, duodenum, and portal pedicle on the right. It is important to avoid dissection of both flexures before proceeding to perform the transverse colectomy, because all the tension will fall on the middle colic vessels. Therefore, the surgeon would decide which flexure to dissect first, then proceed to transect the middle colic vessels, and lastly take down the other flexure. The middle colic vessels are short, hence meticulous dissection is pivotal. Another approach is to dissect the right side of the colon and continue the dissection through the transverse colectomy followed by the left colectomy. The best approach is usually the one the surgeon is most comfortable with.

Division of the bowel is performed with a laparoscopic linear stapler at the level of the terminal ileum proximally and at the conversion of the taenia at the rectosigmoid junction. The specimen is removed through a small Pfannenstiel incision in straight laparoscopy or by opening the Gelport (Applied Medical; Rancho Santa Margarita, CA) during hand-assisted cases. The ileorectal anastomosis is then created and either handsewn or stapled side to side, end to end, side to end, or end to side (Fig. 7). At the same time, stapled anastomosis can be performed using circular or linear surgical staplers. Lastly, after reestablishment of the pneumoperitoneum, a leak test must be performed using warm saline irrigation of the pelvis and a flexible sigmoidoscope. The anastomosis should satisfy the principles of being free of tension, well vascularized, and with a confirmed negative leak test. In patients in whom an IRA anastomosis is not possible or wanted (e.g., poor

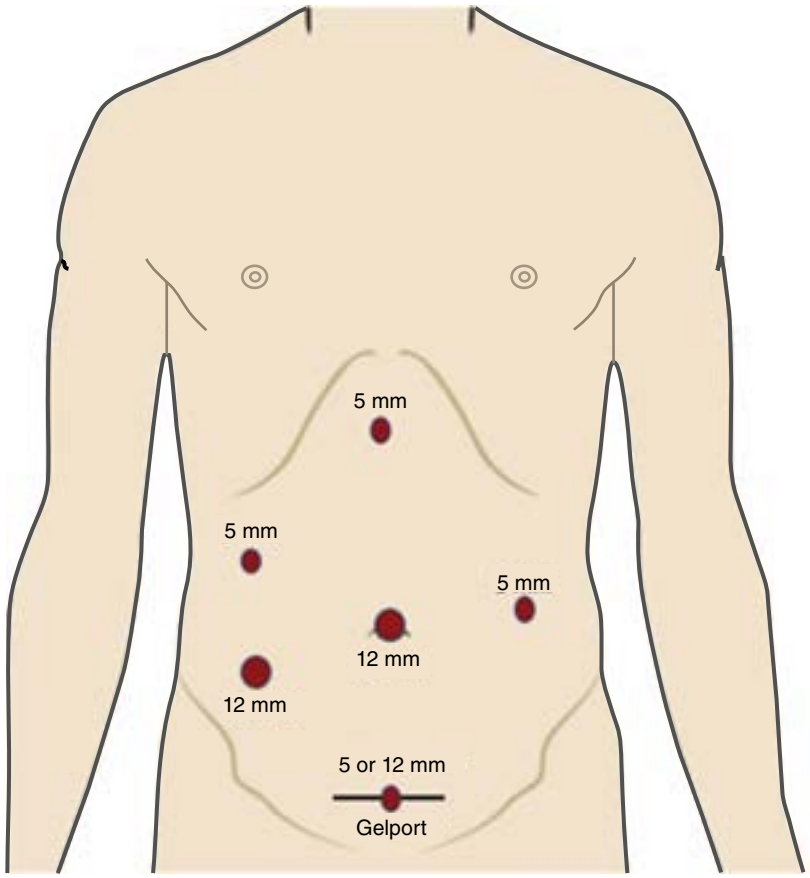


FIG. 6 Laparoscopic port placement.

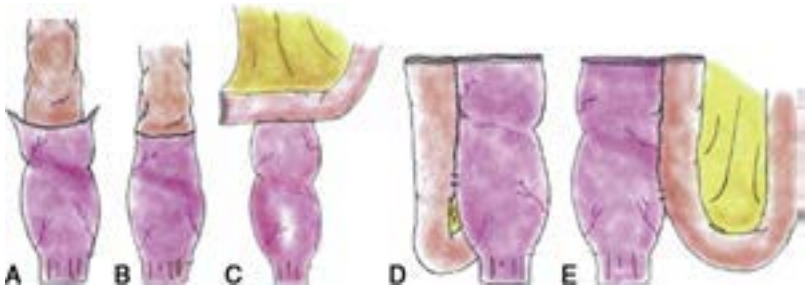


FIG. 7 Variations of ileorectal anastomosis. **(A)** End-to-end (EE) anastomosis with a double-stapled anastomosis. **(B)** EE anastomosis with a double purse-string anastomosis. **(C)** Side-to-end anastomosis. **(D)** Side-to-side anastomosis with the small bowel on the right side. **(E)** Side-to-side anastomosis with the small bowel on the left side. *(From Jolly S, Dudi-Venkata NN, Hanna-Rivero N, et al. Four different ileorectal anastomotic configurations following total colectomy.* ANZ J Surg. *2020;90[9]:1588–1591.)*

sphincter function with fecal incontinence), an alternative is the creation of an end ileostomy.

Robotic port placement will depend on the robotic platform used. However, the technical aspects of the surgery are essentially the same.

Cecorectal Anastomosis

Alternatively, other surgical options are a side-to-side cecorectal anastomosis and antiperistaltic cecorectal anastomosis with subtotal colectomy. The benefit of a subtotal total colectomy with cecorectal anastomosis (Jinling procedure) is the resolution of the obstructive defecation symptoms with less likelihood of consequence diarrhea due to preservation of the ileocecal valve (Fig. 8).

Completion Proctectomy with Ileal Pouch–Anal Anastomosis (IPAA)

Completion proctectomy with ileal pouch–anal anastomosis (IPAA) is typically not recommended as first-line treatment but instead is reserved for patients who have failed all other available options. Usually, IPAA is offered before committing to a permanent stoma. Most patients undergoing IPAA have undergone an abdominal TAC-IRA and present recurrent symptoms of constipation. Pouch

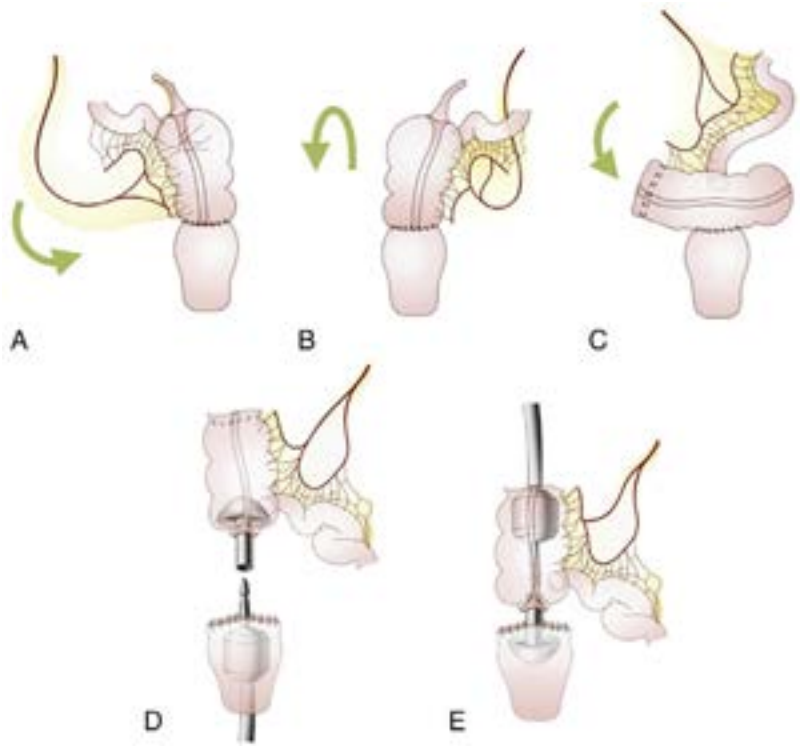


FIG. 8 Types of reconstructive surgery after subtotal colectomy with ileocecal junction preservation. **(A)** Isoperistaltic ascendo- or cecorectal anastomosis, proposed by Lillehei and Wangensteen. **(B)** Counterclockwise rotation of the cecum and ascending colon (Deloyers procedure). **(C)** Ascendo- or cecorectal anastomosis, side-to-end. **(D, E)** Cecorectal anastomosis. *(From Efetov SK, Zubayraeva AA, Nekoval VM, et al. Extended colectomy followed by cecorectal anastomosis as a surgical treatment modality in synchronous colorectal cancer. Case Rep Oncol. 2020;13(2):813–821.)*

excision and poor functional outcomes are some of the complications associated with an IPAA; therefore, the authors recommend a full workup (including ruling out Hirschsprung's disease) and comprehensive discussion and counseling of possible risks and benefits with the patient before committing to the procedure. Careful patient selection is key.

Diverting Ileostomy

Creation of a stoma is usually reserved as a last resort in patients in whom all other alternatives have failed (up to 25% of cases), those with associated fecal incontinence, or those deemed poor surgical candidates unfit to undergo major surgery. The type of stoma will depend on the etiology of the constipation. A diverting loop ileostomy is preferred for patients suffering from colonic slow-transit constipation. It allows symptomatic relief while offering information about the function of the upper gastrointestinal tract. This can be extremely helpful in cases such as global gastrointestinal dysmotility disorders.

Outlet Obstruction Constipation. Obstructed defecation is generally a complex problem due to the presence of concurrent conditions that may engender frustration in patients and treating physicians. This occurs because of slow treatment response, poor resolution of debilitating symptoms, and consequent negative impact on the quality of life. The primary treatment of obstructive defecation constipation is nonoperative. However, in cases of rectal intussusception or large rectoceles refractory to nonoperative management, surgery may be considered. Although it may resolve associated anatomic problems (e.g., rectal ulcers), it may not improve or, in some cases, may potentially worsen functional outcomes.

Rectocele Repair

Rectoceles are the result of an abnormal rectovaginal fascia, typically caused by obstetric trauma. Most symptomatic rectoceles are successfully managed with conservative treatment such as an adequate bowel regimen, changing toilet habits, and biofeedback therapy. Conventionally, only large (>4 cm) symptomatic rectoceles or those in which nonoperative treatments have failed are offered surgical repair. Nonetheless, the decision should be individualized after a thorough discussion with the patient, understanding the symptoms and setting clear postoperative expectations. Transvaginal, transrectal, or transperineal approaches have shown similar outcomes. The selection will be based on the surgeon's experience and preference. The authors prefer transvaginal repair since it is a rather simple technique that allows better access to the endopelvic fascia and levator muscle, and it is associated with fewer complications such as infection and fistula formation because it does not violate the rectal mucosa. Transvaginal repairs include the midline plication (traditional technique) and the site-specific repair.

Preoperative. A mechanical bowel preparation with polyethylene glycol or sodium phosphate in addition to a Nichols and Condon prep is used preoperatively in case the rectal wall is injured inadvertently during the dissection.

Intraoperative. The procedure can be performed under spinal or general anesthesia; the authors prefer the latter. Patients are placed in a modified lithotomy position. The rectum should be irrigated, and extra gloves should be available on the instrument table in anticipation of digital rectal examinations during the procedure. SCD should be placed on both legs unless otherwise

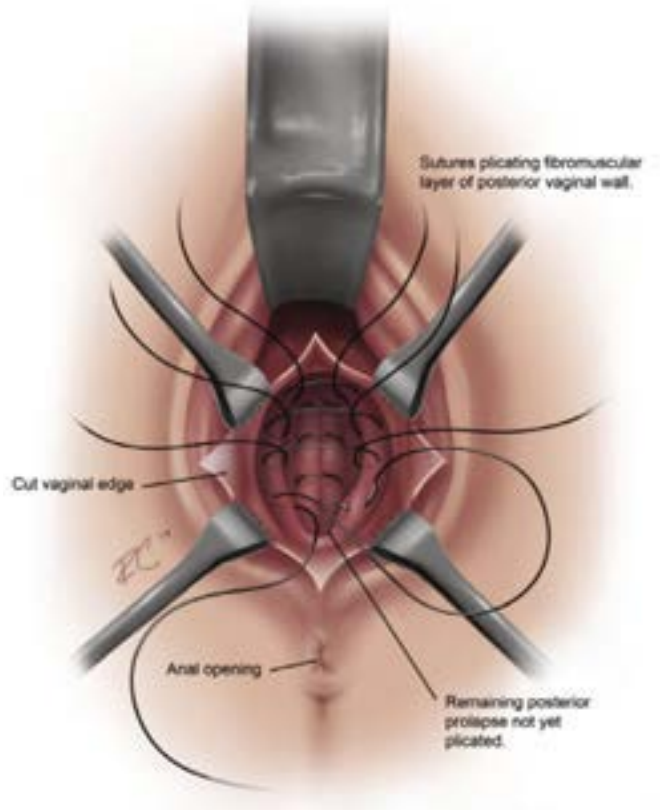


FIG. 9 Posterior vaginal repair of rectocele. *(From Joint Report on Terminology for Surgical Procedures to Treat Pelvic Organ Prolapse [published correction appears in* Female Pelvic Med Reconstr Surg. *2020;26(6):407].* Female Pelvic Med Reconstr Surg. *2020;26[3]:173–201.)*

contraindicated before anesthetic induction. Surgical prophylactic antibiotics should be administered within one hour of the skin incision to reduce surgical site infections. Antibiotics selection will depend on each institution, as well as the patient's allergies. The authors prefer ceftriaxone and metronidazole in the absence of contraindications. All patients should undergo a VTE risk assessment perioperatively and be managed accordingly. A Foley catheter should be inserted under sterile conditions and placed over one of the legs. Using a marking pen, a longitudinal mark is made over the longest axis of the rectocele in the center of the posterior vaginal wall. Then, a local anesthetic with dilute epinephrine (lidocaine 1% with 1:200,000 units of epinephrine) is injected to aid with hemostasis. With the use of a 15-blade scalpel, a midline incision is made over the vaginal mucosa, which is deepened using electrocautery, and the fibromuscular layer of the vagina is dissected. Upon creation of vaginal wall flaps on each side, clamps are placed to facilitate gentle traction. In cases of associated enteroceles, the sac should be opened, the content reduced, and then the sac is closed with a purse-string, delayed-absorbable suture. Once the dissection reaches the extent of the rectocele on both sides and the rectal wall has been examined and confirmed intact, the surgeon proceeds to plicate the vaginal muscularis and rectovaginal tissues in the midline using 2-0 or 0 absorbable or delayed-absorbable interrupted sutures. In the event of a rectal wall injury, it should be immediately repaired using delayed-absorbable suture. If deemed necessary by digital rectal examination, the levator muscles are plicated in the midline, avoiding overcorrection. Lastly, after verifying hemostasis, the redundant vaginal mucosal edges are trimmed on both sides and reapproximated using a 2-0 absorbable suture. A vaginal packing is placed and removed 24 hours postoperatively.

Patients can be placed in 24-hour observation and should be offered laxatives to avoid straining. Figure 9 shows a transvaginal rectocele repair.

There is supporting data on the use of reinforcement of rectocele repairs using synthetic or biological mesh products, particularly for rectocele repairs performed with a transvaginal or transperineal approach. Similar postoperative results have been described.

Transrectal stapled repair of rectoceles and rectal intussusception lost popularity over the years due to the high rate of complications.

Reporting of short-term results shows improvement of constipation symptoms in greater than 80% of patients, with low complication and recurrence rates.

Colostomy Creation

In patients with outlet obstruction constipation who are not compliant or have failed nonoperative therapy, or those who are not candidates for other available treatment options, a colostomy can be considered. If workup reveals a normal colonic transit, a descending colostomy is generally a good alternative with much less morbidity than ileostomies.

Other Surgical Options

Colonic Disimpaction

Not all patients tolerate bedside enemas or disimpaction, in which cases disimpaction under anesthesia may be necessary. These are relatively simple procedures that commonly require only sedation and irrigation. It also allows an opportunity to perform endoscopic procedures and biopsies when deemed necessary.

Malone Antegrade Colonic Enema

Originally described to treat fecal incontinence in children, the antegrade colonic enema uses an appendicostomy or cecostomy to manage constipation symptoms in carefully selected and highly motivated patients who are not interested in or are not candidates for colectomy. Although this technique has been abandoned by many surgeons due to the high rates of malfunction due to stenosis (almost 100%) or leakage, it continues to be an alternative treatment option.

Sacral Nerve Stimulation

This therapy is not currently approved by the Food and Drug Administration (FDA) for the management of constipation; however, it is widely used in the treatment of urinary and fecal incontinence. However, sacral neuromodulation (SNM) or acral nerve stimulation (SNS) has been used for the treatment of slow-transit or outlet obstruction constipation outside of the United States. Success rates are widely variable, ranging between 42% and 100%.

ADULT HIRSCHSPRUNG'S DISEASE

In adult patients with constipation symptoms since childhood and poor or no response to treatment, Hirschsprung's disease should be suspected and ruled out. A disease known to be caused by the congenital absence of submucosal and myenteric ganglion cells, it is confirmed by biopsy of the affected bowel segment. Frequently unrecognized among the adult population because it is considered a children's disease, an absent rectoanal inhibitory reflex during ARM is pathognomonic. It can be surgically managed with the following procedures: Duhamel's, Swenson's, myectomy, Soave's, and low

anterior resection. There is a paucity of data comparing success rates between these techniques in adults.

CONCLUSION

Constipation is a chronic disease with a significant impact on the quality of life of those who suffer from it. Most cases respond successfully to conservative management. However, those who are refractory to medical treatment may benefit from surgical procedures. Individualized workup and treatment are key to achieving resolution of symptoms and improving quality of life.

Suggested Readings

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Surgical Management of the Polyposis Syndromes

Scott R. Kelley, MD, and Sacha P. Broccard, MD

INTRODUCTION

Colorectal polyps can be classified as adenomatous, hamartomatous, hyperplastic, neoplastic, and inflammatory. The development of multiple polyps is considered a polyposis syndrome, and several have been described. Each syndrome has different characteristics including presentation, genetic basis, extracolonic manifestations, and malignancy risk (Table 1). Management options include strict surveillance for the early detection of cancer, chemopreventive medications, and surgery. A detailed family history and genetic evaluation are imperative, and siblings and offspring should be offered genetic counseling and testing. Multidisciplinary care (clinical services, support, counseling) and referral to a polyposis registry is recommended. This chapter focuses on the most common polyposis syndromes.

ADENOMATOUS POLYPOSIS SYNDROMES

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease resulting from a mutation in the adenomatous polyposis coli (APC) tumor suppressor gene located on chromosome 5q21. Most mutations are found between codons 168 and 1640, with two of the most significant being 1061 and 1309. FAP is defined as greater than 100 synchronous adenomas or fewer than 100 with a positive family history. Polyps, predominately found in the rectum and left colon, develop in adolescence and are present in up to 15% of patients by 10 years of age and 75% by 20. If untreated, the risk of colorectal malignancy is nearly 100% by 35 to 40 years of age. Approximately 25% to 30% do not have a family history and will develop FAP de novo. The most common presenting symptoms are bleeding, diarrhea, abdominal pain, and mucous discharge.

For those with a family history or identified APC mutation, a screening colonoscopy should be performed at 10 to 12 years of age and continue annually. With the predilection for polyp development in the left colon and rectum, a yearly flexible proctosigmoidoscopy can be completed instead of a formal colonoscopy. If adenomatous polyps are appreciated on sigmoidoscopy, a formal colonoscopy should ensue.

Extracolonic Intestinal Disease

Extracolonic intestinal disease is a common manifestation of FAP. Hyperplastic gastric fundic glad polyps (FGPs), which have low malignant potential, will develop in 30% to 90% of patients. They affect women and men equally and commonly present in the third or fourth decade of life. In contrast to FGPs, gastric adenomas have the potential for malignant progression, are rare (10%–30%), and typically occur in the antrum. They are more commonly associated with the Japanese and Korean population where the risk of gastric cancer is three to four times higher than western FAP patients.

Duodenal adenomas, most commonly found around the ampulla of Vater and macroscopically different than colonic adenomas, are found in more than 95% of patients with FAP and develop approximately 15 years later than colonic polyps. Duodenal cancer, typically diagnosed around 50 years of age, occurs in 5% to 10% and is the second leading cause of death associated with FAP. A screening esophagogastroduodenoscopy (EGD) is typically performed around 20 years of age, and the Spigelman severity score and staging system (Table 2) is used to determine surveillance intervals (Table 3). The risk of developing cancer after 10 years of follow-up for stage I is 0, stage II and III 2%, and 36% for stage IV. Small tubular adenomas, as well as those with low-grade dysplasia, can be biopsied and observed. High-risk adenomas (villous, >1 cm), severe duodenal

TABLE 1 Summary of Colorectal Polyposis Syndromes

Syndrome	Gene	Inheritance Pattern	Clinical Presentation	Extraintestinal Manifestations	CRC Risk (%)
FAP	*APC*	AD	Left colon and rectum >100 adenomas Duodenal adenomas (95%) Fundic gland hyperplasia (90%) Gastric adenomas (10%)	Benign osteomas (80%) CHRPE (75%) Epidermoid cysts (50%) Dermoid tumors (30%) Supernumerary teeth Cerebellar medulloblastoma	100
aFAP	*APC*	AD	Right colon <100 adenomas	Fundic gland hyperplasia Duodenal adenomas	100
MUTYH	*MYH*	AR	Left colon 10s to 100s of adenomas	Fundic gland hyperplasia Duodenal adenomas	80
Peutz-Jeghers	*LKB1 (STK11)*	AD	Entire GI tract Hamartomatous polyps	Mucocutaneous pigmentation	30-40
Juvenile Polyposis	*SMAD4* *BMPR1A*	AD	Entire GI tract Hamartomatous polyps	Cleft lip/palate Polydactyly Hydrocephalus GU anomalies Congenital heart disease AVMs Hemorrhagic telangiectasias	40
Cowden's	*PTEN*	AD	Colon and stomach Combination of hamartomas, fibromas, adenomas, lipomas, neurofibromas	Trichilemmomas Macrocephaly Hamartomas	NG
Bannayan-Riley-Ruvalcaba	*PTEN*	AD	Entire GI tract Combination of hamartomas and lipomas	Pigmented penile macules Macrocephaly Hamartomas Hemangiomas Mental retardation	NG
Cronkhite-Canada	*PTEN*	Sporadic	Entire GI tract Hamartomatous polyps Diffuse GI inflammation resulting in malabsorption, diarrhea, protein-losing enteropathy	Alopecia Hypogeusia Macrocephaly Onycholysis Cutaneous pigmentation	NG
Hereditary Mixed Polyposis	Unknown	Unknown	Colon and rectum Combination of adenomatous, hamartomatous, hyperplastic polyps	None	NG
Serrated Polyposis	Unknown	Unknown	Colon and rectum At least 5 serrated polyps, all greater than 5 mm in size and proximal to the rectum, 2 of which are greater than 10 mm in diameter -OR- More than 20 serrated polyps of any size distributed throughout the large intestine with 5 being proximal to the rectum	None	30-50

AD, Autosomal dominant; *AR*, autosomal recessive; *AVMs*, arteriovenous malformations; *CHRPE*, congenital hypertrophy of the retinal pigment epithelium; *CRC*, colorectal cancer; *aFAP*, attenuated FAP; *FAP*, familial adenomatous polyposis; *GI*, gastrointestinal; *GU*, genitourinary; *MUTYH*, mutation-Y-homologue associated polyposis; *NG*, no greater than general population.

polyposis, high-grade dysplasia, or stage IV disease should be offered a pancreas-preserving duodenectomy, and those with cancer a pancreaticoduodenectomy. Chemoprevention with nonsteroidal antiinflammatory agents (sulindac, celecoxib) can result in polyp regression in those with a lesser polyp burden, though overall the effect is minimal at best.

Extraintestinal Manifestations

Common extraintestinal manifestations of FAP include osteomas, congenital hypertrophy of the retinal pigmented epithelium (CHRPE), epidermoid cyst, and dermoids. Benign osteomas of the mandible, skull, and tibia are the most common extraintestinal finding occurring in upward of 80% of patients. Although CHRPE

TABLE 2 Spigelman Staging System* for Upper Gastrointestinal Manifestations of Familial Adenomatous Polyposis

Points	I	2	3
Number of polyps	1–4	5–20	>20
Size of polyps (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

*Spigelman stage I, score 1–4; stage II, score 5–6; stage III, score 7–8; stage IV, score 9–12.

TABLE 3 Derivation of Spigelman Stage from Scores

Total Points	Spigelman Stage	Suggested Interval to Next Duodenoscopy (Years)
0	0	5
1–4	I	3–5
5–6	II	3
7–8	III	1
9–12	IV	Duodenectomy; if not, rescope in 6 months

is not specific to FAP, four or more areas of large patchy fundic discoloration is pathognomonic and will be present in around 75% of individuals. Epidermoid cysts occur approximately 50% of the time.

Other extraintestinal manifestations, though rare, include supernumerary teeth, cerebellar medulloblastoma, and cancers of the liver, biliary tree, adrenal glands, and thyroid.

Desmoid Tumors

Desmoids develop in 15% to 30% of patients and are locally invasive abdominal wall and intraabdominal/retroperitoneal myofibroblastic tumors that typically develop 2 to 3 years after surgery and occur around 30 years of age. They can develop spontaneously, are the third most common cause of death associated with FAP, and have been noted to be associated with trauma. Risk factors associated with the development of desmoids are mutations in the 3′ end of the APC gene, female gender, extraintestinal manifestations, and a family history of desmoid disease. Ten percent of desmoids grow rapidly, 10% resolve spontaneously, 30% vacillate between cycles of growth and regression, and 50% remain stable or grow very slowly.

Extraabdominal desmoids are best treated with surgical extirpation with a 1-cm margin, though recurrence is high with documented rates of 20% to 50%. Early excision is recommended to decrease the size of the resultant abdominal wall defect.

Intraabdominal/retroperitoneal desmoids can invade the mesentery and surrounding structures resulting in obstruction, hemorrhage, fistulization, ischemia, and perforation. The primary treatment is medical and includes nonsteroidal antiinflammatory agents (sulindac, celecoxib), estrogen antagonists (tamoxifen, toremifene, raloxifene), and chemotherapy (vinblastine, methotrexate, doxorubicin, Adriamycin, dacarbazine). Radiotherapy can be used for palliative measures but is associated with small bowel necrosis and fistulas. Surgical removal is difficult and often impossible if the root of the mesentery is involved. Resection with completely uninvolved margins (R0) will result in recurrence 50% of the time. FAP-associated desmoid tumors are more likely to recur than their sporadic or pregnancy-associated counterparts. If possible, nonresective procedures such as diversion and bypass can be pursued for palliation. Ureteral obstruction is best treated with stenting.

There is not a defined screening regimen for desmoid tumors, although computed tomography (CT) and magnetic resonance imaging (MRI) can be utilized, especially for those with an increased risk of developing desmoids.

Attenuated Familial Adenomatous Polyposis

In contrast to classic FAP, attenuated FAP (aFAP) presents at a later age (30s–40s) with fewer than 100 polyps predominantly found in the right colon. If untreated, the risk of colorectal malignancy is nearly 100% by 59 years of age. Extracolonic and intestinal manifestations including gastric adenomas, desmoids, and CHRPE are typically not seen in aFAP. Gastrointestinal (GI) malignancy from duodenal polyps has been described in patients with aFAP.

For those with a family history or identified APC mutation suggestive of aFAP, screening colonoscopy should begin between 18 to 20 years of age and repeated every 1 to 2 years. With the predilection for polyp development in the right colon, a formal colonoscopy is recommended. Screening EGD should begin between the ages of 20 to 25, or before colectomy, with repeat interval based on Spigelman stage.

Mutation Y-Homolog Associated Polyposis

Mutation Y-homolog (MYH)-associated polyposis (MAP) is an autosomal recessive inherited form of FAP resulting from a biallelic mutation in the *MYH* gene located on chromosome 1p34. The number of polyps associated with MAP is variable (tens to hundreds) with a median around 50. Polyps are most commonly found in the left colon and present at a median age of 48. If untreated, the risk of colorectal malignancy is around 80% by 70 years of age. Extraintestinal manifestations are associated with MAP, though exceedingly rare.

Due to the phenotypic overlap with FAP, genetic testing for the MYH is typically performed when no APC mutation is detected, there are fewer than 100 adenomatous polyps, and the family history is irrelevant or does not reveal a dominant mode of inheritance.

Screening colonoscopy should begin between ages 18 to 20 and repeated every 1 to 2 years. Screening EGD should begin between ages 30 to 35, or before colectomy, with repeat interval based on Spigelman stage.

CHEMOPREVENTION

Although clinical trials have shown that nonsteroidal antiinflammatory drugs (sulindac, exisulind, celecoxib) and aspirin can reduce the size and number of adenomas in the colon and rectum, there was not an appreciable reduction in cancer. Chemoprevention is not recommended as a primary therapy for polyposis syndromes and is not an appropriate alternative to prophylactic surgery. Situations where chemoprevention can be entertained include treating ileal pouch anal anastomosis (IPAA) polyps, a high family risk of desmoid tumors, delayed surgery, and unwillingness or inability to tolerate polypectomy or completion proctectomy.

SURGERY

The primary goal of surgery is to prevent colorectal cancer. The timing and type of surgery offered depends on a multitude of factors including clinical presentation, family history, and, if known, the site of the chromosomal mutation. Severe polyposis (>1000 colonic or 20 rectal polyps) and *APC* mutations between codons 1250–1464 carry a higher risk of cancer, and surgery should be offered as early as possible. Surgery should also be pursued early for symptomatic disease. For those with a high risk of desmoid disease (family history, mutation in the 3′ end of the *APC* gene, female gender, extracolonic manifestations), surgery should be delayed as long as possible to decrease the chance of desmoid tumors developing. Young patients

should have surgery delayed, if possible, to allow for adequate physical, social, and intellectual maturity. For patients with classic FAP, surgery should be pursued well before cancer develops and typically occurs around 16 to 20 years of age.

Surgical options include an open or minimally invasive total proctocolectomy (TPC) with creation of an end or continent ileostomy, total abdominal colectomy (TAC) with creation of an ileorectal anastomosis (IRA), and a TPC with creation of an IPAA.

Proctocolectomy with End Ileostomy

A proctocolectomy with end Brooke ileostomy has a low rate of complications but leaves the patient with an incontinent stoma. Indications for this approach are patient preference, low rectal cancer requiring an abdominoperineal resection, rectal cancer requiring postoperative pelvic radiation, inability to create an IPAA (inadequate mesenteric length), and poor sphincter function.

The procedure is carried out in an oncologic approach secondary to the risk of a preoperatively unrecognized cancer. A perineal intersphincteric dissection is carried out preserving the external sphincter and levator ani muscles. The perineum is closed in layers, and the greater omentum, if present, is mobilized and placed in the pelvis to prevent future bowel obstructions. After closure of the abdomen, the ileostomy is matured in a standard evaginated Brooke fashion, with an attempted ideal projection of 2.5 cm.

Proctocolectomy with Continent Ileostomy

Initially described by Nils Kock in 1969, the continent ileostomy still remains a viable alternative for motivated patients who are not candidates for an IPAA. Modifications and revisions to the original Kock continent ileostomy have been described (Barnett continent ileostomy reservoir and T-pouch) though without evidence to suggest they are better than the Kock pouch. Contraindications to construction of a continent ileostomy include Crohn's disease, obesity, marginal small bowel length, and anyone with a psychological or physical disability that would preclude understanding or being able to perform daily stomal intubation.

Total Abdominal Colectomy with Ileorectal Anastomosis

Colectomy with ileorectostomy should only be considered in cases of attenuated or mild polyposis (<20 rectal, <1000 colonic adenomas), rectal polyps less than 3 cm in size, no colorectal dysplasia or cancer, a distensible and compliant rectum, and in patients with an intact sphincter mechanism who are willing to adhere to strict follow-up. Ileoproctostomy is an appealing alternative in younger patients of reproductive age to decrease the risk of impotence and reduced fecundity. Strict rectal surveillance (every 6–12 months) must be adhered to due to the increased risk of future neoplastic changes. The risk of rectal carcinoma can reach up to 40% by 30 years, though this is based on literature from the pre-IPAA era. In patients who require a completion proctectomy, an end ileostomy, restorative IPAA, or continent ileostomy are all options.

Restorative Proctocolectomy/Ileal Pouch Anal Anastomosis

Initially described in 1978 by Parks and Nicholls, the restorative proctocolectomy has become the most common continence-preserving procedure performed in patients who are appropriate candidates. Indications include severe polyposis (>20 rectal, >1000 colonic adenomas), rectal polyps larger than 3 cm in size, colonic dysplasia or cancer, dysplastic rectal polyps, and patients with an intact sphincter mechanism willing to adhere to strict follow-up. The restorative pouch can be fashioned in two limbs (J), three limbs (S), four limbs (W), or isoperistaltic (H) configurations. The J-pouch, due to its ease of construction and excellent functional outcomes, has become the most common choice for surgeons.

A total colectomy is performed in an oncologic fashion, and the ileum is transected flush with the cecum (Fig. 1). To provide adequate perfusion to the pouch, it is imperative to preserve the ileal branches of the ileocolic and distal mesenteric arteries. Evaluation for adequacy of reach of the small bowel to the deep pelvis should be undertaken before creation of the pouch. The proposed point of the pouch-anal anastomosis can be pulled down to the pubis, and if this point can be easily advanced 3 to 4 cm below the inferior edge of the pubis, one can feel confident of successful reach for anastomosis. Strategies to decrease tension at the anastomosis include complete mobilization of the small bowel mesentery to the root of the superior mesenteric artery cephalad to the head of the pancreas (Fig. 2), proximal division of the ileocolic artery (Fig. 3), and relaxing incisions of the mesentery over tension points along the superior mesenteric artery (Fig. 4). Rectal dissection is completed in the TME plane, and transection of the rectum with a 30- to 40-mm transverse stapler

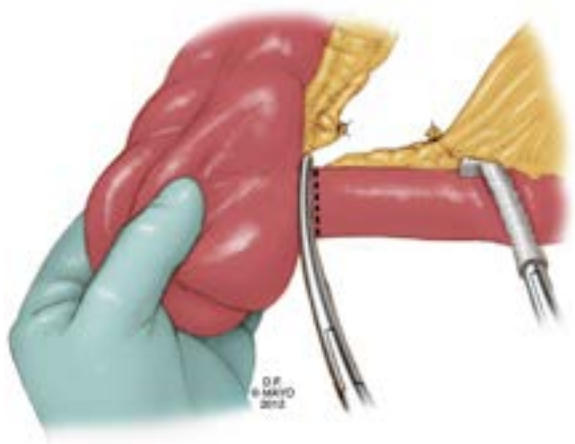


FIG. 1 Transection of ileum flush with cecum. *(From Kelley SR, Dozois EJ. Ulcerative colitis. In* A Companion to Specialist Surgical Practice: Colorectal Surgery. *5th ed. Edinburgh: Elsevier; 2014:129.)*

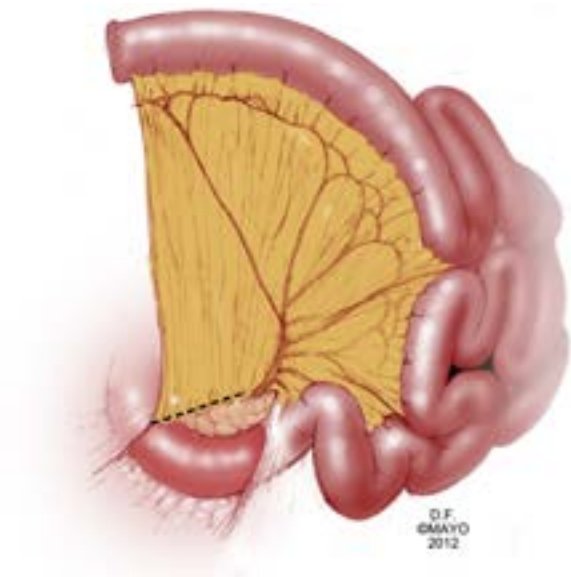


FIG. 2 Mobilization of the small bowel mesentery to the root of the superior mesenteric artery. *(From Kelley SR, Dozois EJ. Ulcerative colitis. In* A Companion to Specialist Surgical Practice: Colorectal Surgery. *5th ed. Edinburgh: Elsevier; 2014:131.)*

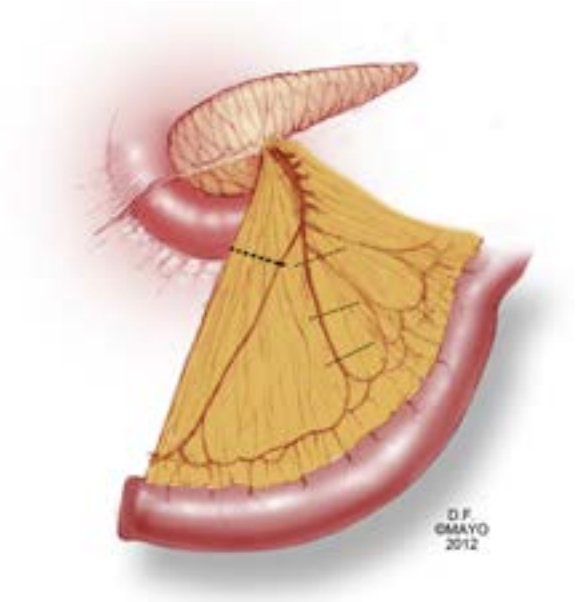


FIG. 3 Division of the ileocolic artery. *(From Mayo Foundation for Medical Education and Research.)*

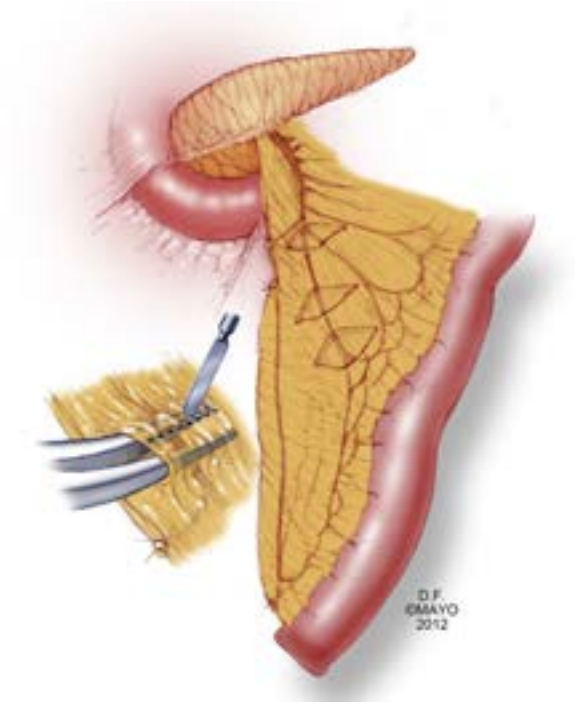


FIG. 4 Mesenteric relaxing incisions. *(From Mayo Foundation for Medical Education and Research.)*

should occur 2 to 3 cm above the dentate line in the anal transition zone (ATZ) (Fig. 5). After reach has been verified, a J-configuration is fashioned with each limb measuring between 12 to 15 cm in length. The limbs are paired in an antimesenteric fashion and held in orientation with interrupted stay sutures. For those without evidence of adenomas in the ATZ or dysplasia in the lower rectum, a double-stapled IPAA can be fashioned, otherwise an anal mucosectomy and handsewn IPAA is recommended. Following creation of the IPAA, an air insufflation leak test is performed and, if necessary, a protective loop ileostomy fashioned, which should be created as close

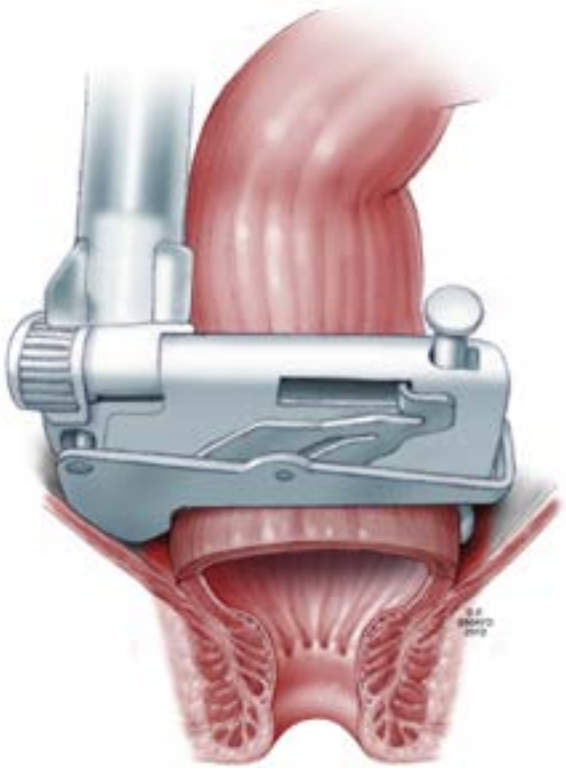


FIG. 5 Rectal transection. *(From Kelley SR, Dozois EJ. Ulcerative Colitis. In* A Companion to Specialist Surgical Practice: Colorectal Surgery. *5th ed. Edinburgh: Elsevier; 2014:132.)*

to the pouch as possible to decrease issues with high output and in the unlikely case that a redo-IPAA would need to be performed. In selected patients, the operation can be completed with good results without the creation of a diverting loop ileostomy.

Double-Stapled Technique

An enterotomy is made in the antimesenteric apex of the pouch, and a linear cutting stapler is used to divide the walls of the two limbs creating a common channel (Fig. 6). A purse-string suture is then fashioned around the enterotomy, and the anvil from a circular stapler is placed inside the pouch where it is held in place by tightening the purse string (Fig. 7). The circular stapler is then placed transanally. After appropriate orientation, the circular stapler cartridge spike is advanced either above or below the transverse rectal staple line and attached to the anvil. The stapler is then closed, approximating the pouch and anus (Fig. 8).

Handsewn Technique

An anal canal mucosectomy is performed starting at the dentate line. Raising the mucosa with a submucosal injection (Fig. 9) of dilute saline and epinephrine (1:200,000) facilitates dissection of the mucosa away from the internal sphincter muscle (Fig. 10), which can be completed sharply or with electrocautery. After the mucosa and proximal rectum have been removed circumferentially, the pouch is gently brought down to the level of the dentate line. An enterotomy is made in the apex of the pouch, if not already created, and it is anchored in position by placing a suture in each of the four quadrants incorporating a full thickness bite of the pouch, internal sphincter muscle, and mucosa. Sutures are placed between the anchoring stitches to complete the anastomosis (Fig. 11).

Postoperative Surveillance

After the creation of an IPAA or IRA, lifelong interval lower endoscopic surveillance is required for adenomas, dysplasia, and



FIG. 6 J-pouch creation. *(From Mayo Foundation for Medical Education and Research.)*



FIG. 7 Anvil in J-pouch. *(From Mayo Foundation for Medical Education and Research.)*

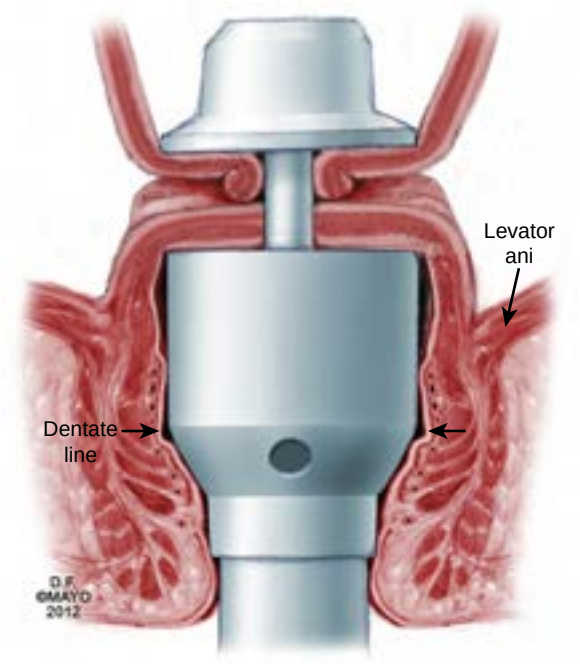


FIG. 8 Stapled ileal pouch anal anastomosis. *(From Mayo Foundation for Medical Education and Research.)*

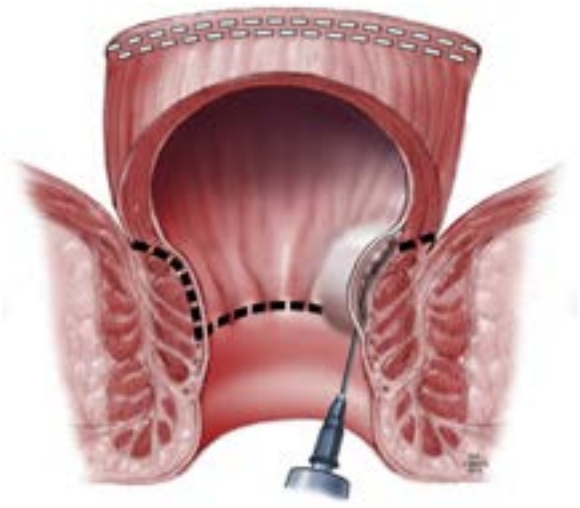


FIG. 9 Submucosal injection. *(From Mayo Foundation for Medical Education and Research.)*

carcinomas at 1- to 2-year or 6-month to 1-year intervals, respectively. Histologic evaluation of random biopsies and polyps should be performed to exclude dysplasia and cancer. More frequent surveillance is performed for increased numbers or size of polyps. Severe dysplasia and villous adenomas >1 cm in size should prompt a completion proctectomy in those with an IRA. Following TPC with end ileostomy, yearly stoma site surveillance by a stoma nurse or experienced practitioner is recommended due to the rare development of ileal adenocarcinoma, most commonly near the mucocutaneous junction in the setting of long-standing ileostomies.

OTHER POLYPOSIS SYNDROMES

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited disease resulting most commonly from a mutation in the *LKB1* (*STK11*) tumor suppressor gene located on chromosome 19p13. Anywhere from 30% to 40% will occur de novo. Hamartomatous polyps are found throughout the GI tract, though most commonly in the small intestine. Extraintestinal manifestations are common

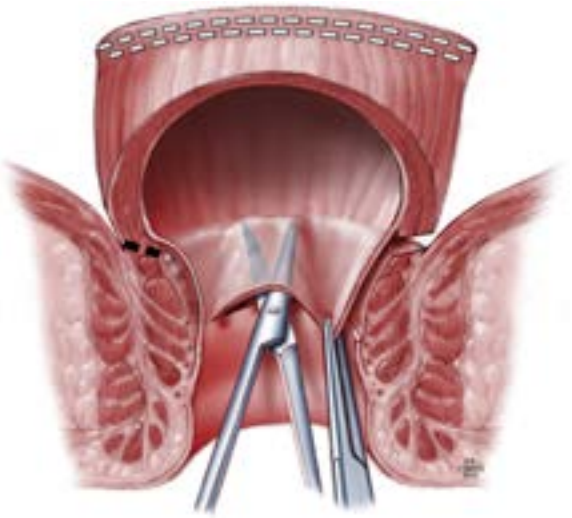


FIG. 10 Anal mucosectomy. *(From Kelley SR, Dozois EJ. Ulcerative Colitis. In* A Companion to Specialist Surgical Practice: Colorectal Surgery. *5th ed. Edinburgh: Elsevier; 2014:134.)*

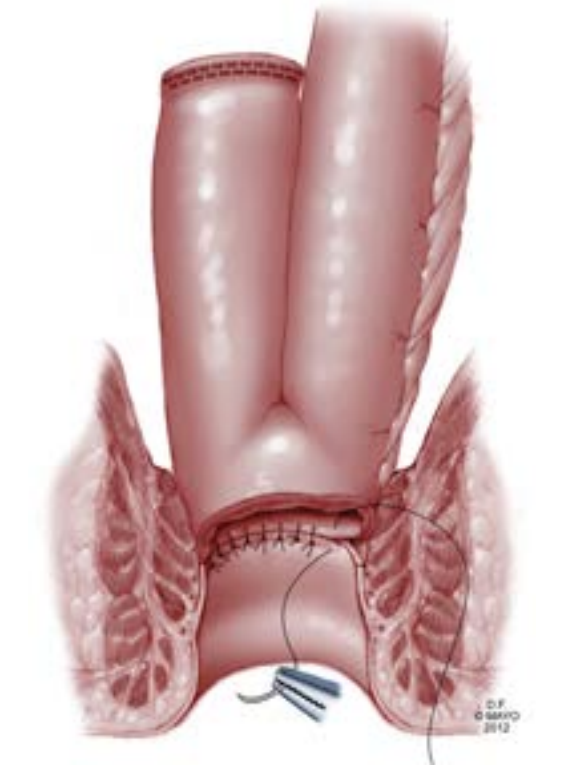


FIG. 11 Hand sewn ileal pouch anal anastomosis. *(From Mayo Foundation for Medical Education and Research.)*

with the hallmark phenotypic feature in adolescence being mucocutaneous hyperpigmentation that can affect the perioral and buccal region, eyes, nostrils, perianal region, fingers and toes, and hands and feet. Hyperpigmentation dissipates as one ages. Hamartomatous polyps and mucocutaneous pigmentation confirms a diagnosis of PJS. Presenting symptoms can include abdominal pain, alteration in bowel habits, weight loss, bowel intussusception, anemia, hematochezia and melanotic stools, and small bowel obstruction. The risk of malignancy increases with age (13-fold higher than the general population) with the most common cancers being colorectal, breast, pancreatic, and genitourinary.

Colonoscopy and EGD should be initiated at 8 years of age. If polyps are detected, endoscopic evaluation should continue every 2 to 3 years. If no polyps are found, repeat endoscopy and small bowel follow-through or capsule enteroscopy should be initiated by 20 years of age and repeated every 2 to 3 years. Other surveillance recommendations with low levels of evidence include an annual clinical exam, annual testicular ultrasound starting at age 10, monthly breast exam and annual breast MRI starting at 18 years of age, cervical smear starting at age 25, and magnetic resonance cholangiopancreatography (MRCP) of the pancreas starting at 25 years of age.

GI surgery is reserved for symptomatic disease or cancer. Any polyp larger than 1.5 cm should be removed, if possible, at the time of surgery. Intraoperative on-table endoscopy can be utilized to evaluate the entire GI tract.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant inherited disease resulting most commonly from mutations in the *SMAD4* and *BMPR1A* genes, which are respectively located on chromosomes 18q21 and 10q22. Polyps can be found throughout the GI system with the colon being affected 100% of the time. Extraintestinal manifestations occur around 15% of the time and can include cleft lip and palate, polydactyly, genitourinary anomalies, intestinal malrotation, hydrocephalus, and congenital heart disease. Hereditary hemorrhagic telangiectasia and bleeding arteriovenous malformations (AVMs) are associated with some *SMAD4* mutations and are found in the GI tract, lungs, brain, and mediastinum. Diagnosis of JPS is confirmed when five or more juvenile polyps are found in the colon or rectum, multiple polyps are appreciated in other regions of the GI tract, or after identification of polyps with a positive family history. Presenting symptoms can include hematochezia and melanotic stools, anemia, intussusception, obstruction, and passage of autoamputated or prolapsed polyps. Colorectal cancer is the most common associated malignancy with lifetime rates as high as 39%. Other malignancies include gastric, duodenal, and pancreatic.

Asymptomatic patients should begin with screening colonoscopy by 12 to 15 years of age and earlier for those with symptoms. If no polyps are detected, evaluation can be repeated every 2 to 3 years, otherwise annually. EGD is recommended by age 15. Those with a *SMAD4* mutation should have periodic screening for AVMs.

Colorectal surgery is reserved for symptomatic disease, dysplasia, cancer, or significant polyp burden (>100 polyps). For those with a relatively spared rectum, a TAC with IRA can be pursued, and if the rectum is significantly involved, a TPC with IPAA is advisable. Surgeries in the remaining GI tract may also be warranted.

Cowden's Syndrome

Cowden's syndrome (CS) is an autosomal dominant disorder resulting from a mutation in the *PTEN* tumor suppressor gene located on chromosome 10q23. Polyps typically occur in the colon and stomach, and colonic polyps can include hamartomas, fibromas, adenomas, lipomas, and neurofibromas. Extraintestinal manifestations include pathognomonic trichilemmomas, macrocephaly, and a wide variety of tumors and hamartomas of various organ systems (breast, thyroid, uterus).

The increased risk of colorectal cancer is estimated to be two or three times the general population (9%–16%). National Comprehensive Cancer Network (NCCN) guidelines recommend a screening colonoscopy starting at the age of 35. Thyroid screening with physical exam and ultrasound should be performed annually and begin at age 15. Annual mammography, with MRI for suspicious findings, should begin at the age of 30. Treatment is based on symptoms and pathology.

Bannayan-Riley-Ruvalcaba Syndrome

Bannayan-Riley-Ruvalcaba syndrome (BRRS) is an autosomal dominant disorder resulting from a mutation in the *PTEN* tumor

suppressor gene located on chromosome 10q23. Common findings associated with BRRS include pigmented penile macules, macrocephaly, hamartomas, hemangiomas, and mental retardation in upward of 50%.

The risk of developing colon and rectal cancer is thought to be no greater than the general population. Treatment is based on symptoms.

Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome (CCS) is a noninherited disorder resulting from a mutation in the *PTEN* tumor suppressor gene located on chromosome 10q23. Hamartomatous GI polyps in addition to alopecia, macrocephaly, onycholysis, and cutaneous pigmentation are common findings. Diffuse GI inflammation resulting in malabsorption, diarrhea, and protein-losing enteropathy can occur.

The risk of developing colon and rectal cancer is thought to be greater than the general population. Treatment is based on symptoms and pathology.

Hereditary Mixed Polyposis Syndrome

Hereditary mixed polyposis syndrome (HMPS) is thought to be an autosomal dominant inherited syndrome, though a specific mutation has yet to be identified. HMPS presents with multiple different colon and rectal polyps (adenomatous, hamartomatous, and hyperplastic).

The risk of developing colon and rectal cancer is thought to be greater than the general population, although this is unsubstantiated at this time. Screening colonoscopy should begin between the ages of 25 to 30. Treatment is based on symptoms and pathology.

Serrated Polyposis Syndrome

Serrated polyposis syndrome (SPS) is a disorder characterized by multiple polyps (hyperplastic or serrated) throughout the colon. A heritable pattern and genetic cause has not been identified. The World Health Organization has proposed two criteria for diagnosing SPS, of which diagnosis is made upon fulfillment of either of the criteria. The criteria include (1) at least five serrated polyps, all greater than 5 mm in size and proximal to the rectum, two of which are greater than 10 mm in diameter, or (2) more than 20 serrated polyps of any size distributed throughout the large intestine with five being proximal to the rectum. These criteria distinguish the two SPS phenotypes; large serrated polyp proximal disease and distal small serrated polyp distal disease.

The risk of developing colon and rectal cancer is increased with rates of up to 25% to 70% documented in those with multiple polyps. The average age for developing colon and rectal cancer is 50 to 60. Treatment is based on polyp burden and dysplastic or neoplastic changes.

Strict surveillance with colonoscopy every 1 to 2 years is advisable. First-degree relatives are at an increased risk of SPS and developing colon and rectal cancer (5-fold), and should be offered the same surveillance starting at 40 years of age or 10 years younger than the index case.

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Surgical Management of Colon Cancer

Mohamad A. Abdulhai, MD, and Michael A. Choti, MD

Colon cancer is the third most common cancer and cause of cancer death in the United States. An estimated 4.5% of the US population will be diagnosed with colon cancer in their lifetime. Fortunately, the mortality from colon cancer has been declining in recent decades, in part as a result of improvements in screening, surgical management, and chemotherapeutic options. The incidence of colon cancer in older adult patients has been steadily declining; however, we have been seeing an increase in frequency in patients younger than 50 years of age. More than two-thirds of colorectal cancers arise in the colon, defined as the intraabdominal portion of the large bowel that extends from the cecum to the peritoneal reflection. Although the biologic distinction between the colon and rectum is somewhat arbitrary, the oncologic behavior and cancer management differs considerably. Yet, similar to rectal malignancies, colon cancer is also best managed using a multidisciplinary team approach to optimize outcome. This chapter reviews the preoperative evaluation, clinical staging, and management of patients with colon cancer, highlighting the importance of a multidisciplinary approach.

CLINICAL PRESENTATION AND SCREENING

Colon cancer patients can present with a variety of gastrointestinal symptoms, depending on the size and location of the tumor. This can include abdominal pain, hematochezia, weight loss, anemia, constipation, diarrhea, or change in the caliber of stools. Classically, right-sided tumors tend to present with anemia, whereas, left-sided cancers are more likely to present with obstructive symptoms. However, many patients with colon cancer are asymptomatic at the time of diagnosis and identified by screening. This highlights the importance of screening to detect colon cancer before it becomes symptomatic. Implementation of increased screening, including colonoscopy, has contributed to the decline in colon cancer-related mortality seen in the past 20 years.

Screening for average-risk adults is now recommended to begin at age 45. There are several options for screening, including colonoscopy every 10 years, multitarget stool DNA testing every 3 years, annual fecal immunochemical testing, annual fecal occult blood testing with flexible sigmoidoscopy every 5 years, or double-contrast enema and CT colonography every 5 years. Those at higher risk for the development of colorectal cancer may require more frequent screening. In some conditions such as familial polyposis syndromes or hereditary nonpolyposis (Lynch syndrome), prophylactic colectomy may be indicated. Options for screening for colorectal cancer may be changing in the future, particularly with the application of newer technologies for the detection of minute fragments of circulating tumor DNA (ctDNA) in the bloodstream. Studies are underway evaluating the role of ctDNA for cancer screening.

PREOPERATIVE EVALUATION AND STAGING

The initial evaluation may depend on the type and severity of symptoms the patient is experiencing, in some cases necessitating more urgent intervention. In most cases, colon cancer presents more electively, affording the opportunity for careful evaluation and staging. Adequate preoperative colonoscopy is important to assess the details of the colon tumor, including the size, location, and extent. Biopsy provides histologic confirmation and characterization of pathologic features such as tumor grade, microsatellite status, and in some cases molecular sequencing. However, in some cases of invasive cancer, the biopsy may miss the invasive component. In such cases, one must be careful not to assume no malignancy if the biopsy is negative, particularly with a presentation or appearance consistent with cancer. During colonoscopy, it is important to ensure that the entire colon is examined when possible as ~5% of patients have a synchronous cancer and ~10% to 20% have a synchronous advanced polyp, which might alter the surgical plan. In some cases, an endoscopically obstructing distal tumor may prevent the ability to evaluate the proximal colon. In such cases, one can evaluate the proximal colon intraoperatively or with a colonoscopy 3 to 6 months after resection. During colonoscopy, tattooing should be considered in some cases to facilitate intraoperative detection.

Routine blood analysis should be obtained, including a complete blood count and metabolic profile. In addition, a preoperative carcinoembryonic antigen (CEA) level should be measured. It is important to obtain a baseline CEA level to compare with postoperative levels on surveillance and to alert to the increased probability of advanced disease. Cross-sectional imaging, most commonly CT, is also important before surgical intervention to determine the extent of local disease and assess for metastatic disease. Fluorodeoxyglucose positron emission tomography (FDG-PET) is not routinely recommended for the initial evaluation and should be used only selectively when the imaging is inconclusive or preoperative CEA is high (>20 ng/mL).

SURGICAL MANAGEMENT

Preoperative Preparation

The management of colon cancer depends on the stage at presentation. The majority of patients with stage I to III colon cancer can be managed with initial surgical resection with curative intent. The goal of surgical resection is removal of the primary tumor in its entirety with negative margins in addition to performing a complete lymphadenectomy of the draining lymph nodes. In cases in which the tumor involves adjacent organs, en bloc resection of those structures should also be considered. In cases of more advanced disease (stage IV), surgical resection of the primary tumor is done selectively, either palliatively for those with significant symptoms or as part of a curative-intent approach combined with metastatectomy.

The patient should undergo medical optimization before surgery to ensure safety of proceeding with an abdominal operation under general anesthesia. Both mechanical and oral antibiotic bowel preparations should be performed to decrease the risk of infectious complications. This includes a clear liquid diet the day before surgery and consumption of a purging solution such as polyethylene glycol (GoLYTELY or MiraLAX). In addition, patients are given oral antibiotics (e.g., neomycin and metronidazole) concurrently with the mechanical bowel preparation.

As with other complex operative procedures, the perioperative management of patients undergoing elective colorectal surgery should be guided by enhanced recovery protocols to improve outcomes, standardize care, and lower healthcare costs. Such pathways focus on improved pain management and minimizing narcotics by using a multimodal pain regimen. In addition, early mobilization, early feeding, and limiting fluid administration is important to hasten the return of bowel function and improve recovery.

The patient should receive prophylactic intravenous antibiotics before skin incision to reduce the risk of surgical site infection. In addition, patients should receive subcutaneous heparin and a sequential compression device placed before induction of anesthesia for venous thromboembolism prophylaxis. An indwelling urinary catheter is typically used. The patient is positioned supine for right-sided lesions and in the modified lithotomy position for left-sided lesions to allow access to the perineum for use of the end-to-end stapler and intraoperative endoscopy.

Operative Approach

The choice of operative method for colon resection can vary based on surgeon experience and patient/tumor factors. Several large multicenter randomized controlled trials have shown equivalent oncologic outcomes (e.g., nodal harvest, recurrence, survival) between open and laparoscopic colectomy. In most cases, a minimally invasive approach results in less pain, shorter hospital stay, and faster recovery, and it is recommended whenever the appropriate expertise is available. More recently, the use of robot-assisted surgery has been advocated as an alternative minimally invasive approach. Although few randomized trials have been conducted comparing robotic versus laparoscopic colectomy, improved visualization, facilitated intracorporeal anastomosis, and lower conversion rates may promote the robotic technique, albeit at a higher cost. In cases of large and locally advanced tumors requiring multivisceral resection, an open colectomy remains the preferred approach in most cases.

Colon Resection

Regardless of whether a minimally invasive or open approach is used, the technical and oncologic principles during surgery are the same. A thorough exploration of the abdomen should be initially performed to assess for metastatic disease. This includes visual inspection and, when possible, palpation of the peritoneal cavity along with the abdominal and pelvic organs, including the liver, omentum, and peritoneal surfaces. A curative resection of colon cancer entails removal of the involved segment of colon along with its mesentery at the origin of the feeding vessel. A 5- to 7-cm proximal and distal margin is typically recommended to ensure adequate removal of the pericolic lymph nodes. Histologic evaluation of a minimum of 12 lymph nodes is recommended to accurately determine nodal stage. Following extirpation, bowel continuity is restored using a tension-free, well-vascularized anastomosis. The alignment of the mesentery should be verified to avoid any torsion or internal hernia. Anastomotic technique can differ based on surgeon preference. Randomized studies have shown no difference in outcomes between stapled and handsewn techniques. Ileocolonic anastomoses are usually performed in a side-to-side functional end-to-end fashion. Colocolonic and colorectal anastomoses can be performed using either an end-to-end or side-to-end technique.

The extent of colonic resection depends on the location of the primary tumor and its draining lymphatic basin (Fig. 1). Tumors of the cecum, ascending colon, and hepatic flexure are managed with

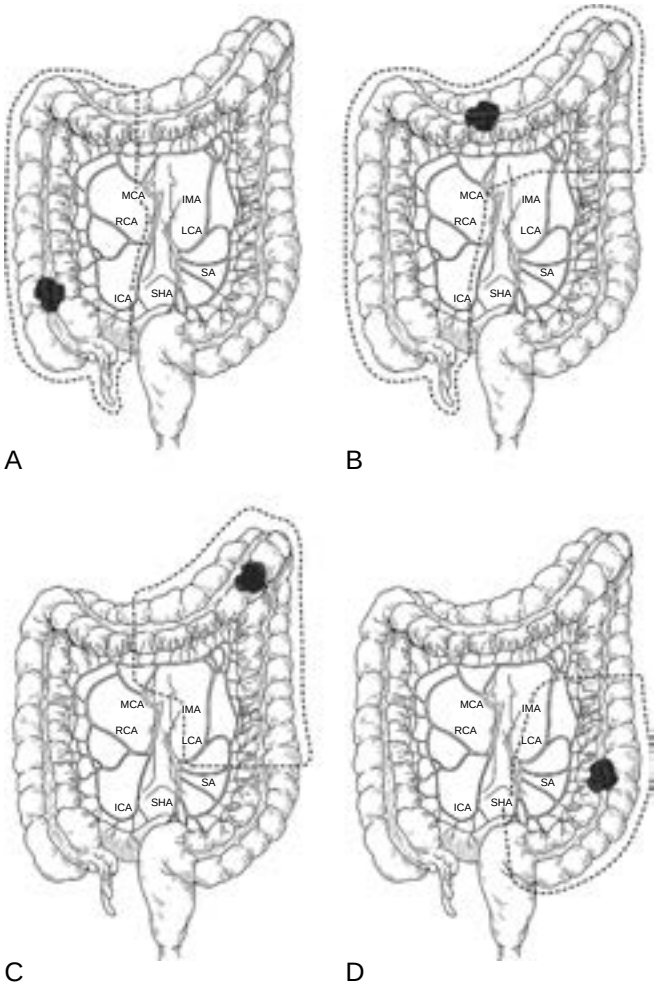


FIG. 1 Extent of resection for colon carcinoma. **(A)** Cecal or ascending colon cancer. **(B)** Transverse colon cancer. **(C)** Splenic flexure colon cancer. **(D)** Sigmoid colon cancer. *ICA*, Ileocolic artery; *IMA*, inferior mesenteric artery; *LCA*, left colic artery; *MCA*, middle colic artery; *RCA*, right colic artery; *SA*, sigmoidal arteries; *SHA*, superior hemorrhoidal artery. *(From Ruo L, Guillem JG. Cancer of the colon. In: Bland KI, Daly JM, Karakousis CP, eds. Surgical Oncology: Contemporary Principles and Practice. New York: McGraw-Hill; 2001.)*

a right hemicolectomy. This entails high ligation of the ileocolic and right colic vascular pedicles and preservation of the middle colic vessels. This is followed by removal of the terminal ileum, cecum, ascending colon, and hepatic flexure and construction of an ileotransverse anastomosis. Transverse colon cancers are managed depending on their location. Tumors of the mid or distal transverse colon are managed with an extended right hemicolectomy, which involves ligation of the ileocolic, right colic, and middle colic pedicles and removal of the cecum, ascending colon, transverse colon, and construction with an ileodescending anastomosis. Tumors of the splenic flexure or descending colon can be managed with either a left hemicolectomy or an extended left hemicolectomy. The former entails takedown of the splenic flexure with ligation of the left colic artery along with the left branch of the middle colic artery and construction of a transverse-to-sigmoid anastomosis. The latter involves ligation of the inferior mesenteric artery with anastomosis of the distal transverse colon to the upper rectum. The oncologic outcomes for either approach are considered equivalent. Sigmoid tumors are managed with anterior resection of the sigmoid colon performed by high ligation of the inferior mesenteric pedicle with anastomosis of the descending colon to the upper rectum.

SPECIAL SCENARIOS

Malignant Polyp

A malignant polyp is defined as an adenoma containing a focus of adenocarcinoma invading the muscularis mucosa into the submucosa (T1). About 5% of all endoscopically resected adenomas will contain invasive adenocarcinoma. Management of these polyps relies on detailed histopathologic examination of the specimen to estimate the risk of residual luminal cancer and the risk of lymph node metastasis. This in turn will determine whether endoscopic resection is sufficient or an oncologic segmental resection is warranted. If a negative histologic margin cannot be assessed, repeat endoscopy or segmental resection may be required. High-risk features for lymph node involvement include poor differentiation, deep submucosal invasion, presence of lymphovascular or perineural invasion, high tumor budding score, and positive endoscopic resection margin. Sessile polyps in general confer a higher risk of lymph node metastasis compared with pedunculated polyps. A 2-mm negative resection margin is considered adequate. The depth of invasion into the submucosa is also predictive of occult lymph node metastasis, and several classification systems have been developed to estimate the risk. The first is the Haggit classification for pedunculated polyps. In the absence of other high-risk features, the risk of lymph node metastasis in Haggit level 1, 2, and 3 lesions is less than 1%, but it can be up to 30% in Haggit level 4 polyps. The other commonly used classification system is the Kikuchi system, which evaluates the depth of invasion into the submucosa. The submucosa is divided into thirds: upper (Sm1), middle (Sm2), and lower (Sm3). The risk of lymph node metastasis for Sm1 tumors is 1% to 2%, Sm2 is <10%, and Sm3 is 20% to 25%. The application of the Kikuchi classification following endoscopic resection can be problematic as the muscularis propria layer is usually not included in the specimen. Therefore, alternatively the absolute depth of invasion into the submucosa is used with depth of invasion less than or equal to 1 mm conferring a low risk of lymph node metastasis.

Patients who undergo complete adequate endoscopic resection and are considered to have a very low risk of occult lymph node metastasis must be closely monitored for recurrence. There is currently no established standard for surveillance after endoscopic resection of malignant polyps in patients who do not undergo surgery. However, most experts recommend surveillance colonoscopy in 3 to 6 months. It is crucial to ensure that the site of the polypectomy is marked with a tattoo at the time of polypectomy or soon after (within 2 weeks) to allow for identification of the polypectomy scar on subsequent surveillance colonoscopies.

Locally Advanced Cancer

Locally advanced colon cancers with invasion of surrounding structures (T4) are seen in 5% to 10% of cases. Some of the most commonly involved organs include the small bowel, bladder, spleen, duodenum, and stomach. Detailed evaluation using cross-sectional imaging (CT scan or MRI) is important preoperatively to recognize multivisceral involvement. When possible, an en bloc multivisceral resection should be done to achieve an R0 resection and offer the best chance for cure. In such cases, neoadjuvant chemotherapy and sometimes radiation therapy can be used to improve the ability to achieve complete resection. This is reported in the FOxTROT international randomized controlled trial, which showed a 59% evidence of histologic downstaging and halving the rate of incomplete resections when using neoadjuvant chemotherapy. In addition, neoadjuvant chemotherapy was well tolerated and did not increase perioperative morbidity. The long-term oncologic outcomes using this approach are yet to be determined.

Stage IV Cancer

About 20% to 25% of patients will present with synchronous metastatic disease. Colon cancer most commonly metastasizes to the liver,

followed by the lung and peritoneal cavity. The management of stage IV colon cancer can be complex. First, it is important to identify if the metastatic disease burden is considered resectable to determine if the patient falls under a curative intent paradigm of treatment. Second, one should evaluate if the primary tumor is symptomatic, resulting in significant bleeding or obstruction. Recent evidence suggests less need for early palliative colectomy than in the past. Only if the primary cancer is appreciably symptomatic should the patient have this addressed with resection, diversion, or stenting before considering systemic therapy. Otherwise, early surgery is not indicated, and systemic chemotherapy is initiated. Even in symptomatic patients, it is not uncommon for the symptoms to improve following response to chemotherapy. The choice of first-line chemotherapy for advanced colon cancer typically includes a combination regimen of fluoropyrimidine, oxaliplatin, and/or irinotecan. In some cases, a biologic therapy such as bevacizumab may be included. Caution must be used, however, when administering bevacizumab with a bleeding or partially obstructing colon cancer in situ as this agent may increase the risk of wound complications or bleeding.

If curative resection of the oligometastatic disease is being considered, surgical resection both of the primary tumor and metastases should be done, either in a staged or synchronous approach. The decision to proceed with which approach should be tailored to the individual patient and surgical availability, considering the patient's physical condition and the extent and magnitude of the primary resection and proposed metastatectomy. In general, one can perform a limited metastatectomy (e.g., minor hepatectomy) with primary resection in a single stage. More complex surgery such as a major hepatectomy can be combined with a simple primary resection, but extensive metastatectomy along with complex primary resection is best managed with a staged approach.

TUMOR-RELATED EMERGENCIES

Perforation

The management of perforated colon cancers can be quite challenging as the surgeon must address both the sepsis and contamination associated with the perforated colon while adhering to the oncologic principles of complete cancer resection when possible. Moreover, perforated tumors are associated with a higher risk of recurrence. Because emergent colectomy for perforation with primary anastomosis is associated with a higher risk of anastomotic leak, consideration of a proximal diversion (loop ileostomy) or resection with end colostomy/ileostomy with a Hartmann pouch may be prudent. When making this decision, one must consider the clinical condition and stability of the patient along with the quality of the bowel and degree of abdominal contamination.

Bowel Obstruction

Large bowel obstruction can be seen in up to one-third of newly diagnosed colon cancers. Left-sided tumors are more likely to cause obstruction compared with right-sided lesions. The management of obstructing colon cancer varies by location, degree of obstruction, and the clinical condition of the patient. The first step is to assess the acuity and degree of obstruction, determined by clinical examination and imaging. It is important to assess the degree of proximal colonic dilation on imaging and look for signs of impending perforation (significant dilation of the cecum to >10 cm or evidence of pneumatosis). One must also evaluate whether the ileocecal valve is competent as this can result in a closed-loop large bowel obstruction and a higher risk of perforation.

In general, obstructing right-sided lesions can be managed with a right or extended right hemicolectomy, often with primary anastomosis. In patients who are hemodynamically unstable, frail, or malnourished, end ileostomy or proximal diversion should be considered. The management of left-sided obstructing lesions can be more challenging. One must consider whether the tumor is resectable as well as the presence and extent of metastatic disease. When performing urgent surgery for an obstructing left-sided cancer, options for resection with anastomosis and diverting ileostomy, resection and end colostomy, simply diverting proximal colostomy without resection should be entertained.

Endoscopic stenting can also have a role in the management of obstructing left-sided tumors. In selected cases, stenting can allow for temporary decompression and bowel preparation and is followed by elective single-stage colectomy. In situations with more advanced disease, palliative stenting followed by systemic chemotherapy can be considered. Stenting should only be performed by experienced endoscopists to mitigate the risks of perforation, occlusion, and migration. Stenting therefore can be considered either as a bridge to curative intent surgical resection or in palliative cases in which patients have incurable disease, limited life expectancy, and poor surgical candidacy.

ADJUVANT THERAPY

The goal of adjuvant systemic chemotherapy following curative-intent resection of colon cancer is eradicating micrometastatic disease and increasing the probability for cure. The decision to offer adjuvant chemotherapy is largely based on nodal status. However, the final shared decision should be individualized, considering other risk factors for recurrence and the patient's general physical condition. In general, systemic adjuvant chemotherapy is indicated in stage III disease. Several large randomized clinical trials have demonstrated improvement in survival, with a 30% reduction in recurrence risk and mortality. In some cases, adjuvant chemotherapy can also be considered for patients with high-risk stage II colon cancer as their recurrence risk is similar to that of stage IIIA disease. The high-risk features include T4 tumors, poorly differentiated histology, <12 lymph node harvest, presence of lymphovascular or perineural invasion, obstructed or perforated tumors, and positive margins. A regimen including a fluoropyrimidine and oxaliplatin (FOLFOX or CapeOX) is typically recommended for adjuvant therapy following colectomy, most commonly for a 6-month duration. Recent randomized trials have found comparable benefit with shorter duration (3 months) in select cases. Studies are ongoing to evaluate the emerging role of ctDNA to detect minimal residual disease following resection of colon cancer. This technology may help more clearly identify which patients will derive benefit from chemotherapy and can reduce its use in those with a higher probability of surgical cure.

SURVEILLANCE

Postoperative surveillance is important to allow for early identification of recurrent disease. Based on guidelines from the National Comprehensive Cancer Network, patients with stage II or III colon cancer should undergo serial serum CEA testing every 3 to 6 months for the first 2 years, then every 6 months up to 5 years. CT scanning is recommended every 6 to 12 months for 5 years. Surveillance colonoscopy is recommended 1 year after resection and again in 3 years if no polyps are found.

CONCLUSION

Improvement in early detection, surgical techniques, and multidisciplinary management have led to improved outcomes for patients with colon cancer. Although operative approaches to colon resection can vary, the principles of oncologically adequate surgery remain standard. Importantly, adherence to evidence-based perioperative management can contribute to safer surgery, more rapid postoperative recovery, and improved long-term outcome. Beyond surgical technique, future discoveries in molecular genetics, screening, improved detection, risk determination, and systemic therapies will likely continue to improve outcomes in the next decade.

Suggested Readings

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PET Scanning in the Management of Colorectal Cancer

Joy Zhou Done, MD, and Sandy Hwang Fang, MD

INTRODUCTION

Accurate staging of disease is crucial to the management of colorectal cancers. Widely disseminated disease is a contraindication to surgical resection of a primary tumor, and thus the detection of metastatic disease provides important information to guide therapeutic goals. According to National Comprehensive Cancer Network (NCCN) guidelines, computed tomography (CT) and magnetic resonance imaging (MRI) play a significant role in the initial diagnosis, staging, and management of colorectal cancer (CRC); however, these imaging techniques provide only anatomic information about the tumor. The use of positron emission tomography (PET) as a hybrid to tomographic imaging, such as CT and MRI, adds functional data to these imaging modalities (Figs. 1 to 3; Table 1). The combined acquisition of PET CT provides more accurate information than either study alone by capturing quantitative data from regions of interest (ROI) to provide information about the entire cancer phenotype or microenvironment. Parametric analysis (PA) allows the extraction of numerical data contained in the voxels of each image to determine tumor biology of a specified ROI. PA can characterize tumor perfusion, heterogeneity, cellularity and fibrosis, oxygenation, and glucose consumption within an ROI using quantitative data on spatial complexity, density, signal intensity, activity, and distributions. This chapter describes the functional utility of PET scanning in the management of CRC, which gives information beyond what is delineated through visual inspection by CT or MRI alone.

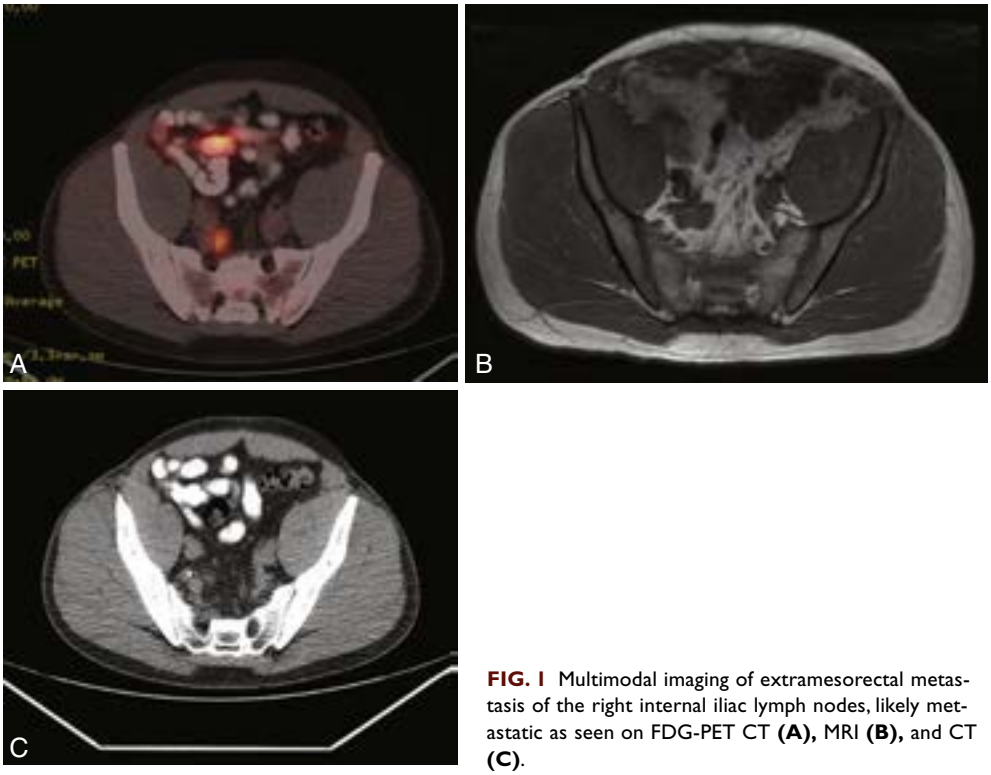


FIG. 1 Multimodal imaging of extramesorectal metastasis of the right internal iliac lymph nodes, likely metastatic as seen on FDG-PET CT **(A),** MRI **(B),** and CT **(C)**.

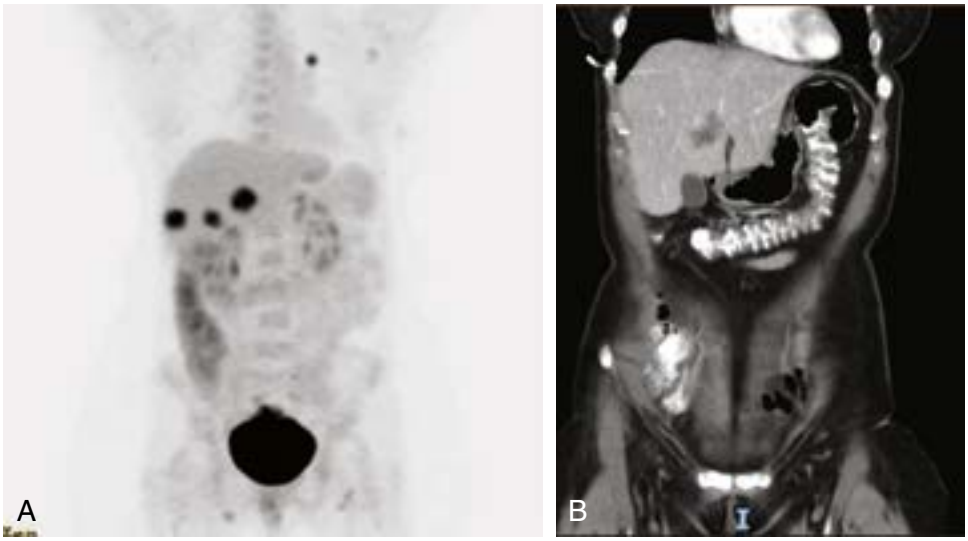


FIG. 2 Multiple FDG-avid hepatic lesions representing metastatic disease as seen on FDG-PET scan **(A)**; ill-defined hypodense hepatic mass as seen on CT **(B)**.

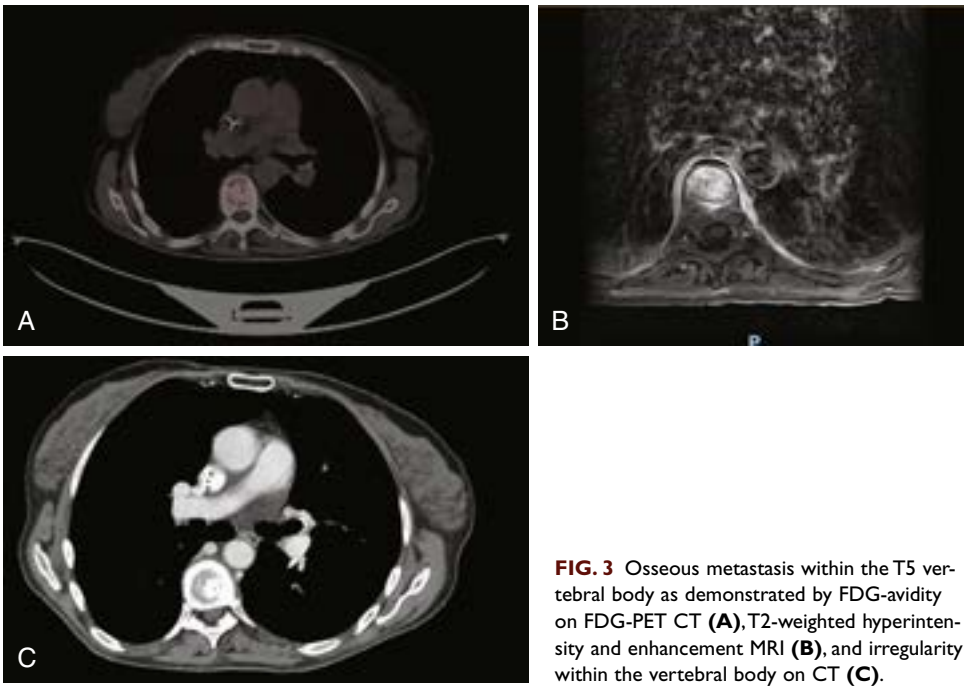


FIG. 3 Osseous metastasis within the T5 vertebral body as demonstrated by FDG-avidity on FDG-PET CT **(A)**, T2-weighted hyperintensity and enhancement MRI **(B)**, and irregularity within the vertebral body on CT **(C)**.

TABLE 1 Sensitivity and Specificity of Imaging Modalities Used in Detection of Hepatic Metastases in CRC

	Sensitivity (%)	Specificity (%)
Contrast-enhanced CT	84	95
MRI	88	93
FDG-PET/CT	97	97

From Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG-PET, and/or FDG-PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology.* 2010;257(3):674–684.

POSITRON EMISSION TOMOGRAPHY CONCEPTS AND DEFINITIONS

PET is a diagnostic nuclear imaging study that measures uptake of 2-deoxy-2-[fluorine-18]fluoro-D-glucose (18F-FDG), an analogue of glucose, to detect metabolic abnormalities based on increased glucose uptake and glycolysis in cells of the body. Cancer cells have increased glucose metabolism compared with normal cells and thus higher FDG uptake in viable cancer cells. Standardized uptake value (SUV) evaluates the metabolic uptake of FDG in tumor cells. SUV may be quantified as the standardized maximum (SUV_{max}) or mean (SUV_{mean}) uptake. SUV_{max} is defined as the highest uptake value of the most intense pixel inside an ROI divided by the injected dose (corrected for decay and normalized for the patient's body weight or body surface area). SUV_{max} does not reflect overall tumor behavior because several confounding factors might affect SUV measurement: tumor heterogeneity, body size, image acquisition time, and partial volume effects. The SUV_{mean} is the average of all the pixel uptake values within an ROI. Increased SUV_{mean} values represent higher metabolic rates, which correlate with more aggressive tumor histology and worse overall survival (OS). Volumetric parameters of PET CT studies reflect the burden of the metabolically active tumor. The metabolic tumor volume (MTV) is the volume of tumor tissue with pathologic FDG uptake within a three-dimensional ROI. Total lesion glycolysis (TLG) is calculated by multiplying the SUV_{mean} by MTV.

INITIAL DIAGNOSIS, WORKUP, AND STAGING OF COLORECTAL CANCER

In the most current NCCN guidelines, initial staging of CRC involves a CT of the chest, abdomen, and pelvis to evaluate for the presence of distant metastasis. In rectal cancer, MRI is used for initial tumor and nodal staging. PET CT is not indicated in the initial workup of a pedunculated or sessile polyp with invasive cancer or resectable CRC (nonmetastatic) (stages I–III). Of note, mucinous tumors have no FDG uptake and account for ~17% of CRCs. PET CT also has limited sensitivity in detecting metastatic tumors less than 10 mm. Special consideration may be given to patients with a significant allergy to iodinated or gadolinium contrast or renal failure. In these circumstances, MRI without contrast or FDG-PET CT is recommended. FDG-PET CT may also be considered in cases where CT or MRI yields equivocal or nondiagnostic information to assist in percutaneous or surgical biopsy for a tissue diagnosis.

There is no established consensus regarding criteria to differentiate between benign, premalignant, or malignant lesions based on standard CT or MRI imaging. A small series evaluating 76 rectal cancer patients with preoperative FDG-PET CT determined that an MTV threshold of 2.5 predicted pathologic T3 and T4 staging as opposed to T1 and T2 staging (odds ratio, 1.81; 95% confidence interval, 1.26-2.60; $P = 0.001$).

Preoperative nodal staging (N-staging) with FDG-PET CT requires accurate identification of pericolorectal and mesenteric lymph nodes with metastatic disease. Studies have evaluated the cut-off value of SUV_{max} of 1.5 or 2.0, both values significantly increasing the identification of malignant lymph nodes. FDG-PET CT has been found to increase the accuracy of N-staging from 48% to 66% when compared to CT, with a potential change in rectal cancer management by 26%. False-negative FDG-PET CT results can be due to intense FDG uptake by the primary tumor, which can obscure adjacent structures, as well as low FDG uptake in microscopically positive nodes. For this reason, FDG-PET CT has been found to have low sensitivity for regional lymph node metastases. In two small, prospective studies comparing contrast enhanced CT with FDG-PET CT in patients with rectal cancer, PET CT altered the staging in nearly one-third of cases, and altered staging (primarily due to revised nodal status). This changed the management strategy and/or surgical plan in up to 14% of the cases. Despite a handful of positive studies, others have found that the routine use of PET CT for preoperative staging in colon and rectal cancers did not impact disease management in more than 96% of patients.

The major advantage of FDG-PET CT compared with contrast-enhanced CT is its superiority in identifying extrahepatic metastatic lesions with a high accuracy of up to 97%. Regarding lung metastases, some studies demonstrate high positive predictive value (PPV) and negative predictive value (NPV) for FDG-PET CT (90% and 94%, respectively), whereas other studies show similar low accuracy both for FDG-PET CT and CT. For liver metastases, a meta-analysis reported the sensitivity and specificity of FDG-PET CT to be 74.1% and 93.9%, respectively. The role of FDG-PET CT in the diagnosis, workup, and preoperative management of liver metastases will be discussed further in this chapter.

THE ROLE OF PREOPERATIVE FDG-PET CT IN COLORECTAL MALIGNANCY

The panel for NCCN strongly discourages the routine use of FDG-PET CT scanning for staging, baseline imaging, or routine follow-up. However, the panel recommends consideration of a preoperative FDG-PET CT at baseline if prior anatomic imaging indicates the presence of potentially surgically curable metastatic disease (M1). Two different meta-analyses studying more than 3000 study participants have demonstrated that FDG-PET CT may identify unrecognized metastatic disease that would preclude the possibility of surgical management, such as hepatic resection or radiofrequency ablation.

POSTTREATMENT EVALUATION OF COLORECTAL MALIGNANCY

In the past decade, overall survival has improved as a result of the introduction of treatment options, such as new chemoradiation therapy techniques (e.g., total neoadjuvant therapy [TNT]) and immunotherapy. However, it remains a challenge to determine which patients are optimal candidates for what type of therapy. Currently, we rely on response evaluation after treatment. It is difficult to predict response to treatment at treatment outset and long-term outcomes. Imaging is routinely used during diagnosis and follow-up and may aid in identifying noninvasive biomarkers that could determine response and long-term outcomes and ultimately tailor treatment regimens for CRC.

Standard assessment of the response to chemotherapy utilizes Response Evaluation Criteria in Solid Tumor (RECIST) to measure the change in size of the posttreatment tumor. However, these criteria do not take into account information about intralesional features, such as tumor necrosis.

In the posttreatment setting, a decrease in SUV on FDG-PET CT following treatment correlates to a greater chance of a complete response and improved long-term survival. A preliminary case series evaluated response to neoadjuvant chemoradiation therapy (nCRT) for rectal cancer 12 days after beginning nCRT identified a ≥52% decrease in SUV_{mean} for responders, of whom responders had a 5-year recurrence-free survival that was significantly higher than that of nonresponders.

On a cautionary note, PET CT may be transiently negative after chemotherapy, despite the presence of residual microscopic cancer cells that may not allow for sufficient FDG uptake. In addition, false-positive PET CT results can occur in the presence of tissue inflammation after surgery or infection.

COLORECTAL CANCER SURVEILLANCE

NCCN guidelines recommend that serial carcinoembryonic antigen (CEA) levels, colonoscopies, and CT scans are obtained for

CRC surveillance. FDG-PET CT is not indicated in standard CRC surveillance.

As per NCCN guidelines, circumstances that may warrant FDG-PET CT are reserved for select patients, in which distant recurrence workup with metachronous metastases is documented by CT, MRI, or biopsy. In this situation, FDG-PET CT determines whether there are other distant metastases that would disqualify the patient from surgery and thus make the patient a candidate for systemic chemotherapy. FDG-PET CT plays an important role in the detection of recurrence in patients who have an unexplained rise in their CEA levels. Residual soft tissue abnormalities are frequently seen in the tumor bed after treatment, which can complicate the interpretation of follow-up scans using conventional imaging techniques; therefore, FDG-PET CT may be considered as the next step in the workup of cancer recurrence. A soft tissue lesion identified using FDG-PET CT 6 months after completion of therapy likely represents recurrence, and the PPV of such a finding increases if it has been more than 12 months since the completion of therapy. The sensitivity and specificity of detection varies by anatomic location, with the highest sensitivity, specificity, and accuracy for the detection of extraabdominal and hepatic recurrence (sensitivity 95%, specificity 100%, and accuracy 99%). For intraabdominal but extrahepatic recurrence, the sensitivity is 88%, specificity 94%, and accuracy 92%. After image-guided liver-directed therapies (i.e., ablation, radioembolization), FDG-PET CT can be considered for assessment of treatment response and liver recurrence.

FDG-PET CT may also be helpful in determining local recurrence of rectal cancer. In a meta-analysis, detection of local recurrence (i.e., recurrence at the anastomosis or in the presacral region for rectal cancers) or distant metastasis, sensitivity of detection by PET CT was 94%, with a specificity of 93%. Postchemoradiation therapy and surgery yields presacral soft tissue findings on surveillance imaging in up to half of rectal cancer patients. FDG-PET CT may be useful in determining whether this presacral or anastomotic thickening represents fibrosis that is metabolically inactive versus recurrent cancer. However, FDG avidity in the pelvis may also be due to benign inflammatory changes from previous postoperative complications such as abscess or anastomotic leak or fistula. Thus, FDG-PET CT false-positive results of local recurrence may require further investigation via endoscopic, percutaneous, or image-guided biopsy.

THE ROLE OF PET CT IN COLORECTAL LIVER METASTASES

There is evolving evidence in the literature to support the utilization of FDG-PET CT in the preoperative evaluation of colorectal liver metastases (CRLM) and surveillance in a select population of patients. A randomized controlled trial evaluating preoperative CRLM, FDG-PET CT on surgical management for metastatic Colorectal Adenocarcinoma to liver Metastases ("PET-CAM"), was a multicenter study that aimed to identify the effect of preoperative PET CT vs. no PET CT on the surgical management of patients with resectable CRC liver metastases as determined by CT scan and/or MRI. Of the 263 participants who underwent FDG-PET CT in the trial, 21 (8%) had a change in surgical management with 7 (2.7%) avoiding futile laparotomy after the discovery of additional loci of metastatic disease (i.e., within the bone, peritoneum/omentum, and lymph nodes). In addition, 1.5% of patients underwent more extensive hepatic resections and 3.4% underwent extrahepatic surgery for distant metastases. A meta-analysis of 18 studies including 1059 patients with hepatic colorectal metastases found that PET or PET CT results changed management in 24% of patients. Controlling for similar baseline patient characteristics, the proportion of major liver resection (defined as greater than two liver segments) performed was higher in the PET-CT arm compared with the no PET-CT arm (76% vs. 67%, respectively). Preoperative staging PET CT improves survival in patients with resectable liver metastases primarily by demonstrating the presence of extrahepatic metastases, thereby identifying patients with inoperable disease who would not benefit from undergoing surgical resection and may instead benefit from neoadjuvant chemotherapy. Thus, these data support the use of FDG-PET CT before hepatic surgery among patients with otherwise resectable CRC liver metastases, as identified on CT scan or MRI. FDG-PET CT is highly accurate for detection of liver metastases on a per-patient basis but less accurate on a per-lesion basis. Notably, PET CT is limited in its ability to demonstrate lesions smaller than 1 cm; these lesions are best detected with MRI. PET CT may be especially useful in guiding liver biopsies, ablations, or hepatic resections in patients with indeterminate or suspicious findings on CT. PET CT is also used to detect occult recurrence and liver metastases in patients with a history of CRC, rising or abnormal CEA level, and otherwise negative imaging studies.

The Ontario Clinical Oncology Group (OCOG) performed a follow-up study evaluating long-term oncologic data (cancer recurrence events and death) for 7 years after the last day of follow-up of the original PET-CAM trial. However, they found no difference in median disease-free survival or OS between both trial arms among those patients who underwent liver resection. Most first recurrences were isolated to one organ site, primarily the lung or the liver, and the majority of recurrences happened more than 1 year following liver resection. These results are similar to prior published literature.

FDG-PET MRI

The use of FDG-PET combined with MRI has recently been introduced as a diagnostic method of detecting CRC metastasis. One retrospective study demonstrated the added value of PET MRI to CT to detect extrahepatic CRC metastasis, whereas another study reported that PET MRI can improve the limited sensitivity of PET CT to detect small lesions. In general, the combination of PET and MRI can improve the detection of both intra- and extrahepatic lesions over PET CT alone.

CONCLUSION

The imaging modalities of CT and MRI remain mainstays of the initial diagnosis, workup, and preoperative planning in management of CRC. Hybrid imaging modalities combining PET and either CT or MRI continue to evolve and has proven utility in a select population of CRC patients. Although CT and MRI are the preferred modalities in detecting extrahepatic and hepatic metastasis, the combination of functional and anatomical imaging modalities such as FDG-PET CT and/or FDG-PET MRI can improve the diagnostic detection of intrahepatic and extrahepatic CRC metastases and aid in the preoperative evaluation of CRC.

Suggested Readings

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Neoadjuvant and Adjuvant Therapy for Colorectal Cancer

Yilin (Linda) Cao, MD, and Nilofer Azad, MD

Colon and rectal cancer, or colorectal cancer (CRC), is a common disease in the United States with an estimated 104,610 new cases of colon cancer and 43,340 new cases of rectal cancer in 2020. The lifetime risk of developing CRC is approximately 1 in 23 (4.4%) for men and 1 in 25 (4.1%) for women. Although the mortality and incidence rates have been declining over the last few decades, CRC remains the second leading cause of cancer-related deaths in the United States, expected to cause nearly 53,000 deaths during 2021. Moreover, deaths from CRC among individuals under the age of 55 have actually increased 1% annually from 2008 to 2017.

For early-stage CRC (stages I–III), surgical resection remains the basis of curative treatment. Distant recurrence, despite appropriate surgical resection, increases based on stage and is thought to be due to micrometastatic disease that is not readily detectable by current methods. For this reason, neoadjuvant and adjuvant therapies are often utilized to target micrometastases with the goal of complete eradication and prolonged survival. The challenge lies in determining which patients will benefit from additional therapy beyond surgical resection. The decision to add neoadjuvant or adjuvant therapy is based in large part on evaluating risk factors, which take into consideration not only clinical tumor stage but also patient-specific data like clinicopathologic features, such as lymphovascular invasion, and molecular profiling, such as microsatellite instability (MSI) status. Adjuvant and neoadjuvant therapeutic approaches to CRC are different for colon versus rectal cancer and are discussed separately in this chapter.

STAGING

Formal CRC staging is essential to risk stratification for guiding clinician treatment decisions for individual patients. Guidelines from the National Comprehensive Cancer Network (NCCN) for preoperative workup of newly diagnosed CRC should include the following: colonoscopy (plus consideration of rigid proctoscopy for rectal cancer) with biopsy and pathology review; complete blood counts, chemistry profile, and carcinoembryonic antigen (CEA) serum level; and computed tomographic (CT) scan of chest, abdomen, and pelvis for colon cancer versus CT chest with magnetic resonance imaging (MRI) of the abdomen and pelvis with contrast for rectal cancer. Endorectal ultrasound for rectal cancer is no longer indicated unless a patient has contraindications to MRI, such as an incompatible pacemaker. Preoperative staging is particularly important in rectal cancer because it determines whether patients receive neoadjuvant radiation therapy (RT), with the goal of both improved long-term local control as well as down-staging, allowing for less morbidity from curative surgical resection. Per the 2021 NCCN Guidelines, positron emission tomography is not recommended. CRC is staged based on the TNM staging system (T, primary tumor; N, regional lymph nodes; M, distant metastasis) adopted by the American Joint Committee on Cancer (AJCC). In the most recent version of the AJCC Cancer Staging Manual (eighth edition, 2017), several modifications were made to assist clinicians with prognostication, including the additional subdivision of M1c, which qualifies peritoneal carcinomatosis as a poor prognostic factor; clarification as to how tumor deposits in lymph nodes are defined; reintroduction of the "L" and "V" elements to better identify lymphatic and vessel invasion; and the identification of MSI status, KRAS, NRAS, and BRAF mutations as additional prognostic and predictive factors. The importance of accurate staging is reflected in Figure 1, which outlines the predicted 2-year overall survival rates by stage.

Colon Cancer

Stage II Colon Cancer

Adjuvant chemotherapy in stage II disease remains controversial due to a lack of demonstrated survival benefit in subset analyses of large clinical trials encompassing stage II–III colon cancer patients. However, stage II colon cancer is a highly heterogeneous group, and accordingly, stratification into a low-risk and high-risk group has been established. Based on NCCN 2021, high-risk factors for recurrence include poorly differentiated/undifferentiated histology, lymphovascular invasion, perineural invasion, emergency presentation such as bowel obstruction or perforation, inadequate lymph node sampling (<12 nodes in the surgical specimen), tumor budding, and indeterminate/close/positive margins. Tumor budding is the presence of single tumor cells or small clusters of tumor cells in the stroma at the invasive front of the tumor (i.e., "buds" that have detached from the main mass) and is thought to reflect epithelial-mesenchymal transition.

Unfortunately, there is currently no consensus for interpreting the relative importance of these diverse factors and how each should impact adjuvant chemotherapy selection in stage II disease. Studies do suggest that pT4 staging may be one of the most prognostic of these factors, with T4 accounting for a loss of 10% to 15% in 5-year overall survival (OS) compared with T3. A particularly pertinent risk factor within the surgeon's purview is that of lymph node sample size. The minimum number of 12 noted in NCCN stems from a 1989 publication reporting that this was an adequate number to determine node positivity in 94% of specimens. Furthermore, the importance

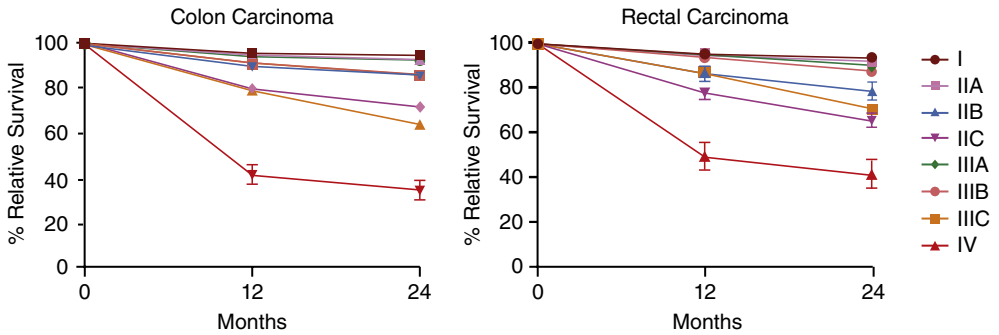


FIG. 1 Survival by stage for colon and rectal cancer patients in the SEER database since 2010. *(Data from* AJCC Cancer Staging Manual. *8th ed. New York: Springer; 2017.)*

of adequate lymph node sampling was demonstrated clinically by the Intergroup 0089 study, which found an absolute 5-year OS difference of 14% in stage II patients who had <10 negative lymph nodes examined compared with those with >20. These data and similar patterns demonstrated by other studies may be enough to warrant surgical reassessment in cases of particularly low-yielding lymph node dissection.

Generally, the presence of any of these high-risk features supports at least the consideration of adjuvant chemotherapy in stage II patients. The most common regimens are 6 months of FOLFOX (folinic acid, 5-FU, and oxaliplatin) or 3 months of XELOX (also known as CAPOX, capecitabine and oxaliplatin). An analysis of high-risk stage II patients from four of the six studies in the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration published in 2021 found that, while noninferiority of 3 vs. 6 months of therapy could not be demonstrated, the decreased cost and toxicity of 3 months of adjuvant therapy made it a reasonable choice in this population given the small relative difference in outcomes. DNA mismatch repair status is another emerging prognostic factor, where MSI-high (i.e., mismatch repair deficient or *dMMR*) tumors portend a survival advantage, favoring observation over adjuvant therapy due to high rates of resistance.

There are also molecular assays that predict recurrence of CRC in the stage II setting. Five assays are commercially available, with the most data available for Oncotype-DX colon, a 12-gene recurrence score that has been validated to predict recurrence in mismatch repair proficient stage II disease. However, the assay has not been validated to show which patients benefit from adjuvant therapy. Multiple assays are in development and will require prospective studies to show that they have both a prognostic and predictive benefit, the latter of which could help in clinical decision making regarding adjuvant therapy.

Stage III Colon Cancer

In stage III colon cancer, adjuvant chemotherapy has been the standard of care since 1990, with several large randomized clinical trials showing benefits in both OS and disease-free survival (DFS). The addition of adjuvant chemotherapy to surgical resection in patients with stage III colon cancer leads to an approximately 40% to 50% reduction in recurrence and 22% to 32% reduction in mortality. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01, conducted from 1977 to 1983, was the first trial to demonstrate 5-year OS benefit for adjuvant therapy in colon cancer, specifically with the regimen of semustine, vincristine, and 5-FU (MOF). The NSABP C-03 trial, along with other similar studies, later demonstrated inferiority of MOF to intravenous 5-FU/LV regimens.

The benefit of the addition of oxaliplatin to 5-FU/LV (i.e., to become modern-day FOLFOX) was demonstrated by the MOSAIC trial. The primary endpoint of 5-year DFS was significantly higher with FOLFOX (73% vs. 67%, hazard ratio [HR]: 0.8). However, this came at the cost of increased rates of febrile neutropenia, peripheral neuropathy, and grade 3 to 4 diarrhea. OS rates were significantly higher for stage III disease (60% of the cohort) with FOLFOX but not in stage II disease. Subsequently, when capecitabine was combined with oxaliplatin (i.e., XELOX or CAPOX) in the NO16968 trial and compared with bolus 5-FU/LV, this demonstrated significantly improved 7-year DFS (63% vs. 56%, HR: 0.8), which translated to a 7-year OS benefit.

The current recommendation for adjuvant therapy for stage III colon cancer is 3 to 6 months of an oxaliplatin-containing regimen such as FOLFOX or XELOX. The IDEA collaboration analyzed six randomized trials of 3 versus 6 months of oxaliplatin-based adjuvant therapy. Results suggested that 6 months of therapy remains the standard of care for high-risk stage III colon cancer (T4N1-2; or any N2 disease). However, in low-risk disease (T1-3N1), 3 months of XELOX is considered noninferior to 6 months while conferring significantly less neuropathy. For patients with significant comorbidities, peripheral neuropathy, or age greater than 70 years, 3 to 6 months of infusional 5-FU/LV or capecitabine without oxaliplatin can be considered.

As new biomarkers and predictors of recurrence/prognosis are discovered and more antineoplastic agents are developed, recommendations will continue to be updated. A promising tool in its infancy is the use of cell-free DNA (cfDNA) for minimal residual disease detection after surgery to guide adjuvant therapy. One biomarker study by Tie et al. in 100 stage III colon cancer patients found that detectable cfDNA in postoperative plasma samples was significantly associated with inferior recurrence-free survival (HR 3.8), which remained independently predictive after adjusting for known clinicopathologic risk factors. Tools such as this will likely lead to more highly individualized cancer therapy algorithms in the coming years, but a graphical summary of current clinical decision making can be found in Figure 2.

RECTAL CANCER

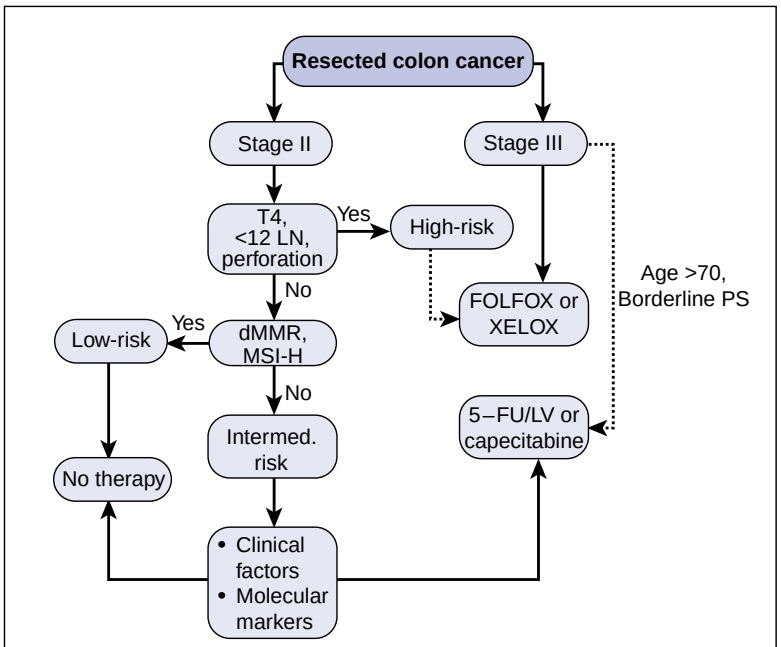
Although rectal cancer has similar pathogenesis and molecular phenotypes to colon cancer, local recurrence rates in rectal cancer are significantly higher than in colon cancer. This discrepancy may be secondary to differences in both tumor factors, such as vasculature and lymphatic drainage patterns associated with the anatomic location, and surgical factors, such as completeness of mesorectal excision and extent of lymphadenectomy. As many as 10% of patients with T1 or T2 rectal cancer, 15% to 35% of patients with T3N0 rectal cancer, and 45% to 65% of patients with node positive T3 or T4 rectal cancer will experience local recurrence with standard resection, which can be significantly decreased with total mesorectal excision (TME) and neoadjuvant or adjuvant radiation.

In terms of the adjuvant/neoadjuvant therapy approach, two significant factors distinguish the management of rectal cancer from colon cancer. The first is that, in rectal cancer, there has been increasing emphasis of neoadjuvant as opposed to adjuvant therapy, termed "total neoadjuvant therapy" or TNT. The second is that RT and radiation therapy with concurrent chemotherapy (chemoRT) play a significant role in rectal cancer, whereas it is not standardly indicated in colon cancer. Concurrent chemotherapy refers to chemotherapy that overlaps the RT course (altogether termed chemoRT), which is delivered at lower than standard doses to help potentiate the ability of RT to kill tumor cells, or "radiosensitization".

Adjuvant Therapy for Rectal Cancer

Although neoadjuvant therapy is now the standard of care, historically, adjuvant therapy was intended to address the high rates of local recurrence and low rates of survival in rectal cancer. In 1985, the Gastrointestinal Tumor Study Group (GITSG) published a prospective randomized control trial of 227 patients with T3-4 or node-positive disease and negative margins on resection who were randomized to (1) surgery alone, (2) post-op bolus 5-FU/lomustine, (3) post-op RT alone, or (4) post-op chemoRT with 5-FU followed by 5-FU/lomustine. In this trial, recurrence rates were significantly reduced with combined chemoRT (33%) versus observation (55%), and OS was longer for chemoRT as well, although it did not reach statistical significance.

It was not until the mid-2000s and the era of TME that the German Rectal Study established the role of neoadjuvant chemoRT in cT3-4 or node-positive disease. It compared 50.4 Gy in 28 fractions (~5.5 weeks of RT) with concurrent infusional 5-FU *preoperatively* 6 weeks before TME to *postoperatively* 4 weeks after TME. All patients had four cycles of IV bolus 5-FU after completion of trial arm therapy. Although the study did not show any benefit in the primary endpoint of OS (~60% at 10 years for both arms), several advantages of the neoadjuvant setting led to this becoming the prevailing paradigm for chemoradiation therapy. Specifically, the study found that the neoadjuvant arm had much higher compliance (90% vs. 50%), decreased nodal involvement rate (25% vs. 40%), significantly improved acute and late grade ≧3 toxicity rates, 3% absolute reduction in 10-year local recurrence rate (7% vs. 10%), and improved likelihood of sphincter-preservation surgery in those initially felt to require abdominal perineal resection (39% vs. 19%).



FOLFOX	FOL = Folinic acid (Leucovorin) F = Fluorouracil OX = Oxaliplatin
CAPOX or XELOX	CAP = Capecitabine OX = Oxaliplatin
FOLFIRI	FOL = Folinic acid (Leucovorin) F = Fluorouracil IRI = Irinotecan
5FU/LV	FU = Fluorouracil LV = Leucovorin (Folinic acid)

FIG. 2 Algorithm for use of adjuvant treatment for colon cancer. *dMMR,* Defective mismatch repair; *LN,* lymph nodes; *MSI-H*, microsatellite instability high; *PS*, performance status.

Neoadjuvant Therapy for Rectal Cancer

Currently, the majority of United States cancer centers utilize a combined modality approach to neoadjuvant therapy with radiotherapy (50.4 Gy total radiation dose over the course of ~5.5 weeks) and concurrent chemotherapy (5-FU/LV or capecitabine), followed by surgical resection 4 to 6 weeks after completion of chemoRT. An emerging alternative strategy that is quickly gaining increasing utilization is short-course (or hypofractionated) radiotherapy of 5 Gy × 5 fractions (25 Gy total dose), which is not delivered with concurrent chemotherapy but is generally followed by a variable number of cycles of neoadjuvant chemotherapy. The need for adjuvant chemotherapy after TNT is still being assessed, with recent trials described in the following sections suggesting that it may not be necessary.

RT is most clearly indicated in stage II–III rectal cancers (i.e., T3-4 disease or node-positive disease). The goal of RT is two fold: to shrink the primary disease and to sterilize the draining lymph nodes. The typical radiation field will cover the perirectal, presacral, and internal iliac lymph nodes to a dose of 45 Gy followed by a more focused field on the primary tumor and mesorectum to 50.4 Gy when using standard chemoRT. For the short-course RT approach, the entire volume receives 25 Gy over 5 fractions (Fig. 3). If there is tumor extension to the prostate or vagina, one would consider adding the external iliac nodal region to the RT treatment volume as well. The Polish II trial established oncologic equivalence of neoadjuvant short-course RT and standard chemoRT in patients with cT3-4 disease, with no difference in sphincter preservation, local recurrence, and disease-free or overall survival. Short-course RT was associated with significantly lower grade ≧3 acute toxicity, but both regimens are considered to be acceptable and largely dependent on institutional practice preferences.

Preoperative therapy offers the opportunity to achieve pathologic complete response, with rates as high as 12% to 16% in the aforementioned Polish II trial. There has been increasing interest in modifying perioperative therapy to optimize pathologic complete response (pCR) rates and oncologic outcomes, potentially even opening a window for patients who may qualify for nonoperative treatment strategies aimed at organ preservation. The Timing of Rectal Cancer Response to Chemoradiation Consortium designed a phase II trial to investigate the effect of extending the interval between neoadjuvant chemoRT and surgery while administering additional chemotherapy (modified-FOLFOX) during the waiting period. Nearly 300 patients with stage II–III locally advanced rectal cancer were assigned to four treatment groups ranging from standard therapy (chemoRT followed by TME in 6–8 weeks), to groups receiving two, four, or six cycles of mFOLFOX6 following chemoRT. The pCR rate increased linearly by number of chemotherapy cycles, ranging from 18% in standard

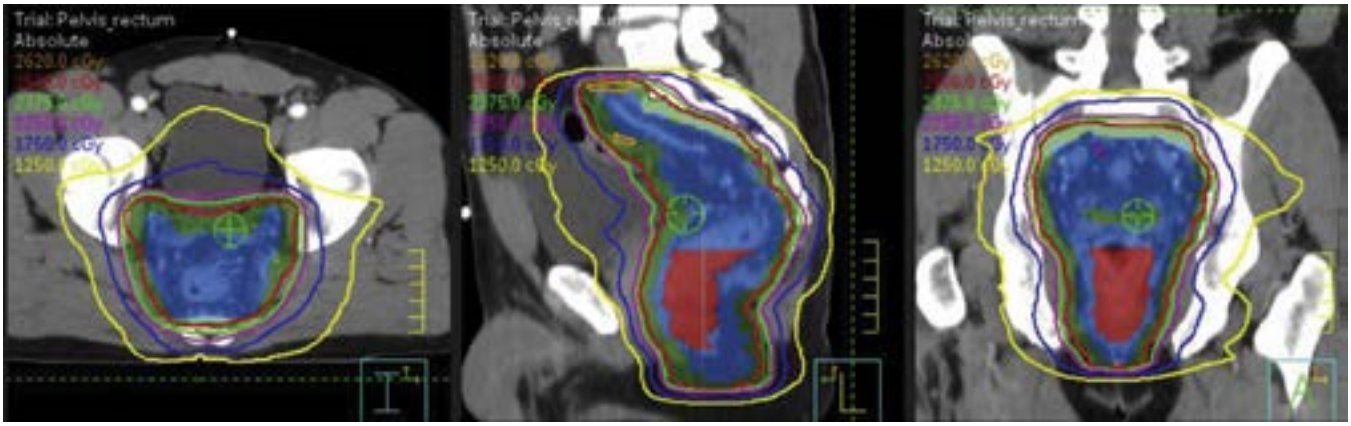


FIG. 3 An example of a preoperative short-course radiation therapy field for rectal cancer, including the perirectal, presacral, and internal iliac nodes *(blue colorwash)* and gross disease *(red colorwash)*.

chemoRT alone to 38% in the group receiving six additional cycles of neoadjuvant mFOLFOX. This promising data encouraged further studies in TNT. The RADIPO trial enrolled 920 patients with high-risk, locally advanced rectal cancer based on pelvic MRI features. Patients received 50 to 50.4 Gy of chemoRT with concurrent oral capecitabine and postoperative chemotherapy (XELOX or FOLFOX) vs. the experimental arm of short-course RT followed by preoperative chemotherapy. The 3-year treatment failure rate was significantly lower in the experimental arm (23.7% vs. 30.4%). The PRODIGE 23 trial corroborated the improvement in oncologic results with TNT, although it utilized a more rigorous chemotherapy regimen (FOLFIRINOX), and chemoRT therapy in both arms and allowed both low- and high-risk rectal cancer, with a 7% absolute benefit in 3-year DFS for the neoadjuvant group. These key trials for TNT are summarized in Table 1.

Treatment deescalation is also being actively investigated. Currently, a large phase III randomized prospective trial (PROSPECT-N1048) is ongoing to assess R0 resection rate and DFS for neoadjuvant chemotherapy alone vs. chemotherapy plus RT in patients with locally advanced rectal cancer (T2N1, T3N0, T3N1). The "watch and wait" strategy for organ preservation has also gained increasing academic interest. A case series of 113 patients at Memorial Sloan Kettering who elected for a watchful waiting approach after clinical complete response to neoadjuvant therapy demonstrated excellent rectal preservation and pelvic tumor control rates (82% and 91%, respectively). However, when compared with a surgical group that achieved pCR, the watchful waiting group had worse overall survival (73% vs. 94%), potentially owing to a high rate of distant metastasis in patients who had local recurrence (36%). These data suggest that better tools for risk stratification are necessary to identify optimal candidates for organ preservation strategies.

SURVEILLANCE

Despite the ever-evolving therapies for CRC, distant and local recurrence rates can be as high as 40%, with the majority of recurrences occurring in the first 2 years after completion of initial definitive therapy. Early identification of recurrence or new primary tumors may allow for potentially curative therapy (surgical resection or systemic therapy) and improved outcomes. For this reason, appropriate

TABLE 1 Key Trials Investigating Total Neoadjuvant Therapy in Rectal Cancer

Trial	Patient Population	Neoadjuvant Treatment Regimen	Time to Surgery	pCR Rate	Result
RAPIDO	920 high-risk patients*	Short course RT → CAPOX 6c or FOLFOX 9c → surgery vs. ChemoRT → surgery → optional adjuvant chemo	4–6 weeks	28% vs. 14%	No differences in complication rates, TNT improved pCR and 3-yr disease-related failure rates
TIMING	259 patients w/ T3-4, N1-2 disease <12 cm from anal verge	Concurrent chemoRT with 5-FU → FOLFOX for 0c, 2c, 4c, or 6c → surgery	6–8 weeks	0c = 18% 2c = 25% 4c = 30% 6c = 38%	No significant differences in surgical complications when bridging with FOLFOX during increasing interval to surgery
PRODIGE 23	461 patients w/ cT3-4 disease <15 cm from anal verge	FOLFIRINOX × 6c → concurrent chemoRT with capecitabine → surgery → adjuvant FOLFOX × 3c vs. Concurrent chemoRT → surgery → adjuvant chemo × 6 months	6–8 weeks	28% vs. 12%	Significant improvement in 3-yr disease-free survival and increased pCR rate with neoadjuvant FOLFIRINOX

*High risk was defined as at least one of the following MRI features: cT4, cN2, enlarged lateral lymph nodes, extramural vascular invasion, or mesorectal fascia involvement.*c,* Cycles; *CAPOX,* capecitabine and oxaliplatin; *FOLFOX,* folinic acid, fluorouracil, oxaliplatin; *FOLFIRINOX,* folinic acid, fluorouracil, irinotecan, oxaliplatin; *pCR*, pathologic complete response; *TNT,* total neoadjuvant therapy.

aggressive surveillance is imperative. Although there are subtle differences among professional organizations, most guidelines are generally in line with those published by NCCN.

For patients with stage I–III colon or rectal cancer, recommended surveillance is colonoscopy 1 year after resection, with subsequent colonoscopy in 3 years, then followed by every 5 years assuming no advanced adenomas are detected. For patients with rectal cancer who underwent transanal local excision only, the addition of proctoscopy with endoscopic ultrasound scan or MRI with contrast is recommended every 3 to 6 months for the first 2 years, then every 6 months through year 5.

For patients with stages II–III colon or rectal cancer, serum CEA is recommended every 3 to 6 months for 2 years, then every 6 months until year 5. CT chest, abdomen, and pelvis should be performed every 6 to 12 months for 5 years. Positron emission tomography/CT is not indicated for routine surveillance.

Suggested Readings

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Management of Colorectal Polyps

Gifty Kwakye, MD, MPH, and Genevieve B. Melton-Meaux, MD, PhD

OVERVIEW

Colorectal cancer (CRC) remains the second leading cause of cancer deaths in the United States for men and women combined. Rates of early-onset CRC have also increased steadily over the past several decades, with 1 in 10 CRC patients diagnosed under the age of 50 years associated with a 58% greater risk of presenting with late-stage disease than their older counterparts. Identifying and removing premalignant colorectal polyps forms the basis of CRC screening programs using a variety of approaches. Of those approved by governing bodies, colonoscopy is the only one that allows for both detection and simultaneous removal of polyps, facilitating CRC prevention.

A colorectal polyp is a macroscopically visible lesion or mass that results from pathologic epithelial elevation of the colonic mucosa. Several other lesions can present as luminal masses, such as lipomas, carcinoid tumors, and leiomyomas. These lesions are covered by normal mucosa and, by definition, are not polyps. Most colonic polyps are asymptomatic; however, they are of clinical concern because of their malignant potential. The term *polyp* is nonspecific, and the importance of any one colorectal polyp is based on its histopathology, which determines the patient's risk of malignancy and, therefore, further treatment and follow-up. Colorectal polyps can be classified as either *sporadic* (approximately 60%) or *hereditary,* with the latter comprising a variety of familial syndromes that are potentially malignant conditions. A variety of approaches are used to address polyps, as outlined.

HISTOPATHOLOGY OF POLYPS

Adenomas

Adenomas are the most common neoplastic polyp identified in patients undergoing colonoscopy, representing 50% to 65% of all colonic polyps. Of sporadic CRC, approximately 80% develop from adenomas. The adenoma-carcinoma sequence, also known as the *loss of heterozygosity* or *chromosomal instability pathway,* is a cascade of sequentially accumulated genetic mutations (Fig. 1). Approximately 10% to 25% of asymptomatic patients at average risk and older than 50 years of age have an adenomatous polyp. The histology of these adenomas is most commonly tubular (65% to 85%), but they may also be tubulovillous (10%–25%) or villous (10%). Advanced adenomas are those that are greater than 1 cm or having a villous architecture, severe dysplasia, or carcinoma. The prevalence rate of advanced adenomas ranges from 3.5% to 9.5%, depending on gender and age. Identification of an adenoma should prompt a complete colonoscopy because of the 20% to 40% risk of proximal neoplastic lesions. Recommendations for follow-up colonoscopy are made based on the number, size, and histopathology of the adenomas and other clinical factors such as personal risk factors and family history. Removal of adenomas reduces future CRC and the development of advanced adenomas.

Serrated Polyps

In addition to the adenoma-carcinoma sequence, an increasingly recognized CRC carcinogenesis process is the serrated pathway (see Fig. 1). In fact, recent studies show that prevalence of serrated polyps in average-risk individuals is as high as 20% to 40%, accounting for almost 25% of sporadic CRCs. As outlined by the updated World Health Organization (WHO) classification system, serrated polyps include hyperplastic polyps (HPs), sessile serrated lesions (SSLs) and traditional serrated adenomas (TSAs). HPs are small, diminutive polyps, typically located in the left side of the colon and are identified by the absence of SSL architectural features on pathology. They have traditionally been thought of as benign but in special situations can have an increased malignant potential. These include large size (>1 cm diameter), location in the right colon, mixed adenoma/hyperplastic histology, more than 20 hyperplastic colonic polyps, familial hyperplastic polyposis, and a family history of CRC.

SSL is the recommended terminology for polyps previously called *sessile serrated adenoma, sessile serrated polyp,* or *sessile serrated adenoma/polyp.* Unlike HPs, SSLs have crypt distortion, presence of mucosal prolapse, or stromal proliferations. TSAs have distinct features that include ectopic crypts with narrow slits, prominent eosinophilic cytoplasm, and penicillate nuclei. Serrated polyposis syndrome can occur, characterized by the presence of either (1) ≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size or (2) >20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum.

Hamartomas

A hamartoma is an outgrowth composed of normal mature cells that originate from below the mucosa. When sporadic, hamartomas

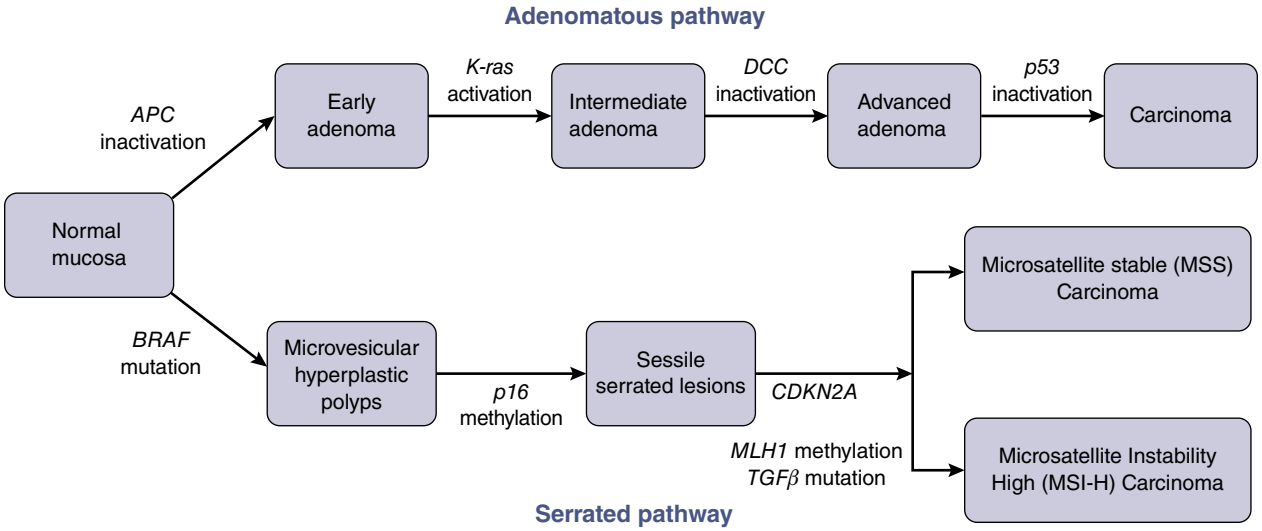


FIG. 1 Colorectal carcinogenesis pathways.

are frequently called *juvenile polyps* because they are relatively common in children. This second histologic category of colorectal polyps is mostly associated with one of three autosomal-dominant familial syndromes: Peutz-Jeghers syndrome, juvenile polyposis, and Cowden's syndrome. Although sporadic hamartomatous polyps are not considered premalignant, the familial syndromes have a significant rate of cancer development; therefore patients with these syndromes should undergo regular colonoscopic surveillance.

The typical phenotype of patients with Peutz-Jeghers syndrome includes perioral hyperpigmentation and multiple hamartomatous polyps located in the small or large bowel. These polyps may cause intussusception, bleeding, or obstruction at a young age. After the third decade, patients with Peutz-Jeghers syndrome have a 2% to 13% risk of gastrointestinal (GI) cancer and therefore should undergo regular endoscopic surveillance.

Juvenile polyposis is diagnosed when a young patient has 10 or more hamartomatous GI polyps. Lesions may occur anywhere within the GI tract, although they are frequently in the colon. These polyps may twist and auto-amputate, causing bleeding. Colon cancer affects up to 50% of those afflicted with juvenile polyposis and may occur in the fourth decade of life.

Cowden's disease, also known as *multiple hamartoma syndrome,* is characterized by hamartomatous neoplasms of the skin and mucosa, GI tract, bones, central nervous system, eyes, and genitourinary tract. A significant risk exists for skin, thyroid, endometrial, and breast cancer in Cowden's syndrome. Emerging evidence suggests an increased incidence of CRC as well.

TECHNIQUES FOR EXCISING POLYPS

Colonoscopic Approach

Polypectomy has proven to be an effective means of CRC prevention, allowing for identification, removal, and histopathologic evaluation of polyps. Most colorectal polyps are treated with endoscopic polypectomy, either with biopsy forceps or snare polypectomy, both of which can be either hot with electrocautery or cold. Snare excision typically provides a larger specimen, and the stalk (or base) can be evaluated histopathologically to better define the level of superficial malignancy if present. Large lesions may be removed with a piecemeal excisional technique, which allows for sequential excision of the entire lesion or en bloc with more advanced endoscopic techniques described in the next section.

Relative contraindications to colonoscopic polypectomy include anticoagulation therapy, bleeding diathesis, acute colitis, and evidence of invasive malignancy, such as central ulceration, a hard or fixed lesion, necrosis, or inability to raise the lesion with submucosal injection.

Complications related to colonoscopic polypectomy are uncommon and typically minor. The risk of death is 1 in 14,000. The most common serious complications are bleeding and perforation. Bleeding occurs in 4.8 in 1000 patients after colonoscopic polypectomy and may occur immediately or days later when clot dissolution occurs. Most post-polypectomy bleeds stop spontaneously and, when persistent, can usually be controlled with endoscopic clipping or cauterization. Rarely, interventional angiography or colectomy is necessary. Bleeding risk should be minimized by stopping warfarin and aspirin 5 days before polypectomy and clopidogrel 7 days before and possibly holding these agents for several days after polypectomy, although stopping any of these agents must be tailored to the patient's risk profile (e.g., patient with a mechanical mitral valve with a high risk of stroke off anticoagulation therapy).

Colonic perforation after conventional polypectomy occurs in 0.1% of patients, most of whom undergo successful treatment with conservative therapy that includes inpatient observation, bowel rest, and intravenous antibiotics. These patients must be followed closely as inpatients for any sign of clinical deterioration warranting laparotomy. One alternative approach is early laparoscopic primary repair of the defect, with colonoscopic assistance if the perforation is not easily identified on laparoscopy. The patient should be in the lithotomy position, and if colonoscopy is necessary, minimal insufflation with carbon dioxide should be used. Contraindications to this approach include peritonitis, malignancy, and the presence of significant fecal soilage.

Post-polypectomy syndrome has been reported to occur in up to 0.3% of patients after polypectomy, most often when cauterization has been used. The etiology is believed to be that the cautery causes a microperforation in the colonic wall and results in bacterial translocation. Patients typically present anywhere from 0 to 3 days after the polypectomy with abdominal pain and tenderness, fever, and leukocytosis. On computerized tomographic scan, fat stranding is typically seen in the mesentery, and the colonic wall of the polypectomy site is thickened; however, unlike with colonic perforation, pneumoperitoneum is not present. Patients should be treated with bowel rest, intravenous antibiotics, and close observation until symptoms resolve. Recognition of post-polypectomy syndrome is important to avoid unnecessary laparotomy in these patients, who may present with localized peritonitis.



FIG. 2 Endoscopic mucosal resection (EMR) of a large multilobar colonic polyp. **(A)** Polyp. **(B)** Injection of a lifting agent. **(C)** Resection bed after polyp removal. *(Photographs courtesy Dr. Allison Schulman, Advanced Gastrointestinal Endoscopist, University of Michigan).*

Endoscopic Mucosal Resection

Initially described in Japan, endoscopic mucosal resection (EMR) is one of two advanced endoscopy techniques gaining traction that allows for removal of large superficial polyps within the GI tract. A solution is injected into the submucosa, right underneath the polyp (Fig. 2). This raises the mucosal layer, facilitating better encirclement with the snare device. Solutions typically used include saline (normal or hypertonic), glycerol, hyaluronic acid, and diluted epinephrine. EMR improves the safety of polypectomy by increasing the distance between the mucosa and the muscularis propria. It is critical to tattoo the area with India ink when large or suspicious polyps are removed because typically further endoscopic evaluation or resection is indicated. For larger lesions, a piecemeal polypectomy typically still occurs because of the limitations of the procedure. This affects the ability to perform accurate pathologic staging, resulting in the need for a segmental colectomy that could potentially have been avoided.

Endoscopic Submucosal Dissection

Compared with EMR, endoscopic submucosal dissection (ESD) better allows for en bloc resection of even large polyps. The border of the polyp is typically marked by injecting indigo carmine. The polyp is then lifted with introduction of solution into the submucosal layer, like in EMR. Using special endoscopic knives and electrocautery, the lesion is excised in one piece. Because of violation of the submucosal layer, bleeding is quite common and can be easily controlled with electrocautery or placement of endoscopic hemoclips. Caution should however be used when applying any heat device in the thin-walled colon because this could lead to perforation. Although ESD allows for en bloc polyp excision consistent with oncologic principles, it has a higher perforation rate, takes longer to complete, and has a steeper learning curve, which have affected widespread adoption.

Combined Endo-Laparoscopic Surgery

Even with advanced endoscopic techniques described earlier, removal of large colonic polyps is not always feasible. Traditionally, these cases have been referred for segmental colectomy, which has an associated increased risk for morbidity and, in select patients, even mortality. In combined endo-laparoscopic surgery (CELS), endoscopic resection of the polyp is performed while manipulating the bowel laparoscopically by either invaginating the bowel wall to allow for easier polyp snaring or mobilizing the bowel to improve reach endoscopically. One of its advantages is immediate detection of full-thickness bowel injury, which can be repaired laparoscopically in experienced hands. However, it is limited by the challenges presented by combining two very different techniques. For instance, insufflation of the bowel lumen endoscopically might limit the ability to visualize and maneuver laparoscopic instruments, increasing the risk for injury to underlying intraabdominal structures. Clamping the terminal ileum during endoscopic insufflation could limit distension of the small bowel but fails to address colonic distension. At the end of the case, an air leak test can be performed to identify any injury not detected previously. With careful patient selection, CELS has been shown to be successful in 70% to 97% of cases.

Surgical Approach

Large polyps or early rectal cancers not amendable to endoscopic excision can be addressed using surgical techniques performed transanally. These allow for complete en bloc excision of the lesion, which is important for pathologic evaluation. This also potentially avoids the morbidity and mortality of a more invasive low anterior resection or abdominoperineal resection in patients with benign disease or early cancers. The surgical approach used is determined by location of the polyp relative to the anal verge. In addition to routine history and physical examination, patients should have a proctoscopy completed to assess the location of the polyp and its size to assist with both patient positioning intraoperatively but also choice of surgical technique to use. Placement of the patient in the lithotomy position, prone with split legs or lateral decubitus should be performed aiming to have the lesion located inferiorly in the 5 to 7 o'clock position. Orientation of the specimen once removed needs to be always maintained in case additional margin(s) must be resected after pathology review. An easy strategy to accomplish this involves pinning the specimen to the white pad found in most surgical needle boxes and labeling the cardinal points with permanent ink. Complications related to surgical polypectomy include urinary retention, bleeding, infections, and bowel perforation. There is also a chance for incomplete resection or need to convert to a different more invasive approach. Both can be avoided with proper patient selection following careful review of perioperative workup. The surgery can be done as an outpatient or with a short period of inpatient observation depending on practice preferences.

Conventional Transanal Excision

For large polyps in the distal rectum, local excision has been shown to be effective at complete removal, where lymph node sampling is not required. Polyps amendable to standard conventional transanal excision (TAE) must be located within 6 to 8 cm from the anal verge, be <3 cm in size, and occupy less than 30% of the rectal circumference. For known malignant polyps, recommendation is to proceed with TAE in tumors with T1 depth of invasion only. Because of the tendency for suboptimal visualization, higher rates of positive margins and recurrence following conventional TAE resections have been reported.

Transanal Endoscopic Microsurgery

Transanal endoscopic microsurgery (TEM) allows for excision of lesions higher up in the rectum than conventional TAE, including up to the distal sigmoid colon per published reports. It requires a reusable, rigid 4-cm-diameter proctoscope, which comes in either a 12-cm or 20-cm length; a laparoscopic camera; and modified angled laparoscopic instruments. The rigid platform has three additional 5- to 9-mm ports through which instruments and a suction device can be passed. CO_2 pneumorectum is established through a port on the proctoscope to help maintain distension of the bowel wall while operating. Electrocautery is used to demarcate a 5- to 10-mm margin around the lesion. Then, using an instrument to grasp and adjust the distal edge, an energy device is used to perform submucosal or full-thickness dissection of the outlined area. For mainly posterior tumors, a partial resection of the mesorectum can be performed en bloc with the polyp. Care must be taken to avoid grasping the lesion directly because this could result in tissue breakage. Also, it is important to remain perpendicular to the lesion during dissection to avoid early tunneling, which could compromise the deep margin. Once the specimen is removed, hemostasis is achieved.

If a full-thickness excision was performed, it is recommended that the defect be closed transversely using a running or interrupted figure-of-8 absorbable suture. This tends to be a more time-consuming aspect of the procedure and requires some comfort with laparoscopic suturing to complete successfully. One could consider using barbed suture (e.g., V-lock), a knot pusher, or laparoscopic suture clips to eliminate the need to tie intracorporal knots, which can be challenging. Studies show that lesions located anteriorly in the upper or middle rectum tend to have a higher rate of intraperitoneal entry during dissection. In experienced hands, this can be sutured closed using the TEM platform with the patient placed in the steep Trendelenburg position to shift the bowel out from the pelvis. If unable, a transabdominal approach might be required.

The main limitation of TEM is the cost of the equipment. In addition, the rigid proctoscope can make it difficult to manipulate instruments when operating, requiring a steep learning curve to troubleshoot. Patients should complete a full bowel prep before the procedure to avoid stool interfering with visualization during the intraluminal portion of the case. This is also important if one anticipates a higher risk for intraperitoneal entry, with the potential need for transabdominal surgery based on lesion location.

Transanal Minimally Invasive Surgery

Because of the limitations associated with TEM, transanal minimally invasive surgery (TAMIS) was introduced as an alternative. It combines TEM principles with single-site laparoscopy, without the need for expensive specialized equipment or complex learning curves. The setup includes a flexible disposable single-site laparoscopic platform along with standard laparoscopic cameras, insufflators, and instruments. The more commonly used GelPOINT Path access channel comes in three lengths: 4 cm, 5.5 cm, and 9 cm. Channel length selection again is based on lesion location from the anal verge. The kit comes with self-retaining sleeves that are inserted into the gel cap, which can accommodate 5- to 10-mm standard instruments, in addition to frequently used needle sizes. Pneumorectum is established through a side port using standard insufflation equipment. If available, the AirSeal device can be used instead with the added advantage of providing stable bowel distension, even during suctioning activities. Dissection is performed in a similar fashion as in TEM.

Although the flexible platform allows easier maneuvering of instruments, the most challenging part of the procedure remains suturing the defect close at the end of the case because of the confined intraluminal space. To navigate this issue, many have turned to using the robotic platform with the TAMIS setup, capitalizing on the increased degree of articulation at the wrist of the robotic instruments.

Even though most vendors offer a shorter channel length, lesions in the distal rectum just above the dentate line might still be difficult to resect completely because of the platform. A hybrid approach using TAMIS for the proximal margin and then removing the platform to facilitate a conventional TAE can allow for complete excision and closure of the defect.

APPROACH TO THE MALIGNANT POLYP

Up to 5% of polyps that appear benign contain invasive cancer. This risk of cancer correlates with increasing polyp size such that polyps greater than 2 cm have an approximately 30% risk of cancer. For this reason, as mentioned previously, the colon should be tattooed at the site of any large polyp or any suspicious polyp if further treatment and evaluation are necessary.

Malignant polyps with deeper depth of invasion (i.e., >T1) have increased risk for lymph node metastases and should proceed to formal segmental resection. Even superficial or T1 early cancers can have higher risk for lymph node involvement based on the location within the polyp. To assist with risk prediction in this setting, the Haggitt level and Kikuchi submucosal (Sm) classification systems are used (Table 1). Haggitt levels 1 to 3 correspond with Sm1, but Haggitt level 4 can be Sm1, Sm2, or Sm3. A malignant polyp with an Sm3 classification is an indication for formal resection. Other factors predictive of lymph node metastases or recurrence are high tumor grade, extensive tumor budding, and lymphovascular invasion. In the absence of any of these features, the risk of adverse outcome is less than 1%; however, if a malignant polyp has one of these features, the risk increases to 20%. If two or more of these adverse features are present, the risk of adverse outcomes increases to 36%. Further evaluation of these features may better define patients who can be spared major surgery.

TABLE 1 Classification of Invasion Level

Haggitt Classification (Pedunculated Polyps)	Definition	Kikuchi Classification (Sessile Polyps)	Definition	Risk of Lymph Node Metastasis
1	Invades submucosa but limited to the head of the polyp	Sm1	Invades into the upper third of the submucosa	3%
2	Invades the neck of the polyp	Sm2	Invades into the middle third of the submucosa	8%
3	Invades the stalk of the polyp	Sm3	Invades into the lower third of the submucosa	23%
4	Invades the submucosa of the bowel wall below the stalk			

Haggit 1-3 corresponds to Sm1. Haggit 4 corresponds to Sm1, Sm2, or Sm3 levels.

Criteria for close surveillance after endoscopic removal of a malignant polyp include complete excision, a microscopic margin greater than 2 mm, no lymphatic or vascular invasion, moderate to well differentiation, Haggitt level 1 to 3, or Sm level 1 to 2.

All other malignant polyps that do not meet the aforementioned criteria should be considered for surgical resection. However, even with some high-risk features, patients with serious medical comorbidities may be best managed with close surveillance and nonsurgical treatment. An alternative to patients at high risk with a malignant rectal polyp may be full-thickness surgical excision (TAE, TEM, or TAMIS) with adjuvant chemoradiation.

Suggested Reading

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Management of Peritoneal Surface Malignancies

Fabian M. Johnston, MD, and Juliet Siena Lumati, MD

Peritoneal surface malignancies represent a heterogenous group of intraperitoneal malignancies arising from the lining of the abdominal and pelvic cavity. They include primary malignancies of the peritoneum such as diffuse malignant peritoneal mesothelioma, peritoneal serous papillary carcinoma, desmoplastic small round cell tumors, and metastases from other primary tumors typically involving the colon, stomach, and ovaries. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have evolved over the past decade to provide a therapeutic advantage to patients who otherwise have limited options beyond systemic chemoradiation for locoregional control or palliation. The purpose of this chapter is to review the epidemiology of peritoneal surface malignancies as well as current treatment guidelines.

EPIDEMIOLOGY AND CLASSIFICATION

Appendiceal Neoplasm

The true incidence of appendiceal neoplasms is unknown but is thought to be about 0.12 cases per 100,000 people per year in the United States. They are more commonly diagnosed incidentally on pathology in about 1% to 2% of appendectomy specimens. These tumors can be of mucinous or non-mucinous histology and may contain a signet ring cell component. Signet ring cell carcinomas are very aggressive, with up to 60% of cases already showing distant metastasis at the time of diagnosis. Patients with mucinous tumors may clinically present with *pseudomyxoma peritonei* (PMP), which is a condition characterized by mucinous ascites and peritoneal implants. Because of the rarity of these neoplasms, histologic classification had been challenging until 2010, when the World Health Organization recognized three categories of primary appendiceal neoplasms: *mucinous adenoma, low-grade appendiceal mucinous neoplasm* (LAMN), and *mucinous adenocarcinoma*. Subsequently in 2016, The Peritoneal Surface Oncology Group International Consensus developed a classification system to describe both the primary lesion and peritoneal disease. It also classified noncarcinoid epithelial neoplasms of the appendix itself and added a new term, *high-grade appendiceal mucinous neoplasm* (HAMN) for lesions with the low-grade architectural features of low-grade appendiceal mucinous neoplasm but with high-grade cytologic features (Box 1).

CLINICAL MANIFESTATION

Clinical symptoms on presentation can be quite nonspecific. Common presentations include increasing abdominal girth, weight loss, fatigue, bloating, constipation, and pain. Not uncommonly the diagnosis is made on presentation with acute appendicitis obstruction of the appendiceal lumen by malignant cells, which may lead to inflammation and infection of the appendix. Similarly, mucinous tumors may present with cystic dilation of the appendix, which could also mimic symptoms of appendicitis or be found incidentally on imaging for a different etiology. Men may also present with hernias and women with a bulky pelvic mass. Anorexia, early satiety, and massive ascites are also common manifestations, and in some ways, likely underestimate the true incidence of the disease given the late clinical presentation of these neoplasms.

PREOPERATIVE WORKUP

Preoperative workup should include staging CT of the chest, abdomen, and pelvis. Routine CBC, basic metabolic panel, and nutritional markers are often helpful. Other parameters include serum tumor markers including CEA, CA 19-9, CA125, and chromogranin A as well as obtaining a preoperative colonoscopy to evaluate for synchronous or metachronous colonic lesions, which at times may be negative. A diagnostic laparoscopy may be useful in determining eligibility for cytoreductive surgery in addition to obtaining histologic assessment, which may help guide treatment plans.

PATIENT SELECTION

Patient selection is extremely important in deciding who will most benefit from CRS and HIPEC and to avoid significant morbidity and mortality in patients who are not expected to benefit. Surgeons

BOX 1 PSOGI 2016 Classification of Noncarcinoid Appendiceal Epithelial Neoplasms

- Tubular, tubulovillous or villous adenoma, low- or high-grade dysplasia
- Serrated polyp with or without dysplasia (low or high grade)
- Low-grade appendiceal mucinous neoplasm
- High-grade appendiceal mucinous neoplasm
- Mucinous adenocarcinoma: well, moderately, or poorly differentiated
- Poorly differentiated (mucinous) adenocarcinoma with signet ring cells
- (Mucinous) signet ring cell carcinoma
- Adenocarcinoma: well, moderately, or poorly differentiated

should consider the extent of disease, tumor biology, physiologic age, comorbidities, and the ECOG/WHO functional and frailty status when selecting patients. Scoring systems such as the peritoneal disease severity score (PDSC), which was devised to stage patients with colon cancer based on clinical symptoms, extent of carcinomatosis based on radiographic evidence, and tumor histopathology may be useful to facilitate appropriate patient selection. For patients with LAMN (grade 1) CRS + HIPEC is the treatment of choice if complete cytoreduction can be achieved. Patients with adenocarcinoma and peritoneal metastasis are less likely to have complete cytoreduction and overall have poorer survival than those with LAMN. It is important to note that not all LAMNs or well-differentiated mucinous adenocarcinomas require a right hemicolectomy unless there is clear involvement of the colon serosa, which would necessitate colectomy. Furthermore, The American College of Surgeons' NSQIP surgical risk calculator may also be used to estimate perioperative risk, especially in patients with significant cardiopulmonary comorbidities not captured by the PDSC. It is important to note that no risk calculator is absolute; therefore, it is the combination of risk factors and expected net benefit that guides preoperative discussions with patients to set appropriate expectations. Furthermore, all patients should be presented at multidisciplinary team with considerations given to probability of extensive organ resection, morbidity, quality of life, and recurrence risk. The Chicago Consensus Guidelines on the management of appendiceal neoplasms are highlighted in Figures 1 and 2.

COLORECTAL CANCERS

The care of patients with advanced colorectal cancer has evolved over the past several decades, with overall improvement in the median survival for patients with stage IV disease. This has been largely attributed to improvements in the use of multimodal targeted therapy (i.e., neoadjuvant chemotherapy [NACT] and chemoradiation for rectal tumors), surgical technique, adjuvant chemotherapy for colon cancer, and improved patient selection. This is in addition to improving evidence that metastasectomy of liver and lung metastases improves 5-year survivorship.

In 2003, Verwall et al. randomized 105 patients with metastatic colon cancer with peritoneal carcinomatosis to receive CRS + HIPEC or systemic therapy alone that consisted of monotherapy 5FU/leucovorin. Results from this clinical trial showed an improvement in median survival in the HIPEC arm at 22.3 months compared with 12 months in the standard group at the median follow-up of 22 months. However, a subsequent follow-up study published in 2008 found no difference at the 8-year follow-up. Similarly, the COLOPEC trial, which was a multicenter randomized controlled trial (RCT) of 204 patients compared adjuvant HIPEC + systemic chemotherapy to systemic chemotherapy alone. The authors found no difference in metastasis-free survival at 18 months and a slight increase in postoperative complications in the HIPEC + chemotherapy group. Given that HIPEC is typically performed concurrently with CRS, the first study to evaluate HIPEC + CRS versus CRS alone was the PRODIGE trial with results recently published as of February 2021. This was an RCT comparing HIPEC + CRS versus CRS alone and recruited 265 patients across 7 centers. The authors found no significant difference in the median survival in the HIPEC + CRS group versus the CRS group (41 months vs. 40 months, respectively) at a median follow-up of 63 months. In a subgroup analysis, patients with a moderate burden of peritoneal disease (peritoneal cancer index [PCI] 11–15) who received HIPEC had a significant improvement in overall survival at 41 months compared with 32 months in CRS, though outpatient complication rates were higher in the HIPEC + CRS group versus

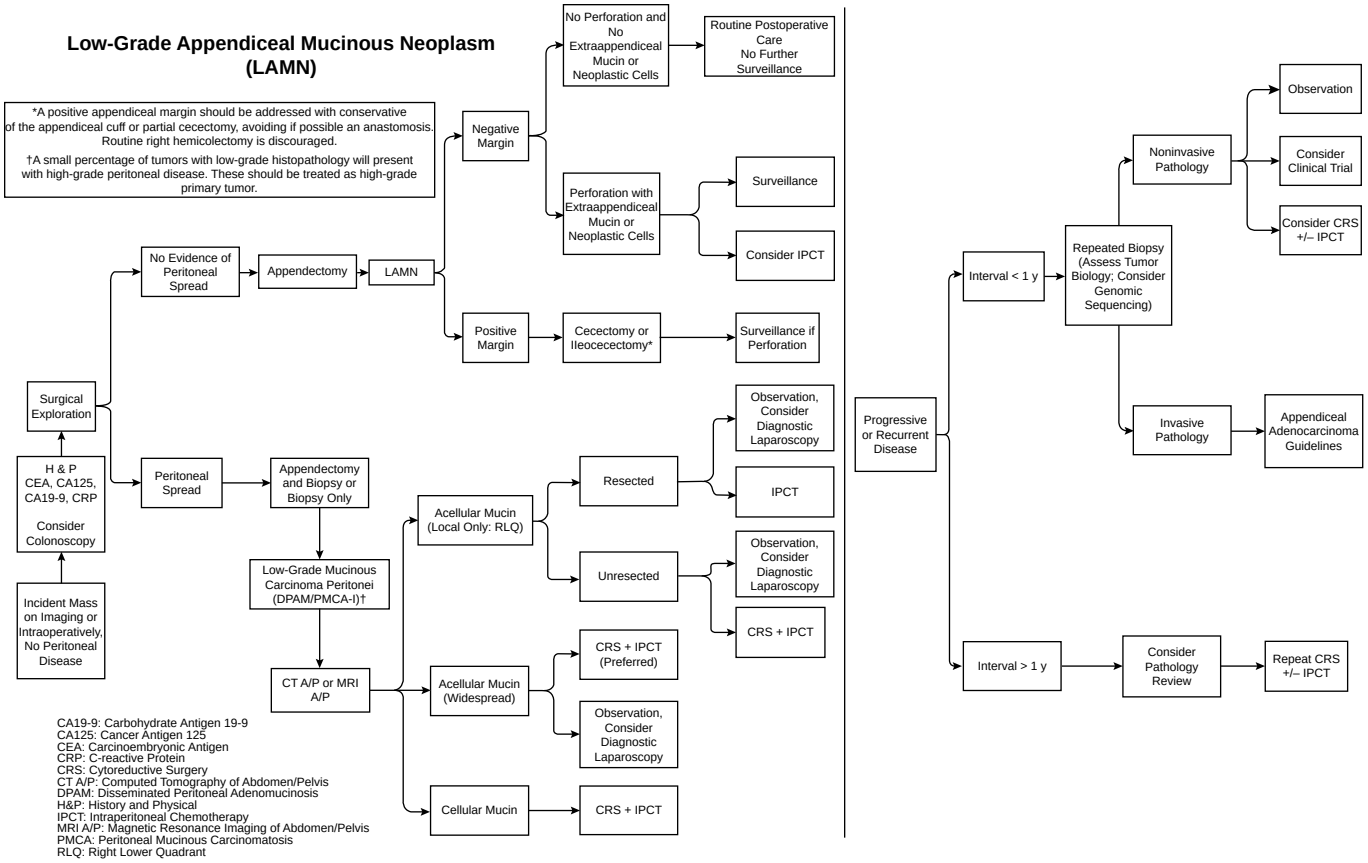


FIG. 1 The 2018 Chicago Consensus Guidelines on the Management of Low-Grade Appendiceal Mucinous Neoplasm (LAMN). *(From Chicago Consensus Working Group. The Chicago consensus on peritoneal surface malignancies: standards. Cancer. 2020;126:2516–2524.)*

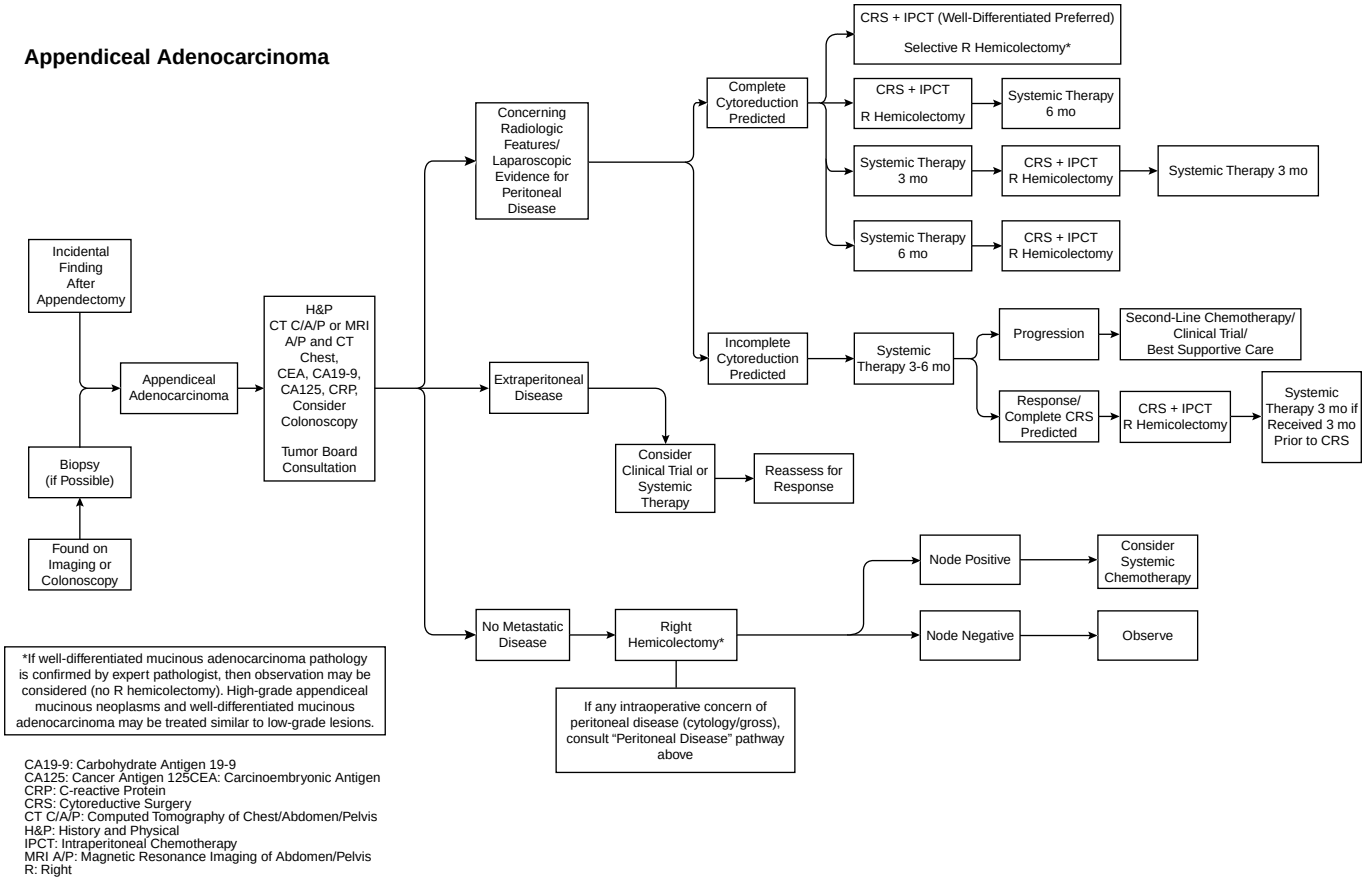


FIG. 2 The 2018 Chicago Consensus Guidelines on the Management of Appendiceal Adenocarcinomas. *(From Chicago Consensus Working Group. The Chicago consensus on peritoneal surface malignancies: standards.* Cancer. *2020;126:2516–2524.)*

the CRS group (24% vs. 13%, respectively). The results of these studies on prospective clinical trials highlight the need for a multidisciplinary approach to selecting patients who will maximally benefit from CRS versus HIPEC+ CRS. It also highlights the benefit of cytoreduction in combination with NACT.

Epidemiology

Peritoneal disease is present in about 8% of CRC patients at the time of primary resection, and up to 25% of patients with recurrent CRS will develop metastatic disease confined to the peritoneal surface. Risk factors for peritoneal metastases include mucinous histology, T4 cancers, vascular invasion, spontaneous or iatrogenic perforation, and right-sided tumors, which overall confer a worse prognosis. The presence of untreated visceral solid organ metastasis is a relative contraindication to HIPEC and CRS.

Clinical Manifestations

Peritoneal metastases secondary to CRC may present with ascites manifesting as increasing intraabdominal girth, pain, or small bowel obstruction. However, just as often, synchronous peritoneal disease may be asymptomatic and detected at the time of primary surgery or on staging imaging. For patients with metachronous disease, it is most common to identify peritoneal metastases during surveillance given the intensity of imaging use in current practice.

Preoperative Workup

Patient selection is very important in determining the appropriateness of cytoreductive surgery and HIPEC. Preoperative evaluation should include a thorough history and physical examination along with axial imaging including CT of the chest, abdomen, and pelvis. PET/CT may be useful in patients with non-mucinous tumors. Laboratory workup includes CEA, CA-19, and CA-125 levels and nutritional markers. A complete colonoscopy is also recommended if not already completed. Diagnostic laparoscopy may be helpful for staging and assessment of surgical eligibility given the poor sensitivity of axial imaging for detecting peritoneal metastasis. In addition, small tumors in specific locations such as the root of the mesentery and serosal surface of the small bowel are harder to detect on CT scan. PET/CT has a sensitivity of 78% to 100% and is not uncommonly ordered before surgery. It is however associated with false-negative results for tumors that are not PET/CT avid (mucinous tumors) or false-positive results for inflammatory processes. There have been limited studies evaluating the role of diffusion weight MRI in detecting subcentimeter deposits in difficult anatomic locations, though it is not widely adopted given the contraindications, costs, and availability.

Patient Selection for Surgery

Patient selection is critical in determining who would most benefit from CRS + HIPEC. Generally, good candidates for CRS + HIPEC are patients with good performance status who have an ECOG/WHO status of 1 or less, have adequate physiologic and organ function, have a low/moderate PCI, and can receive systemic chemotherapy. In fact, response to initial chemotherapy is often used as prognostic marker to screen patients with rapidly evolving tumor biology. PCI scores range from 0 to 39, with a score less than 12 considered most favorable for resection. A PCI greater than 20 is typically considered a contraindication to resection. Patients with a PCI between 12 and 20 may be determined on a case-by-case basis depending on

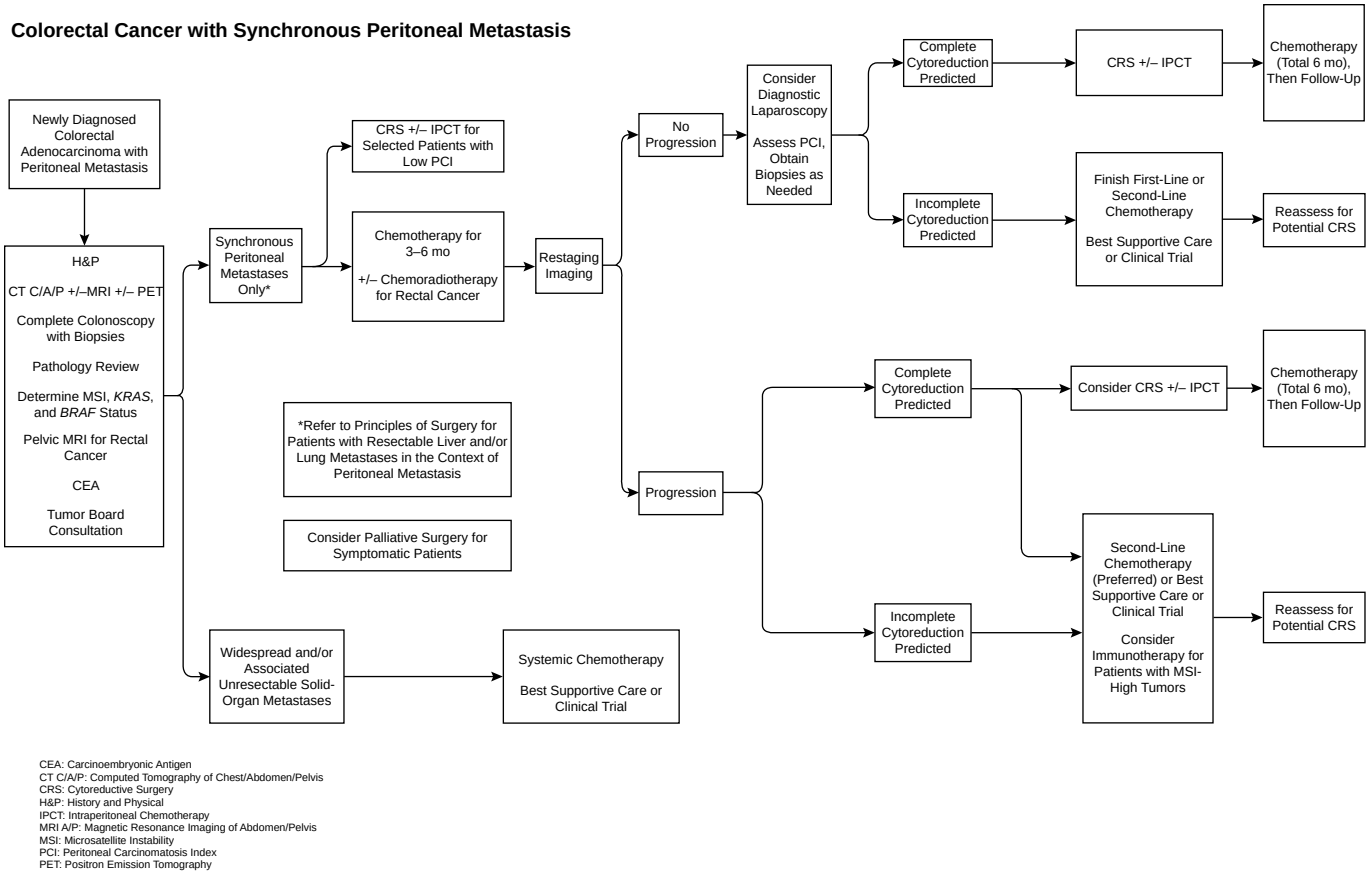


FIG. 3 The 2018 Chicago Consensus Guidelines on the Management of Colorectal Cancers with Synchronous Peritoneal Metastasis. *(From Chicago Consensus Working Group. The Chicago consensus on peritoneal surface malignancies: standards. Cancer. 2020;126:2516–2524.)*

additional clinical parameters, such as extent of extraperitoneal metastasis and tumor biology. A more conservative PCI cutoff of 17 has been proposed based on results of a prospective study by Goere et al., which showed no benefit of HIPEC + CRS in patients with a PCI greater than 17. It is important to note that a preoperative radiologic PCI score may not always correlate with an intraoperative PCI score, hence staging laparoscopy can be used as an adjunct to assess borderline cases. The presence of malignant ascites, large tumor burden, or multifocal bowel obstructions are relative contraindications to curative intent surgery in addition to the presence of liver or lung metastasis that are untreated. Visceral metastases should be considered for therapy on an individualized basis. Lastly, the treatment options and timing for patients with synchronous or metachronous lesions similar to appendiceal neoplasms should be discussed among a multidisciplinary team. Figure 3 summarizes the Chicago Consensus Guidelines on CRS and HIPEC in colorectal cancers.

GASTRIC CANCER

Epidemiology and Clinical Manifestation

Gastric cancer is a leading cause of cancer-related deaths, with a mortality rate of 8.9% after lung cancer (19.7%) and breast cancer (12.9%), respectively. Overall 5-year survival approaches 90% in countries like Japan and varies between 10% and 30% in Western countries. Peritoneal carcinomatosis occurs synchronously with primary tumors in 14%% to 43% of patients with gastric cancer and accounts for 35% of synchronous metastasis. Risk factors for peritoneal metastasis include extranodal involvement, diffuse infiltrated type, signet cell histology, higher CEA levels, liver involvement, young age, and female gender. Prognosis of untreated gastric cancer with peritoneal carcinomatous is quite poor, with a median 5-year survival that approaches 0%.

Preoperative Workup

Preoperative workup includes history and physical examination, upper endoscopic ultrasound, and endoscopic ultrasound with biopsy for local regional staging. Imaging includes CT of the chest, abdomen, and pelvis with contrast and PET/CT if there is no evidence of M1 disease. HER2/NEU testing should be obtained if metastatic disease is suspected. Molecular profiling to assess for microsatellite stability and PDL1 positivity maybe helpful for patients with unresectable disease. Genetic counseling is recommended in young patients to evaluate for *CDH1* mutations given their high penetrance. Nutritional markers should be considered in addition to smoking cessation and counseling. Patients typically receive the most commonly used perioperative chemotherapy, which includes FOLFOX, XELOX, FLOT, ECF, +/– radiation for 3 to 6 months followed by restaging and diagnostic laparoscopy with peritoneal washings. Patients with advanced tumors, clinical T3 or greater, or node-positive disease should undergo laparoscopic staging with peritoneal washings to evaluate for extent of peritoneal disease.

Patient Selection for Surgery

All patients with biopsy-proven gastric cancer should be presented to a multidisciplinary tumor board to discuss a tailored treatment plan, which is largely dependent on the patient's functional status and

tumor biology. Generally, patients with low peritoneal disease burden and lack of progression of disease after systemic therapy should be restaged and considered for HIPEC + CRS. Various options include early postoperative chemotherapy (EPIC) or bidirectional intraperitoneal and systemic induction chemotherapy before CRS + HIPEC. Ideal candidates should be young (<70 years of age) and have a good performance status, a PCI score <10, small nodules, a resectable primary tumor, no evidence of paraaortic lymphadenopathy, no liver or extraperitoneal metastasis, and have responded well to NACT.

Hoptopp et al. found an overall increase in survival in patients with gastric cancer and confirmed peritoneal metastasis who underwent NACT with FLOT followed by CRS + HIPEC versus chemotherapy alone (17 months vs. 6 months) in a single-center study. A more recent advancement is the use of neoadjuvant intraperitoneal and systemic chemotherapy protocol/bidirectional intraperitoneal and systemic induction chemotherapy (NIPS/BISIC), which aims to reduce the stage and increase the incidence of complete cytoreduction. By simultaneously administering intravenous and intraperitoneal chemotherapy, the cancer cells are targeted both from the peritoneal cavity and subperitoneal blood vessels. Several studies have examined the effectiveness of this therapy in complete cytoreduction and improving survivorship. Yonemura et al published a prospective study of 194 patients who had BIPSC followed by CRS + HIPEC. Patients had (1) biopsy-proven peritoneal carcinomatosis, (2) no evidence of liver or lung metastasis, and (3) good performance scores. In this study, 152 patients responded to BIPSC and subsequently underwent CRS + HIPEC. Complete cytoreduction was achieved in about 70% of these patients. Median survival was 15.8 months in patients who had CRS + HIPEC after BIPSC versus patients who did not (7 months). Completeness of cytoreduction, pathologic response to NIPS, and PCI on multivariate analysis overall predicted survivorship. It is important to note that the complication rate was 24%, which is similar to that found in a study by Hultman et al., which also showed an improvement in median survivorship (19 months vs. 14 months) but reported a higher complication rate of 63%. This is most commonly caused by anastomotic leak, sepsis, wound infections, and organ failure. These studies show that appropriate patient selection and identification of patients with unresectable or disseminated disease who are eligible for complete cytoreduction is paramount.

PERITONEAL MESOTHELIOMA

Epidemiology and Clinical Manifestation

Mesothelioma is a rare malignancy of serosal membranes. This includes the pleura, peritoneum, pericardium, and the tunica vaginalis testes. The peritoneum is the second most common location and is estimated to represent about 10% to 15% of all mesotheliomas. The highest incidence is reported in countries such as New Zealand, the United Kingdom, and Australia, and the lowest incidence is reported in countries such as Japan, Slovenia, and Central Europe. The estimated incidence is 1.94 per 100,0000 and 0.41 per 100,000 for men and women, respectively, in the United States. Mesothelioma is commonly associated with exposure to asbestos, but 33% to 50% of patients diagnosed with malignant pleural mesothelioma (MPM) have no prior asbestos exposures. Other risk factors include exposure to radiation minerals such as thorium, chronic peritonitis, and germline BRCA-1–associated protein *(BAP-1)* gene mutation. Histologic classifications include epithelioid, sarcomatous, and biphasic/mixed. About 75% of all mesotheliomas are epithelioid in origin, which overall have the most favorable prognosis.

Perioperative Workup

Making the diagnosis is often challenging as patients present with mostly vague abdominal symptoms. On imaging, patients may have ascites, evidence of omental caking, or mesenteric fatty infiltration. Definitive diagnosis is based on histology and pathologic assessment, which could be obtained on percutaneous biopsy or diagnostic laparoscopy. Diagnostic laparoscopy is indicated to evaluate the extent of disease amenable to surgery. Pathologic assessment is essential to differentiating subtypes of mesothelioma that may be more amenable to surgery versus chemotherapy alone. Epithelioid histology has overall the most favorable response to HIPEC + CRS in contrast with sarcomatoid, biphasic subtypes, which overall have a poorer prognosis and for which surgery is less likely to offer a survival benefit. Furthermore, the CA-125 and Ki-67 index are often obtained in addition to germline testing for a *BAP-1* gene mutation.

Patient Selection for Surgery

The natural history of MPM is aggressive; without treatment, median survival is approximately 6 months. Median survival with systemic chemotherapy alone is approximately 16 months; however, it improves to approximately 40 months with HIPEC + CRS. Patients with MPM are considered for surgical therapy with CRS/HIPEC if their disease burden is amenable to resection of all or nearly all (CC-0 or CC-1) visible disease and are suitably fit for such extensive resection.

OVARIAN CANCER

Epidemiology and Clinical Manifestation

Ovarian cancer is associated with one of the highest mortalities from gynecologic cancers in the world, with an estimated 5-year survival rate of 39%. Despite efforts to screen for ovarian cancer, 35% to 43% of patients still present with advanced disease involving the peritoneum at the time of diagnosis. Risk factors for peritoneal disease include germline mutations, incomplete resection at initial cytoreductive surgery, shorter treatment-free survival, higher FIGO (International Federation of Gynecology and Obstetrics) stage, and the present of malignant ascites. The most common type of ovarian cancer is epithelial in origin; less common types include clear cell, mucinous, carcinosarcoma, endometroid carcinoma, and malignant germ cell tumors. Symptoms include early satiety, bloating, nonspecific abdominal pain, and urinary symptoms. Others may present with massive ascites, which is typically associated with mucinous neoplasms.

Preoperative Workup

The diagnosis is made based on clinical suspicion, imaging, and tumor markers, with elevation of CA-125, inhibin, B-HCG, LDH, and CEA levels being pathognomonic. Nutritional parameters, CBC, and liver function tests and chemistries are routinely ordered. A complete colonoscopy is recommended to evaluate for synchronous gastrointestinal malignancies that can present similarly. Genetic counseling is recommended for all patients given the incidence of *BRCA* mutation, which may help guide adjuvant systemic therapy. Surgery is the mainstay therapy and typically includes extensive debulking and cytoreduction with a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) but can include appendectomy, colon or small bowel resection, cholecystectomy, and omentectomy. Diagnostic laparoscopy is essential to quantify tumor burden and identify patients whose disease is amenable to adequate cytoreduction. The presence of omental caking, peritoneal and diaphragmatic extensive carcinomatosis, mesenteric retraction, bowel and stomach infiltration, and spleen and/or liver superficial metastasis are typically assessed on laparoscopy. Importantly, these operations are typically conducted using a multidisciplinary approach involving gynecology oncology and surgical oncology to improve the chances of complete cytoreduction.

Patient Selection for Surgery

HIPEC is typically considered in patients with stage III disease of epithelial origin as the other cell types are less chemosensitive. Furthermore, NACT with interval CRS is considered in patients with advanced-stage ovarian cancer who are not good candidates for upfront primary debulking surgery (PDS) because of advanced age, frailty, poor performance status, or for those in whom the disease is unlikely to be optimally cytoreduced. This has the potential to facilitate medical optimization and to downstage the disease. The addition of HIPEC to CRS has been evaluated in several studies in the recurrent setting. In a 2015 RCT, Spilotis found a 13-month improvement in survival with HIPEC + CRS versus CRS alone. In a retrospective cohort study of 584 patients with stage III epithelial ovarian cancer, Lei et al. found an overall 15-month improvement in survival in patients undergoing CRS + HIPEC versus CRS alone, and patients with complete CRS had the most favorable survival outcomes. In an RCT of 245 patients randomized to HIPEC + CRS versus CRS alone, Van Driel et al. found an increase in overall median survival in the HIPEC + CRS group at 45.7 months versus 33.9 months in the CRS group alone. The CHIPPI-1808 trial comparing HIPEC + NACT + CRS versus NACT + CRS should have results by 2026 and perhaps may help improve patient selection and justify the use of upfront HIPEC in the primary setting versus the current standard of care, which is typically in the recurrent setting with interval CRS.

Intraoperative Management and Technique

The Chicago Consensus Working group publishes a consensus on peritoneal surface malignancies that includes guidelines for standard operations and metrics. Generally speaking, a fellowship experience with CRS + HIPEC, documentation of number of cases, and availability of two surgeons are necessary in addition to established criteria for institutional credentials. Process standards include confirmed tissue diagnosis, relevant tumor markers depending on the cancer type, cross-sectional imaging, and ideally registry of all patients in a data repository. Quality standards also exist for reporting of pathology, intraoperative monitoring, perfusion equipment used, and rating of the completeness of intraoperative cytoreduction. A complete list of standards, quality, and process measures is available online.

Preoperatively patients undergo mechanical bowel preparation with oral antibiotics before surgery. Patients are positioned supine for lithotomy if any concern of needing lower pelvic work; DVT prophylaxis with SCDs and subcutaneous heparin in addition to perioperative IV antibiotics are administered. It is important to maintain good communication with anesthesia and the intraoperative room staff to ensure that the patient's core body temperature is maintained and that the patient is adequately being resuscitated to maintain good urine output given insensible losses that can occur during the operation. Adequate monitoring of cardiovascular and fluid resuscitation is crucial in the intraoperative and postoperative period. If not closely monitored and managed, patients are at risk for abdominal hypertension, coagulopathy, decreased systemic vascular resistance, and high-output cardiac failure in addition to toxicities directly related to the chemotherapy agent being used. Therefore, early determination of the need for recovery in the intensive care unit (ICU) should be determined intraoperatively. Increasingly, intraoperative goal-directed fluid therapy and enhanced recovery pathways have been implemented in various institutions with the goal to improve postoperative outcomes. For example, tools such as stroke volume variation are used to guide fluid management and maintain urine output. This strategy overall leads to less overall fluid administration and is associated with less postoperative morbidity.

The procedure begins with an exploratory laparotomy with complete evaluation of the extent of peritoneal metastasizes and probability of complete cytoreduction through a midline incision. Diagnostic laparoscopy may be undertaken before laparotomy if there is concern that the extent of disease may preclude cytoreduction. Lysis of adhesions may be required if the patient already had prior surgeries or malignant adhesions that may preclude safe entry. A pre-cytoreduction PCI is assessed followed by complete cytoreductive surgery with the intent of removing all tumors greater than 0.25 cm. (CC-0 or CC-1). We generally inspect systematically the bilateral diaphragm surfaces, lesser sac, small bowel and its mesentery, porta hepatis, aortocaval groove (IVC bursa) near the caudate and pelvis, and all solid organs. Once all sites have been inspected, we recommend running the small bowel in its entirety from the ligament of Treitz to the ileocecal valve as well as inspecting the right and left colon and its mesentery to the level of the sacral promontory. All prior anastomoses should also be inspected in addition to incising the nodal tissue at the ligament of Treitz, falciform ligament, and triangular ligament for liver mobilization. Small lesions can be removed sharply, but larger lesions that are infiltrative or cannot be separated easily require formal resection. Generally, extensive small bowel disease or nodal disease involving the root of the mesentery are contraindications to complete cytoreduction. Complete cytoreduction typically requires an omentectomy, selective peritonectomy, and visceral resection.

For HIPEC, most units prefer a closed technique, which overall reduces exposure of the operative room team and decreases heat dissipation. Other institutions utilize an open technique for delivery. Mitomycin C, oxaliplatin, or doxorubicin is typically used. Selection of the type of chemotherapy agent is typically based on tumor histology and institutional protocol. Several studies have shown no difference in progression-free survival comparing HIPEC with mitomycin C versus oxaliplatin, the two most used chemotherapy agents. These studies also suggest differences in side-effect profiles, suggesting that more studies are needed.

The inflow and outflow cannulas as well as a temperature probe are placed into the abdomen, and the incision is temporary closed. Using a hyperthermia perfusion pump, 3 to 6 L of warm fluid is instilled until abdominal distension based on intraoperative determination of peritoneal volume. The fluid is heated to about 40° to 43°C. Once the target temperature is achieved, the chemotherapy agent is infused over 30 to 120 minutes. Once this is complete, the abdomen is opened and reinspected. There is no known difference in outcomes based on anastomosis pre- or post-HIPEC. The fascia is closed, and a completeness cytoreduction score is assigned at the end of the case. In early postoperative intraperitoneal chemotherapy (EPIC), the abdomen is filled with 1 L of lactated Ringer solution, then mitomycin +/– cisplatin is given continuously or on postoperative day 1 and 2 at varying doses. In NIPs + HIPEC + CRS, patients are given intravenous chemotherapy preoperatively and administered docetaxel and/or cisplatin intraperitoneally on day 1 and day 8. This is repeated three times, and laparotomy with cytoreduction is performed 2 weeks after the last administration of intravenous chemotherapy. These alternatives have shown some promising results in select populations.

Postoperative Management

Depending on institutional support (e.g., nursing levels, telemetry) patients are admitted to the floor, step-down unit, or ICU. Patients with larger cytoreductions or significant comorbidities benefit from ICU management. Patients are generally at risk of postoperative ileus. Commonly, a nasogastric tube is placed at the time of surgery. Early ambulation and incentive spirometry are strongly encouraged. If extensive diaphragm stripping or resection is performed, some patients with respiratory comorbidities may benefit from chest tubes. Patients are typically managed with fluid restriction after the initial resuscitative phase, which typically is in the first 72 hours. Early discontinuation of intravenous fluids when

tolerating a regular diet and/or adequately resuscitated is encouraged. Though ERAS protocols for HIPEC + CRS have not been widely adopted, they do show some promising results in reducing length of stay for patients undergoing HIPEC + CRS, though no RCT has been conducted to date. In general, patients remain in the hospital until they have adequate return of bowel function and pain control. Initially some patients may have electrolyte and metabolic derangement caused by fluid shifts and should be monitored closely. Risk factors associated with increased risk of complications include number of anastomosis performed, diaphragm resection, number of blood transfusions required, and thermal bowel injuries. Overall postcomplication rates are described between 10% and 40%, depending on the series. Average length of stay is approximately 7 to 10 days. Advanced age, malnutrition, and multiple visceral resections are associated with an increased length of stay, hence early intervention to identify patients at most risk is crucial to obtaining quality long-term outcomes for HIPEC and CRS.

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Management of Lower Gastrointestinal Bleeding

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INTRODUCTION

Lower gastrointestinal bleeding (LGIB) is a frequently encountered and complex clinical problem for surgeons. Classically defined as gastrointestinal (GI) bleeding emanating from any point distal to the ligament of Treitz, LGIB can originate anywhere from the small bowel to the anus and accounts for an estimated 30% of all GI bleeding. Nearly all LGIB can be isolated to the colon and rectum, with diverticular bleeding being the most common cause. Less than 10% of LGIB originates from the small bowel or anus. Aggressive resuscitation, accurate localization, and control of bleeding are the primary goals of treatment for patients who present with hemorrhagic shock. A systematic approach to diagnosis and management is pivotal in reducing morbidity and mortality.

Etiology

LGIB can be further categorized as massive, moderate, or occult. Massive bleeds are the most life-threatening, with mortality rates approaching 20%. Despite this, more than 80% of all LGIB will resolve spontaneously, and the overall mortality rate is about 4%. Patients presenting with massive LGIB are usually >65 years and present with hematochezia or bright red blood per rectum in the setting of hemodynamic instability. The most common causes are diverticulosis and angiodysplasia. Interestingly, one-third of patients with presumed massive LGIB will have an upper GI source, so assessing for risk factors of peptic ulcer disease is important.

Moderate and occult bleeding can occur at any age. Moderate LGIB presents as hematochezia or melena in a hemodynamically stable patient. The differential diagnosis is broad (Table 1). Occult LGIB is otherwise asymptomatic, except for microcytic anemia resulting from chronic blood loss. The differential diagnosis of these patients includes malignancy, inflammatory conditions, ischemia, and congenital causes such as bleeding Meckel's diverticula.

Epidemiology

Approximately 30% of all patients presenting with major GI bleeding are found to have bleeding distal to the ligament of Treitz. Among patients with presumed LGIB, 80% originate distal to the ileocecal valve, with only 10% originating from the small bowel. The remaining cases usually arise in the upper GI tract. The overall incidence of LGIB is notably higher in older adult patients, particularly those who are on multiple medications.

Diverticulosis accounts for over 40% cases of LGIB and often presents as painless hematochezia. Diverticular bleeding frequently recurs, and the prevalence increases in patients older than 80 years of age or in those with chronic constipation. Ischemic colitis accounts for 20% of LGIB and is also more prevalent in the elderly. This may occur in response to reduced mesenteric flow to the colon caused by decreased cardiac output, vasospasm, or atherosclerotic disease. Treatment is generally supportive and conservative unless there is evidence of full-thickness necrosis and/or peritonitis. The watershed area of the splenic flexure is a common location for ischemic colitis, and involvement of this area on imaging should alert the clinician to the possibility of this diagnosis. The most common cause of LGIB in patients younger than 50 years of age is benign anorectal disease, usually hemorrhoids or anal fissures. The possibility of inflammatory bowel disease (IBD) or NSAID-induced mucosal ulceration should also be considered in these patients. Post-polypectomy bleeding can result in brisk bleeding following colonoscopy and polypectomy. Risk factors include age greater than 65 years and polyp size larger than 1 cm. Though the bleeding is usually self-limited, presentation can be delayed for up to 1 week after the procedure; therefore ascertaining the history of colonoscopy with polypectomy is crucial.

TABLE 1 Differential Diagnosis of Lower Gastrointestinal Bleeding

Anatomic Source of Bleeding	Etiologies
Small intestine	Angiodysplasia Crohn's disease Mesenteric ischemia Recent surgery/trauma Meckel's diverticulum Dieulafoy's lesion Aortoenteric fistula Intussusception
Colon	Diverticulosis Neoplasm Angiodysplasia Inflammatory bowel disease Recent colorectal surgery/trauma Recent colonoscopy/ polypectomy Ischemic colitis Infectious colitis Enterohemorrhagic *Escherichia coli* (EHEC) *Salmonella* *Campylobacter* *Shigella* *Cytomegalovirus* *Entamoeba histolytica* Fecal impaction Aortoenteric fistula
Rectum	Radiation proctitis Neoplasm Angiodysplasia Rectal varices Fecal impaction Inflammatory bowel disease Solitary rectal ulcer Rectal prolapse Recent colorectal surgery/trauma
Anus	Hemorrhoids Anal fissure Inflammatory bowel disease Local trauma Perianal variceal disease

History and Physical Examination

The differential diagnosis for LGIB is broad, so a thorough history and physical examination is necessary. The history may suggest a cause of LGIB and can inform decision-making regarding

diagnostic evaluation and management. Key details in the history should include the quantity, quality, and frequency of the bleeding, specifically whether the bleeding is recurrent or sporadic. Inquiry into other associated symptoms such as presence of abdominal pain, nausea, vomiting, or a recent change in bowel habits is also warranted. The clinician should specifically inquire about prior episodes of LGIB, history of abdominopelvic radiation, trauma, symptomatic arrhythmias, liver disease or cirrhosis, HIV status, and recent endoscopic or surgical procedures. A detailed review of the patient's medications including antiplatelet agents, anticoagulants, and NSAIDs as well as a family history of colon cancer or inflammatory bowel disease should also be noted.

Abdominal examination and digital rectal examination should be completed in all patients presenting with LGIB. Abdominal examination may reveal tenderness, distension, or a mass. Digital rectal examination is important to inspect for anorectal pathology such as hemorrhoids or fissures. Additionally, the quality of the stool in the rectal vault, whether it is impacted, dark melena, maroon-colored, or frank blood, should be documented. Importantly, the clinician should pay close attention to the patient's vital signs at all points during the history and physical examination as any hemodynamic instability warrants a rapid resuscitation and aggressive diagnostic effort.

MANAGEMENT

All patients presenting with LGIB should be triaged and evaluated immediately as decompensation can be rapid. Administration of supplemental oxygen, the establishment of intravenous lines access with two large-bore peripheral venous catheters, and placement on a cardiopulmonary monitor should be performed initially. Infusion of crystalloid solutions should be started immediately to resuscitate the patient. Laboratory examination should include a complete blood count, metabolic panel, liver function tests, lactate, coagulation studies, and a type and screen.

Resuscitation and Transfusion

Appropriate resuscitation of a patient with LGIB is crucial to minimize morbidity. The process should begin as described earlier as soon as it is recognized that the patient is actively bleeding. For patients with evidence of multiple comorbidities or massive LGIB, a critical care consultation and monitoring in a critical care setting is warranted.

Most patients with moderate or occult LGIB present without signs of instability. These patients may warrant less aggressive resuscitation with crystalloid during their initial workup and evaluation. Transfusion should be initiated to correct any overt coagulopathy and to maintain a hemoglobin >7 g/dL for most patients. Some patients, particularly those with other comorbidities, may require a higher goal hemoglobin and should be treated on an individual basis. International normalized ratio (INR) should be corrected to <1.5, and platelets should be transfused to >50,000/μL.

The massive LGIB patient who presents in hemorrhagic shock is similar to a trauma patient. Therefore, activation of a massive transfusion protocol and the use of empiric blood product ratios of 1:1:1 of packed red blood cells to fresh-frozen plasma to platelets in order to correct coagulopathy is effective. Early use of fresh-frozen plasma and platelets should be considered. The end goals of resuscitation are correction of coagulopathy and hemodynamic support. A policy of permissive hypotension with systolic blood pressure >90 mm Hg is sufficient for most patients. Although crystalloid solutions may be indicated in other cases of LGIB, care should be taken to avoid the overuse of crystalloids in this subset of patients because this may contribute to bowel edema and other complications such as abdominal compartment syndrome or respiratory failure. The use of thromboelastography (TEG) may also be a useful adjunct for the care of the hemodynamically unstable LGIB patient in centers where this technology is available. Prompt progression to the next phases of management, bleeding localization and hemorrhagic control, is important to minimize mortality. Aggressive efforts to correct coagulopathy and metabolic derangements before surgical intervention should be undertaken, although salvage procedures may be required in rare cases. This will be discussed further in later sections.

Special Hematologic Considerations

Early identification of hematologic disorders or medications is mandatory during the resuscitative process. Laboratory studies, including traditional coagulation studies and possibly TEG, should be obtained during the initial workup. Anticoagulants and antiplatelet agents should be discontinued, and reversal should be considered in patients with hemodynamic instability or ongoing bleeding. For patients who are therapeutic or supratherapeutic on warfarin, a prothrombin concentrate complex should be considered. Vitamin K and fresh-frozen plasma can also be utilized for this purpose, but prothrombin complex concentrate has the advantage of rapid reversal with lower fluid volumes. In recent years, idarucizumab has become more readily available to reverse dabigatran. Although not widely available yet, andexanet alfa has also been approved by the US Food and Drug Administration (FDA) for the reversal of apixaban and rivaroxaban. Currently, there is no specific reversal agent for antiplatelet agents such as aspirin and clopidogrel. Most clinicians favor early platelet transfusion and/or desmopressin administration in the setting of active hemorrhage. Cardiology consultation should be considered for patients who have had drug-eluting cardiac stents placed within the past year because they are at risk for stent thrombosis if dual antiplatelet agents are discontinued, and this can contribute to mortality. It may be reasonable to continue aspirin therapy in some of these patients. Desmopressin administration can be particularly useful to reverse coagulopathy in the uremic patient. For patients with inherited or acquired coagulation disorders, specific reversal agents and therapies should be guided in consultation with the hematology service. More specialized laboratory studies may be indicated in some patients.

Localization

The first step in management and hemorrhage control is localization of the bleeding site. As previously discussed, LGIB has a broad differential, and identifying the source of bleeding is tantamount to further management.

Nasogastric Lavage

An upper GI source should always be considered in patients with suspected LGIB, particularly in patients with hemodynamic instability, brisk bleeding, or unrevealing evaluation of the lower GI tract. Bleeding peptic ulcers, angiodysplasia, or esophageal varices can often manifest as visible blood in the stool. Clearly, management diverges drastically if the source of bleeding is in the upper GI tract. Nasogastric lavage has classically been recommended as the first step in determining an upper versus lower GI source, particularly in the unstable patient. A nasogastric tube is inserted bedside, and then the contents of the stomach are suctioned. Alternatively, 200 to 300 mL saline is instilled into the tube and then suctioned back to look for blood or coffee grounds in the stomach. Fluid with bile present but without blood is considered to be a negative lavage. The lack of bilious fluid suggests inadequate evaluation of the post-pyloric region. A clear effluent is considered nondiagnostic and is not uncommon. Disadvantages of nasogastric lavage include patient discomfort and lack of therapeutic benefit. Nasogastric lavage has fallen out of favor in recent years and should be reserved for cases of suspected upper GI hemorrhage to improve visualization at the time of endoscopy. The authors liberally employ the use of upper endoscopy for the evaluation and management of GI bleeding because of its numerous advantages.

Anoscopy/Rigid Sigmoidoscopy

In patients with a strong suspicion for GI bleeding from the anorectum or distal sigmoid, anoscopy or rigid sigmoidoscopy should

be considered. Anoscopy can be quickly performed with little to no sedation at the bedside by inserting a tubular instrument into the patient's anus to visualize hemorrhoids, anal fissures, fecal impaction, or local trauma to the anus. Anoscopy can also be therapeutic as it can be used to assist with banding or other treatment of bleeding hemorrhoids. Rigid sigmoidoscopy is also a technically simple bedside procedure but generally requires additional sedation. The instrument is longer and allows for insufflation, which can facilitate visualization of the rectal and distal sigmoid mucosa. Both procedures can be uncomfortable for the patient and provide limited visualization of the most distal GI tract. When possible, flexible sigmoidoscopy or colonoscopy is preferred.

Colonoscopy

When there is a high degree of suspicion for a colorectal source of LGIB, colonoscopy is the modality of choice to localize the source if possible. It has been shown to correctly identify the location of LGIB in more than 75% of patients. Colonoscopy is performed using a flexible scope guided from the anus through the entirety of the rectum and colon until the ileocecal valve is reached. Colonoscopy can detect discrete sources of bleeding, such diverticula, angiodysplasia, and tumors, as well as more diffuse sources of bleeding, such as inflammatory bowel disease, ischemic colitis, and radiation proctitis.

An important benefit of the procedure is the ability to perform therapeutic intervention. Bleeding should only be ascribed to lesions with stigmata of recent hemorrhage, including visualized bleeding, exposed blood vessels, or adherent clots. Colonoscopic hemostasis can be achieved with dilute epinephrine injections (1:10,000) in 1 to 2 mL aliquots up to 30 mL total. This result is usually temporary, and a second hemostatic method is recommended. Epinephrine injections are best suited to facilitate site identification in cases of active or copious bleeding. Endoclip placement results in hemostasis for nearly all diverticular bleeds with stigmata of recent hemorrhage and in nearly 70% with other forms of LGIB (Fig. 1). Other endoscopic techniques for hemostasis include bipolar electrocoagulation, heater probe cautery, argon plasma coagulation, and rubber band ligation. Angiodysplasia is particularly amenable to argon plasma coagulation (Fig. 2). Rubber band ligation has the highest rates of rebleeding and can add significant procedure time depending on the site. Tattooing is recommended to expedite site identification in the event of recurrent bleeding, particularly if surgical intervention is determined to be necessary.

The timing of colonoscopy in the evaluation of LGIB remains controversial. Ideally, a bowel prep should be attempted to maximize visualization during the procedure. Notably, early colonoscopy performed while the patient is actively bleeding has been shown to improve diagnostic yield. Colonoscopic evaluation following bowel

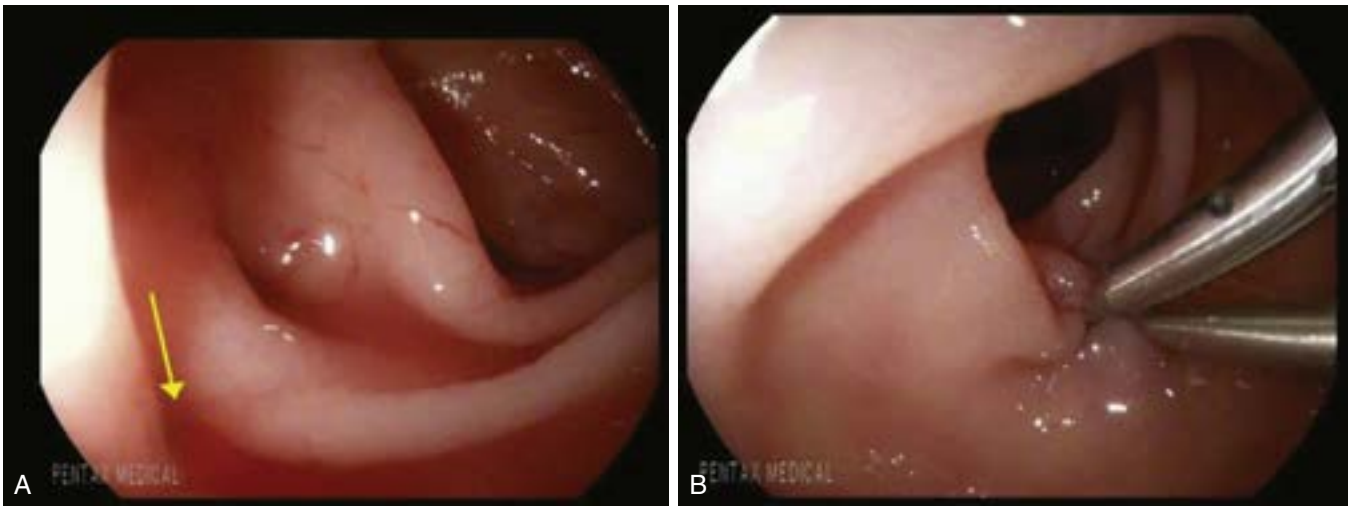


FIG. 1 **(A)** Colonic diverticulum with stigmata of recent hemorrhage. **(B)** Successful endoscopic clipping of bleeding diverticulum. *(Courtesy Daniel S. Behin, MD, Montefiore Medical Center/Albert Einstein College of Medicine, New York.)*

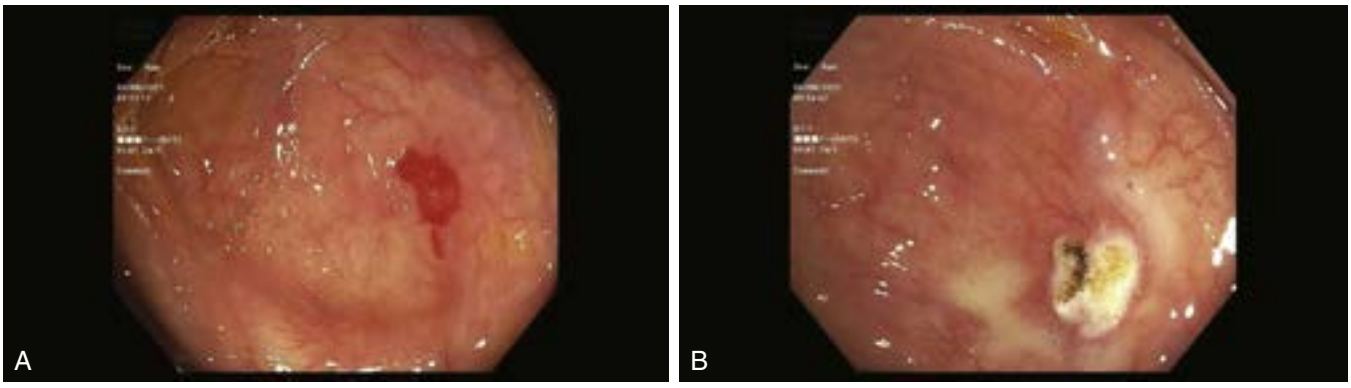


FIG. 2 Cecal angiodysplasia before **(A)** and after **(B)** endoscopic argon beam plasma coagulation. *(Courtesy Daniel S. Behin, MD, Montefiore Medical Center/Albert Einstein College of Medicine, New York.)*

preparation is generally recommended within the first 24 hours of admission for patients with LGIB.

If the patient is not stable enough for endoscopic evaluation, radiologic evaluation or surgical intervention should be considered as an alternative. Colonoscopy should also be deferred if there is suspicion for active diverticulitis as this reportedly increases the risk of perforation. Other procedural risks include mucosal injury and the general risks of anesthesia/sedation.

Computed Tomographic Angiography

Computed tomographic angiography (CTA) is an important diagnostic tool for the evaluation of active LGIB. The study is performed using intravenous contrast timed such that active arterial extravasation from a vessel into the lumen of the small bowel can be visualized on a multidetector helical CT scanner. Extravasation of intravenous contrast into the lumen of the bowel, or an active "blush," constitutes a positive finding (Fig. 3). This study has a sensitivity close to 90% and can detect bleeding rates as low as 0.3 mL/min to 0.5 mL/min. Localization accuracy is as high as 97% in patients with high transfusion requirements and/or hemodynamic instability. Unfortunately, CTA has a relatively low specificity of 85%.

CTA is widely available, fast, minimally invasive, and does not require any bowel preparation or oral contrast administration. As a result, it is very useful in hemodynamically unstable patients who do not have time to undergo bowel preparation before intervention and are transiently responding to resuscitation. CTA is also useful in identifying other causes of LGIB such as ischemic colitis and can be used to evaluate the small bowel. Disadvantages include the requisite for active hemorrhage at the time of the study, possible allergic reaction to intravenous contrast, radiation exposure, difficulty with precise localization of a small-intestinal source, and lack of direct therapeutic application.

Nuclear Scintigraphy with Technetium-99m

Like CTA, nuclear scintigraphy allows for radiographic location of LGIB and is purely a diagnostic test. The patient's red blood cells are tagged with the radiotracer Technetium-99m (^{99m}Tc) and re-injected into the patient followed by sequential imaging. Nuclear scintigraphy is a far more sensitive test than CTA as it can detect bleeding rates as low as 0.1 mL/min. An important advantage of this study is its ability to detect bleeding occurring up to 24 hours after tracer injection as the radio-labeled red blood cells remain detectable. The half-life of ^{99m}Tc allows for sequential imaging several times in a 24-hour period.

Despite the high sensitivity rates, nuclear scintigraphy results in false localization rates approaching 25% have been reported, making it less accurate than CTA. This study is best suited as a screening tool for hemodynamically stable patients with scant, intermittent bleeding and not for definitive localization. Arteriography is generally warranted in the event of a positive study for localization and possible therapeutic intervention. Surgical intervention, particularly segmental resection, should not be guided by the results of nuclear scintigraphy.

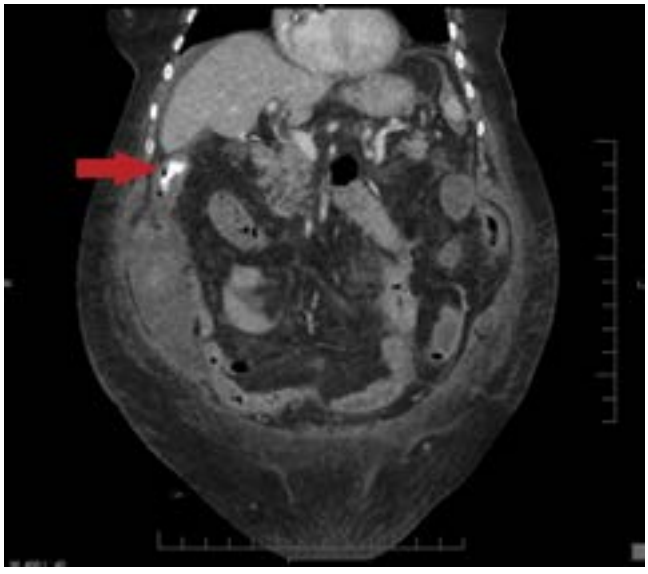


FIG. 3 Active extravasation of contrast in the hepatic flexure of a patient with lower gastrointestinal bleeding identified by CTA. *(Courtesy Michael F Petroziello, MD, Roswell Park Cancer Institute Hospital, Buffalo, NY.)*

Angiography

Angiography offers the advantages of accurate localization and the opportunity for therapeutic intervention, and it is a particularly useful option in patients with unstable vital signs requiring ongoing blood transfusions. Appropriate indications include copious bleeding precluding colonoscopic evaluation and positive extravasation on CTA or nuclear scintigraphy. For the latter, angiography further localizes the source of bleeding and potentially allows for hemorrhage control. These patients require little to no sedation, and access is usually obtained through the femoral artery. Fluoroscopic visualization is used to identify extravasation following selective mesenteric arterial cannulation and injection of contrast material. Angiography can detect bleeding at rates as low as 0.5 mL/min and has a high sensitivity for LGIB. Overall, it is a better test for patients with profuse, active bleeding than for those with scant, intermittent bleeding.

Embolization can be attempted for patients with positive localization during angiography. Super subselection with microcatheters and microcoil embolization are preferred when possible. Embolization, including highly selective embolization, is clinically successful in the majority of cases, with demonstrated bleeding resolution rates of 75% to 90%, depending on the location (Fig. 4). Other therapeutic options include intraarterial infusion with vasopressin, a potent vasoconstrictor, which is effective in substantially decreasing bleeding. These maneuvers may eliminate the need for emergent operation and facilitate continued resuscitation followed by surgical intervention under more controlled circumstances. For cases of venous bleeding, embolization of the venous system is possible, though not frequently undertaken.

Many have advocated for the preferential use of angiography in frail patients with severe comorbidities for whom an emergent operation would carry a prohibitively high mortality. Angiography is usually reserved for hemodynamically unstable patients or patients with a continued transfusion requirement. Unfortunately, the rebleeding rate is not insignificant and approaches 20% in some studies. Potential risks of angiography include bowel ischemia, contrast allergy or nephropathy, the risks of sedation, pseudoaneurysm, hematoma, and other vascular complications at the access site. Table 2 outlines and compares salient characteristic features of the various radiologic diagnostic and treatment options.

For patients with intermittent, obscure LGIB that has not been identified via other methods, provocative angiography is a technique that can be utilized. During this procedure, a therapeutic dose of anticoagulant is administered with the goal of provoking the bleeding lesion into an active hemorrhage so it can be captured on angiography. The lesion is then embolized in the same fashion as described previously. Systemic anticoagulation is usually achieved with heparin and followed by incremental and selective transcatheter injection of urokinase and a vasodilator, such as nicardipine. Multiple studies have shown that this procedure has an acceptable risk profile, including minimal risk of bleeding complications from the anticoagulant.

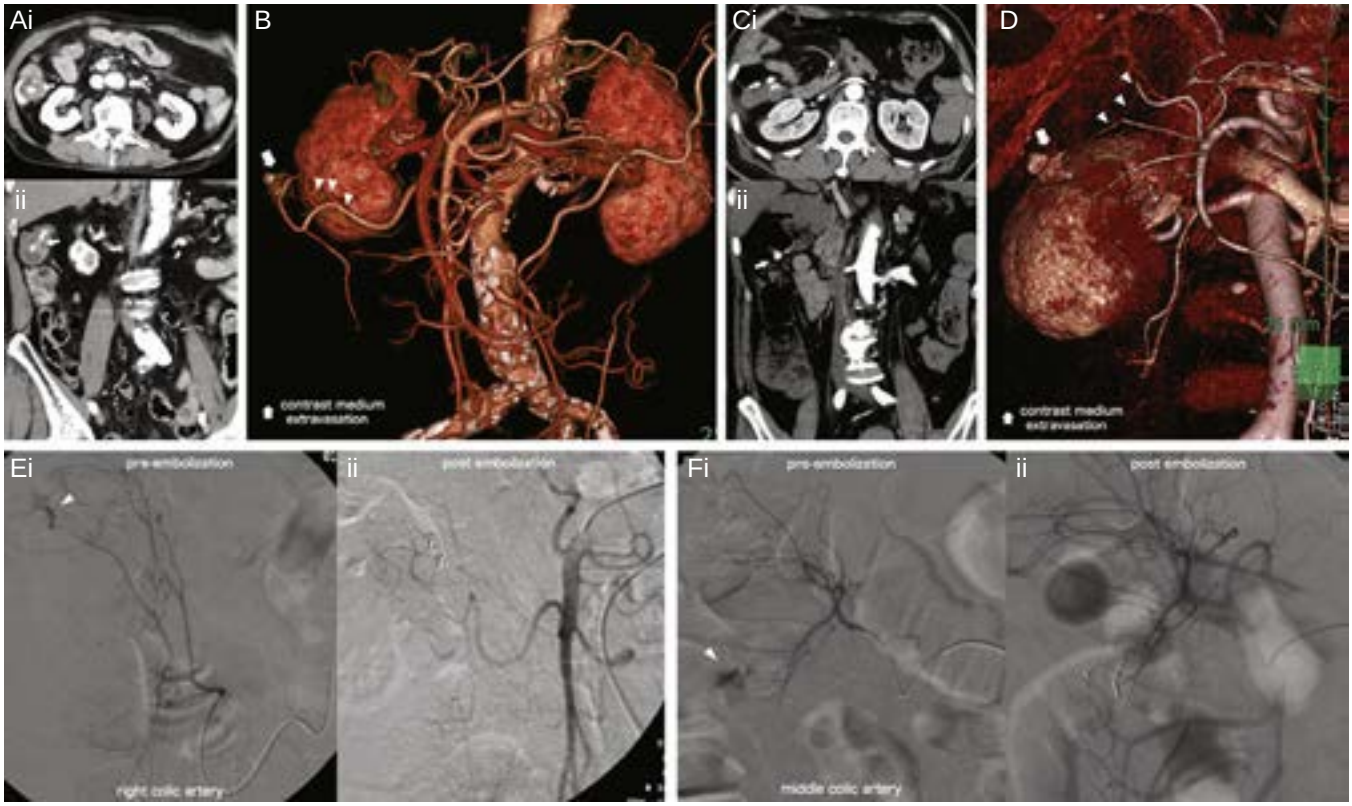


FIG. 4 Bleeding at the hepatic flexure of the colon secondary to diverticulosis in two patients. Multiplanar reconstruction (MPR) and volume-rendered 3D reconstruction of arterial-phase CT images reveal arterial bleeding from the peripheral branch of the right colic artery **(A** and **B)** and the middle colic artery **(C** and **D).** Pre- and postembolization images demonstrate extravasation of contrast from the involved vessels and resolution of bleeding, respectively **(E** and **F).** *(From Tsurukiri J, Ueno M, Kaneko N. Bleeding at the hepatic flexure of the colon secondary to diverticulosis.* Clin Gastroenterol Hepatol. *2012;10:e11–e12.)*

TABLE 2 Radiologic Imaging Tests for Evaluation of Lower Gastrointestinal Bleeding with Their Associated Characteristics

Study	Invasive Procedure	Bleeding Detection Rate (mL/min)	Capacity for	
			Localization	Intervention
CTA	–	0.3–0.5	+	–
NS	–	0.1	–	–
Angiography	+	0.5	+	+

CTA, Computed tomographic angiography; *NS,* nuclear scintigraphy.

Nearly one-third of patients with a previously unidentified source of LGIB have a source identified with provocative angiography. Bleeding lesions can be treated by embolization or surgical resection. Resection is the preferred treatment for hypervascular neoplasms and can be useful for selected patients with angiodysplasia. If surgical resection is being considered and no mass lesion is identified at the time of selective arteriography, a microcatheter should be left in the feeding artery. The patient should be brought to the operating room in an expeditious fashion for surgical exploration. Injection of the catheter with blue dye will allow for visualization of the involved segment and can be used to guide the extent of resection.

Capsule Endoscopy

Although the majority of LGIB is colonic in origin, some cases of obscure bleeding originate from the small bowel. Capsule endoscopy is a useful modality for the subset of patients who have persistent bleeding and negative endoscopic evaluations of the colon and foregut. The patient swallows a pill-sized capsule that contains a small camera. The camera takes intermittent photographs as it travels through the patient's GI tract, and the photos are retrieved after the capsule is returned. The images are reviewed carefully to determine the source of bleeding. Capsule endoscopy is therefore best suited for hemodynamically normal patients who have chronic GI bleeding with a suspected small intestinal source. Diagnostic accuracy is good with sensitivities and specificities of approximately 90% and 95%, respectively. Diagnostic yield is improved in patients with acute bleeding and in those taking anticoagulants. The procedure is noninvasive and has an overall low complication rate; however, complications may include battery failure, capsule retention, and bowel perforation. Other disadvantages include the lack of potential for localization or therapeutic intervention. Patients may be administered a test capsule made of absorbable material before the

actual pill camera if the patient is at high risk for a retained capsule. Surgical intervention is required for retained capsules but may result in accurate identification and treatment of the bleeding pathology in rare circumstances.

Double Balloon Enteroscopy

Similar to capsule endoscopy, double balloon enteroscopy allows for visualization of the small bowel. The study is performed under anesthesia/sedation. An endoscope is utilized with the addition of an overtube. Both the endoscope and overtube have balloons at their distal aspects. The procedure begins like any other endoscopy, and the endoscope is advanced into the proximal small bowel. The overtube balloon is then inflated and the overtube retracted, thus pulling the small bowel toward the endoscope and allowing the latter to advance further into the small bowel. To pass further, the endoscope's balloon is inflated, and the overtube's balloon deflated advancing it forward to meet the endoscope. This tedious process allows the endoscope to advance though the small bowel as a result of retraction of the overtube.

Frequently, patients have already undergone CTA or capsule endoscopy to identify an area of interest. The major advantages over capsule endoscopy include the potential for therapeutic intervention and tissue sampling. In addition, double balloon endoscopy can be performed via the transoral or transanal routes. Disadvantages include the risk of bowel perforation and the risks associated with anesthesia as well as prolonged duration of the procedures, often lasting 60 to 90 minutes.

Management Algorithm for LGIB

Further management of the patient presenting with LGIB depends on the results of the aforementioned localization studies. A treatment algorithm is proposed to guide management for these complex patients (Fig. 5). We recommend colonoscopy as a first-line test for stable patients with mild or moderate LGIB. Many of these patients will have diverticular bleeding, and this has been shown to resolve spontaneously in 80% of cases, with most patients receiving fewer than 4 units of blood. This is irrespective of colonoscopic intervention. Up to one-third of spontaneously resolving diverticular bleeds

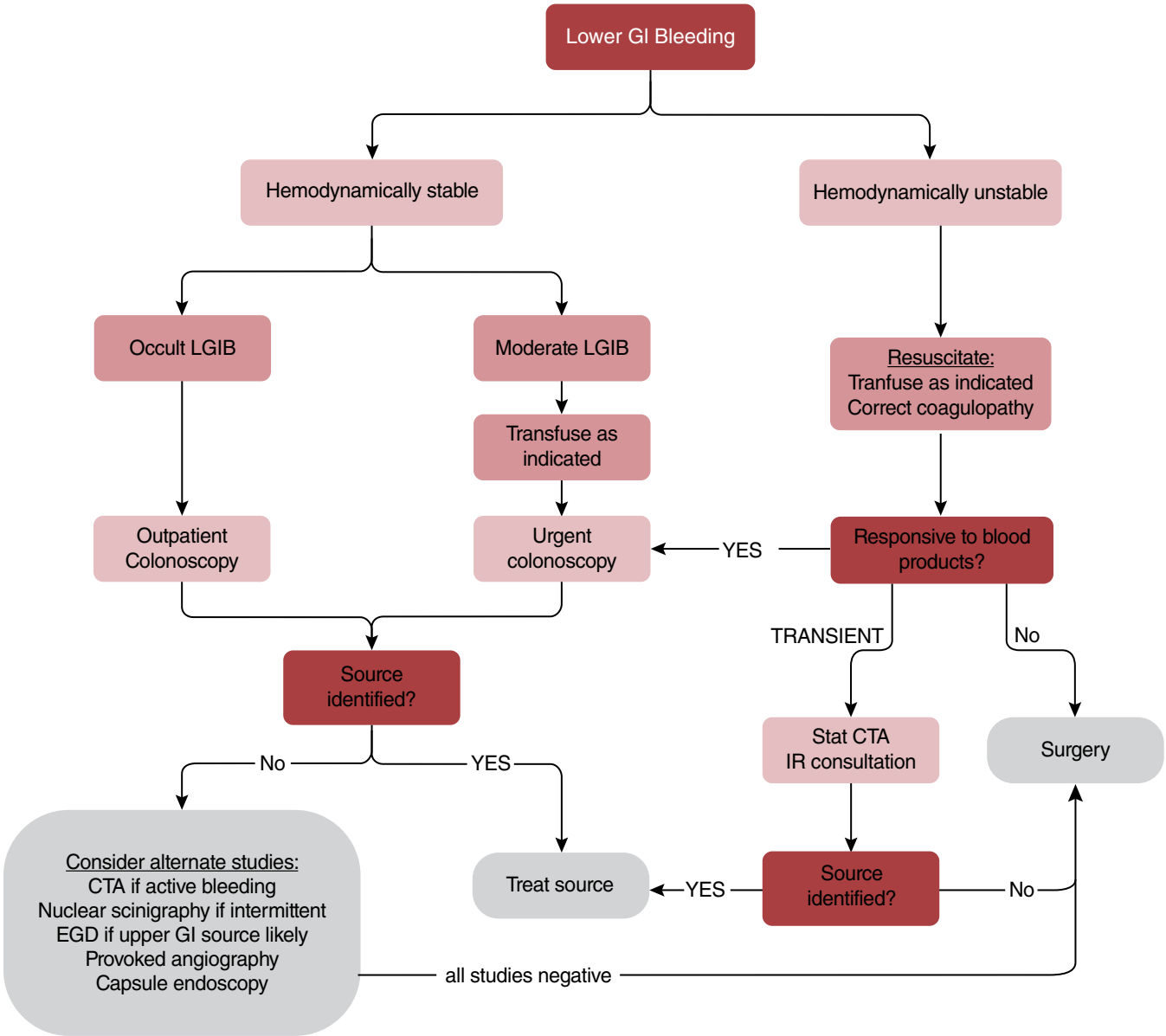


FIG. 5 Algorithm for the management of lower gastrointestinal bleeding. *CTA,* Computed tomography angiography; *EGD,* endoscopy; *GI,* gastrointestinal; *IR,* interventional radiology *LGIB,* lower gastrointestinal bleeding.

will recur within 6 to 12 months. Other forms of LGIB will also spontaneously resolve at high rates, including angiodysplasias, the most common cause of obscure LGIB. These may also recur at rates nearing 50% within 1 year. Although observation and serial hemoglobin monitoring may be an acceptable monitoring plan in some patients, therapeutic intervention with endoscopic or interventional techniques is preferred by surgeons whenever possible.

In patients with massive LGIB or moderate LGIB with instability, emergent CTA should be performed if the patient transiently responds to blood transfusion. Early notification of the interventional radiology team for possible angiography with embolization is crucial in the critically ill patient, and CTA can be bypassed altogether if the patient is increasingly unstable with minimal response to blood transfusion. Emergent esophagogastroduodenoscopy (EGD) should be considered if an upper GI source is suspected based on the history and physical examination. Aggressive resuscitation in a critical care setting along with reversal of coagulopathy and appropriate transfusion should be performed concurrently.

Emergent surgical intervention is a last resort in the management of LGIB because of high mortality rates but can be necessary and life-saving for some patients. Consequently, it is important for surgeons to be involved in the management of these patients early in their treatment as patients can decompensate quickly, leaving only a small window of opportunity for optimization. In general, emergent surgery is reserved for hemodynamically unstable patients or for those who have undergone failed interventions.

SURGICAL CONSIDERATIONS

Indications

Improvements in endoscopic and interventional radiology hemostatic techniques during recent years has resulted in a decreased role for emergent surgical intervention in patients with LGIB. Current indications for emergency surgical management are limited to failure of nonoperative intervention with a confirmed or presumed source and ongoing bleeding or hemodynamic instability, particularly in patients who have received transfusion of more than 6 units of blood products. In a hemodynamically stable patient, nonurgent surgical intervention may also be warranted in select cases, such as malignancy, bleeding hemorrhoids, or Meckel's diverticulum.

Operative Technique

Operative planning relies heavily on localization of the bleeding source and stability of the patient. For most patients with a presumed colonic source, surgical options include either a segmental resection or a subtotal colectomy. For patients with bleeding that cannot be controlled endoscopically, one consideration is to have the endoscopist tattoo the segment to facilitate intraoperative identification, which is an otherwise a difficult task.

Localization of the bleeding lesion before surgery is helpful to prevent excess mortality from a subtotal colectomy. In most studies, the mortality from this procedure approaches 40%, whereas segmental resection carries only a 20% mortality risk. Additionally, localization ensures that rebleeding from an unresected lesion is prevented. In contrast with the mortality risk, subtotal colectomy carries only a 4% risk of rebleeding, whereas segmental resection has a close to 20% risk. These risks and benefits should be considered on an individual basis with the understanding that the primary goal of surgery is to provide immediate control of the bleeding. If there is any question at all about localization, the surgeon should strongly consider performing a subtotal colectomy.

Patients requiring emergent colectomy for acute LGIB are at high risk for morbidity and mortality, with close to 60% suffering complications such as respiratory or renal failure. The surgeon should have a low threshold to perform a damage-control operation and delay formal closure of the abdomen. This will allow for ongoing resuscitation of the patient and monitoring for ongoing bleeding in a critical care setting. Temporarily packing the abdomen with laparotomy sponges can be considered for coagulopathic patients with diffuse hemorrhage from surgical surfaces to minimize time in the operating room. The patient can be returned to the operating room in 24 to 48 hours for reexploration and formal closure. The decision whether to create an ostomy or reconstruct the GI tract with an anastomosis can be made at that time. Since an anastomotic leak can be catastrophic, the creation of an anastomosis at the time of initial emergent surgery in the setting of coagulopathy and hemodynamic instability should be discouraged.

CONCLUSION

LGIB is a heterogeneous disease state consisting of a broad differential diagnosis with a range of severity. Owing to this complexity, a thorough history and physical examination is most important to narrow the differential diagnosis and proceed through a thoughtful diagnostic algorithm. Resuscitation, correction of coagulopathy, and blood transfusion are the cornerstones of management of LGIB and are often the only therapeutic maneuvers necessary given that most patients presenting with LGIB will spontaneously resolve. Endoscopic and interventional radiology procedures should be the initial localization and therapeutic modalities for most patients with LGIB depending on the clinical status of the patient. Surgery is reserved for a small subset of patients with continued hemodynamic instability or failure of less-invasive techniques, but it can be life-saving. Surgeons should be actively engaged in the management of patients with LGIB and should be prepared to intervene in the rare circumstance that this becomes necessary.

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Appendicitis: Diagnosis and Management

Elaa Mahdi, MD, MPH, and Walter Pegoli Jr., MD

Appendicitis continues to be one of the most common causes of the acute surgical abdomen treated by general surgeons. The global incidence of appendicitis ranges from 100 to 150 per 100,000 persons per year, with a lifetime risk of 7% to 10%. In the United States, there are about 400,000 cases diagnosed each year, of which 16% to 40% are perforated. The pathogenesis of appendicitis remains unclear, with the thought being that obstruction of the appendiceal lumen results in inflammation and bacterial infection. The diagnosis is made on patient history, physical examination, laboratory tests, and various imaging modalities. Traditionally, treatment has included the initiation of antibiotics followed by surgical resection of the appendix. However, recent studies have demonstrated efficacy for the treatment of uncomplicated appendicitis using antibiotics alone. In this chapter, we discuss the pathophysiology, diagnostic workup, and most recent recommendations regarding management of patients with appendicitis.

ANATOMY OF THE APPENDIX

The appendix is an approximately 9 cm long and 0.6 cm wide vermiform or "worm-shaped" hollow viscus structure originating from the terminal cecum, where the three taenia coli converge. Upon completion of normal antenatal rotation of the intestine, the cecum and appendix are typically found in the right lower quadrant (RLQ). However, their location can be varied in patients with nonrotation or malrotation of their intestines. Although the base of the appendix always emanates from the cecum, the location of the tip of the appendix is often more variable (Fig. 1). It can be found retrocecal, subcecal, pelvic, preileal, or postileal, accounting for the diversity of presenting signs and symptoms. The blood supply to the appendix and mesoappendix is from the appendiceal artery, a branch off the ileocolic artery.

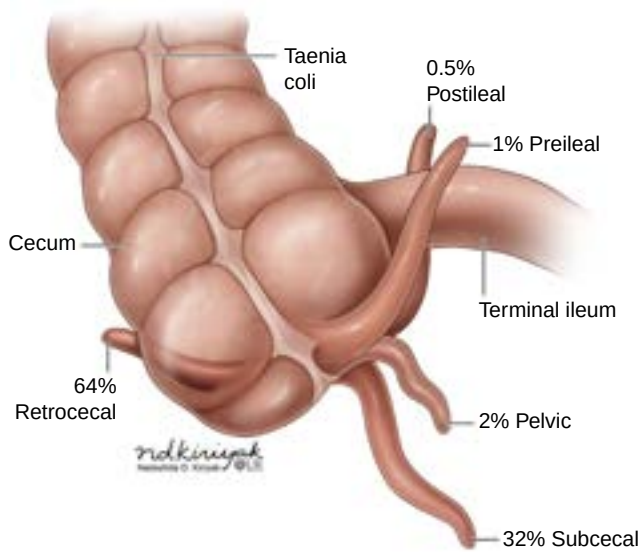


FIG. 1 Variations in the positions of the vermiform appendix.

PATHOLOGY OF ACUTE APPENDICITIS

The etiology of acute appendicitis is thought to be caused by obstruction of the appendiceal lumen. The most common cause of luminal obstruction is mechanical obstruction from a fecalith or appendicolith. Other causes include lymphoid hyperplasia, parasitic infections, neoplasm, or a foreign body. If left untreated, the ongoing obstruction results in a cycle of increased bacterial overgrowth, mucus production, inflammation, and venous congestion. The subsequent distension of the normally narrow-caliber appendix causes stretching of the visceral afferent nerve fibers, resulting in the vague periumbilical abdominal pain that is often described as one of the first symptoms. Similarly, distension of the appendix can result in nausea and vomiting early in the course of the disease. The increasing congestion eventually leads to obstruction of arterial inflow, resulting in ischemia, with progression to necrosis, gangrene, and eventually perforation with or without abscess formation. Organisms isolated in patients with acute appendicitis include *Escherichia coli, Bacteroides fragilis, Klebsiella pneumoniae, Streptococcus, Enterococcus,* and *Pseudomonas aeruginosa*. In cases of gangrenous or perforated appendicitis, *E. coli* and *Bacteroides* spp. are found in a majority of patients. Knowing the most common bacterial culprits helps guide antibiotic management in the treatment of appendicitis, especially if a nonoperative approach is chosen or postoperative antibiotics are required.

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

History and Physical Examination

The diagnosis of appendicitis has typically been a clinical diagnosis based on history and physical examination. Patients will often complain of a vague onset of symptoms including anorexia, malaise, and epigastric or periumbilical abdominal pain/discomfort. This will typically progress to nausea and/or vomiting associated with abdominal pain that migrates to the RLQ. Findings on physical examination include fever, tachycardia, RLQ tenderness, guarding, and percussion tenderness. The tenderness usually is most intense at McBurney's point, which is located one-third of the distance between the right anterior superior iliac spine and the umbilicus. The patient may exhibit a positive Rovsing's sign, which is defined as palpation of the left lower quadrant (LLQ) resulting in RLQ pain. Additionally, physical examination findings will differ based on the location of the appendiceal tip and the degree of inflammation. A patient with a retrocecal appendix may not present with RLQ pain, but will have a positive psoas sign when extension of the right hip produces pain. A patient with a pelvic appendix may have an obturator sign, when internal rotation of the right hip causes pain. However, recent data suggest that although these signs are specific, they are not very sensitive for diagnosing acute appendicitis (Tables 1 and 2). Multiple

TABLE 1 Clinical Signs and Symptoms of Acute Appendicitis

History	**Onset of vague abdominal discomfort, cramping, nausea, progressing to right lower quadrant pain, with associated anorexia, vomiting, and general malaise**
Physical examination	Right lower quadrant tenderness, voluntary and involuntary guarding, fever, tachycardia, occasionally palpable mass
Laboratory examination	Leukocytosis, No bacteria on urinalysis, negative pregnancy testing
Diagnostic imaging	Distended fluid-filled appendix with surrounding inflammation, perforation, abscess, fecalith

TABLE 2 Clinical Examination Operating Characteristics for Diagnosis of Acute Appendicitis

	Sensitivity (%)	Specificity (%)
Rovsing's sign	30–68	58–91
Obturator sign	21–34	79–96
Psoas sign	16–39	50–95

TABLE 3 Pediatric Appendicitis Score Variables

Sign/Symptom	Score
Nausea/vomiting	1
Anorexia	1
Fever (≥38.0 C)	1
Migration of pain	1
Leukocytosis (WBC >10,000 mm3)	1
Neutrophilia (>75%)	1
Right lower quadrant pain	2
Tenderness with hopping/coughing/percussion	2
Total	10

WBC, White blood cell.

clinical scoring systems have been developed to aid in the diagnosis of appendicitis. The Appendicitis Inflammatory Response (AIR) and the Alvarado score are used in adults, with the AIR found to have the superior performance. In children, the Pediatric Appendicitis Score (PAS) was developed to help identify patients with appendicitis using eight signs, symptoms, and laboratory values often associated with appendicitis (Table 3).

However, even when a patient presents with the "classic" signs and symptoms of appendicitis, a broad differential diagnosis including inflammatory bowel disease, urinary stones, Meckel's diverticulitis, and other potential etiologies should also be considered.

Laboratory Examination

On laboratory examination, patients are typically found to have a leukocytosis (>10,000 cells/mm^3), a left shift (>75% neutrophilia), and elevated markers of inflammation such as C-reactive protein (CRP). Although these are nonspecific findings of appendicitis, a normal laboratory value for them is less likely to be indicative of appendicitis. A urinalysis should be obtained to evaluate for a possible urologic source. Of note, sterile pyuria can result from the proximity of an inflamed appendix to the bladder.

Diagnostic Imaging

Different imaging modalities can be used to assist in the diagnosis of acute appendicitis, depending on patient age, body habitus, and risk of radiation exposure. In the pediatric patient, ultrasound (US) remains the initial imaging study of choice. It is easy to perform, inexpensive, and does not expose patients to harmful radiation. However, it is user-dependent and has limited visualization in obese patients. The overall specificity is 83% and sensitivity is 78%. Ultrasound findings typically include a distended, noncompressible appendix >6 mm in diameter with hypervascularity on Doppler studies (Fig. 2). Computed tomography (CT) is the most widely used study in the adult population. It is quick, not user-dependent, and has a specificity of 90% and sensitivity of 94%. However, it is more expensive than US and exposes patients to ionizing radiation. Of note, when used in children, low-dose radiation techniques should be utilized. Findings typically include a distended, fluid-filled appendix, periappendiceal fat stranding, and appendicoliths when present (Fig. 3). It can also demonstrate free fluid, abscess, phlegmon, and other findings associated with complicated appendicitis. In addition, colitis, diverticulitis, inflammatory bowel disease, gynecologic pathology, and other maladies in the differential diagnoses can be elucidated by CT. Magnetic resonance imaging (MRI) is gaining popularity as an imaging modality in children and in pregnant women. The diagnostic accuracy is similar to CT, without the exposure to ionizing radiation. However, it is associated with increased cost compared with CT. In their meta-analysis of second-line imaging after equivocal initial US, Eng et al. reported pooled MRI sensitivities and specificities of 97.4% and 97.1% in children, and 89.9% and 93.6% in adults, respectively. MRI is a viable alternative to CT in children or pregnant women with inconclusive findings on US.

MANAGEMENT OF ACUTE APPENDICITIS

The management of acute appendicitis has continued to evolve over time. Whereas the diagnosis of acute appendicitis would have traditionally meant the initiation of antibiotics and an emergent trip to the operating room, more recently the trend has been to delay surgical intervention until convenient for up to 24 hours. Some practitioners are now even managing patients with uncomplicated appendicitis nonoperatively using antibiotics alone.

Once the diagnosis of appendicitis has been made, patients should be resuscitated with intravenous crystalloid fluids (if necessary) and started on broad-spectrum intravenous antibiotics with gram-negative and anaerobic coverage as some of the most common organisms associated with acute appendicitis are *E. coli*, *B. fragilis,* and *K. pneumoniae.* Popular broad-spectrum antibiotics include piperacillin-tazobactam, ampicillin-sulbactam, and imipenem-cilastatin. Alternative antibiotics include ceftriaxone-metronidazole or cefoxitin. Cameron et al. compared the effectiveness of extended-spectrum antibiotics (piperacillin-tazobactam) versus narrow-spectrum antibiotics (cefoxitin or ceftriaxone-metronidazole) on rate of surgical site infections and hospital readmission rates in children with uncomplicated appendicitis. They found no difference in the outcomes, supporting the use of narrow-spectrum antibiotics in an era of increasing incidence of antibiotic-resistant bacteria. The duration of antibiotic therapy should be dependent on the severity of disease and whether the patient undergoes an appendectomy. For those with uncomplicated appendicitis who undergo appendectomy, antibiotics need not be continued postoperatively. Patients with complicated appendicitis will require a longer course of antibiotic therapy predicated upon extent of disease and clinical condition.

Timing of Surgery

The diagnosis of uncomplicated appendicitis is no longer considered an acute surgical emergency. Van Dijk et al. found no significantly higher risk for developing complicated appendicitis when surgery was delayed for up to 24 hours from hospital presentation. Data from the National Surgical Quality Improvement Program (NSQIP) reported similar outcomes, even when appendectomy was delayed until hospital day 2. However, those who underwent appendectomy on hospital day 3 had increased 30-day mortality and major postoperative complications. The WSES Jerusalem 2020 guidelines recommend operating within 24 hours of presentation in children and adults with uncomplicated acute appendicitis. In addition, they state that in pregnant patients with equivocal findings, a short in-hospital delay with repeat abdominal US is acceptable without a significant increased risk of adverse maternal or fetal outcomes.

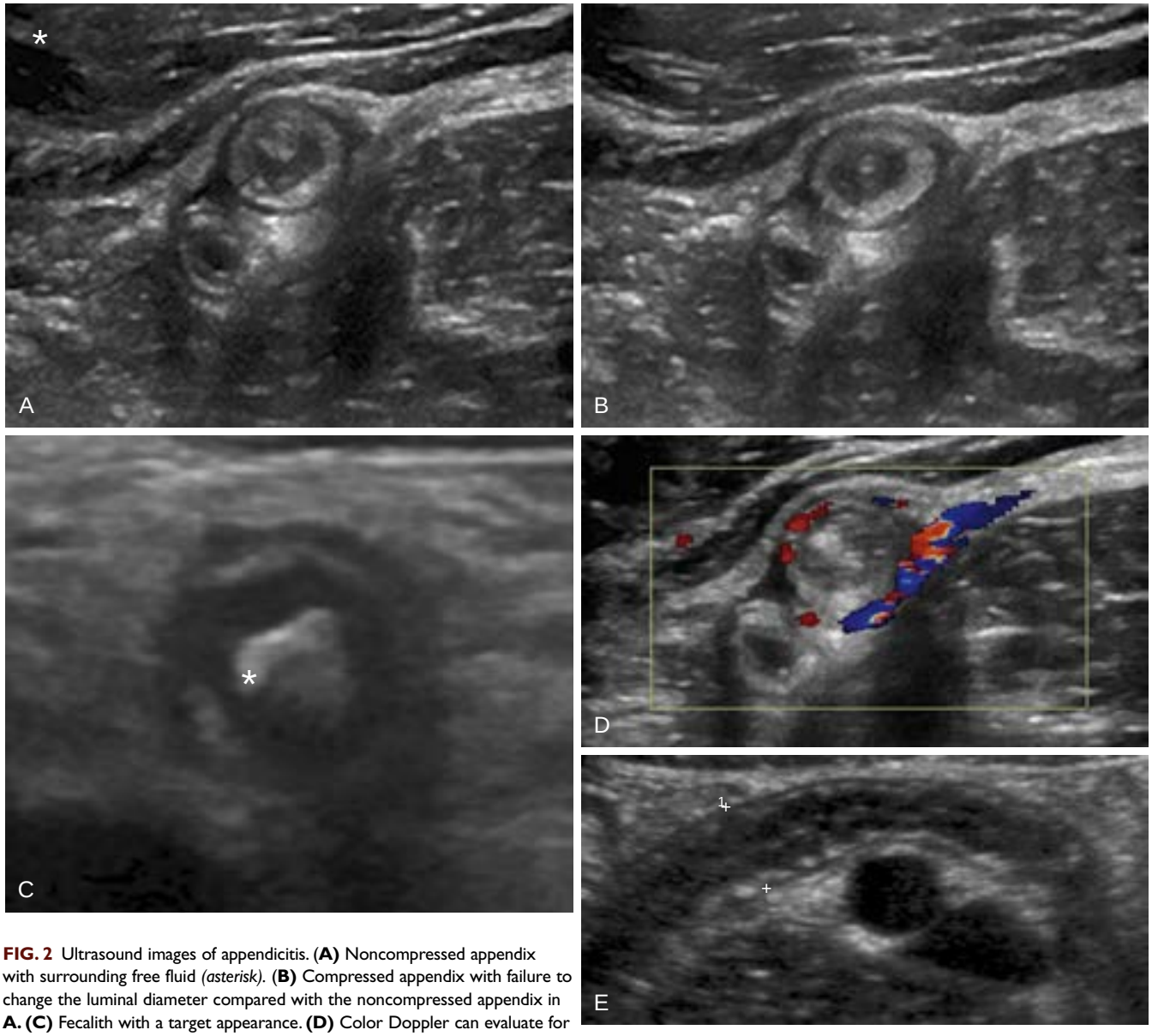


FIG. 2 Ultrasound images of appendicitis. **(A)** Noncompressed appendix with surrounding free fluid *(asterisk)*. **(B)** Compressed appendix with failure to change the luminal diameter compared with the noncompressed appendix in **A. (C)** Fecalith with a target appearance. **(D)** Color Doppler can evaluate for the presence or absence of blood flow within the wall of an inflamed appendix. **(E)** Dilated appendix. *(Images courtesy Dr. Katherine Kaproth-Joslin.)*

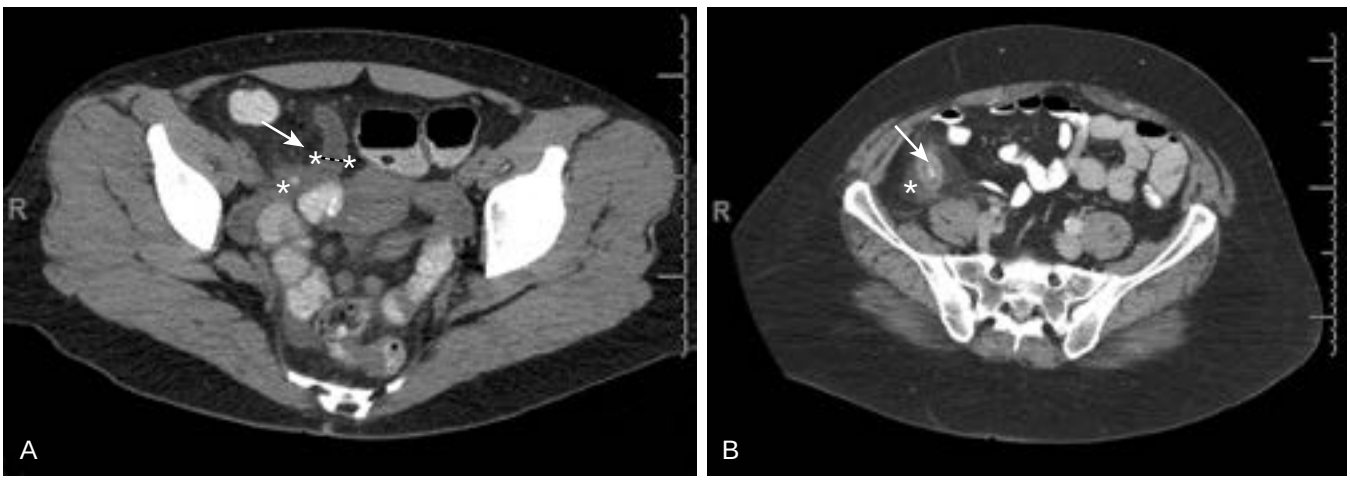


FIG. 3 CT images of appendicitis. **(A)** Dilated appendix *(arrow)*.**(B)** Appendicolith *(arrow)*. *(Images courtesy Dr. Katherine Kaproth-Joslin.)*

Laparoscopic Appendectomy

The patient is placed in the supine position on the operating table with the left arm or both arms tucked. A Foley catheter should be considered if the patient was not confirmed to have voided before the case. The patient is prepped from the xiphoid process to the pubis. The abdomen is accessed through the umbilicus either with an open technique using a Hasson trocar or closed technique with a Veress needle. For placement of the Veress needle, the umbilicus is elevated with two towel clips, and an incision is made through the skin. The Veress needle is inserted perpendicular to the skin and advanced until two audible clicks as the spring-loaded needle retracts are appreciated. The first click occurs as the needle transverses the fascia, and the second click occurs as the needle transverses the peritoneum. A saline drop test is then performed to confirm entry into the peritoneal cavity. The abdomen is insufflated with carbon dioxide until intraabdominal pressure is 12 to 15 mm Hg. The Veress needle is retracted, followed by either a blind entry with a 12-mm closed conventional trocar or radially expanding trocar versus visual entry with an optical trocar (Optiview, Visiport). For the Hasson open technique, an incision is made into the infraumbilical or supraumbilical fold and carried through the subcutaneous tissue. Dissection is then performed through the subcutaneous tissue with S-retractors or a Kelly clamp until the rectus fascia is visualized. Two retention sutures are placed into the fascia on either side of the midline. With a knife, scissors, or electrocautery, a vertical incision is made through the fascia elevated with the retention sutures. The peritoneal cavity is entered bluntly with a Kelly clamp. The Hasson port is inserted under direct visualization and anchored in place with the stay sutures. The abdomen is insufflated and inspected to ensure that no injury occurred during entrance. The placement of subsequent trocars can be variable, depending on patient size, age, and pregnancy (Fig. 4). However, our preference is the use of an umbilical camera port and the working 5-mm ports at the right upper quadrant and LLQ (see Fig. 4A). A four-quadrant exploration is first done to quickly rule out other intraabdominal abnormalities before the patient is placed in reverse Trendelenburg with the right side up. Atraumatic graspers are used to follow the cecum to the convergence of the taenia coli. The cecum is lifted toward the left upper quadrant to better expose the base of the appendix. The mesoappendix is grasped/elevated, and peritoneal and/or omental attachments are lysed to expose the entirety of the appendix. For the retrocecal appendix, the white line of Toldt must be divided to mobilize the cecum and expose the appendix. A window is created through the mesoappendix. A linear gastrointestinal endoscopic stapler with a white load or an electrosurgical device (cautery or LigaSure) is introduced through the umbilical port, and the mesoappendix is divided, leaving the base of the appendix exposed (Fig. 5A). A blue load on the stapler is then used to divide the appendix (Fig. 5B; Fig. 6). Of note, an Endoloop may also be used to control the appendiceal base. The appendix is placed in a retrieval bag and withdrawn through the umbilical port. The staple line is then inspected, and hemostasis is achieved, as necessary. If murky, turbid fluid is observed in the pelvis, consideration should be given to obtaining a sample for Gram stain, culture, and sensitivities. Information gained may influence the choice of postoperative antibiotics. Recent data discourage peritoneal irrigation as it shows no benefit and may lead to an increased incidence of postoperative abscess formation. The working ports are removed under direct visualization, followed by desufflation through the umbilical port and closure of the trocar sites.

Open Appendectomy

Although the laparoscopic approach to appendectomy is most commonly used, the ability to perform an open appendectomy is essential. The patient is placed in the supine position and prepped in the usual sterile fashion. An imaginary line is drawn between the anterior superior iliac spine (ASIS) and the umbilicus. McBurney's point is identified and marked (see Fig. 4D). A skin incision is made within a natural crease. The dissection is carried down to the external oblique aponeurosis. The muscle is incised in the direction of its fibers and spread bluntly to expose the underlying internal oblique muscle. It too is dissected similarly to expose the transversus abdominis, which is split to expose the peritoneum. The peritoneum is elevated and sharply incised with care taken to avoid injury to the underlying bowel.

Once inside the abdomen, the cecum is identified and elevated into the wound. The appendiceal base is located at the confluence of the tenia. The appendix is dissected free from surrounding structures. A stapling device can be used to ligate/divide the mesoappendix and the appendiceal base. The "classic" technique divides the mesoappendix between Kelly clamps and ligating the ends using 3-0 silk. The base of the appendix is crushed with a Kelly clamp. The clamp is then relocated on the appendix 1 cm distal to the crushed zone (CZ). The appendix is ligated at the CZ with an 0 Chromic suture. The appendix is divided just proximal to the clamp. The stump may be cauterized or invaginated with a purse-string suture or a *Z*-stitch.

The incision is closed in layers. First, the peritoneum and transversus abdominis are closed with a running absorbable suture. Next, the internal and external oblique muscles are anatomically approximated with interrupted absorbable sutures. Finally, the skin is closed with a running absorbable subcuticular suture. In the case of perforation, the skin may be left open or loosely approximated.

Management of Perforated (Complicated) Appendicitis

Perforated appendicitis occurs in up to 40% of cases of appendicitis. Such patients will usually have had a longer duration of symptoms before presentation. The findings on abdominal examination may range from a tender RLQ abdominal mass to a rigid distended abdomen with diffuse peritonitis. Imaging findings may range from pneumoperitoneum and free fluid to an RLQ phlegmon or abscess. Patients diagnosed with complicated appendicitis should be resuscitated with intravenous fluids and immediately started on intravenous antibiotics such as piperacillin-tazobactam alone or a ceftriaxone with metronidazole. The decision to proceed with surgical intervention will depend on their clinical picture. Patients who are diffusely peritonitic and hemodynamically unstable should be aggressively resuscitated and taken to the operating room when adequately resuscitated. Patients who are found to have phlegmon or abscess formation can be considered for nonoperative management, which consists of intravenous antibiotics, percutaneous drainage (for patients with a drainable collection), and nutritional support for those who are unable to aliment orally. Appendectomy in the setting of an abscess or phlegmon is technically challenging and has been associated with a higher incidence of intraoperative and postoperative complications. Antibiotic therapy should be dictated by culture results, if available. Once patients are tolerating a regular diet, they can be transitioned to oral amoxicillin/clavulanate (Augmentin) for a total 5-day course, which has been shown to be as efficacious as 7 days of antibiotics, with no increase in the risk of abscess formation.

CURRENT CONTROVERIES

Nonoperative Management of Nonperforated Appendicitis

Although appendectomy remains the treatment of choice in patients with uncomplicated acute appendicitis, nonoperative management with antibiotics has become a viable alternative. O'Leary et al. performed a randomized clinical trial comparing the efficacy of antibiotic only versus appendectomy in uncomplicated acute appendicitis. They found that 25% of their antibiotic-only group experienced recurrence within 1 year. Of note, the antibiotic-only group also reported a decreased quality of life when compared with the surgical cohort. They concluded that surgery remains the mainstay of treatment. In their randomized clinical trial, the CODA Collaborative

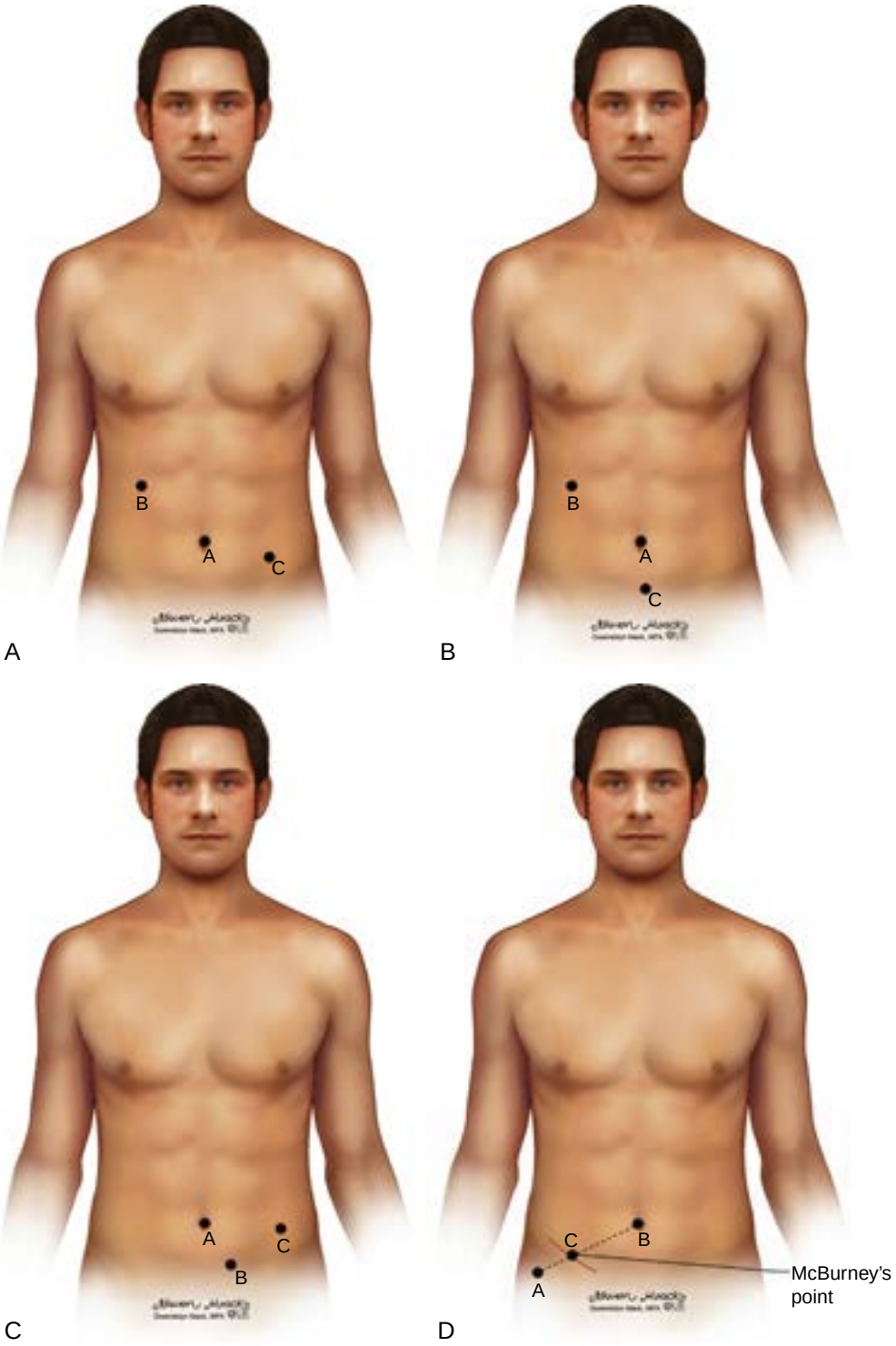


FIG. 4 Laparoscopic and open incisions for appendectomy. **(A)** Umbilical port *(A)*, RUQ port *(B)*, and LLQ port *(C)*. **(B)** Umbilical port *(A)*, RUQ port *(B)*, and suprapubic port *(C)*. **(C)** Umbilical port *(A)*, suprapubic port *(B)*, and LLQ port *(C)*. **(D)** McBurney's point one third the distance from the ASIS and umbilicus, with a surgical incision made over McBurney's point in a natural skin crease. *LLQ,* Left lower quadrant; *RUQ,* right upper quadrant.

compared a 10-day antibiotic course verses appendectomy at 25 centers in the United States. They found that although antibiotics were not inferior to appendectomy for the 30-day health status, the antibiotic-only group had higher failure rates, with 29% undergoing appendectomy by 90 days (41% of those with appendicolith and 25% of without appendicolith). Of note, most recent studies have shown a 5-year recurrence rate approaching 50% in both children and adults who were treated with antibiotics alone. Careful patient selection must be utilized in selecting which patient is an appropriate candidate for nonoperative management. Appropriate candidates should have a small appendix that does not contain an appendicolith on diagnostic imaging, CRP < 60 g/L, WBC < 12, and age < 60 years to

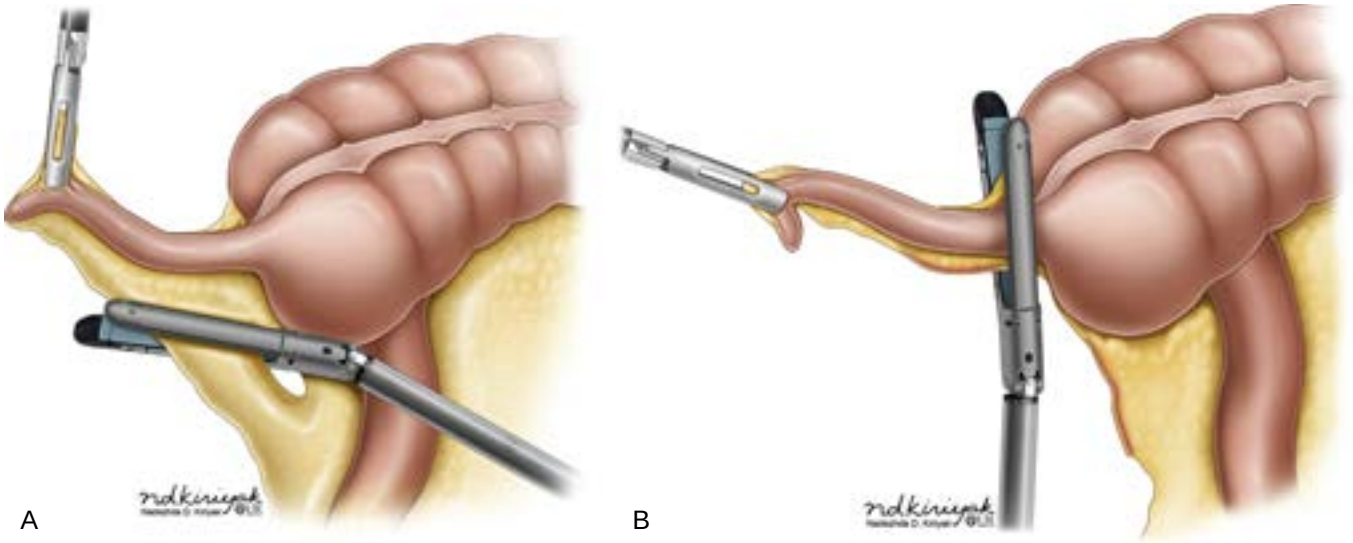


FIG. 5 **(A)** A window is created in the mesoappendix between the base of the appendix and the cecum, and the mesoappendix is divided with a white, vascular load. **(B)** The base of the appendix is stapled and divided with a blue gastrointestinal staple load.



FIG. 6 The base of the appendix is stapled and divided.

have a chance of successful recovery based on studies by Hansson et al. and Loftus et al. Antibiotic duration for these patients ranges from 7 to 10 total days, with transition from intravenous to oral antibiotics following clinical improvement.

Interval Appendectomy

Interval appendectomy in patients who underwent initial nonoperative management of complicated appendicitis remains a controversial subject. It is typically considered safe to perform 6 weeks after successful treatment, as the acute inflammatory process has resolved by that time. Some argue that such patients have a very low rate of recurrence after their initial presentation and that surgery, with its 11% complication rate, is unnecessary. Proponents of interval appendectomy argue that there is a significant rate of recurrence and stress the importance of excluding an underlying appendiceal malignancy. At present, there is still no strong evidence to recommend for or against it in adults. However, it is recommended that adults 40 years of age and older undergo interval CT and colonoscopy to rule out malignancy. In children, several studies have shown that interval appendectomy is indicated. A 2017 multicenter randomized study found that 23% of children initially treated nonoperatively recurred and required appendectomy within 1 year, with a morbidity rate of 6%. Of note, the performance of interval appendectomy is often driven by parental concerns.

SUMMARY

Acute appendicitis continues to be a common, but complex, diagnostic and management challenge to surgeons. The variability in clinical presentation across ages and the broad differentials can cloud the diagnosis. No one clinical finding, laboratory study, or imaging finding can reliably make the diagnosis 100% of the time. Surgeons must combine these findings and resources to discern the diagnosis. Even then, the management can be complex and is ever evolving. Preoperative antibiotics and appendectomy remain the gold standard in the management of uncomplicated cases. In complicated cases, those patients with uncontrolled intraabdominal sepsis should be resuscitated, given broad-spectrum antibiotics, and taken to the operating room as soon as possible. Controversy exists on how to best treat those patients with complicated appendicitis who are clinically stable. Some clinicians advocate the use of antibiotics with or without percutaneous drainage in those with abscess formation, while others advocate for early surgical intervention. Further studies are needed to delineate which approach is truly superior. For now, all agree that appendicitis still remains a surgical disease.

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Management of Hemorrhoids

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INTRODUCTION

Hemorrhoids are specialized vascular cushions in the anal canal or at the anal verge. These cushions are composed of blood vessels, connective tissue, and smooth muscle fibers. Hemorrhoids are a normal part of human anatomy and are responsible for 15% to 20% of anal resting pressure. Hemorrhoids are typically paired and located in the right posterior, right anterior, and left lateral locations. Internal hemorrhoids are positioned cephalad to the dentate line and are covered with mucosa, and external hemorrhoids are located caudal to the dentate line and are covered with anoderm, and most distally, skin. (Fig. 1). Internal hemorrhoids are classified based on their degree of prolapse (Table 1).

ETIOLOGY AND SYMPTOMS

Hemorrhoids are a normal part of human anatomy. Pathologic hemorrhoids occur as such through increased abdominal pressure, usually caused by constipation, straining, and poor toileting hygiene. Other causes for hemorrhoid enlargement and complications are diarrhea, pregnancy, chronic obstructive pulmonary disease (COPD), and portal hypertension (PH). Approximately 10 million Americans are affected by symptomatic hemorrhoids, making it roughly 4.4% of the population affected. The majority of these patients are over the age of 50.

Most patients with anorectal complaints will be labeled as having "hemorrhoids." It is imperative that the practitioner differentiate hemorrhoidal symptoms from other benign or malignant anorectal conditions. Patients with rectal bleeding from hemorrhoids will describe bright red bleeding, usually with defecation. The blood can be minor and seen on the paper with wiping, or can fill the toilet bowl and include clots. Symptoms of constipation and straining or diarrhea should be elicited, and documenting bowel and toileting habits is a good place to start when evaluating these patients. Time spent on the toilet should be noted, and it should be discerned if this time is spent defecating, engaging in reading, and so on. It should be documented if the patient feels a prolapse of tissue and whether they need to manually reduce this. Hemorrhoidal prolapse should be easily differentiated from true rectal prolapse by the absence of circumferential folds and the presence of radial folds (Fig. 2). A family history of colon cancer, polyps, or inflammatory bowel disease should be documented. Thorough examination of the anorectum (externally, digitally, and with anoscopy) should be performed. All patients with bleeding should have a discussion regarding colonoscopy. Patients with symptomatic external hemorrhoids are almost always suffering from thrombosis, and this may be solitary or in conjunction with strangulated internal hemorrhoids (Fig. 3). It may be difficult to examine these patients because of discomfort and fear, and examination under anesthesia may be warranted. Skin tags are common and asymptomatic but may contribute to hygiene problems and pruritus ani.

TREATMENT

Dietary and Lifestyle Modifications

Once the patient has been diagnosed with symptomatic hemorrhoids and other conditions fully ruled out, first-line treatment with conservative, nonoperative therapy should commence. The vast majority of patients are started on a fiber supplement such as psyllium or methylcellulose and a stool softener such as docusate. Patients are encouraged to drink eight or more glasses of water per day, cut back on caffeinated beverages, and increase dietary fiber. Patients should also be advised on proper toileting hygiene as reducing pressure to the pelvic floor by avoiding straining is imperative. Patients are encouraged to reduce time on the toilet to less than 3 minutes and not to sit longer than necessary (no reading, cell phone, crossword puzzles). In a large systematic review, these simple measures were sufficient to decrease symptoms in the majority of patients with grade I and II hemorrhoids. Warm sitz baths two to three times daily may also help with symptom relief, as may application of cotton soaked with witch hazel to reduce edema. Over-the-counter topical remedies usually contain hydrocortisone or *-caine* analgesics and may provide temporary relief, but they do not help reduce symptoms in the long run.

The use of phlebotonics including the natural plant extract flavonoids are thought to improve hemorrhoids through an unknown mechanism of action. Studies report increased venous drainage and decreased hemorrhoidal inflammation. Patients report less bleeding, less pruritus, and overall symptom improvement. Long-term data do not exist to support durability at this time.

Some patients will fail conservative treatment and require procedural intervention. Office-based procedures include rubber band ligation (RBL), sclerotherapy, infrared coagulation (IRC), and use of the HET bipolar system. Operative procedures are also included in the algorithm of treatment and may be employed as more conservative treatments fail.

Office-Based Procedures

Rubber Band Ligation

RBL is the most common office-based procedure for symptomatic hemorrhoids. It is appropriate for use on grade I, II, or III hemorrhoids and requires no anesthetic or bowel preparation. Patients who are on anticoagulation, on antiplatelet therapy, or are allergic to latex are not eligible for this procedure. With the former, there is a risk of

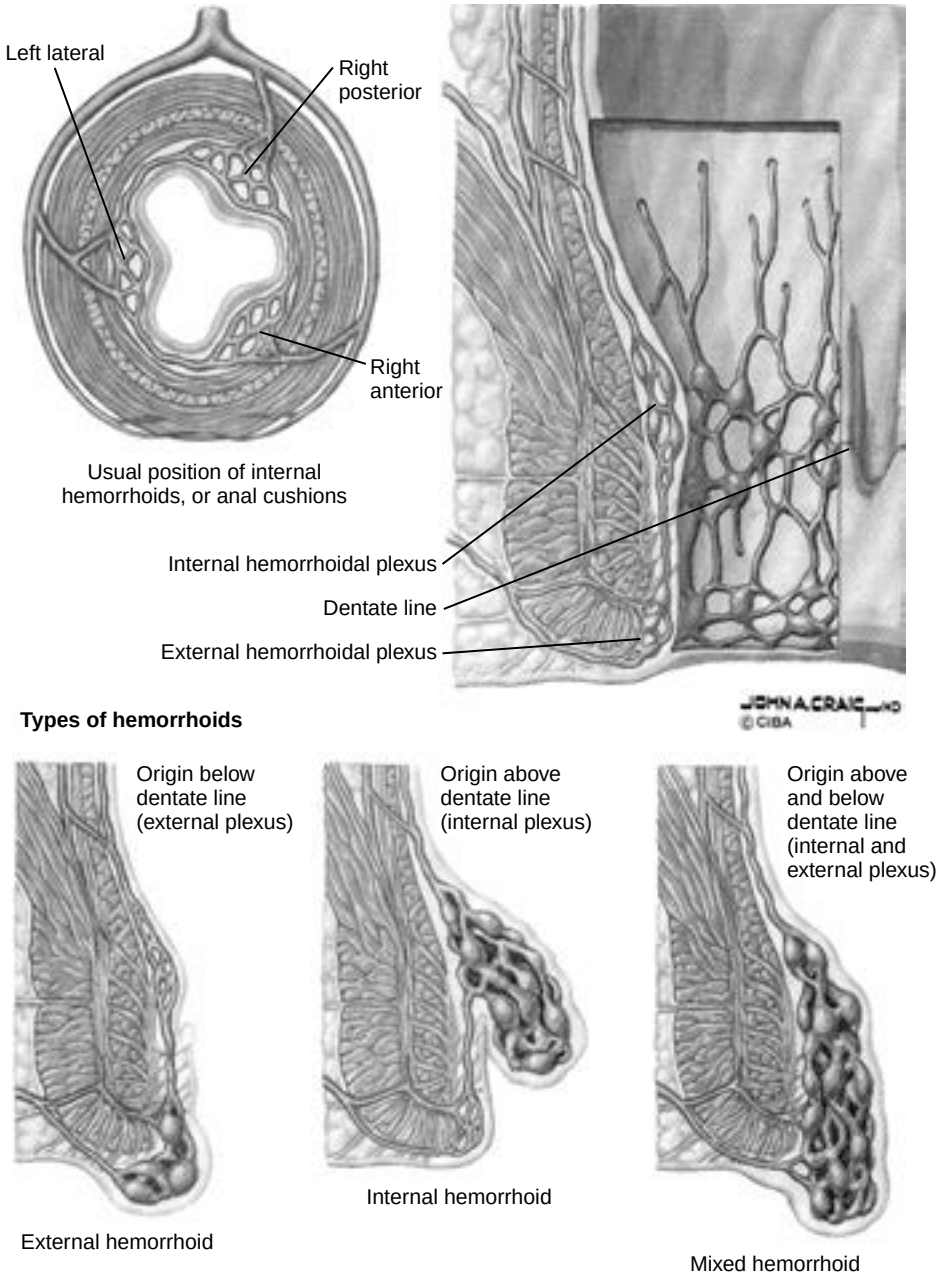


FIG. 1 Location and types of hemorrhoids.

TABLE 1 Classification of Internal Hemorrhoids

Grade	Location	Symptoms
1	Bulge into anal canal	Painless bleeding
2	Prolapse, reduce spontaneously	Bleeding, pressure, itching
3	Prolapse, require manual reduction	Bleeding, pressure, mucoid drainage
4	Prolapse, cannot be reduced	Pain, bleeding, pressure, mucoid drainage

delayed bleeding. Patients are asked to abstain from aspirin-containing products at home for 7 days before the procedure. They are placed in the left lateral decubitus or prone jack-knife (preferred) position on a procto table. Anoscopy is performed, and the hemorrhoids are visualized. The largest or most excoriated hemorrhoid is addressed at the first session. The rubber band is placed approximately 2 cm above the dentate line at the apex of the hemorrhoid (Fig. 4). There is no somatic pain sensation at this level, and many patients report dull pelvic pressure.

There are several types of rubber band ligators available; our preference is shown. Suction ligators have the benefit of not needing an assistant. RBL helps reduce hemorrhoid size by reducing blood flow to the hemorrhoidal cushion and by removing a small portion of rectal mucosa. Over time, fibrosis and scarring occur, which help pull the hemorrhoid cephalad and further reduce size and prolapse symptoms. Hemorrhoid banding has a high success rate of over 90%. Many patients may need a series of bandings to fully address symptoms; these should be scheduled roughly 3 to 4 weeks apart. Our preference is to band one hemorrhoid at the first occasion and up to two thereafter. We avoid banding all three hemorrhoidal columns to reduce pelvic pressure and pain. The band will slough in approximately 1 week, causing some minor bleeding. Again, it is this part

of the procedure that makes it unsuitable for those on anticoagulants or aspirin. For those who can stop anticoagulation 1 week before and after, banding is a good option. For those who cannot, sclerotherapy can be offered.

RBL is safe, and its most common complications are pain, bleeding, vasovagal symptoms, or thrombosis of the contiguous external hemorrhoid. Severe pain immediately after banding indicates the band was placed too low, and band removal is required either in the operating room or with a band-removing tool in the office. Rarely, pelvic sepsis can occur with fever, increasing and severe pain, and urinary retention. It is a rare but serious complication and requires immediate operative intervention to control sepsis with wide debridement of necrotic tissue.



FIG. 2 Prolapsed external and internal hemorrhoids.

Sclerotherapy

Sclerotherapy is an office-based procedure used for grade I and II hemorrhoids and is a viable option for patients on anticoagulants and antiplatelet agents. A sclerosant is injected into the hemorrhoid, resulting in shrinkage, fibrosis, scarring, and fixation. Sclerosing agents include 5% phenol (suspended in almond oil), hypertonic saline, or ethanolamine. Anoscopy is performed and, using a 25-gauge needle, the surgeon injects the sclerosant 1 cm above the dentate line in the submucosa of the hemorrhoid. The volume injected varies based on the sclerosant but is typically 2 to 3 mL when using phenol and 1 mL when using ethanolamine, and all three hemorrhoids can be treated in one session. Digital pressure is used to control needle site bleeding in patients who are anticoagulated. Sclerotherapy, like RBL, can be repeated to achieve the desired effect. Complications are similar to RBL and arise usually from injecting the sclerosant into the muscle or mucosa, which leads to pain, ulceration, and eventual sloughing of the mucosa.

Other Office-Based Procedures

IRC and bipolar diathermy are also utilized for grade I and II hemorrhoids. Like sclerotherapy, both can treat all hemorrhoid columns in one setting. In IRC, the tip of the infrared coagulator (IRC 2100, Redfield Corporation) is placed at the apex of the hemorrhoid. A 1- to 1.5-second pulse is applied, resulting in a 4-mm^2 focus of coagulation. This creates a 2.5-mm-deep ulcer. Typically three to four applications are made on each hemorrhoid. The overall effect is thrombosis and tissue destruction, which leads to shrinkage, scarring, and fixation of the hemorrhoid. IRC is well tolerated and has similar side effects to RBL and sclerotherapy (Fig. 5).

The HET system (HET bipolar system, Covidien) is also used in the office setting. Using specialized forceps, the hemorrhoid is grasped, and bipolar energy is applied. HET is well tolerated and has similar side effects to RBL and sclerotherapy.

Operative Treatment

Operative treatment is indicated for patients with grade III and grade IV hemorrhoids and for those who have persistent symptoms

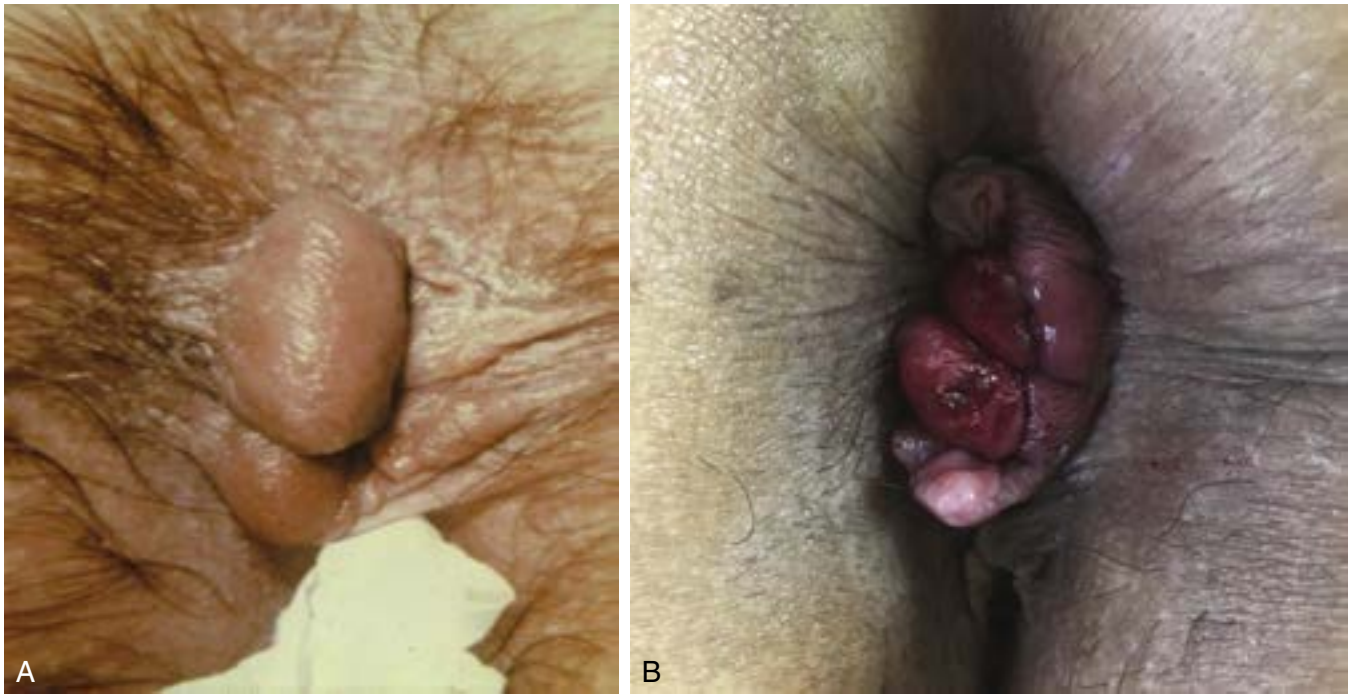


FIG. 3 (A) An acute, thrombosed external hemorrhoid. **(B)** Prolapsed and strangulated internal hemorrhoids with an external component.

despite conservative and office-based procedures. Some patients are suitable to go directly to an operation in the nonurgent setting. Only about 5% to 10% of patients with symptomatic hemorrhoids will require an operation. Surgery is superior to office-based procedures in terms of durability but has more potential complications including pain, urinary retention, bleeding, anal stenosis, infection, and changes in continence. Use of long-acting injectable anesthetics is helpful. Detailed postoperative instructions including pain management, local wound care, controlling constipation, and return precautions are important for patient satisfaction and comfort in the postoperative period.

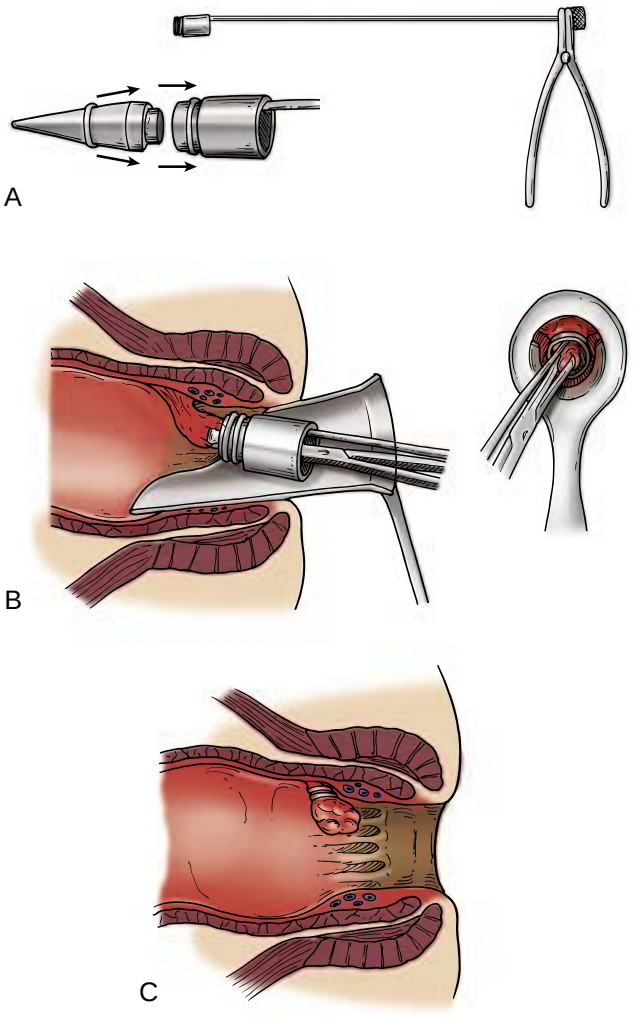


FIG. 4 Rubber band ligation of internal hemorrhoids. (A) A rubber band is placed onto a banding gun. **(B)** The hemorrhoid is grasped 2 cm above the dentate line, and the band is advanced over the hemorrhoid. **(C)** The band is shown in the correct position after ligation.

Acute Hemorrhoidal Crisis

The term *acute hemorrhoidal crisis* is attributed to Dr. Eugene Salvati, whose robust practice of over 50 years focused heavily on proctology. Acute hemorrhoidal crisis refers to circumferential prolapsed, thrombosed, and incarcerated internal and external hemorrhoids, with or without necrosis. In the absence of necrosis, the patient can be treated definitively or temporized with the use of an injected mixture of 1% lidocaine with epinephrine, normal saline, and hyaluronidase. The mixture is injected into all edematous tissues. The area is massaged, and a pressure dressing is applied. We typically have the patient sit on a roll of kerlix. The procedure can be repeated (Fig. 6). With necrosis present, this should be managed operatively with hemorrhoidectomy. Before incision, the hyaluronidase mixture can be injected and the hemorrhoids reduced to better delineate the tissues that are necessary for excision and reduce the chances for overexcision of anoderm. Single-column thrombosis can be excised and the wound left open to granulate. This is best done within the first 72 hours of thrombosis, and patients should be counseled that pain and drainage will be present after the procedure (Fig. 7).

Ferguson Hemorrhoidectomy

The Ferguson or "closed" hemorrhoidectomy is the most common hemorrhoid operation performed in the United States and offers a durable solution to hemorrhoidal symptoms. It involves excision of the hemorrhoidal tissue (internal and external) with ligation of the hemorrhoid pedicle and closure of the mucosal defect and skin. Our preference is to perform this operation under spinal anesthesia with the patient in the prone jack-knife position. The hemorrhoid is marked for excision at the anoderm. It is injected with an equal mixture of lidocaine with epinephrine and bupivacaine. A V-shaped incision is made in the perianal skin, and the hemorrhoid is elevated off the external and internal sphincter as the dissection is carried cephalad. The sphincter muscles should be clearly identified in situ as the incision is continued onto the mucosa. The apex of the hemorrhoid is identified, and the vascular pedicle is clamped before excision of the hemorrhoid. The pedicle is suture ligated (we use 2-0 Vicryl on a tapered needle), and the defect is then closed using a locking running suture until reaching the skin, where simple running sutures complete the closure. The last few millimeters are left open to drain (Fig. 8). The procedure can also be performed using a bipolar

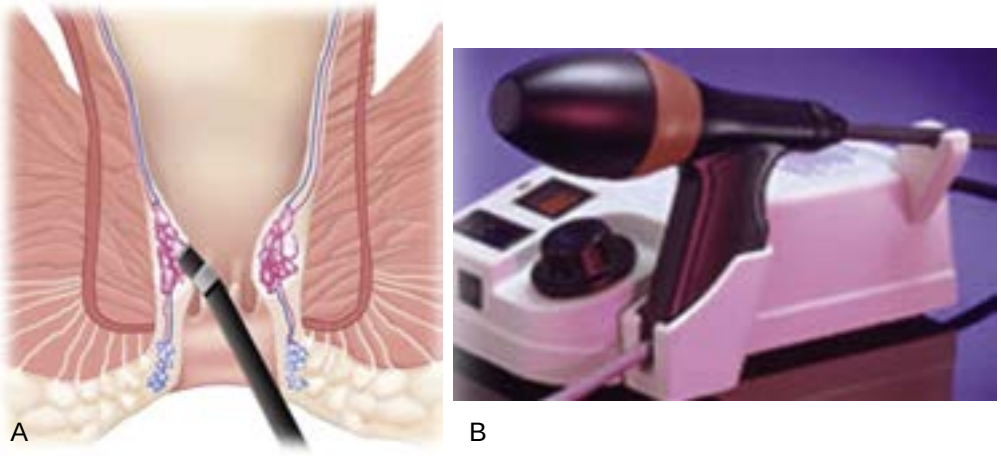


FIG. 5 Infrared coagulation of internal hemorrhoids. (A) The applicator is applied to the apex of the hemorrhoid. **(B)** The IRC 2100 device (Redfield Corporation).



FIG. 6 Acute hemorrhoidal crisis. (A) Thrombosed internal and external hemorrhoids with severe edema before injection. **(B)** After hyaluronidase mixture injection and massage. Note the absence of edema.

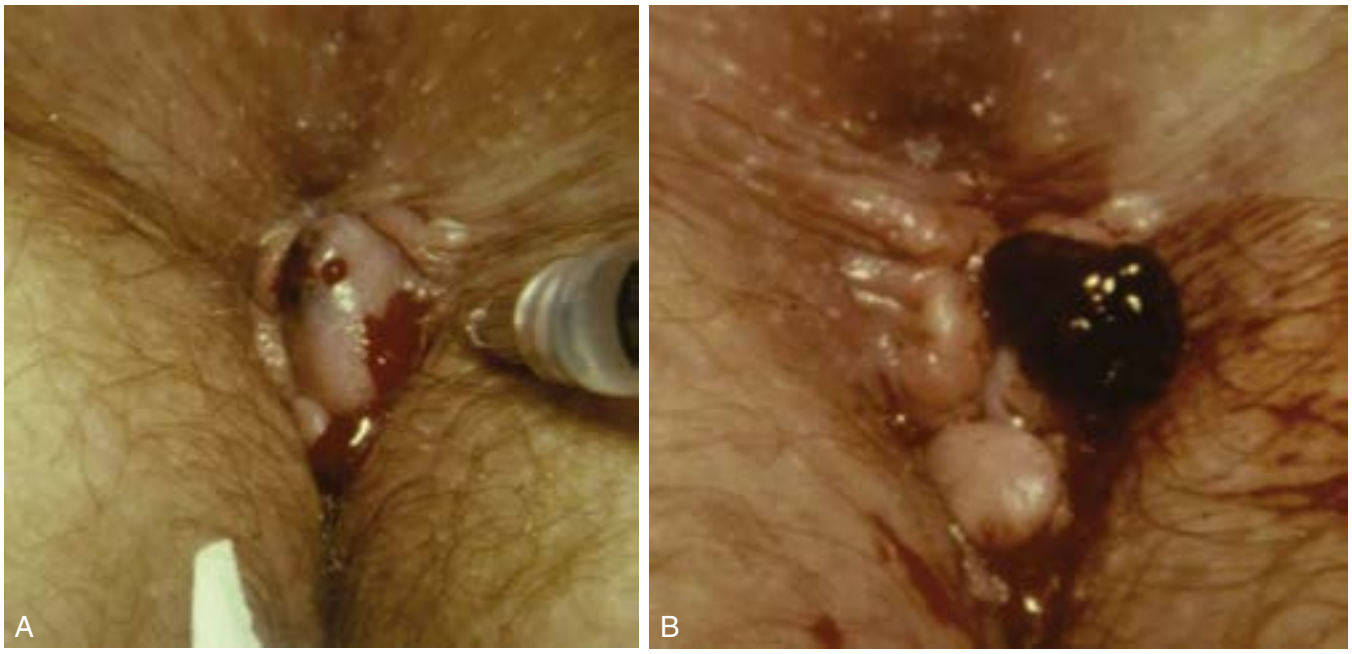


FIG. 7 Acute thrombosed external hemorrhoid. (A) Single thrombosed external hemorrhoid. **(B)** Clot excised with overlying.

sealing device (LigaSure or Harmonic). Careful identification of the internal sphincter is mandatory to proceed safely with this technology, and caution must be used to prevent overexcision of anoderm with resultant anal stenosis. Using an energy device will also significantly increase cost.

Milligan-Morgan Hemorrhoidectomy

The Milligan-Morgan, or "open" hemorrhoidectomy, is performed most commonly in Europe and the United Kingdom. The procedure is identical to the Ferguson hemorrhoidectomy, but after excision the wound is left open to heal by secondary intention.

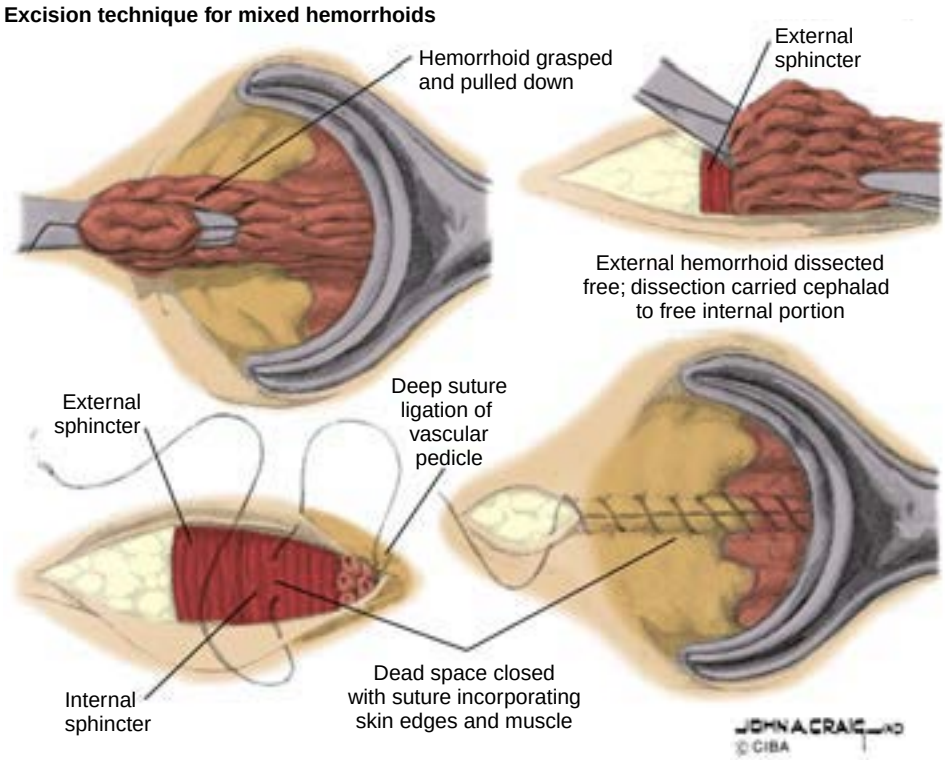


FIG. 8 **Ferguson hemorrhoidectomy.**

Outcomes and overall durability are similar, but wound healing is much longer.

Stapled Hemorrhoidopexy

Stapled hemorrhoidopexy (or procedure for prolapsed hemorrhoids [PPH]) is usually offered to patients with grades I to III circumferential internal hemorrhoids without a bulky external component. It was developed as an alternative to excisional hemorrhoidectomy because of the associated postoperative pain. The technique uses a specialized circular end-to-end anastomosis (EEA) stapler that removes a circumferential band of mucosa and submucosa proximal to the hemorrhoids. It does not remove the hemorrhoids, but flattens them with tension and disruption of the vascular pedicle and helps reposition them back to their normal anatomic position in the anal canal. There are no external wounds, and the staple line is cephalad to the dentate line, thus reducing pain compared with traditional excisional hemorrhoidectomy. PPH can help flatten external disease, but it will not completely address large external hemorrhoids.

Stapled hemorrhoidopexy is also performed under spinal anesthesia in the prone jack-knife position. The hemorrhoidopexy kit contains a dilator, a clear plastic anoscope, an operating anoscope, and stapler (Fig. 9). The dilator is placed in the anal canal, and the clear plastic anoscope is sutured to the perianal skin to evert the dentate line. Next, the operating anoscope with depth markings is used to place a circumferential submucosal purse-string suture 3 to 4 cm proximal to the dentate line, about 2 cm proximal to the hemorrhoidal pedicle. Caution must be taken to avoid placing a full-thickness suture, especially in women as injury to the vagina and subsequent rectovaginal fistula can occur. After placement of the purse-string suture, the vagina should be checked digitally to ensure the absence of suture. Once the purse-string suture is complete, it is tied to the anvil of the stapler. The anvil is then mated with the stapler, and the stapler is fired. The specimen appears as a ring of mucosa and submucosa.

Complications of PPH and excisional hemorrhoidectomy are similar. In some cases, if the staple line is too close to the dentate line, the patient will have significant postoperative pain, so care must be taken to place the purse-string suture at the correct level. Staple line bleeding at the time of the initial operation should be controlled by oversewing the entire staple line. Rare complications such as rectovaginal fistula, pelvic sepsis, staple line stricture, and rectal perforation have been reported, and most complications result from misplacement of the purse-string suture. PPH outcomes are similar to hemorrhoidectomy however; long-term recurrence is higher with stapled hemorrhoidopexy. Overall, PPH patients have less pain, faster recovery, and better quality of life scores compared with excisional hemorrhoidectomy patients.

Doppler-Guided Hemorrhoid Artery Ligation and Mucopexy

Doppler-guided hemorrhoidal artery ligation (DGHAL) is a technique that utilizes one of two patented anoscopes, the THD (transanal hemorrhoid dearterialization) or the HAL (hemorrhoid artery ligation). Both systems utilize Doppler guidance to isolate the hemorrhoidal arteries for ligation. Typically used on grade II to III hemorrhoids, it allows selective and specific ligation of the hemorrhoidal arteries, reducing arterial inflow to the hemorrhoids and returning the tissues to normal physiologic condition. Up to 90% of patients had improved symptoms, with less postoperative pain than other surgical options, because all suturing is done proximal to the dentate line.

Similar to other hemorrhoid procedures, the DGHAL is performed in the operating room in the prone jack-knife position. The proprietary anoscope is placed in the anal canal to 6 to 7 cm from the anorectal junction. The vessels are localized with the attached Doppler, usually about 2 cm above the anorectal junction (Fig. 10). A *Z*-stitch is placed at this location through the slot on the anoscope, and ultimately six sutures are placed. For patients with grade III or IV hemorrhoids, a mucopexy, or "rectoanal repair," can be added to help draw up and flatten out the tissues. Overall complication rates are low and are mostly related to bleeding and recurrence.

Open Transanal Hemorrhoidopexy

Open transanal hemorrhoidopexy can be performed alone or in conjunction with other operative procedures. It involves suturing the

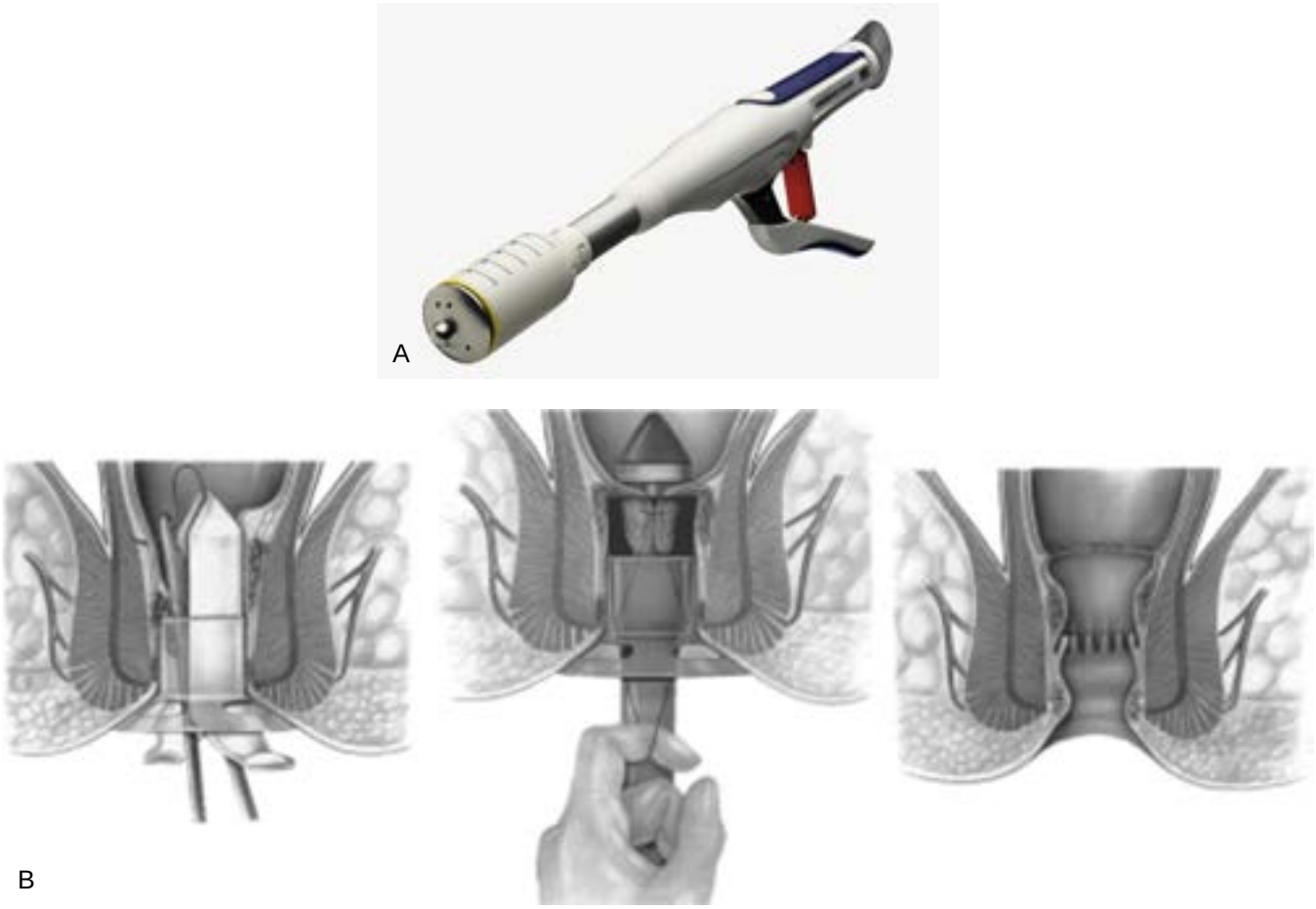


FIG. 9 **(A)** EEA hemorrhoid and prolapse stapler with DST Series technology. **(B)** Stapled hemorrhoidopexy technique. A purse-string suture is applied 4 cm above the dentate line *(left)*. The stapler is advanced into the rectum, and traction is held on the suture *(center)*. The staple line is shown after completion of the procedure *(right)*. (**A** *courtesy Medtronic, copyright 2019.)*

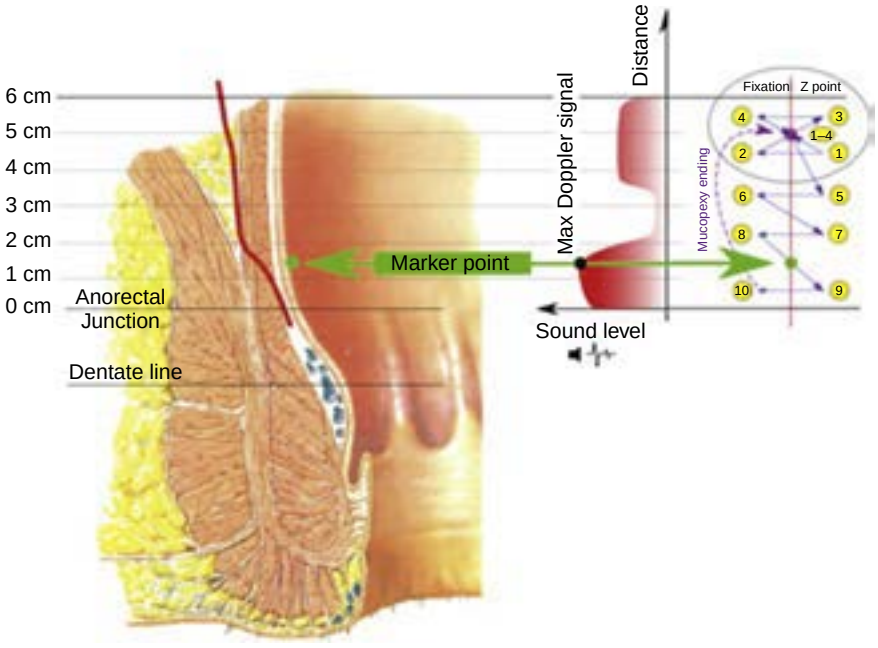


FIG. 10 Schematic of transanal hemorrhoidal dearterialization and mucopexy. *Marker point* denotes the location of the best Doppler signal for hemorrhoidal ligation. A *Z*-stitch is placed at this location for ligation alone. For higher-grade hemorrhoids, mucopexy with running suture is performed starting proximally and encompassing the ligation point, pulling the redundant mucosa up into the rectum *(right side of image). (From Ratto C, de Parades V. Doppler guided ligation of hemorrhoidal arteries with mucopexy: a technique for the future. J Visc Surg. 2015;152:S15–S21.)*

anal mucosa to the rectal wall using a *Z*-stitch. At 4 cm from the anal verge, a suture including mucosa and submucosa is placed through the rectal wall and then at the upper level of the hemorrhoid tissue near the vascular pedicle. Before tying the suture, a 1-cm strip of mucosa between the two sutures is excised after injection of lidocaine with epinephrine. The suture is then tied down, drawing the prolapsing hemorrhoid higher into the anal canal. Our practice is to perform this procedure, with or without excision of the intervening tissue, during other operative treatment for the hemorrhoids, and it can be a useful adjunct. Complications related to bleeding and thrombosis are most common. Recurrences may be managed with a repeat procedure.

Postoperative Considerations

Surgical hemorrhoidectomy is a very safe procedure. Postoperative urinary retention occurs in up to 15% of patients and can be partially mitigated with fluid restriction. Postoperative bleeding occurs in 1% to 2% of patients. Early bleeding is considered an operative complication, but bleeding 7 to 14 days later is a known complication resulting from absorption of sutures. All patients with significant bleeding must return to the operating room. During the examination under anesthesia, most often no active bleeding is seen, but all suture or staple lines should be oversewn. Rarely more serious complications will occur as mentioned previously. Overall, most patients will have postoperative pain and should be given multimodal analgesics to help reduce narcotic usage. Oral regimens of nonsteroidal antiinflammatory drugs (NSAIDs) as well as acetaminophen should be given around the clock. Sitz baths to help reduce discomfort should be utilized liberally. Constipation and diarrhea should be avoided, and appropriate stool modifiers should be offered if necessary. Studies have shown that use of topical calcium channel blockers in the postoperative period reduced overall pain and allowed patients to resume normal activities sooner. Overwhelmingly the greatest improvement has been with the use of liposomal bupivacaine, which has demonstrated overall reduction of pain scores and greater interval in opioid usage in the postoperative period.

SPECIAL SITUATIONS AND COMPOUNDING CONDITIONS

Pregnancy

Pregnant patients are susceptible to increased hemorrhoid symptoms because of the complex physiologic changes that result in increased intraabdominal pressure and reduced venous return. Labor-related straining further complicates the problem. Bleeding and pain are the most common symptoms, and symptoms present at any time during pregnancy, but most often in the third trimester.

Treatment is almost always conservative and nonoperative as most hemorrhoid symptoms will regress in the postpartum period. Unless the hemorrhoids are thrombosed or strangulated, surgery should be avoided. Stool softeners, sitz baths, and cooling ointments should be used liberally.

Portal Hypertension

PH is another condition that will result in increased rectal bleeding, and many of these patients have rectal varices on examination that may resemble hemorrhoids. Bleeding in the setting of PH should be treated conservatively. RBL is contraindicated because of the risk of delayed bleeding. Sclerotherapy and suture ligation of the hemorrhoids can be offered if conservative therapy fails. Ultimately, reducing portal pressure with a transjugular intrahepatic portosystemic shunt is the terminal procedure. Caution should be taken to avoid any bedside or office-based procedures in these patients because bleeding, even from small injection sites, can be brisk and difficult to control.

Immunocompromised Patients

Managing hemorrhoid symptoms in immunocompromised patients can be challenging. Conservative measures are first line as the risk of poor wound healing and pelvic sepsis is increased after surgical hemorrhoidectomy in this cohort. For patients on immunosuppressants that can be stopped, preference is to have 1 week off medication before the procedure. In patients with poorly controlled HIV or AIDS, sclerotherapy is the procedure of choice. Preprocedure antibiotics should be considered in this population and discussed with the patient and the patient's other physicians. Patients with well-controlled HIV have a risk similar to non-HIV patients.

Crohn's Disease

In patients with Crohn's disease, symptomatic hemorrhoids are rare. Symptoms are more likely related to the Crohn's disease when a careful history and examination are made. Anal fissure and anorectal abscess are much more common than symptomatic hemorrhoids. Treatment should always be conservative, and maximal management of the Crohn's disease is imperative. Elective operations for hemorrhoids in patients with proctitis should be avoided. Acute, painful thrombosis may be excised with a small incision.

SUMMARY

Hemorrhoidal disease is very common among adults in the United States given the incidence of constipation and low-fiber diet. Symptoms must be carefully elucidated by the physician, and a thorough physical examination and anoscopy are crucial to confirming the diagnosis. Colonoscopy should be ordered to confirm outlet bleeding and rule out proximal source. Conservative management with dietary and lifestyle changes are the mainstay of treatment in every patient. Fiber supplementation and proper toilet hygiene are imperative. When failure of conservative therapy is noted, patients with grade I to II hemorrhoids and some with grade III will benefit from office-based procedures. They can be repeated safely to obtain optimal results. Those with grade III and IV hemorrhoids or who fail office-based procedures have multiple surgical options depending on anatomy and patient preference. The operation should be tailored to the patient. Care should be taken when managing patients with special circumstances as not every procedure is suitable.

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Management of Fissure-In-Ano

Vernissia Tam, MD, MS, and Heather L. Yeo, MD, MHS

INTRODUCTION

Anal fissures are one of the most common conditions seen in a colorectal surgery practice. Patients present with sharp tearing or cutting pain during and after bowel movements, often accompanied by hematochezia. The pathogenesis is believed to be precipitated by hard stool or diarrhea passing through the anal canal, causing mucosal trauma. The trauma causes pain and tightening of the sphincter. Increased sphincter tone and decreased blood flow along with repeated trauma prevent fissures from healing, forming the key targets for treatment.

On anorectal examination, 75% to 90% are located in the posterior midline, and acute fissures appear as a longitudinal tear in the anal canal, distal to the dentate line (Fig. 1A). After 6 to 8 weeks, chronic fissures may present with a skin tag or sentinel pile, with exposed fibers of the internal sphincter visible at the base, and heaped-up granulation tissue at the edges (Fig. 1B). Up to 20% may be located in the anterior midline, and off-midline fissures should prompt evaluation into other underlying infectious, immunosuppressive, or malignant etiologies (Fig. 1C).

NONOPERATIVE MANAGEMENT

Dietary and Lifestyle Modifications

There is no single recommendation for treatment that is best for all patients. Nonoperative treatment success will partially depend on patient compliance with lifestyle modifications and topical agents. The decision to escalate to surgery involves the degree of improvement with conservative measures, the risk for incontinence, and patient preference. For severely symptomatic patients who do not have risk factors for incontinence and can accept a small risk of long-term incontinence, surgery may be offered up front for the highest likelihood of healing and lowest risk of recurrence. It is our preference to only use this in very select cases.

Over 50% of acute fissures will resolve with conservative measures and warrant a trial of nonoperative management. Initial recommendations include increased fiber intake (25 to 35 g per day) via diet or supplements, increased hydration, and warm sitz baths. Fiber combined with sitz baths alone has been reported to heal up to 87% of acute fissures. The combination of these conservative measures with a topical analgesic (e.g., 2% lidocaine, EMLA cream) and a sphincter relaxant is a reasonable first-line treatment. Failure of symptoms to improve in 6 to 8 weeks warrants reevaluation and escalation of treatment. A biopsy should be performed on all long-standing fissures to rule out malignancy.



FIG. 1 **(A)** Acute posterior midline fissure. **(B)** Chronic fissure with sentinel tag. **(C)** Off-midline fissure associated with Crohn's disease. *(**B** and **C** courtesy Dr. Kelly Garrett.)*

Topical Sphincter Relaxants

Topical nitroglycerin releases nitric oxide and relaxes the internal anal sphincter (IAS), producing healing rates between 49% and 68%. Doses between 0.2% and 0.8% can be applied 2 to 4 times per day. However, effects are short-lasting (approximately 90 minutes), which may require diligence and frequent reapplication. The most significant side effect is headaches and lightheadedness, which may be mild to severely disabling and can lead to noncompliance and cessation of treatment.

Topical gels containing nifedipine or diltiazem similarly relax the internal sphincter and encourage blood flow. Oral doses are available but may lead to orthostatic hypotension. Studies comparing topical nitrates to calcium channel blockers have showed conflicting results, and both are considered equivalent, with selection largely based on provider preference and pharmacy availability. We prefer a dose of 2% to 5% topical diltiazem cream applied 2 to 3 times daily. If tolerated, oral doses of 60 mg twice-daily have been successfully described.

Chemical Denervation

Botulinum A toxin (Botox, Allergan Inc.) chemically paralyzes the internal sphincter, which lowers the resting anal pressure and increases blood flow. Injections can be performed as an outpatient or clinic-based procedure. We prefer treatment with 60 to 100 units diluted in 2 to 5 mL sterile saline solution. Four divided doses are injected into the intersphincteric groove directed toward the IAS in four quadrants. Depending on sphincter tone, another 1 mL is injected on either side of the fissure (Fig. 2).

Effects of Botox are not compromised with patient noncompliance, and results are longer-lasting than topical relaxants. However, the long-term durability of cure is not as clear, and recurrence has been reported to be as high as 40% at 4 years. Nevertheless, there are decreased rates of permanent incontinence compared with surgical sphincterotomy. In a Cochrane review of nonsurgical therapy for anal fissure including 23 studies and 1236 patients, topical nitroglycerin was found to be better than placebo in healing fissures (49% vs. 36%, $P < 0.0009$), though nearly 50% of those initially cured had a recurrence. Botox and calcium channel blockers were equally efficacious to nitroglycerin and benefited from fewer adverse events. Overall, no medical therapy approached the superior efficacy of surgical sphincterotomy.

OPERATIVE MANAGEMENT

Manual dilation of the sphincter muscle using fingers, various retractors, and pneumatic balloons has been abandoned secondary to poor outcomes including incontinence, recurrence, trauma, and patient discomfort. Fissurectomy has been proposed to address the chronic anatomic changes that may prevent a fissure from healing. Minimal debridement or "trimming" eliminates the fibrosis, sentinel pile, and rolled edges back to healthy tissue that may encourage a fissure to heal. It has limited success when used alone but may be performed in conjunction with chemical denervation, sphincterotomy, or advancement flaps.

Lateral Internal Sphincterotomy

LIS is the gold standard surgical treatment for chronic fissures, offering the highest rates of healing (up to 95%) and low recurrence with durable results. It can be performed as an open or closed approach, with equivalent rates of healing and recurrence. In a Cochrane review of 2056 patients in 27 studies analyzing 13 different procedures, there was no difference between open versus closed LIS in fissure persistence and incontinence risk.

In the open approach, a small radial incision is made over the intersphincteric groove. The internal sphincter muscle is dissected out and exposed before dividing under direct visualization (Fig. 3). The overlying incision can then be closed with an absorbable suture.

Our group favors the closed approach. In the closed approach, a blade is inserted in the intersphincteric groove parallel to the muscle fibers. The blade is then turned 90 degrees, and the IAS muscle fibers are divided against a finger inserted into the anal canal, without going through the mucosa. Manual spreading of the divide fibers in a gentle sweeping motion in the anal canal can confirm adequate division and separation (Fig. 4). The cut typically includes all fibers below the dentate line.

The overall rate of transient disturbed continence from a systematic review was 14% among over 4500 patients, with <1% reporting accidental defecation or stool seepage. Although there are some studies reporting higher rates of permanent incontinence following the open technique, results are inconsistent, and both open and closed sphincterotomies are well-accepted approaches.

To reduce the risk of incontinence, a tailored sphincterotomy has been proposed by dividing the IAS to the height/internal apex of the fissure, rather than the dentate line, which may result in excessive division. This approach should be considered in populations at higher risk for postoperative incontinence, including women who may have shorter anal canals and less muscle, multiple vaginal deliveries, or prior obstetric injuries; individuals with other sphincter or perineal injuries; and individuals with inflammatory bowel disease.

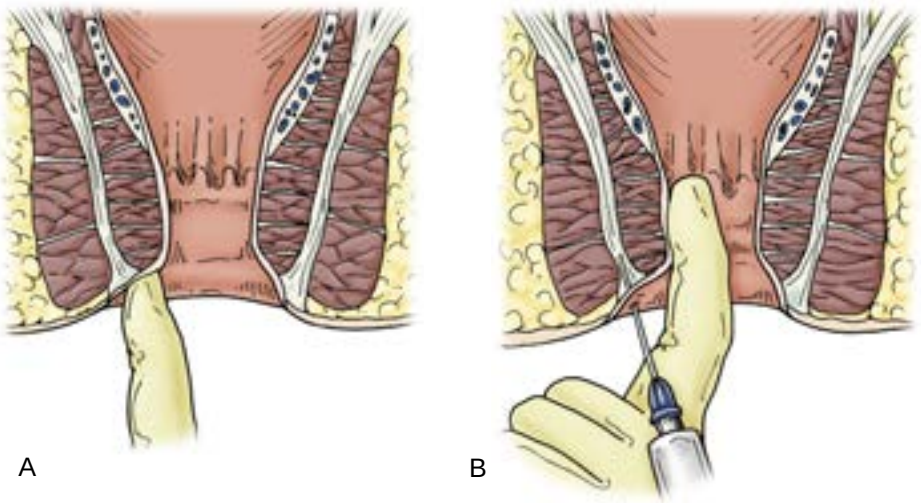


FIG. 2 Chemical denervation. **(A)** Palpation of the intersphincteric groove with a lubricated finger guides **(B)** injection in four quadrants. *(From Braasch JW, Sedgwick CE, Veidenheimer MC, Ellis H, eds.* Atlas of Abdominal Surgery. *Philadelphia: Saunders; 1991:199)*

Advancement Flaps

Patients with persistent or recurrent fissures after LIS are challenging to manage. Repeat LIS is not recommended given the high risk of permanent incontinence, especially in patients without increased sphincter tone. These patients without evidence of increased sphincter tone may benefit from a fissurectomy combined with a dermal advancement flap. Two common advancement flap techniques are the *V-Y flap* and *house flap.* A V-Y flap is created from the perianal skin, where the apex of the *V* is pulled proximally and sutured to the proximal apex of the fissure (Fig. 5). In a house flap, the base of the

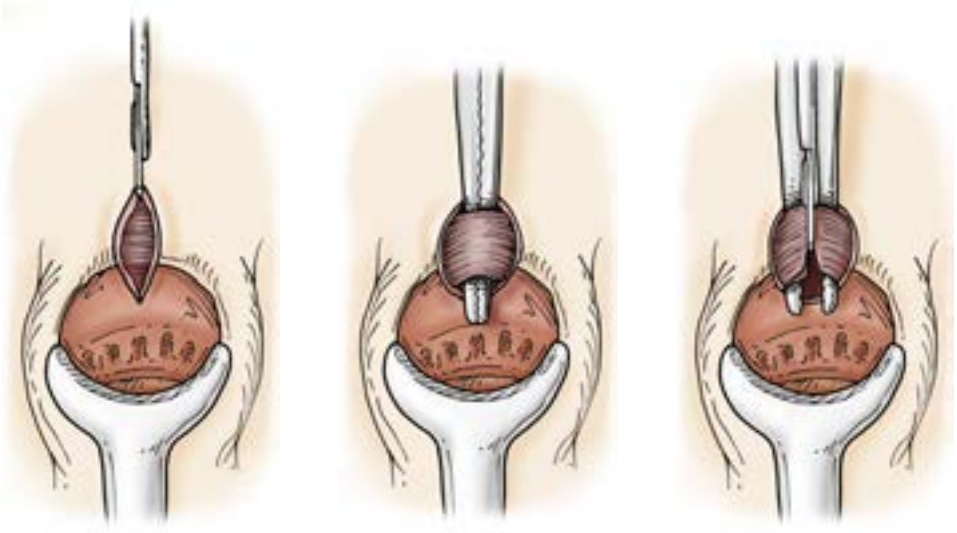


FIG. 3 Open lateral internal sphincterotomy. *(From Wexner SW, Beck DE, eds.* Fundamentals of Anorectal Surgery. *2nd ed. London: Saunders; 1998:214–215.)*

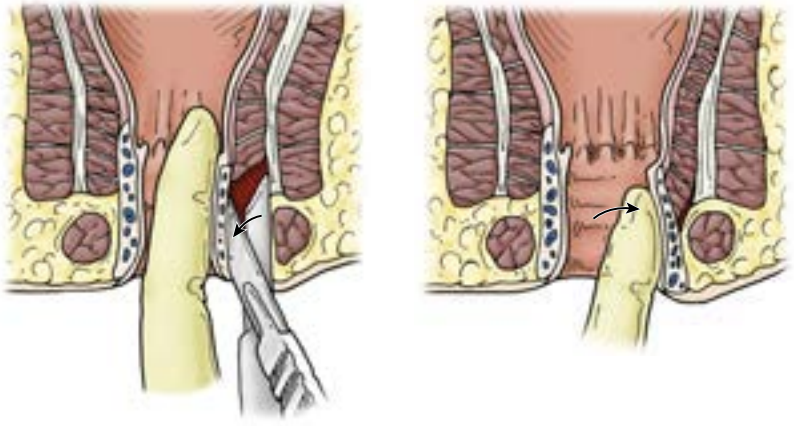


FIG. 4 Closed lateral internal sphincterotomy.

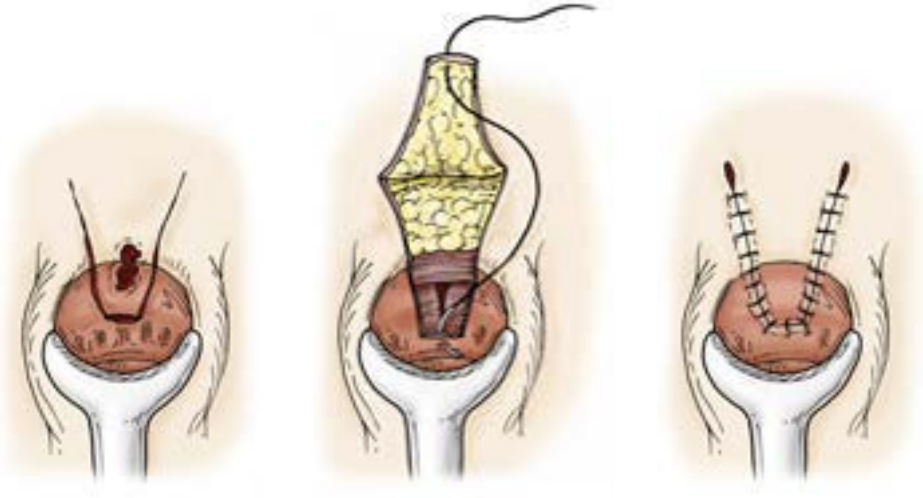


FIG. 5 V-Y advancement flap. *(From Braasch JW, Sedgwick CE, Veidenheimer MC, Ellis H, eds.* Atlas of Abdominal Surgery. *Philadelphia: Saunders; 1991:199)*

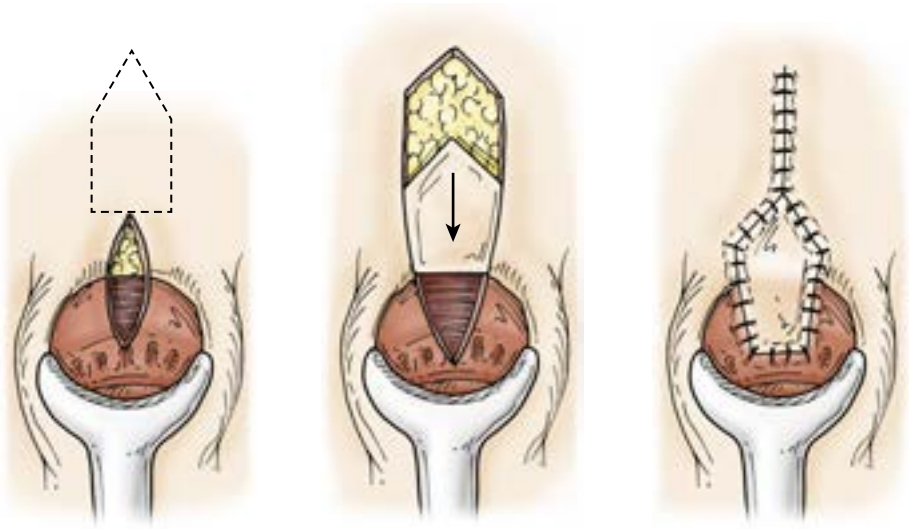


FIG. 6 House advancement flap. *(From Liberman H, Thorson AG. How I do it. Anal stenosis.* Am J Surg. 2000 *Apr;179(4):325–9.)*

pentagon-shaped flap is sutured to the proximal apex of the fissure, while the external "house roof" is closed linearly (Fig. 6).

SPECIAL CONSIDERATIONS

LIS for patients with preexisting fecal incontinence or risk factors should be offered cautiously so as not to worsen or permanently induce incontinence. These would include women with obstetric trauma or previous sphincter injuries.

When fissures are off midline, underlying disorders should be considered such as Crohn's disease, human immunodeficiency virus (HIV), tuberculosis, anal cancer, sexually transmitted infections, or other immunosuppressive or infectious etiologies such as human papilloma virus (HPV) and syphilis. In such cases, biopsies and cultures are helpful for diagnosis. Patients who are immunocompromised secondary to chemotherapy will often present with diarrhea; nonoperative management and chemical denervation with Botox is recommended.

Perianal morbidity is a common phenotype of Crohn's disease, and Crohn's-related fissures generally should not be treated with sphincterotomy. Medical management directed at the patient's Crohn's disease will heal the majority of anal fissures. Patients who are constipated should be treated with fiber supplementation and increased hydration. Topical diltiazem and Botox denervation are recommended for nonoperative management, with early involvement of gastroenterology.

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Management of Anorectal Abscess and Fistula

Amy J. Thorsen, MD

Approximately 100,000 patients in the United States will seek care for anorectal sepsis each year. The mean age of presentation is 40 years (range 20–60 years). Adult males are twice as likely to develop an anorectal abscess and/or fistula compared with females. Anorectal abscesses and fistulas can be thought of as two successive phases of the same infectious process, with an abscess representing the acute phase of infection and a fistula denoting the chronic phase of suppuration and fistulization. Thus it is not surprising that 30% to 70% of anorectal abscesses are associated with a concomitant anorectal fistula, and that 30% to 40% of patients develop an anorectal fistula after undergoing treatment for an anorectal abscess.

Management of anal abscess and fistula includes four basic principles: (1) control the septic process (drain the pus), (2) define the involved anatomy, (3) treat the underlying process without

compromising sphincter function, and (4) minimize recurrence risk. Although many presentations are straightforward, complex and recurrent disease challenge even the most experienced surgeon. It is crucial for surgeons managing this disease to understand the regional anatomy, treat patients in the context of their comorbid conditions (such as Crohn's disease), and apply the appropriate surgical technique. Improper management can lead to potentially life-threatening sepsis or significantly impact a patient's quality of life by causing chronic discomfort and socially-inhibiting problems with personal hygiene.

ANORECTAL ABSCESS

Etiology and Classification

The anal glands lie within the intersphincteric space and empty into the rectum through 10 to 15 crypts of Morgagni located circumferentially at the dentate line. When this drainage is blocked, pressure builds as the septic source grows and propagates along paths of least resistance within or through the intersphincteric space. The potential pathways of suppurative extension delineate the anatomic spaces of anorectal sepsis: intersphincteric, submucosal, perianal, ischiorectal, postanal (subdivided into superficial and deep by the anococcygeal ligament), and supralevator space (Fig. 1).

The intersphincteric abscess, located at the site of the anal glands, tracks craniocaudally between the sphincter layers. A submucosal abscess represents the least extensive suppurative process, located just beneath the mucosa above the dentate line. Perianal abscesses descend through the intersphincteric space to the subcutaneous tissue around the anus and below the sphincter complex. The ischiorectal space encircles the external sphincter caudad to the levator ani

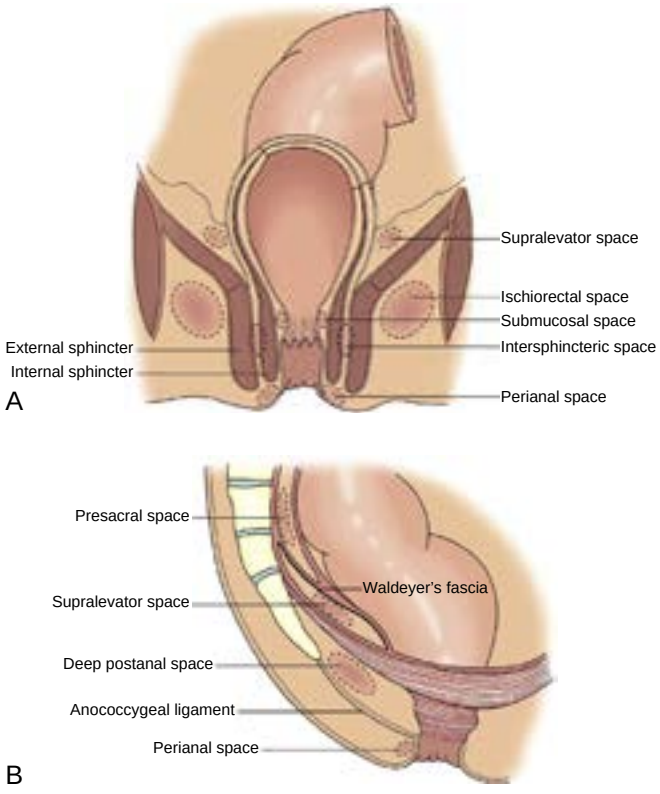


FIG. 1 Anal sepsis and fistula. Classification of anorectal abscesses by location. **(A)** Coronal view. **(B)** Sagittal view. *(From Yeo CJ, et al.* Shackelford's Surgery of the Alimentary Tract. *ed 7. Philadelphia: Saunders; 2007.)*

BOX 1 Causes of Anorectal Abscess

Cryptoglandular
Iatrogenic (anorectal or genitourinary surgery)
Perineal trauma
Radiation injury
Inflammatory bowel disease
Acquired immunodeficiency syndrome
Invasive fungal infection
Hidradenitis suppurativa
Diverticulitis
Anal fissure
Osteomyelitis
Foreign body
Malignancy (carcinoma, adenocarcinoma, hematologic malignancy)

Data from Becks DE, et al, eds. *The ASCRS Textbook of Colon and Rectal Surgery.* 2nd ed. New York: Springer-Verlag; 2011.

complex and medial to the ischial tuberosities; an ischiorectal abscess occurs from the extension of sepsis laterally from the intersphincteric space or caudally from the supralevator space. The postanal space is located posteriorly, between the levators (cranially) and the external sphincter (caudally); this space may be solely involved, or infection may extend laterally to the ischiorectal fossa, forming the so-called *horseshoe abscess.* The postanal space is divided into the superficial and deep postanal spaces by the presence of the anococcygeal ligament. Deep postanal space infections may be missed if this ligament is not penetrated during operative drainage. Supralevator abscesses, located above the levators as the name implies, are caused by cranial extension of cryptoglandular sepsis or by caudal extension of an intraabdominal process, such as diverticular disease, that perforates through the peritoneum.

Understanding the anatomic spaces of anorectal sepsis is imperative in deciphering the patient's presentation and planning the appropriate intervention that attains adequate drainage and reduces complications such as systemic sepsis, recurrence, fecal incontinence, and complex fistula formation. Although the cryptoglandular theory is believed to be responsible for the vast majority of anorectal abscesses, it is crucial to identify contributing conditions or alternate causes such as those displayed in Box 1. The impact of these factors and etiologies on the nature of the disease and treatment strategy will be discussed later in the chapter.

Presentation and Diagnosis

Anal pain independent of defecation is the most common complaint, given almost one-half of anorectal abscesses are in the perianal space. Swelling and fever are often present. Associated symptoms or medical history suggestive of or including inflammatory bowel disease and immunocompromised status should also be gathered. On anorectal examination, an indurated bulge with fluctuance and cellulitis near the anal verge is indicative of perianal abscess. Intersphincteric abscesses are unique in their lack of external examination findings but cause exquisite tenderness on digital rectal examination. Ischiorectal abscesses typically have gluteal findings of induration, tenderness, and fluctuance several centimeters away from the anal verge without tenderness on digital rectal examination. Abscesses limited to the postanal space may have localized tenderness posterior to the anal verge, but without apparent induration or fluctuance. Induration or fluctuance between the posterior anorectum and coccyx will be noted on bimanual examination. Supralevator abscesses may have no anorectal findings unless there is a downward extension of sepsis into the ischiorectal fossa; fluctuance above the levators may be noted on digital rectal examination. Further evaluation with

pelvic imaging should be considered to exclude their presence if a supralevator component is suspected. Anoscopy, rigid proctoscopy, and flexible sigmoidoscopy can be performed to evaluate the rectal mucosa for inflammatory bowel disease, but it is often not tolerated and should not be pressed. Patients who cannot tolerate an examination should undergo an examination under anesthesia (EUA).

The majority of patients with a suggestive history and physical examination can be managed with bedside drainage or operative evaluation and treatment. Radiologic imaging, however, is useful in some acute situations and helpful with more chronic or recurrent anorectal sepsis. CT is helpful in patients with associated abdominal symptoms or findings or with the clinical suspicion of a supralevator abscess. A pelvic CT scan should not be relied upon to exclude drainable anorectal infection; purulence can be present without definitive CT findings. Undrained anorectal infection can lead to severe systemic infection and destruction of the anal sphincter complex, resulting in functional morbidity. Endoanal ultrasound and MRI are not generally available or tolerated in the acute setting of anorectal abscess. Both, however, can be useful adjuncts in delineating the anatomy of complex, multiple, or recurrent fistula-in-ano.

Operative Evaluation and Drainage

Surgical drainage remains the definitive treatment of anorectal abscesses. Bedside drainage under local anesthesia using 1% lidocaine with dilute epinephrine is often well tolerated for perianal abscesses and small ischiorectal abscesses. After infiltrating the area with local anesthetic, a curved incision is made over the abscess. The incision should be oriented over the side of the abscess closest to the anal verge without transgression into the sphincter complex; this is done so if a fistula forms (an estimated 50% occurrence), it is more likely to have a simple, short tract. The temptation to drain an abscess over its most fluctuant point or at the furthest point from the verge should be avoided to prevent potential creation of a long fistula tract. A hemostat or finger is used to probe the wound, breaking down all loculations and defining the extent of disease. An ellipse of skin at least 1 cm in size incorporating the initial incision is excised to prevent premature closure of the skin. Hemostasis can be achieved with direct pressure, silver nitrate, or local anesthesia with epinephrine. The cavity is irrigated, and dry gauze is applied externally with the expectation of ongoing drainage. Packing the wound should be avoided because it subjects the patient to more pain and slower healing without the benefit of improved resolution of sepsis.

Large ischiorectal abscesses and those that must be approached transanally (intersphincteric, some supralevator, horseshoe, and deep postanal space infections) are most appropriately done in the operating room under monitored anesthesia care (MAC) or general anesthesia. A preoperative antibiotic with gram-negative coverage is administered. The anorectal region is best exposed with the patient in the prone jack-knife position and the buttocks taped widely apart, but the high lithotomy position is often adequate. A headlamp to improve visualization is recommended. Commonly used instruments include the Hill-Ferguson, Fansler, or Pratt bivalve retractors, fistula probes, curettes, 16- or 18-gauge angiocaths, and dilute hydrogen peroxide. The perianal region is inspected, noting any induration, fluctuance, or dermatologic abnormalities. A digital rectal examination is performed followed by anoscopy, looking for mucosal bulging, induration, sphincter defects, or other abnormalities. A biopsy should be performed on ulcerations, suspicious nodules, or perianal lesions to exclude neoplasia. A biopsy should be performed on recurrent abscess or fistula tracts as well in an effort to diagnose underlying inflammatory bowel disease, chronic infections (such as tuberculosis or actinomyces), or the rare malignancy. If the site of purulence is not obvious, an 18-gauge needle can be used to aspirate in suspected areas. Culture data is rarely helpful, but it may be so in patients with recurrent infections, nonhealing wounds, a history of methicillin-resistant *Staphylococcus aureus,* or underlying HIV infection in whom atypical microbes may be present.

For a large ischiorectal abscess, ipsilateral counterincisions can serve to establish adequate drainage rather than a large incision that resects overlying healthy tissue and prolongs healing unnecessarily. Digital exploration of the abscess cavity is prudent to ensure that extension into the postanal space or the contralateral fossa is not present. Packing is usually unnecessary and impractical for the patient to exchange. An alternate means of drainage utilizes a stab incision overlying the abscess, as close to the anal verge as possible, and the insertion of a 10- to 16-French mushroom catheter into the cavity. The catheter is secured with an anchoring suture and left in place for 1 week. The catheter is removed once a tract is well established, although it can be left in for prolonged periods in cases of large or recurrent infections.

Drainage of a postanal space abscess deserves special note. A radial incision is made from the posterior anal verge toward the coccyx. Subcutaneous tissue is divided, and the underlying fibers of the external sphincter are spread with a hemostat clamp. The anococcygeal ligament is then divided to access the postanal space. This fibrous ligament may take a bit of force to separate. A digit is inserted to explore the extent of suppuration. If a horseshoe abscess is present, elliptical counterincisions over the involved ischiorectal fossa are created. Penrose drains can be looped between incisions to maintain patency. If an underlying fistula is noted, a noncutting seton is placed to prevent recurrent sepsis (Fig. 2). A second staged procedure to later address the fistula can be planned.

Intersphincteric abscesses are addressed transanally. The mucosa overlying the bulging/fluctuant anal canal is vertically divided with cautery. This exposes the underlying internal sphincter muscle with its circumferential transversely oriented muscle fibers. A fine-tipped hemostat is passed through the internal sphincter into the suppurative intersphincteric space and directed cephalad. The internal sphincter is divided over the hemostat with electrocautery. This generally does not compromise fecal continence, but patients should be informed of that small risk as part of informed consent. An alternative but less common method involves a stab incision at the anal verge in the intersphincteric groove and insertion of a small mushroom catheter into the affected intersphincteric space. The catheter is removed or backed out after sepsis has resolved.

The source of the supralevator abscess determines its treatment, which is why preoperative imaging can be helpful when a supralevator component is suspected. Descending abdominal or pelvic sources are typically addressed with CT-guided percutaneous drainage; more complex or severe intraabdominal disease may warrant transabdominal surgery or fecal diversion. Ascending cryptoglandular sepsis travels either through the intersphincteric space or through the levators from the ischiorectal fossa. The intersphincteric source is treated with transanal or transrectal drainage; incorrect surgical drainage through the ischiorectal fossa creates a suprasphincteric fistula. Conversely, the supralevator abscess with an ischiorectal source should be drained via skin incision to drain the ischiorectal fossa; transrectal drainage would be inappropriate and create an extrasphincteric fistula. A Malecot catheter may aid drainage of a supralevator abscess when accessed through the ischiorectal fossa (Fig. 3).

Primary Fistulotomy

Fistulotomy at the time of incision and drainage of the anorectal abscess was once a contentious issue. Proponents argued that the presence of sepsis aided in defining the fistula tract; laying open the tract would reduce recurrence. Edema and inflammation from the suppurative process, however, may increase the risk of creating a false tract when probing and can make it difficult to accurately assess the degree of sphincter involvement. A general consensus has been reached, however, that primary or "prophylactic" fistulotomy submits a majority of patients who would never have recurred or developed a fistula to sphincterotomy and its attendant risks of fecal incontinence. Primary fistulotomy should only be selectively performed in the most straightforward of superficial or low

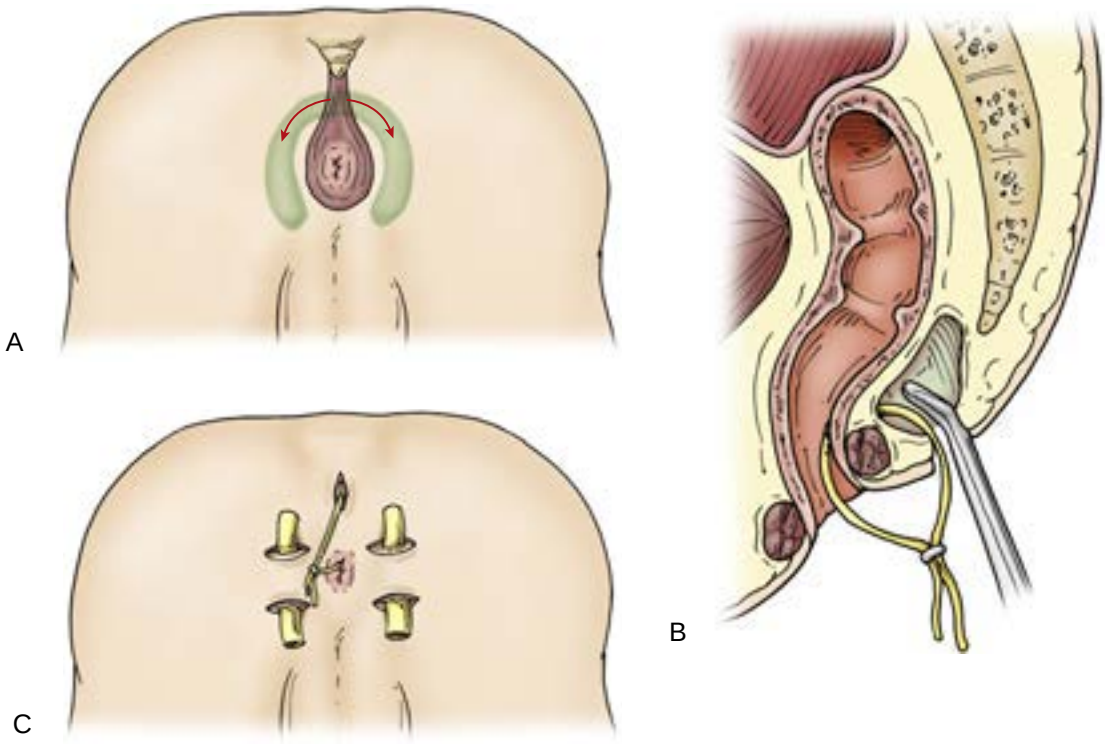


FIG. 2 **(A)** Horseshoe abscess shows that the deep postanal space is a window to the ischiorectal fossa bilaterally *(arrows)*. **(B)** The deep postanal space is drained through a radial incision in the posterior midline. A clamp is placed in the postanal space to ensure adequate drainage. If an internal opening is identified, a seton is placed through the fistula tract, encircling the posterior sphincter. **(C)** Counterincisions drain the ischiorectal fossa. Placement of Penrose drains through the tracts ensures adequate drainage of the abscess cavities without significant soft-tissue loss. *(Courtesy Gaio Lakin, PhD.)*

transsphincteric fistulas, and provided that the anticipated benefit of healing outweighs the potential risk of fecal incontinence. Care must be taken to avoid creating false passages in the inflamed field while searching for the internal opening. Once the tract is cannulated with a fistula probe, the overlying tissue is divided and the wound is left open to drain. Primary fistulotomy is contraindicated in the elderly and in women with anterior fistulas, as well as in patients with compromised fecal continence, Crohn's disease, AIDS, and high transsphincteric fistulas.

If a fistula is easily identified at the time of abscess drainage, an alternative treatment option is partial fistulotomy and seton placement. Although this commits the patient to a second-stage procedure, draining seton placement should prevent recurrent anorectal sepsis and, once healed, allow the surgeon to assess the patient's anorectal function and tolerance of a second-stage fistulotomy or plan for a different fistula repair.

Antibiotics and the Immunocompromised Patient

Most patients do not require antibiotic therapy after surgical drainage; antibiotics in general do not improve healing, reduce recurrence, or definitively decrease fistula formation after appropriate surgical drainage. In certain populations, however, antibiotics are warranted. Patients with large areas of cellulitis, signs of systemic sepsis or shock, prosthetic heart valves, or various conditions of immunocompromise warrant prolonged oral or parenteral antibiotics. Immunocompromised patient groups include those with diabetes mellitus, chronic corticosteroid use, acquired immunodeficiency syndrome, bone marrow transplant recipients, and active chemotherapy.

In contrast with all other patients with anorectal infection, profoundly neutropenic patients are often not addressed with surgery. The degree and duration of neutropenia is directly related to the incidence and prognosis of anorectal infections. In general, patient with absolute neutrophil counts (ANC) below 500 per cubic millimeter often do not mount sufficient immune response to develop suppuration. Therefore, patients with a low ANC and without fluctuance do not have a target for surgical drainage; prolonged, broad-spectrum antibiotics are recommended. Efforts to correct the neutropenia by holding chemotherapy and by administering neutrophil growth factors are employed. This vulnerable patient population must be monitored closely, given that a suppurative process may develop as the neutrophil count increases; imaging or EUA with aspiration may be useful adjuncts to identify a drainable source. Progressive sepsis, obvious fluctuance, or expanding soft tissue infection are indications for surgical evaluation, drainage, or debridement.

Necrotizing Perianal Skin Infection

Necrotizing perianal skin infections are destructive, life-threatening infections that must be quickly differentiated from the more common anorectal abscess and infection on initial presentation because immediate surgical debridement offers the only chance at survival. Rapid development of severe anorectal pain that is out of proportion to findings on examination is the classic harbinger of a necrotizing infection. Risk factors include diabetes, chronic renal disease, obesity, smoking, underlying neurologic disease (such as dementia or spinal cord injury) that prevents early detection or communication of symptoms, and previous anorectal infections. Tender, irregular red, violaceous, or black macules and blisters in the perianal region are early signs of this dangerous process. These infections may be associated with crepitus, induration, or gangrene. Septic shock and electrolyte disturbances may develop. Anorectal sepsis with severe systemic manifestations should be quickly recognized and evaluated in the operating room; radical debridement of all nonviable tissue is

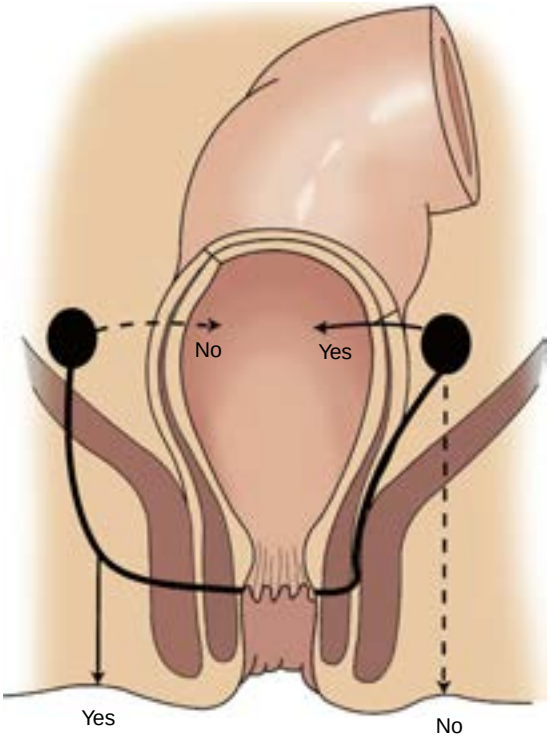


FIG. 3 Drainage of a supralevator abscess *(black ovals).* On the right, the supralevator abscess is associated with a transsphincteric fistula and passage through the ischiorectal fossa; often there are associated findings of an ischiorectal abscess. This abscess is drained via the skin and ischiorectal fossa; transrectal drainage would be inappropriate because it would result in an extrasphincteric fistula. On the left, the supralevator abscess is associated with an intersphincteric fistula and should be drained transrectally; drainage across the ischiorectal fossa would create a suprasphincteric fistula. Supralevator abscesses also may be addressed via computed tomography–guided percutaneous drainage (alone or in combination with transrectal/transgluteal approaches), particularly when they are caused by downward extension of an intraabdominal process such as diverticulitis. *(From Yeo CJ, et al.* Shackelford's Surgery of the Alimentary Tract. *ed 7. Philadelphia: Saunders; 2007.)*

necessary. Patients will require supportive management in the intensive care setting and empiric coverage with broad-spectrum antibiotics. Transfer to a tertiary center with hyperbaric oxygen capability should be considered if infection persists after initial debridement. By limiting the growth of anaerobic and other forms of bacteria and by boosting the effects of antibiotics and the immune system, hyperbaric oxygen is emerging as a powerful adjunct in treating this disease process and promoting healing. The need for fecal diversion is debatable and should only be considered in the subacute setting after hemodynamic stability is well established.

FISTULA-IN-ANO

Etiology and Classification

The cryptoglandular theory suggests that the acute suppurative process of anorectal sepsis originates at one of 8 to 10 anal glands located at the dentate line. These glands originate in the intersphincteric space and penetrate the internal sphincter with their ducts. They can become blocked and allow bacteria to cause infections which propagate along the path of least resistance until the growing pressure is released by surgical or spontaneous drainage. A fistula is the chronic sequelae of this process if the tract fails to heal and epithelializes. Although the cryptoglandular process is responsible for the vast majority of fistulas, other etiologies can instigate chronic inflammation and epithelialization along an abnormal communication between the skin and anorectum (see Box 1).

Although a perianal abscess is described by the anatomic space in which it forms, an anal fistula is most commonly classified in terms of its relationship to the internal and external anal sphincters. In 1976, Park et al. published the classification system that is used currently. Figure 4 depicts the four classes of fistulas. Each of these fistula classes can be further complicated by the presence of circular and/or high blind tracts that branch off the fistula tract into the intersphincteric space or ischiorectal fossa, but do not drain independently. Another type of fistula not included in the anorectal classification scheme is the superficial fistula, which is essentially a skin bridge with an underlying subcutaneous tract that does not involve the sphincter complex; this can be a result of scarring after recurrent infections and surgery, premature healing of an anal fissure, or another process, such as hidradenitis.

Fistulas can be further categorized as "simple" or "complex" fistulas. A complex fistula has features that increase the risk of recurrence and/or incontinence after intervention, either by its own anatomy or by patient factors. Table 1 defines features of complex fistulas, which includes most fistula classes except subcutaneous, intersphincteric, or low transsphincteric fistulas.

Presentation and Diagnosis

Patients will frequently, although not always, have a history of a previous perianal abscess that spontaneously drained or required surgical intervention; patients may experience initial healing and have a recurrent abscess or other symptoms weeks, months, or even years after the index infection. Some patients will experience continual drainage and intermittent swelling months after recovering from an acute abscess, indicating a persistent tract from the internal opening to an either open or closed external opening.

Patients describe intermittent anal pain, pruritis, drainage that is mucoid, bloody, or feculent, or occasionally blood per rectum caused by friable granulation tissue at the internal opening. Cyclic discomfort and swelling that is relieved after spontaneous drainage is a common feature. Patients should be queried regarding gastrointestinal symptoms suggestive of inflammatory bowel disease and their current level of fecal continence. A history of anal surgery, anal infections, radiation, trauma, obstetric trauma, and systemic disease including inflammatory bowel disease, hematologic malignancy, or immunosuppression should be elicited, given these factors may affect continence and healing with many types of surgical interventions. On examination, the external opening is easily identifiable as an inflamed pyogenic granuloma; a palpable cord may be present and suggest the path of the tract. When less active, the external opening may be more subtle and appear more like a subtle dimple or scar. The internal opening can occasionally be palpated on digital rectal examination as a nodule or pit and is usually at the dentate line. Anoscopy, when tolerated, can assist in visualizing the internal opening as well as assess whether a distal proctitis is present. Further endoscopy can be considered in a patient with symptoms suggestive of inflammatory bowel disease.

Routine diagnostic imaging is typically unnecessary for patients with anal fistula, however imaging may be helpful in patients with a suspected occult anorectal abscess, recurrent or complex fistula, an unrevealing EUA, or suspected or confirmed anal Crohn's disease. Preoperative endoanal ultrasound (EAUS) may help preserve anorectal function by measuring sphincter involvement; EAUS can successfully predict the amount of sphincter that would be divided if primary fistulotomy is performed as well as identify undrained sepsis, complex anatomy, and high blind tracts (Fig. 5). MRI appears to have higher sensitivity in evaluating secondary extensions, suprasphincteric tracts, and extrasphincteric tracts in complex fistulas when compared to EAUS and has been shown to alter surgical

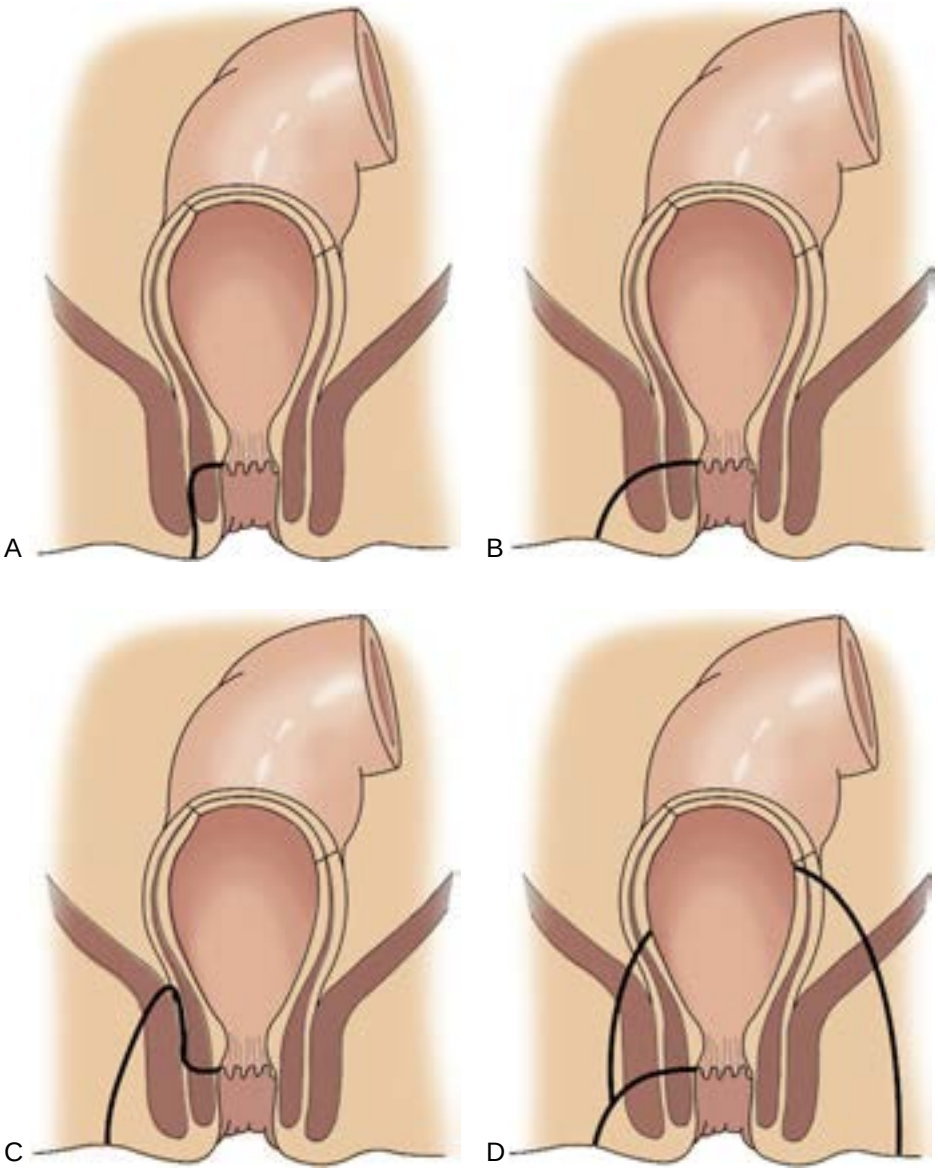


FIG. 4 Classification of anal fistulas. **(A)** Intersphincteric: the tract remains in the intersphincteric plane. **(B)** Transsphincteric: the fistula tract passes from the intersphincteric plane through the external sphincter muscle. *1*, uncomplicated. **(C)** Suprasphincteric: there is an upward extension of the fistula tract in the intersphincteric plane. The tract then passes above the level of the puborectalis muscle and continues downward through the ischiorectal fossa to the perianal area. **(D)** Extrasphincteric: there is a tract that passes from the skin of the perineum through the ischiorectal fossa and the levator muscles before entering the rectal wall. This fistula may be a consequence of an extension of a transsphincteric fistula or secondary to trauma, anorectal disease, or pelvic inflammation. *(Modified from Yeo CJ, et al.* Shackelford's Surgery of the Alimentary Tract. *ed 7. Philadelphia: Saunders; 2007.)*

TABLE 1 Features of Complex Fistulas

Anatomy	Comorbid Conditions
Multiple fistulas	Compromised fecal continence
Suprasphincteric fistulas	Inflammatory bowel disease
Extrasphincteric fistulas	Refractory diarrhea
Associated high blind tract(s)	Anterior fistulas in women
High transsphincteric fistulas (>30% of anal sphincter length)	Immunodeficiency or compromised wound healing
	History of regional radiation
	History of obstetric trauma
	Elderly patients
	Prior anorectal surgery

approach and decrease recurrence rates. Transperineal ultrasound may be a lower-cost, less-invasive imaging option with similar diagnostic accuracy compared to EAUS and MRI, although it is less widely available. CT lacks adequate resolution to identify tracts and their relationship to the sphincters and levators with comparable accuracy. When imaging is indicated, the best option may be based on local radiologic expertise.

Surgical Treatment

There are four tenets of fistula surgery: (1) define the fistula anatomy, (2) ensure the resolution of sepsis, (3) assess and preserve anal sphincter function, and (4) minimize recurrence risk. Maintaining these principles are critical at each step of treatment.

Define Fistula Anatomy

The anatomy of a fistula includes the internal and external openings, the course of the intervening tract(s), and the presence of any blind tracts or sinuses. The internal opening is described by its location

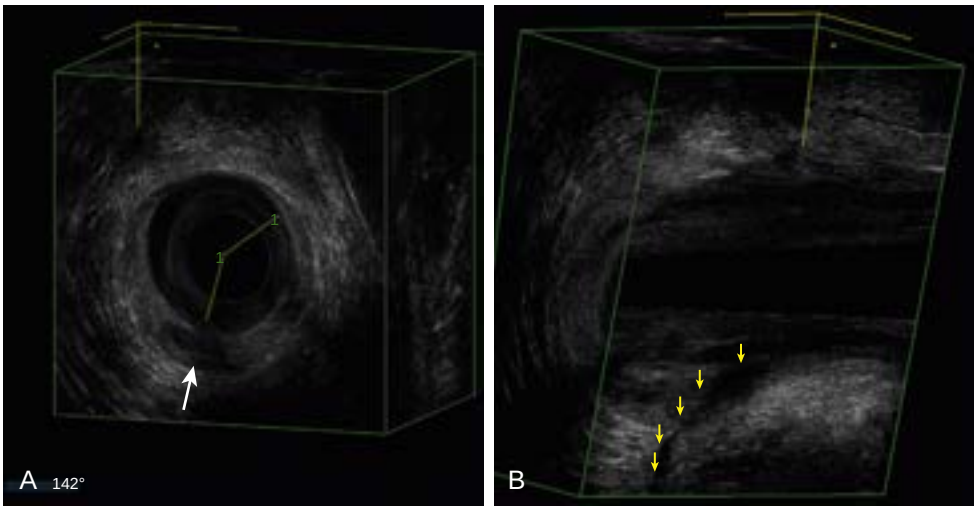


FIG. 5 Ultrasound scan of right posterior transsphincteric fistula. (A) Coronal view revealing a 142-degree internal sphincter defect on the left side from a previous hemorrhoidectomy. The hypoechoic internal opening of a right transsphincteric fistula is noted by the *arrow*. Given the edge of the internal sphincter defect abuts the fistula tract, ligation of the intersphincteric fistula tract procedure may not be feasible. **(B)** Angled sagittal view showing the hypoechoic transsphincteric fistula. Note the internal opening *(arrows)* nears half the length of the hyperechoic external sphincter; therefore, a fistulotomy would not be appropriate. *(Courtesy Amy Thorsen, MD.)*

and relationship to the dentate line, whereas tracts are delineated by their relationship with the sphincter complex and levators. Fistula anatomy can be estimated by office examination but is most definitively assessed in the operating room with an EUA. The patient may usually be consented for a definitive procedure, with the caveat that if a more complex fistula or unexpected findings are discovered during operative evaluation, a staged procedure may be required to preserve sphincter function and ensure successful surgical treatment. The patient is placed in the prone jack-knife position with the buttocks taped widely apart; some surgeons prefer high lithotomy or left lateral positioning. The perianal region is inspected, identifying evident external openings, suspicious lesions, or scars, which can be probed. Goodsall's rule predicts that an external opening posterior to a transverse line across the anus drains to a posterior midline internal opening, while those that open anterior to the line have short, radial courses to the internal opening. Although Goodsall's rule is accurate for a majority of the posterior external openings, it has been shown to be less accurate in women with anterior openings.

Digital rectal examination is performed to assess for undrained sepsis and location of the internal opening. Anoscopy is used to identify the internal opening and to note any signs of proctitis or malignancy. A fistula probe is inserted into the external opening and gently advanced toward the anticipated internal opening with subtle redirection as resistance dictates. The fistula tract should easily accept the probe without the sensation of tissue destruction; a false tract must not be created as it will only serve to complicate the disease and neglect the primary tract. The internal opening may also be identified by injecting dilute hydrogen peroxide into the external opening with an angiocatheter. If the internal opening is not easily identified, the surgeon should not persist to find or create one. Once the internal and external openings are identified, the tract can be cannulated with the fistula probe; if the tract is not cannulated fully, the tract may be curved. Curving the fistula probe or straightening the tract with a Kocher clamp may facilitate cannulation. Once cannulated, the type of fistula is established by determining its relationship to the internal and external sphincter complex, the levators, and presence of multiple fistulas or blind tracts. The percentage of sphincter complex caudal to the tract is determined by palpating the apex of the sphincter complex in relationship to the probe. Low transsphincteric fistulas are defined as those that involve less than 30% of the external sphincter complex.

If the tract cannot be fully cannulated, the external opening is enlarged toward the anal verge, a curette is used to debride the tract, and the operation is terminated. This approach may be associated with a higher risk of recurrence but avoids creating an iatrogenic false internal opening at a false location. Adjunctive imaging with ultrasound or MRI to better identify fistula anatomy is performed after 3 to 6 weeks to allow for inflammation related to surgery to subside.

Ensure the Resolution of Sepsis

For many patients with complex fistulas or an obvious fistula at the time of operative treatment of anorectal sepsis, a conservative, staged approach with the initial placement of a seton is most appropriate. This allows the possibility of multiple options to treat the fistula in the future without compromising sphincter integrity.

For a patient treated initially with a seton, a second-stage procedure can be considered when the internal opening is less than 5 mm and the tract is simple, narrow, and without an associated cavity. Ongoing sepsis, as evidenced by pus, cellulitis, induration, or a persistent cavity, prevents healing and closure of the tract; any efforts to close the fistula definitively will likely fail. In the setting of persistent infection, a fistulotomy can be performed only in a simple intersphincteric or low transsphincteric fistula to simultaneously address the sepsis and the fistula. Complex fistulas with persistent sepsis should be considered to have an undrained source of infection. They can be addressed with debridement of the tract around the seton, widening of the external opening, and a search for a high blind or circular tract. If additional treatable sources of the persistent sepsis cannot be identified or sepsis continues despite these approaches, imaging is pursued.

Assess and Preserve Anal Sphincter Function

Although a controlled anal fistula with or without a seton can cause significant discomfort and problems with personal hygiene, fecal incontinence is far more disruptive to a patient's quality of life. For that reason, preservation of continence is always a priority when choosing the proper management strategy. Division of the internal

TABLE 2 Management Strategy by Fistula Classification

Type of Fistula	Fistulotomy	Seton*	LIFT	Advancement Flap	Fibrin Glue	Collagen Plug	Address Intraabdominal or Pelvic Source
Superficial/intersphincteric	X						
Low transsphincteric	X	X	X	X	X	X	
High transsphincteric		X	X	X	X	X	
Suprasphincteric		X		X		X	X
Extrasphincteric						X	X

LIFT, Ligation of intersphincteric fistula tract.
*Seton placement can be a first stage or definitive treatment option.

sphincter is usually well tolerated without much effect on continence, especially in men. Division of the distal third of the external sphincter is considered "safe" in healthy male individuals; this can be considered in the posterior external sphincter in women without preexisting sphincter dysfunction. The degree of sphincterotomy tolerated without affecting continence is undoubtedly patient-dependent. Careful analysis of a patient's risk for incontinence includes an assessment of their current degree of continence, prior anorectal surgery, trauma, and obstetric history as well as associated conditions that may cause diarrhea or inhibit healing. Women in particular are vulnerable to incontinence as a result of a shorter sphincter complex, anatomic and neurologic injury to the pelvic floor sustained during childbirth, and loss of elasticity and muscle attenuation associated with aging and menopause. Patients with active inflammatory bowel disease involving the anorectum and immunodeficiencies often heal poorly and suffer recurrent or metachronous fistula disease. Sphincter-preserving techniques are preferred in these patient populations. Table 2 provides a guide to choosing the proper surgical technique, although it does not take into account relevant patient factors.

Minimize Recurrence Risk

Complex fistulas are a frustrating disease process because they are prone to recurrence despite meticulous surgical technique. Although primary fistulotomy has the lowest recurrence risk, it also is associated with the highest risk of incontinence because of inherent disruption in the sphincter complex. All other sphincter surgical procedures, although they preserve the muscular anatomy, are associated with much higher recurrence risk. This must be considered in an informed consent discussion with patients. Reported outcomes in many of these described procedures vary widely; a surgeon's personal experience with a procedure may be the most important factor in reducing recurrence.

Fistulotomy

Fistulotomy can be done at the time of abscess presentation, at the time of initial fistula presentation, or as a second-stage procedure in appropriately selected patients. Regardless of timing, a fistulotomy is only appropriate in low-risk patients with a superficial, intersphincteric, or low transsphincteric fistula. Once the anatomy of the fistula is determined, the tract is cannulated and the tissue overlying the probe is divided with electrocautery. The tract is debrided with a curette to remove debris and granulation tissue. The deepithelialized wound, now effectively a ditch instead of a tunnel, is allowed to heal by secondary intention.

For larger wounds, wound healing can be accelerated and bleeding avoided by marsupialization of the wound; this is performed by sewing the wound edges to the base of the wound with a continuous locking absorbable suture. Marsupialization can prevent both the premature epithelization of the wound edges before the deeper base heals and the subsequent formation of a subcutaneous fistula.

Sphincter-sacrificing procedures have the highest success rates, generally over 90%, but are also associated with some degree of fecal incontinence in up to 40% of patients in some series. Hence fistulotomy is usually not appropriate for high or complex fistulas. Factors related to recurrence after fistulotomy include branching of fistulas, failure to accurately identify the internal opening, and fistulas associated with Crohn's disease.

Seton

A noncutting seton allows for ongoing drainage of sepsis and promotes fibrosis and maturation of the fistula tract as well as resolution of any abscess cavity, often in preparation for a second-stage procedure. After the fistula tract has been defined and debrided, the external opening is opened slightly toward the anal verge. Circular, high blind tracts, and long subcutaneous tracts are appropriately laid open or drained and curetted. A thin silastic band, vessel loop, or nonabsorbable suture is threaded through the tract and secured in a loop or omega shape with several interrupted silk sutures. The seton should not be tight; a hemostat should easily fit between the skin and loop without tension. The second-stage procedure, either fistulotomy or a sphincter-preserving operation, is usually performed 6 to 10 weeks later, although a waiting period of 3 to 4 months is advised for more complex fistulas and abscess cavities. Setons used in this fashion for complex fistulas have success rates of 62% to 100%, depending on patient factors and the choice of the secondary procedure. For some Crohn's or other high-risk patients, seton placement can be the definitive operation; it is left in place for prolonged periods (years) to prevent recurrent sepsis without the intention to perform a second-stage procedure due to the likelihood of failure or iatrogenic incontinence.

In rare situations, a seton can be used to perform a slow, controlled fistulotomy in complex fistulas. Historically, a cutting seton was used when the risk of incontinence from a traditional fistulotomy was considered to be too high. The cutting seton is tightened at interval office visits to gradually divide the fistula and involved sphincter muscle. Cutting setons have high success rates in resolving anal fistulas, however some studies report some level of impaired continence in up to 67% of treated patients. Hence cutting setons should be used very selectively.

LIFT

Ligation of the intersphincteric fistula tract (LIFT) is a relatively new sphincter-preserving technique first described in 2007. This procedure is most often performed as a second-stage procedure for a transsphincteric fistula after a mature tract has developed. A draining seton may be used before the LIFT procedure to allow for fibrosis of the tract, but this has not been clearly shown to affect the success rate of the LIFT procedure.

With the patient in the prone jack-knife position with the buttocks taped widely apart, the fistula tract is cannulated with a probe. The external opening is widened to allow for drainage (Fig. 6). A 1- to 2-cm curvilinear incision is made with electrocautery over the palpated intersphincteric groove superficial/distal to the fistula tract. A Lonestar retractor (CooperSurgical) deployed along the anoderm edges provides excellent exposure. The intersphincteric

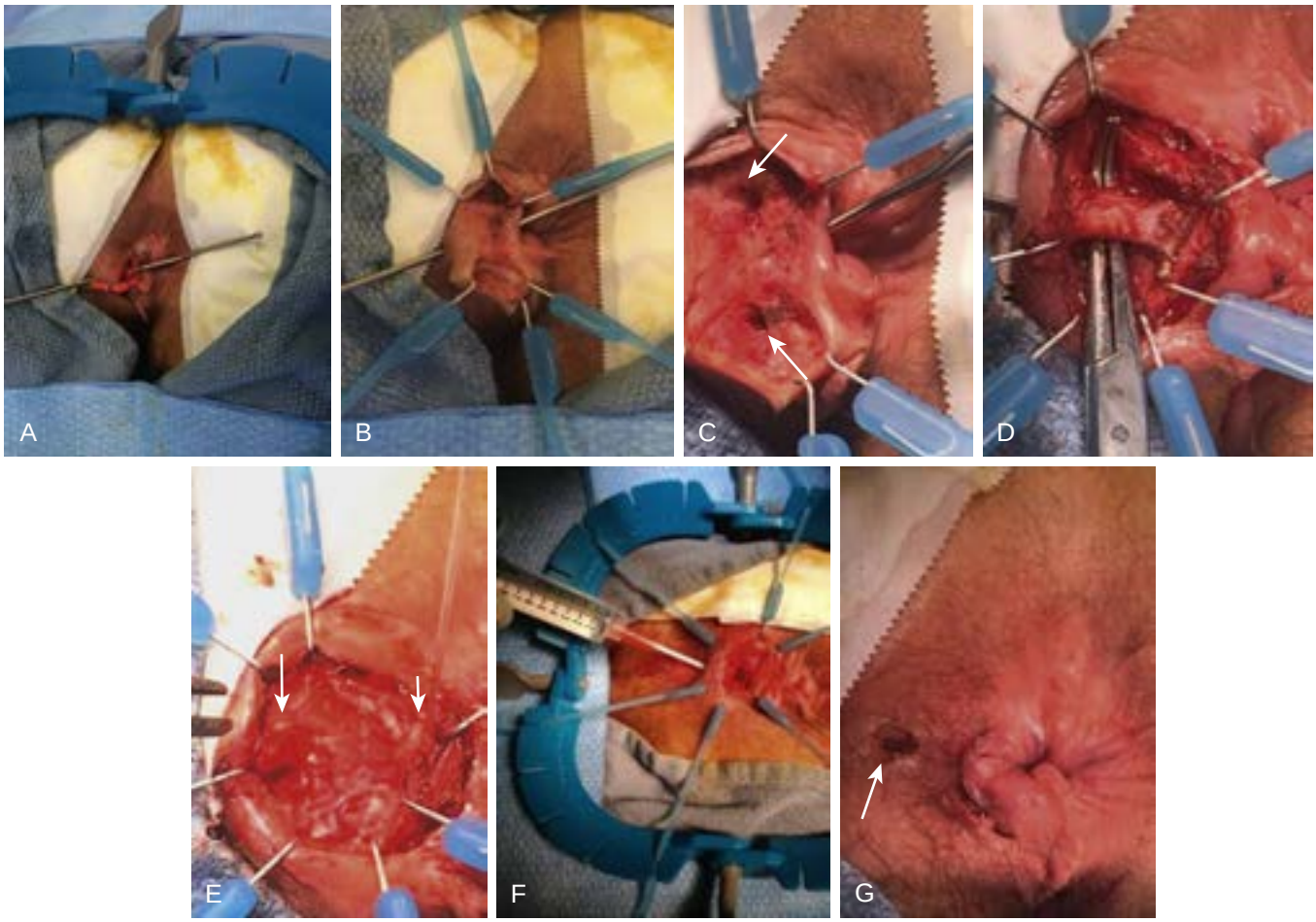


FIG. 6 **(A)** The fistula tract is cannulated. **(B)** A curvilinear incision is made overlying or slightly distal to the intersphincteric groove. A Lone Star retractor (Cooper Surgical) is helpful for exposure. **(C)** The intersphincteric plane is developed on either side of the tract *(arrows)*. **(D)** Dissection continues around the tract until it is isolated. The probe is removed. **(E)** Division and ligation of the fistula tract. The tract is encircled with a Vicryl (Ethicon) tie, and the tract is ligated at the border of the internal anal sphincter *(right arrow)*. If a long tract is present, it can be excised, and the tract near the external anal sphincter is either ligated or imbricated with Vicryl suture *(left arrow)*. **(F)** The repair is tested by injecting hydrogen peroxide into the internal and external openings. The ligated ends can also be probed to ensure closure. If there is a leak, the fistula opening is further imbricated. **(G)** The external opening *(arrow)* is slightly enlarged, and the distal aspect of the tract is debrided with a curette. *(Courtesy Jeffery J. Morken, MD.)*

plane is bluntly developed with a fine-tipped hemostat. The fistula tract is circumferentially isolated with care to avoid disrupting it. The probe is removed, and both distal and proximal ends of the intersphincteric tract are suture-ligated with 3-0 absorbable suture. The tract is sharply divided with a scalpel. The external opening is injected with hydrogen peroxide; if there is a persistent leak, the intersphincteric opening of the external sphincter is oversewn until there is no longer a leak. Some authors test the internal opening with peroxide as well to ensure proper closure of the proximal portion of the tract. The anoderm is reapproximated with a running absorbable suture. Very high fistula tracts or those that track long distances within the intersphincteric space may be difficult to properly isolate in the intersphincteric plane and not good candidates for this approach.

A meta-analysis of 1378 LIFT procedures from 26 studies demonstrated an overall success rate of 76%, an overall complication rate of 14%, and a low rate of fecal incontinence of 1.4%. Horseshoe anatomy, Crohn's disease, and prior fistula surgery were risk factors for failure. Some failures result in resolution of the external sphincter involvement, converting the fistula to a simple intersphincteric fistula that is more amenable to fistulotomy. Because of this, secondary healing after surgical reintervention can be as high as 77% to 86%.

Endorectal Advancement Flap

The endorectal advancement flap is a sphincter-preserving operation used as a second-stage procedure for high fistula tracts, suprasphincteric tracts, and low tracts in high-risk patients with healthy rectal mucosa (see Table 1). For lesions below the dentate line, fistulotomy or a dermal advancement flap is preferred to prevent the creation of a mucosal ectropion that can form if the rectal mucosa is brought down to near the anal verge. Patients may undergo a preoperative bowel preparation. Performed under general anesthesia, the prone jackknife position is preferred for most fistulas, although the lithotomy position is often used to address posterior midline internal openings. The seton is removed, and the internal opening serves to mark the apex of the flap (Fig. 7). Beginning at the internal opening, a flap is created by distal-to-proximal dissection with electrocautery including mucosa, submucosa, and a few fibers of the internal sphincter (partial thickness). To ensure adequate perfusion, it is crucial that



FIG. 7 Mucosal (Martin's) advancement flap. A longitudinal incision is made over the strictured area in the anal canal. Proximal rectal and anal mucosa are then undermined through a transverse incision starting at the proximal end of a previously made longitudinal incision. The flap is then sutured to the distal edge of the internal anal sphincter, leaving open the most distal aspect of the wound. *(From Liberman H, Thorson AG. How I do it: anal stenosis.* Am J Surg. *2000;179:325.)*

the base (proximal end) of the flap is wide, at least two to three times the width of the apex. The trapezoidal-shaped flap is typically 2 to 4 cm long to allow for tension-free closure caudal to the level of the original internal opening. Care should be taken to avoid excessive handling of the flap, which can result in hematoma formation and tissue compromise. The fistula tract is debrided with a curette, and the external opening is widened to allow for drainage. Absorbable suture is used to close the internal opening, and the integrity of the closure is tested with injection of hydrogen peroxide at the external opening. The tip of the flap with the internal opening is excised, and the flap is gently pulled distally over the internal opening to the dentate line, but not below it, to prevent ectropion formation. Wound edges are reapproximated with interrupted absorbable suture.

Fistula healing after endorectal advancement flap repair is reported in 66% to 87% of patients with cryptoglandular disease. Factors associated with failure include prior radiation, Crohn's disease, active proctitis, prior abscess drainage, rectovaginal fistula, smoking, malignancy, obesity, and having more than one prior attempted fistula repair. An endorectal advancement flap may be repeated after a failed flap procedure or performed after other failed approaches including LIFT, with healing rates that range between 57% and 100%. Changes in bowel continence have been reported in up to 35% of patients treated with the procedure.

Other Continence Preserving Procedures

Synthetic and biologic materials such as fibrin glue and fistula plugs were once promising additions to the armamentarium of fistula treatment. Their general principle is obliteration of the internal opening and fistula tract. Their primary benefit was a minimal risk profile, as they pose no risk to continence, are easily repeated in the case of recurrence, and do not preclude subsequent surgical management. However, more recent evaluations reveal low success rates, so the procedures as standalone procedures have been relatively abandoned. The use of fistula plugs or biologic mesh has been described to augment the success of the LIFT repair however evidence that this leads to superior results is limited.

Minimally invasive approaches to anal fistulas that use endoscopic or laser closure techniques such as video-assisted anal fistula treatment (VAAFT), fistula laser closure (FiLaC), and endoscopic clipping using an over-the-scope clip (OTSC) device have been described in small, single-institution series with limited follow-up and various degrees of industry support. Although short-term healing appears comparable to LIFT and endorectal advancement flap repairs, long-term results are unavailable. All of these techniques require specialized equipment and expertise, and their use is generally not recommended at this time.

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Anal Stenosis

Chassidy Grimes, MD, and Dana Hayden, MD

BACKGROUND

Anal stenosis is a narrowing of the anal canal. The narrowing can be anatomic, in which normally pliable anal mucosa is replaced with fibrotic tissue. This scarring can be isolated or circumferential and can vary in length. The narrowing can also be functional as a result of a hypertonic internal sphincter. The causes of anatomic stenosis can be further subdivided into congenital, primary, and secondary causes (Box 1). The most common cause of secondary stenosis is surgery, most likely occurring after multiquadrant hemorrhoidectomy when large areas of anoderm are removed. The literature cites that up to 87% of cases are secondary to hemorrhoidectomy (Liberman & Thorson, 2000; Katdare & Ricciardi, 2010; Khubchandani, 1994). Stenosis may also result after procedures such as low anorectal anastomosis or fistulectomy (Chiarelli et al., 2018). This chapter focuses on the diagnosis and management of anatomic secondary anal stenosis.

DIAGNOSIS

The diagnosis of anal stenosis is largely clinical, taking into consideration the patient's surgical and medical history as well as physical examination findings. The patient will often present with complaints such as constipation, obstipation, painful bowel movements, bleeding, and small-caliber stools (Farid et al., 2010; Chiarelli et al., 2018). Alternatively, they can have diarrhea caused by chronic laxative use or overflow from subsequent upstream rectal dilation. It is recommended that an anorectal examination be performed under anesthesia to both minimize patient discomfort as well as distinguish

BOX 1 Causes of Anatomic Stenosis

Congenital

Imperforate anus
Anal atresia

Primary

Senile

Secondary

Postsurgical
Laxative abuse
Inflammatory bowel diseases (Crohn's disease)
Radiotherapy
Tuberculosis
Sexually transmitted infections
Trauma
Chronic diarrhea
Malignancy

TABLE 1 Grading of Anal Stenosis

Severity	Level of Stenosis
Mild: Anal canal can be examined by a lubricated index finger or medium Hill-Ferguson retractor.	Low: Involvement at least 0.5 cm distal to the dentate line
Moderate: Forceful dilation is required to insert a lubricated index finger or medium Hill-Ferguson retractor.	Middle: Involvement 0.5 cm distal and proximal to the dentate line
Severe: Forceful dilation is required to insert a lubricated little finger or small Hill-Ferguson retractor.	High: Involvement 0.5 cm above the dentate line

between a functional and anatomic cause of stenosis. Under anesthesia, the internal sphincter will relax, leading to resolution of the stenosis if it is functional. With true scarring and stricture, the stenosis will remain regardless of muscle relaxation. Anoscopy and proctoscopy can be useful in determining the extent of stenosis and assess the health of the rectal mucosa (Liberman & Thorson, 2000; Katdare & Ricciardi, 2010). It is important to look for any firm tissue, ulcerations, or outgrowths within or surrounding the area of stenosis and biopsy when appropriate to rule out malignancy as a cause. Grading of anal stenosis proposed by Milson and Mazier is based on severity and level of involvement within the anal canal (Table 1). This classification may help guide the next steps in management (Milsom & Mazier, 1986).

MANAGEMENT

Nonoperative Management

Management of anal stenosis depends on severity of stenosis and the patient's symptoms. It is generally accepted to start with conservative measures. This involves management with a high-fiber diet, adequate hydration, and stool softeners. In addition, gradual manual anal dilation can be performed. The initial dilation can be performed under anesthesia with subsequent serial dilation done by the patient at home with a finger or a small plastic dilator. Dilation may be considered controversial given the risk of incontinence, as it may lead to hematoma formation within the intersphincteric space causing further scarring (Khubchandani, 1994). Although there are associated risks, some patients respond well to dilation. It should be considered particularly in cases of Crohn's disease and radiation therapy where large perineal surgical operations are not advised (Kashkooli et al., 2015; Liberman & Thorson, 2000; Lightner et al., 2020). Most cases of mild and moderate stenosis can be managed conservatively. For cases of severe stenosis, it is still recommended to begin with medical management, although patients are likely to require surgery (Brisinda et al., 2009).

Operative Management

Surgical management is considered in cases of moderate to severe stenosis or for those patients who failed medical management. There is a wide variety of options for surgical management. In cases of anastomotic stricture, a step-up approach should be considered. Initially, dilation can be performed, followed by circular stapler resection or stricturoplasty, and then finally transabdominal resection of the anastomosis with repeat anastomosis as the last option (Kraenzler et al., 2017). For other anatomic strictures, anoplasty is the treatment of choice. The overall goal of anoplasty is to divide the stricture and deliver more pliable, healthy anoderm into the area without tension, thereby relieving the stenosis. This can be done with a variety of surgical techniques.

Stricturoplasty

Stricturoplasty involves release of the stricture. The stricture is divided longitudinally and closed transversely. This method can provide symptom relief for the patient but can lead to subsequent scarring and recurrent stenosis (Duieb et al., 2009; Katdare & Ricciardi, 2010).

Mucosal Advancement Flaps

During mucosal advancement flaps, the scar is excised and if there is also scarring of the underlying sphincter, a sphincterotomy is performed (Fig. 1). A transverse incision is made at the dentate line, and the rectal mucosa is undermined and advanced to the distal edge of the internal sphincter to cover the defect (Rakhmanine et al., 2002). The external portion of the wound is left open. Although there is a small risk of mucosal ectropion, this is a good option for midlevel stenosis because of minimal complications and symptom relief (Casadesus et al., 2007).

Y-V Advancement Flap

This technique begins with a Y-shaped incision at the area of stricture, and then it is carried on to the perianal skin, creating a V (Fig. 2). The V portion of the incision is taken down to the

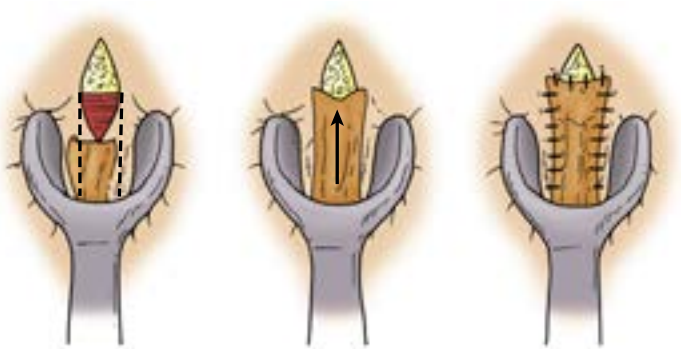


FIG. 1 Mucosal advancement flap. *(From Fleshman JW. Fissure-in-ano and anal stenosis. In: Beck DE, Wexner SD, eds:* Fundamentals of Anorectal Surgery, *ed 2. London: Saunders; 1998.)*

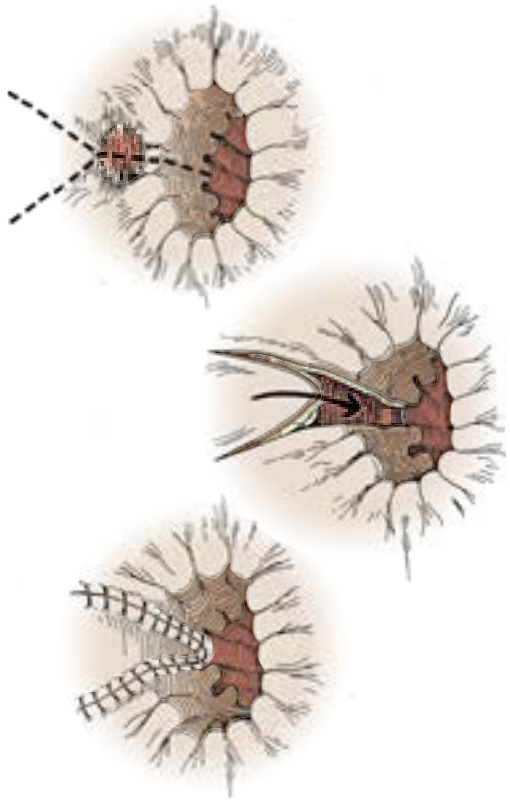


FIG. 2 Y-V advancement flap. *(From Fleshman JW. Fissure-in-ano and anal stenosis. In: Beck DE, Wexner SD, eds:* Fundamentals of Anorectal Surgery, *ed 2. London: Saunders; 1998.)*

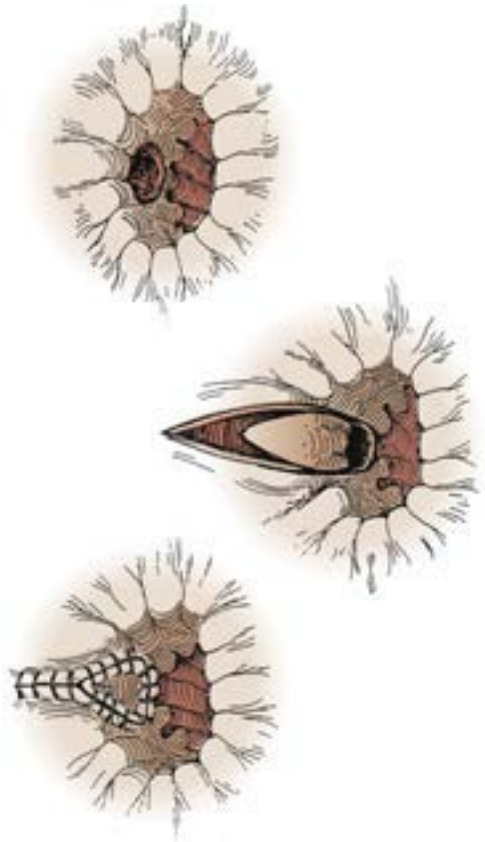


FIG. 3 V-Y flap. *(From Fleshman JW. Fissure-in-ano and anal stenosis. In: Beck DE, Wexner SD, eds:* Fundamentals of Anorectal Surgery, *ed 2. London: Saunders; 1998.)*

subcutaneous tissue, which contains the blood supply to the flap (Gingold & Arvanitis, 1986; Liberman & Thorson, 2000). The apex of the V is advanced into the anal canal and affixed to the internal sphincter and rectal mucosa. This technique can be done bilaterally but is not considered adequate for coverage of a stenosis >25% circumference of the anal canal (Brisinda et al., 2009).

V-Y Advancement Flap

An initial vertical incision is created to incise the scar tissue (Fig. 3). A V-shaped incision is then made with the apex lying on the perianal skin. Similar to the Y-V flap, the V is carried down to the subcutaneous tissue. The broad-based portion is advanced and affixed to the dentate line with the final Y-shaped incision. This technique is useful for the management of low, severe anal stenosis (Angelchik et al., 1993).

House Flap

The initial incision is longitudinal and created from the dentate line to the area of stenosis (Fig. 4). Two transverse incisions of equal width are then created on both ends of the longitudinal incision. A house-shaped flap is then created with the width of the base matching the width of the transverse incisions and is carried down to subcutaneous tissue with the apex overlying the perianal skin. It is then advanced into the anal canal to cover the defect and sutured in place (Christensen et al., 1992). This technique is useful for stenoses that extend from the dentate line onto perianal skin. It also avoids the narrow apex involved in Y-V advancement flaps, which are subject to ischemia (Alver et al., 2008; Casadesus et al., 2007). House flaps can be performed bilaterally and cover large areas of stenosis (Chiarelli et al., 2018).

Diamond-Shaped and U-Shaped Flap

For a diamond-shaped flap, the scar is incised with a vertical incision that is carried on to perianal skin to make a diamond shape (Fig. 5).

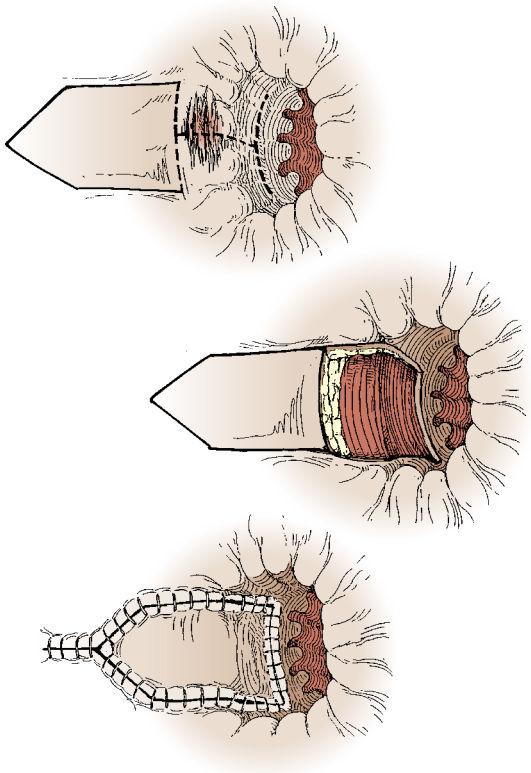


FIG. 4 House flap. *(From Fleshman JW. Fissure-in-ano and anal stenosis. In: Beck DE, Wexner SD, eds:* Fundamentals of Anorectal Surgery, *ed 2. London: Saunders; 1998.)*

The flap is advanced into the anal canal and sutured (Liberman & Thorson, 2000). The U-shaped flap is performed in similar fashion (Fig. 6). It is useful for management of strictures with associated mucosal ectropion, but the donor site is not closed, making it a less desirable technique (Brisinda et al., 2009).

Rotational S Flap

This technique is used is cases of extensive and circumferential anal stenosis that require excision of a large amount of skin (Handaya & Sunardi, 2019) . An S-shaped incision is created, with the midportion carried down to the dentate line transversely (Fig. 7). The wide portions of the S are then rotated down to the dentate line and sutured. One limitation of the S flap is that it does not release the stricture as effectively as the previously described advancement flaps (Brisinda et al., 2009).

POSTOPERATIVE CARE AND COMPLICATIONS

The majority of these procedures can be performed in an outpatient setting but may require admission depending on the extent of dissection or surgeon preference. Postoperative care typically involves adequate pain control, a strict bowel regimen that ensures soft stools, and sitz baths or showers to keep the wounds clean (Chiarelli et al., 2018). Complications include wound infection, flap ischemia, fecal incontinence, failure to correct stenosis, recurrent stenosis, and ectropion (Brisinda et al., 2009; Casadesus et al., 2007). Complication rates are relatively low, and good patient satisfaction has been demonstrated with diamond, Y-V, and house flaps (Farid et al., 2010).

SELECTION OF SURGICAL TECHNIQUE

Given the multitude of options, Duieb et al. described an algorithmic intraoperative approach to deciding which technique to use. First, an initial longitudinal incision through the stricture is created, assessing

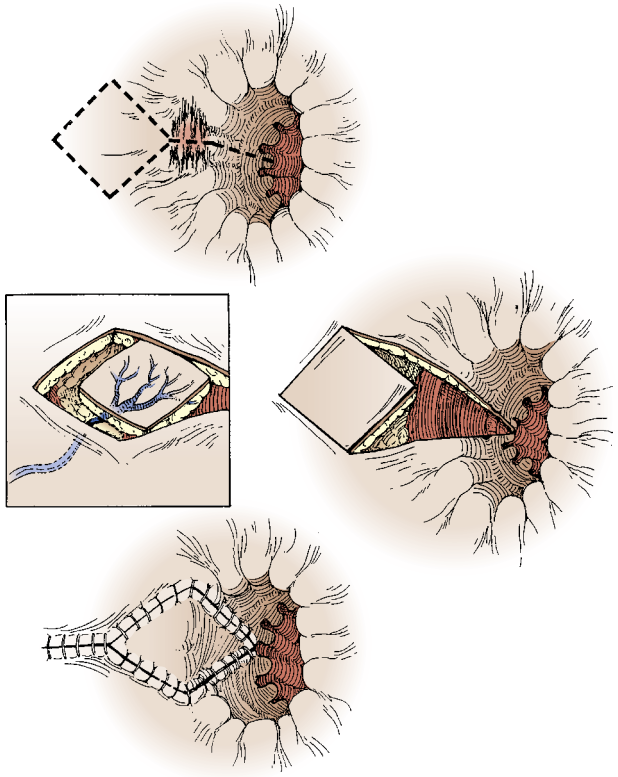


FIG. 5 Diamond flap. *(From Fleshman JW. Fissure-in-ano and anal stenosis. In: Beck DE, Wexner SD, eds:* Fundamentals of Anorectal Surgery, *ed 2. London: Saunders; 1998.)*

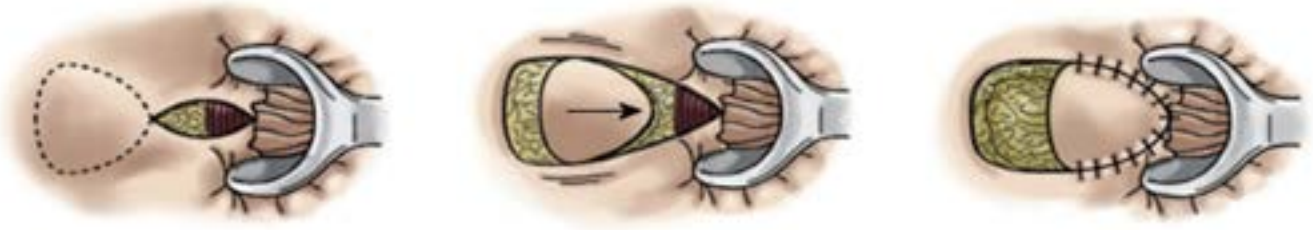


FIG. 6 U flap. *(From Fleshman JW. Fissure-in-ano and anal stenosis. In: Beck DE, Wexner SD, eds:* Fundamentals of Anorectal Surgery, *ed 2. London: Saunders; 1998.)*

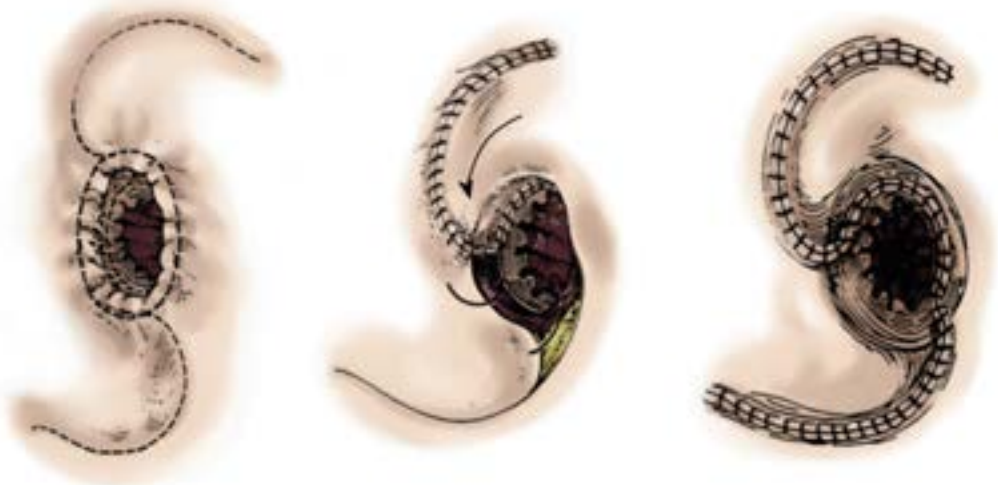


FIG. 7 Rotational flap. *(From Fleshman JW. Fissure-in-ano and anal stenosis. In: Beck DE, Wexner SD, eds:* Fundamentals of Anorectal Surgery, *ed 2. London: Saunders; 1998.)*

for a sphincter component, and sphincterotomy is performed when necessary. Next, primary transverse closure is attempted if there is no tension. If excessive tension is present, then a Y incision is created via extension of the initial longitudinal incision, and a Y-V flap is attempted. If there is continued tension, the Y incision is extended to create a diamond flap. Even though low complication rates were reported, this approach was only performed in a small subset of patients and by only one surgeon (Duieb et al., 2009). It does not consider the different patterns and extent of stenosis and is solely based on tension. Farid et al. reported on 60 patients with anal stenosis. They demonstrated that house flap reconstruction achieved greater anal caliber while maintaining continence and significantly improved quality of life when compared with Y-V and diamond-shaped flaps (Farid et al., 2010). In conclusion, there is no clear consensus on which technique is superior. Selection of approach is ultimately based on surgeon experience and should be individualized based on surgical history and anatomy, taking into consideration the benefits and limitations noted with each of the procedures.

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Management of Pruritus Ani

Matthew D. Price, MD, and Chady Atallah, MD

DEFINITION

Pruritus ani is a dermatologic condition characterized by an itching or burning sensation of the perianal region. Although this condition can be seen in any age group, patients often present in their third to fifth decade of life after having attempted multiple over-the-counter or home remedies with little success. Pruritus ani affects 1% to 5% of the population with a male-to-female ratio of 4:1. Primary idiopathic anal pruritus is responsible 50% to 90% of the time. Secondary causes include infections or infestations, dermatologic inflammatory diseases, premalignant and malignant neoplasms, and benign anorectal or systemic diseases (Box 1).

ETIOLOGY

Primary/Idiopathic Pruritus Ani

Primary or idiopathic pruritus ani is diagnosed after all secondary causes have been ruled out and no pathologic etiology can be identified. Fecal soilage, moisture, and various nonspecific offending agents are thought to act as triggers. C-fibers, a class of nonmyelinated nerve fibers found in the somatic sensory system, are believed to play a key role. Scratching to relieve the itch is known to cause further excoriation and inflammation, which leads to further stimulation of nerve fibers. This process is known as the *itch-scratch cycle*. A key step in treating this condition is breaking the itch-scratch cycle. Additionally, increased levels of histamine, bradykinin, and kallikrein have been associated with the condition.

Certain foods have been associated with primary/idiopathic pruritus ani including coffee, caffeinated beverages, citrus fruits, chocolate, alcoholic beverages, tomatoes, and spicy foods (Box 2). These foods have been shown to alter bowel habits and can act as irritants to the perianal skin.

Secondary Pruritus Ani

Infectious

Fungal infections, particularly Candida, are relatively common causes of pruritus ani with an estimated frequency of 10% to 43%. Similar to most fungal infections, these usually occur in moist or sweaty environments such as skin folds in elderly or obese patients. Immunosuppressed patients or patients taking antibiotics are more prone to developing Candida-related anal pruritus. Antifungal powder, good hygiene, and keeping the affected areas dry are important steps in treatment. Oral antifungals can be used in cases of severe infections. Several case reports have associated streptococci and *Corynebacterium minutissimum* with pruritus ani, but they are found much less commonly than fungal infections.

Sexually transmitted diseases are common causes, particularly in patients practicing anoreceptive intercourse. *Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum,* herpes, *Molluscum contagiosum,* and *Condyloma acuminatum* have all been implicated.

BOX 1 Causes of Secondary Pruritus Ani

Infectious
Bacterial infection (Staphylococcus, Streptococcus, Erythrasma)
Sexually transmitted infection (Gonococcus, Chlamydia)
Fungal infection (Candida, dermatophytes)
Parasites (pinworms, scabies)
Viral infection (Herpes virus, Condylomata, Molluscum)

Dermatologic
Contact dermatitis
Atopic dermatitis
Perianal psoriasis
Lichen sclerosus
Seborrheic dermatitis

Anorectal
Hemorrhoids (external, prolapsing internal)
Fistula-in-ano
Anal fissures
Hidradenitis suppurativa
Fecal incontinence
Perianal Crohn's disease
Skin tags
Chronic diarrhea
Pilonidal disease

Malignant
Anal canal cancer
Anal margin cancer
Rectal cancer
Bowen's disease
Extramammary Paget's disease

Systemic Disease
Diabetes mellitus
Leukemia
Lymphoma
Chronic renal failure
Iron-deficiency anemia
Hyperthyroidism
Hyperbilirubinemia

BOX 2 Food Products That Contribute to Pruritus Ani

Caffeine-containing products (colas, coffee, tea, energy drinks)
Citrus fruits and vegetables
Carbonated beverages
Chocolate
Tomato
Beer
Spicy and acidic foods
Refined carbohydrates
Nuts

Parasitic perianal infections are rare including pinworm *(Enterobius vericularis),* scabies *(Sarcoptes scabiei),* and pediculosis pubis. Nocturnal pruritus ani in children is characteristic of pinworm infections. The nematodes of the pinworm usually reside in the large intestine during the day then lay their eggs in the perianal region at night, resulting in local irritation. Oral albendazole is used for treatment.

Dermatologic

Eczema, or atopic dermatitis, is the most common dermatologic condition responsible for anal pruritus. It is usually an allergic response to a wide variety of inciting agents including laundry detergents or topical creams. Identifying the inciting factor can be difficult, but eliminating exposure is key to treatment.

Psoriasis can cause anal pruritus, although it more commonly affects extensor surfaces of the extremities. Several series show that 4% to 8% of patients presenting with pruritus ani have psoriasis. Treatment of psoriatic anal pruritus involves topical steroids for brief symptomatic improvement followed by maintenance topical calcipotriene, salicylic acid, or ultraviolet light.

Other less common dermatologic causes of pruritus ani include lichen sclerosus, seborrheic dermatitis, lichen planus, and lichen simplex chronicus.

Anorectal Diseases

Benign anorectal conditions such as external and internal hemorrhoids, anal fissures, fistulae, hidradenitis suppurativa, perianal Crohn's disease, anal skin tags, and pilonidal disease are commonly found in patients with pruritus ani. Management of the specific condition is associated with improvement in pruritus.

Malignant or premalignant anorectal processes can result in pruritus ani and should be considered at presentation including cancers of the anal canal, anal margin, or even the lower rectum. Bowen's disease (perianal squamous cell carcinoma in situ) and Paget's disease (cutaneous adenocarcinoma in situ) are the most common premalignant lesions. If Paget's disease of the anal canal is discovered, further endoscopic evaluation of the colon is needed to rule out an underlying carcinoma.

Miscellaneous

Other causes of anal pruritus include radiation-induced perianal dermatitis from cancer treatments, systemic diseases including uremic or cholestatic pruritus, and excessive moisture of the perianal skin from urinary incontinence or vaginal discharge. Treatment is dependent on the specific condition.

EVALUATION AND DIAGNOSIS

History

Evaluation of a patient presenting with anal pruritus begins with a thorough history and physical examination. Patients can present with a range of symptoms from mild irritation to severe, unrelenting pain. Timing of symptoms can vary from worsening pruritus with bowel movements to persistent pruritus throughout the day, or even nocturnal symptoms. Bleeding can be present, though anything more than spotting on toilet paper would warrant further workup for other pathologies. Symptoms can be longstanding or recent onset. Patients usually present to a specialist after having trialed several forms of treatment either on their own or as directed by their previous providers. A patient's bowel and cleansing habits should be discussed, including bowel frequency, diarrhea, anal incontinence, excessive wiping, scented soaps, or prepared wipes. Sexual history should be ascertained. Dietary habits should also be assessed for potential triggers (see Box 2).

Physical

Physical examination begins with inspection of the perianal area, perineum, and genitalia. Physical findings can range from completely normal to severe widespread excoriations. The Washington Criteria has often been used to stage the appearance of perianal skin according to severity of disease and should be documented with each encounter to track treatment response (Table 1). Secondary causes

TABLE 1 Washington Hospital Staging Criteria

Stage 0	Normal-appearing perianal skin
Stage I	Erythematous and inflamed perianal skin
Stage II	White, lichenified perianal skin
Stage III	Lichenified skin with coarse ridges and ulceration

must be ruled out with anoscopy, and when indicated cultures or biopsies should be taken. Indications for biopsy include any nonhealing wounds, ulcerations, or lesions suspicious for malignancy. Microbiologic testing should be pursued based on clinical suspicion. Any perianal drainage should be sent for bacterial and viral culture. Patients with diarrhea should have their stool cultured and evaluated for ova or parasites. Flexible sigmoidoscopy and colonoscopy with biopsies should be performed whenever inflammatory bowel disease or malignancy remain on the differential.

MANAGEMENT

Initial treatment of pruritus ani should be directed toward treatment of any secondary causes identified. Once secondary causes have been treated, symptom relief, healing of impaired skin, and prevention of further damage should be the goals. It is important to inform patients early on that there will likely be a period of trial and error as an instant cure is unlikely.

Education and Lifestyle Modifications

Patients should be instructed to not scratch the area so as to begin to break the "itch-scratch cycle" and prevent further excoriation and irritation. As poor anal hygiene is a known trigger, time should be spent educating on proper anal hygiene including gentle cleansing of the perianal area with water and unscented soaps followed by cool air-drying or dabbing with toilet paper after each bowel movement. Scented soaps and prepared "baby wipes" should be avoided. The anal region should be kept dry. This can be achieved by placing a cotton ball in the gluteal fold after cleansing. Overzealous hygiene with aggressive scrubbing should be cautioned against as this too can lead to further excoriation and worsen the cycle. Though uncommon in the United States, bidets followed by patting dry the area with unscented toilet paper has been shown to be an effective method of maintaining good anal hygiene. If chronic diarrhea impedes proper perianal hygiene, fiber supplements or stool bulking agents should be prescribed.

Loose-fitting clothing should be used to allow for natural aeration. Home and over-the-counter remedies should be discontinued when initiating a stepwise treatment to rule out possible confounding factors. Dietary modifications should be made to avoid foods that have shown to be associated with the condition, including caffeine, spicy and acidic foods, chocolate, tomatoes, and carbonated beverages (see Box 2).

Medical

Following initiation of lifestyle modifications, topical agents can be used for further treatment and symptom management. Hydrophobic barrier creams that include zinc oxide such as Calmoseptine, Desitin, and Balmex are helpful to allow for healing and long-term prevention. Antihistamines, both topical and systemic, have been shown to decrease nocturnal itching. Topical capsaicin, a component of chili peppers, has been shown to suppress the histamine-mediated itch-scratch response. Topical steroids can be considered once infectious causes have been ruled out. Topical cortisone cream is effective in relieving pruritic symptoms, however long-term use is associated with atrophy of the skin, thus treatment is usually limited to 2-week periods. Though steroids are rarely curative, they can be effective in breaking the itch-scratch cycle and allow time for the skin to heal.

Lack of clinical and symptomatic improvement within 2 weeks of full lifestyle modification and topical therapy warrants further evaluation for missed secondary causes. Other treatments that have been studied, though with limited data, include topical tacrolimus ointment for 4 weeks leading to decreased itch intensity and frequency. Intradermal and subcutaneous injection of the perianal region with methylene blue has shown resolution of symptoms in 20% to 88% of patients. Methylene blue is thought to destroy sensory nerve endings resulting in hypoesthesia of the perianal region. Initial trials of methylene blue were complicated by several patients developing full-thickness skin necrosis, though the technique has since been modified. Patients should be counseled that the methylene blue will often permanently color the treated area blue.

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Surgical Management of Fecal Incontinence

Sarah Stringfield, MD, and Alessandro Fichera, MD

INTRODUCTION

Fecal incontinence (FI) is defined as the uncontrolled passage of feces or gas over at least 1 month's duration in an individual who had previously maintained control. Fecal incontinence is a common condition, affecting up to 11% of men and 26% of women older than 50 years of age. It is the second leading reason for admission to nursing homes and is present in up to 50% of institutionalized patients. True prevalence may be even higher, as social stigma surrounding incontinence likely limits reporting. Fecal incontinence has a profound negative impact on quality of life and generates a substantial financial and logistical burden to healthcare and society.

Continence depends on the complex relationship between the anal sphincter and pelvic floor musculature, rectal reservoir function, stool consistency, and neurologic function. Conditions that alter any of these factors may result in FI. General categories of causes of FI include structural abnormalities, functional disorders, neurologic etiologies, and congenital malformations (Table 1). In women, the

TABLE 1 Causes of Fecal Incontinence

Category	Examples
Acquired structural abnormalities	Obstetric injury History of anorectal surgery Rectal or hemorrhoidal prolapse Anal or rectal fistula Sphincter-sparing rectal resection Trauma
Functional disorders	Diarrhea Inflammatory bowel disease Irritable bowel disease Hypersecretory tumors Fecal impaction (paradoxical diarrhea) Radiation proctitis Physical disabilities Psychiatric disorders
Neurologic disorders	Pudendal neuropathy Spinal injury or surgery Multiple sclerosis Dementia Central nervous system disorder Spina bifida
Congenital disorders	Imperforate anus Cloacal defect

leading cause is obstetric injury. Treatment is challenging and must be individualized to each patient based on the underlying cause.

DIAGNOSTIC EVALUATION

A variety of diagnostic tests can be performed to help determine the cause of the patient's fecal incontinence and quantify the severity of their symptoms (Table 2). Patients presenting with FI require a thorough history and physical examination. Direct and specific questions must be asked to understand the type and extent of incontinence. This can include awareness of continence episodes (urge vs. passive incontinence), timing and frequency of symptoms, stool characteristics and habits, and other associated symptoms such as prolapse, drainage, and urinary or sexual dysfunction. A detailed obstetric and surgical history is essential. Underlying disease processes such as diabetes, stroke, inflammatory bowel disease, or certain medications may contribute to FI.

A thorough anorectal physical examination should be performed. Essential components of the examination include assessing the anal sphincter tone and pelvic accessory muscles at rest as well as during squeeze and Valsalva maneuvers. The patient should be evaluated for the presence of pelvic organ prolapse, masses, perianal skin irritation, hemorrhoids, fissures, and fistulas.

There are many validated patient-reported scoring systems that can be used to quantify the severity of fecal incontinence. A commonly used system is the Cleveland Clinic Florida Fecal Incontinence Score (Wexner scale), which assesses the frequency of five parameters (incontinence to solid stool, liquid stool, gas, wears a pad, and lifestyle alteration) and sums it into an aggregate score. Additional scoring instruments include the Fecal Incontinence Severity index, Fecal Incontinence Quality of Life score, and the St. Mark's Incontinence score. All scoring systems emphasize different symptoms and may be limited by the subjectivity of the reporting, failure to include coping mechanisms, and lack of objective physiologic test data. Although the scoring systems provide a useful way to quantify severity of incontinence, they do not have the ability to accurately predict outcomes.

TABLE 2 Diagnostic Evaluation and Workup

Study	Components and Examples
Patient history	Awareness of incontinence episodes Timing and frequency of episodes Stool characteristics Stool habits Other associated symptoms (prolapse, drainage, urinary or sexual dysfunction) Obstetric and surgical history Medications Underlying diseases
Physical examination	Sphincter tone at rest and squeeze Pelvic accessory muscles during squeeze and Valsalva Anatomic abnormalities: prolapse, masses, hemorrhoids, fissure, fistulas Perianal skin irritation
Patient-reported scoring systems	Cleveland Clinic Florida Fecal Incontinence score Fecal Incontinence Severity index Fecal Incontinence Quality of Life score St. Mark's Incontinence score
Endoanal ultrasound	Sphincter integrity
Anorectal physiology	Manometry Anorectal sensation Volume tolerance Compliance Electromyography
Defecography	Prolapse Rectocele/enterocele Positional instability

Objective testing predominantly assesses sphincter integrity and anorectal function. Endoanal ultrasound is the most sensitive means to confirm whether a sphincter defect is present in patients with suspected sphincter injury and determine the size of the defect. Ultrasound can identify defects in both internal and external anal sphincters (Fig. 1). Anorectal physiology testing includes manometry, anorectal sensation, volume tolerance, and compliance, and it helps define the elements of dysfunction. Although findings do not consistently correlate with the severity of FI or predict outcomes, this type of testing can help define the elements of dysfunction and guide management. Pudendal nerve terminal motor latency and electromyography may be useful in select circumstances. Defecography, either with MRI or fluoroscopy, may be useful in cases of pelvic organ prolapse to visualize positional instability and identify involved pelvic compartments. Colonoscopy should be performed in patients with bleeding, those with a change in bowel habits, and those who meet national screening guidelines.

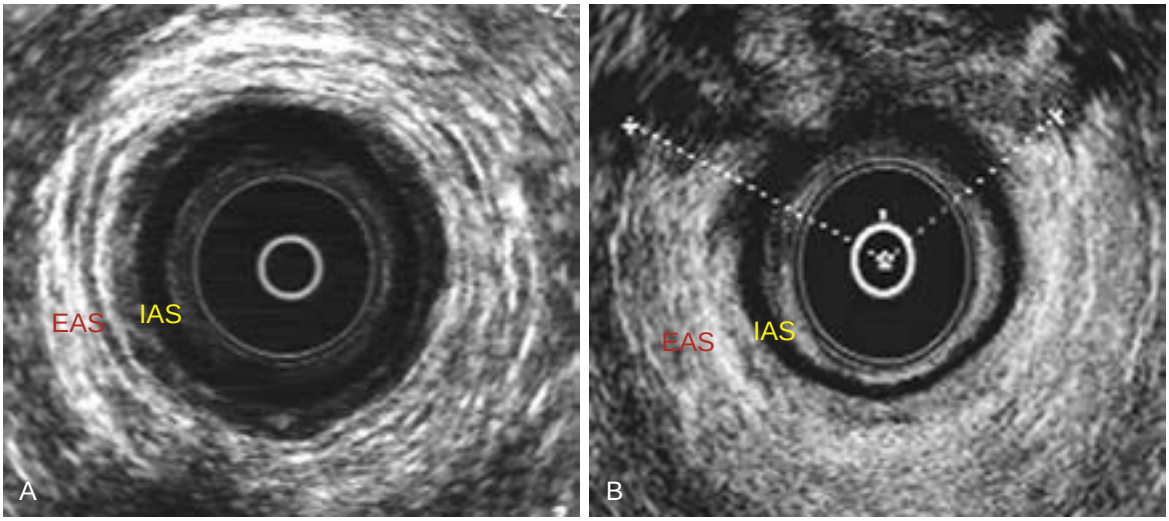


FIG. 1 Endoanal ultrasound evaluation of anal sphincters. (A) Intact sphincter complex. **(B)** Approximately 110-degree anterior sphincter defect. *IAS*, Internal anal sphincter (*dark ring*); *EAS*, external anal sphincter (*white ring*).

NONOPERATIVE MANAGEMENT

Medical Management

Initial management of FI for all patients, regardless of etiology, should be nonoperative. The goal is to control symptoms and attempt to correct any modifiable factors contributing to the patient's presentation. Up to 20% to 50% of patients can improve after starting medical management and lifestyle changes, which avoids surgery in many patients. Initial steps include optimizing stool consistency, slowing bowel motility, and minimizing the average stool load in the rectum, particularly before sleeping or leaving home. These changes can often be accomplished with habit changes and dietary modifications as well as pharmacologic and bowel management interventions. Common foods that promote urgency or diarrhea should be avoided. This includes caffeine, sugar replacements, and lactose. Dietary fiber supplementation may improve stool consistency in patients with diarrhea, prevent seepage, and promote complete evacuation. Antidiarrheal medications such as loperamide and diphenoxylate-atropine can also help thicken stools and decrease frequency. Cholestyramine can be helpful in patients with bile acid diarrhea, usually those with a history of cholecystectomy or terminal ileal resection. Irritable bowel syndrome can be treated with tricyclic antidepressants and drugs such as alosetron or eluxadoline. Bowel management programs start with patient education regarding regularity and timing of bowel movements in relation to the gastrocolic reflex. Timing meals and reducing stool load in accordance with planned events or sleeping can prevent episodes of incontinence in these situations. Scheduled enemas can reduce stool load and are therapeutic in patients with fecal impaction and overflow incontinence. Incontinence pads and barrier creams for perianal skin care are useful adjunctive treatments.

Biofeedback

In patients with some degree of preserved voluntary sphincter contraction, pelvic floor physical therapy and biofeedback therapy can improve symptoms. The sessions focus on strengthening and re-coordinating the pelvic floor and sphincter function in response to rectal distension. The patient is monitored during the biofeedback sessions and counseled on appropriate muscle contraction, relaxation, abdominal pressure, and breathing techniques. Subjective benefits have been noted in up to 64% to 89% of patients who participate in the therapy. Long-term results and objective benefits are less clearly defined. The approach is simple, noninvasive, and without any adverse side effects, and it should be offered to any patient who may be a candidate.

TABLE 3 Surgical Targets and Options

Goal	Options
Correction of anatomic abnormalities	Overlapping sphincteroplasty Prolapse repair Fistula repair Hemorrhoid treatment/excision Cloaca or keyhole deformity repair
Enhancement of sphincter function	Sacral nerve stimulation Radiofrequency energy administration Injection of bulking agents Tibial nerve stimulation
Sphincter replacement or support	Artificial bowel sphincter Implantation of magnetic anal sphincter Graciloplasty Cerclage (Thiersch procedure) Pelvic sling system
Diversion	Colostomy Ileostomy
Reduction of fecal load	Antegrade continence enema

SURGICAL MANAGEMENT

Patients who fail medical management may be offered a surgical option. There are many options for surgical interventions, and the approach typically depends on the etiology of the incontinence, severity of the symptoms, and several patient factors (Table 3). The initial approach should typically correct any anatomic abnormalities that may be contributing to incontinence, as restoration of normal anatomy may normalize function. This can include rectal or hemorrhoidal prolapse, rectovaginal or anal fistulas, and cloacal or keyhole deformities. If symptoms persist, then incontinence-specific approaches may be considered. While many incontinence-specific

options exist, many are not frequently used or require medical devices that have been taken off the market. The most common and efficacious surgical interventions include sacral nerve stimulation, sphincteroplasty, and fecal diversion.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) is a technology initially developed for urinary incontinence but was demonstrated to have benefits for FI as well. The device stimulates the S3 nerve root by delivering mild electrical pulses. The exact mechanism by which it improves urinary and fecal incontinence is not fully understood. SNS has been approved by the US Food and Drug Administration (FDA) for use in treatment of FI in the United States since 2011 and can be performed in most patients with FI. Patients with sphincter defects up to 120 degrees can see a reduction in severity and frequency of FI episodes with implantation of SNS.

The procedure is performed in two stages. During the first stage, a tined lead is placed under fluoroscopic guidance along the S3 nerve root (Figs. 2 and 3). The procedure is performed under monitored anesthesia care or general anesthetic with a short-acting paralytic agent. The patient is placed prone, and exposure of the buttocks and feet are maintained to visualize motor responses. Access to the S3 foramen is obtained with a hollow needle under fluoroscopic guidance. Appropriate needle placement is confirmed by stimulating the needle with an electrical impulse and confirming appropriate motor response. Motor responses of S3 stimulation include pelvic bellows and ipsilateral big toe plantarflexion. Using Seldinger technique, a wire and subsequently a tined lead is placed through the S3 foramen and along the S3 nerve root. The lead is tunneled laterally to a subcutaneous pocket and coupled with an external wire. The external wire is tunneled out of the skin several centimeters removed from the subcutaneous pocket and coupled with an external battery pack. The external wire and battery pack are bandaged, and the patient is instructed to avoid showering during the trial period.

During a 2-week trial period, the patient keeps a diary of incontinence symptoms and compares it to a diary kept before implantation of the SNS. Lead settings are modified in the outpatient setting until the patient has maximum benefit with minimal discomfort. If the patient sees a benefit, typically 50% or greater reduction in the number of incontinence episodes, then the second stage of the procedure is performed. The patient is positioned in the same way. The external wire is uncoupled from the tined lead and removed. The lateral subcutaneous pocket is opened, and the permanent device is connected to the tined lead and implanted. If the patient does not see a reduction in incontinence symptoms or does not tolerate the device during the trial period, then the lead and external wire are removed during the second phase.

Patients now have the option of having a rechargeable battery or a larger, non-rechargeable battery pack placed that lasts approximately

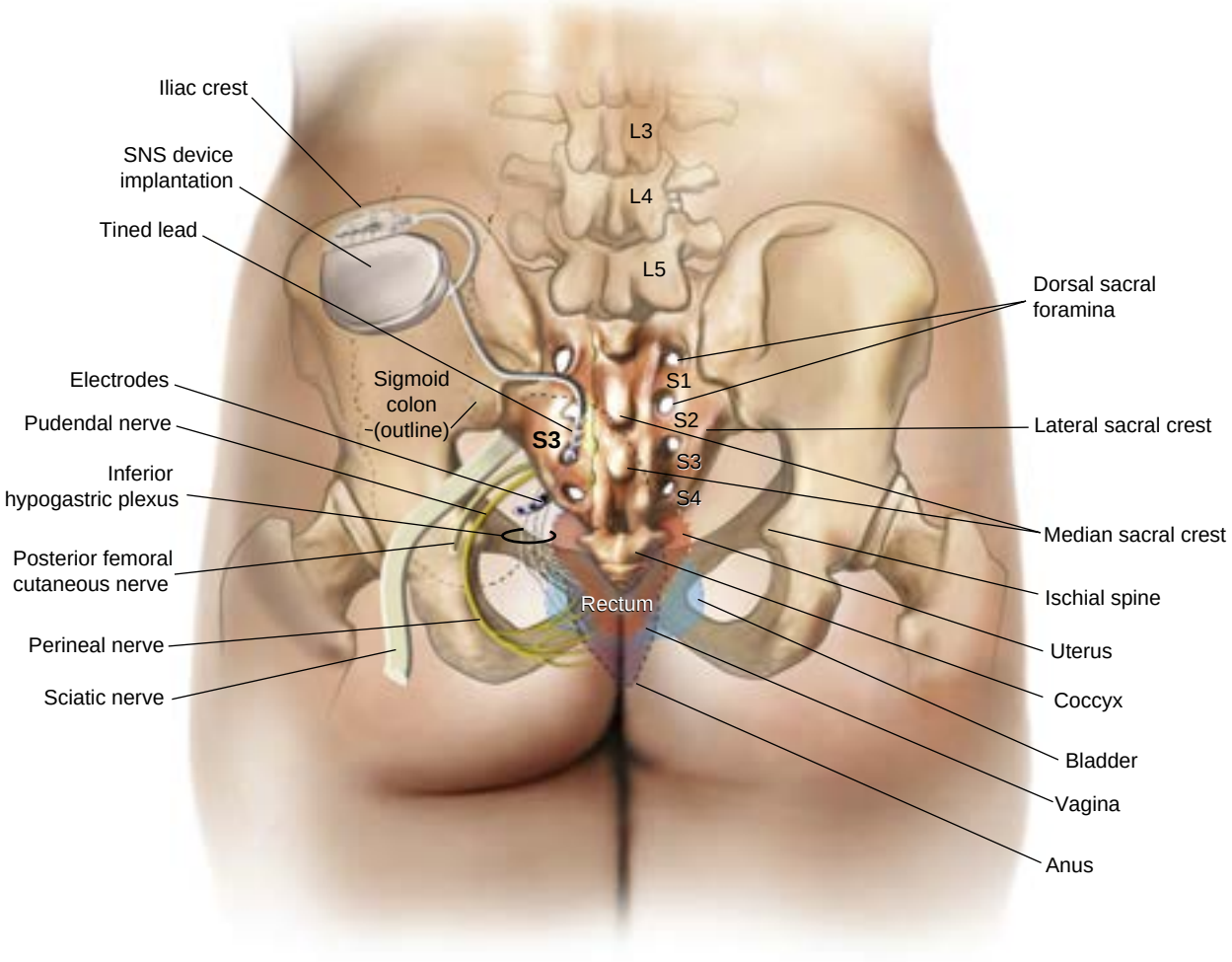


FIG. 2 Sacral nerve stimulator placement and anatomy. *(From Hull T.* Posterior Pelvic Floor Abnormalities. *Philadelphia: Elsevier; 2011).*

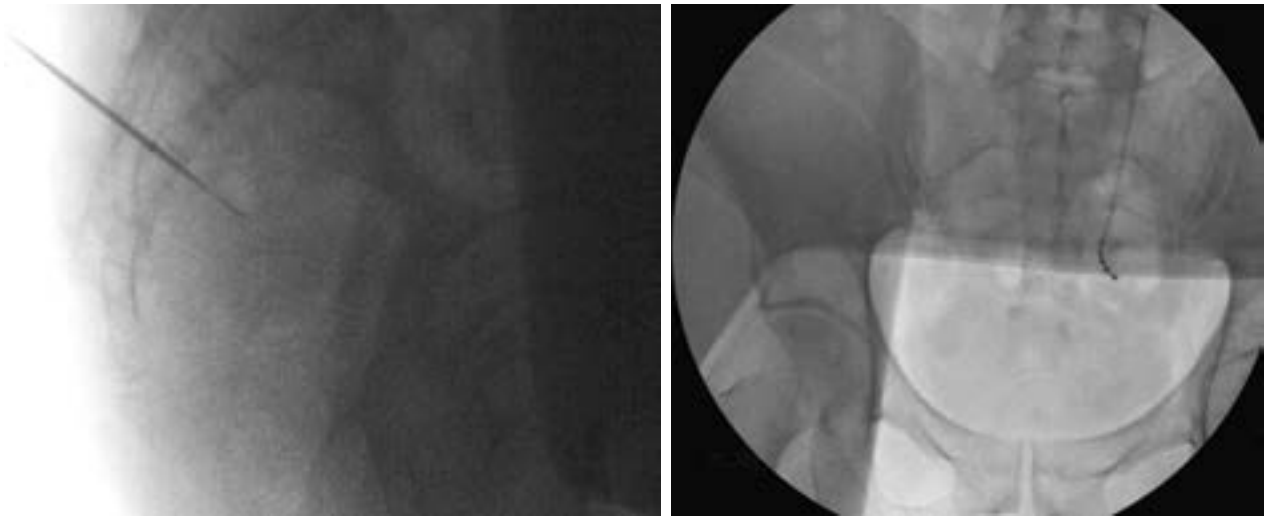


FIG. 3 **Sacral nerve stimulator placement with fluoroscopic guidance.**

5 years. Benefits of the rechargeable battery include smaller size and avoidance of additional operations to change the battery. However, it requires the patient to charge the battery every couple of weeks using a charging device placed on the skin over the battery. The decision of whether to choose a rechargeable or non-rechargeable battery will depend on the patient's ability to charge the device and the risks and benefits of routine battery charging versus surgical replacement every 5 years. Currently marketed SNS devices are MRI-compatible.

The SNS study group reported results of a prospective multi-institutional trial conducted on 133 patients with FI who underwent test stimulation. In this study, 90% of the patients had a 50% or greater reduction in the number of incontinence episodes and underwent permanent battery implantation. At 12 months, 83% of implanted patients reported therapeutic success, which was 75% of overall patients. The mean number of incontinence episodes decreased from 9.4 per week to 1.9 per week at 12 months. At 5 years, 89% of patients had sustained benefit, and 36% reported perfect continence. Risks of SNS are generally minor and include pain and surgical site infection, which are seen in about 10% of patients. Either of these complications can be treated with removal of the device. Reimplantation can be attempted after the infection has cleared, and the contralateral side can be used in either group of patients. At 5 years, 36% of patients required revision or replacement. Overall, SNS placement is an intervention that has low complication rates, is reversible, and has been shown to achieve good long-term improvement in continence. It is now the first-line treatment in many patients who are considered candidates.

Overlapping Anterior Sphincteroplasty

An overlapping anterior sphincteroplasty may be performed in patients with an anterior anatomic defect with the goal of reconstituting the circular configuration of the sphincter muscle around the anal canal. These sphincter defects are most commonly seen in women as a result of obstetric injuries. When sphincter injury is suspected, ultrasound imaging should be performed to confirm. The best postoperative results are seen in patients with defects of 60 to 180 degrees. When defects are seen immediately following delivery, they should be repaired primarily. If the patient continues to have a sphincter defect and symptoms of FI, definitive operative intervention should be delayed for 3 to 6 months to allow time for swelling to subside and for scar tissue to form.

Patients should undergo preoperative mechanical bowel preparation. Patients are placed in the prone jack-knife or lithotomy position. A curvilinear incision is made anterior to the anus within the perineum, and the two sides of the sphincter are identified and mobilized. The ends of the sphincter muscle should be mobilized as much as necessary to allow for an overlap, but not too much in order to avoid pudendal nerve injury or ischemia. An anterior levatorplasty is often performed in conjunction with sphincter repair to approximate the levator muscles. The two sides of the sphincter are reapproximated in an overlapping fashion with 2-0 monofilament sutures. The sutures should be placed within any scar tissue that is present as it holds suture better than muscle. The skin is closed loosely to allow for drainage (Fig. 4).

Short-term results for this procedure are very good, with up to 80% of patients reporting good to excellent functional results. However, the benefits deteriorate over time, and less than half of patients remain continent at 5 to 10 years. This surgical technique is most useful in patients with an associated rectovaginal fistula that requires repair. Repeat anal sphincter reconstruction after a failed sphincteroplasty should be avoided unless other treatment modalities are not possible or have already been attempted and failed. Repeat repairs are unlikely to be more successful than the original repair unless a specific factor responsible for the failure can be identified and avoided.

Fecal Diversion

In patients who fail medical or surgical therapy, those with very large defects that are not amenable to repair, or in cases of patient preference, stoma creation may be offered as an effective solution for FI. In most patients, creation of a sigmoid colostomy is appropriate and provides for an ostomy that is easy to care for. A laparoscopic approach is preferred and feasible in most patients. Stoma placement is important, as many of these ostomies will not be reversed. Trained stoma nurses should be involved in the patient's care both preoperatively and postoperatively. In patients who had a stoma created for FI, 83% reported an improvement in quality of life, and 84% would choose a stoma again.

Additional Surgical Interventions

Several products have been developed to artificially increase anorectal outlet resistance in patients with incontinence caused by a weak or dysfunctional anal sphincter. These include an artificial bowel sphincter, a magnetic sphincter, radiofrequency administration, and injection of bulking agents into the anal canal. Studies of these

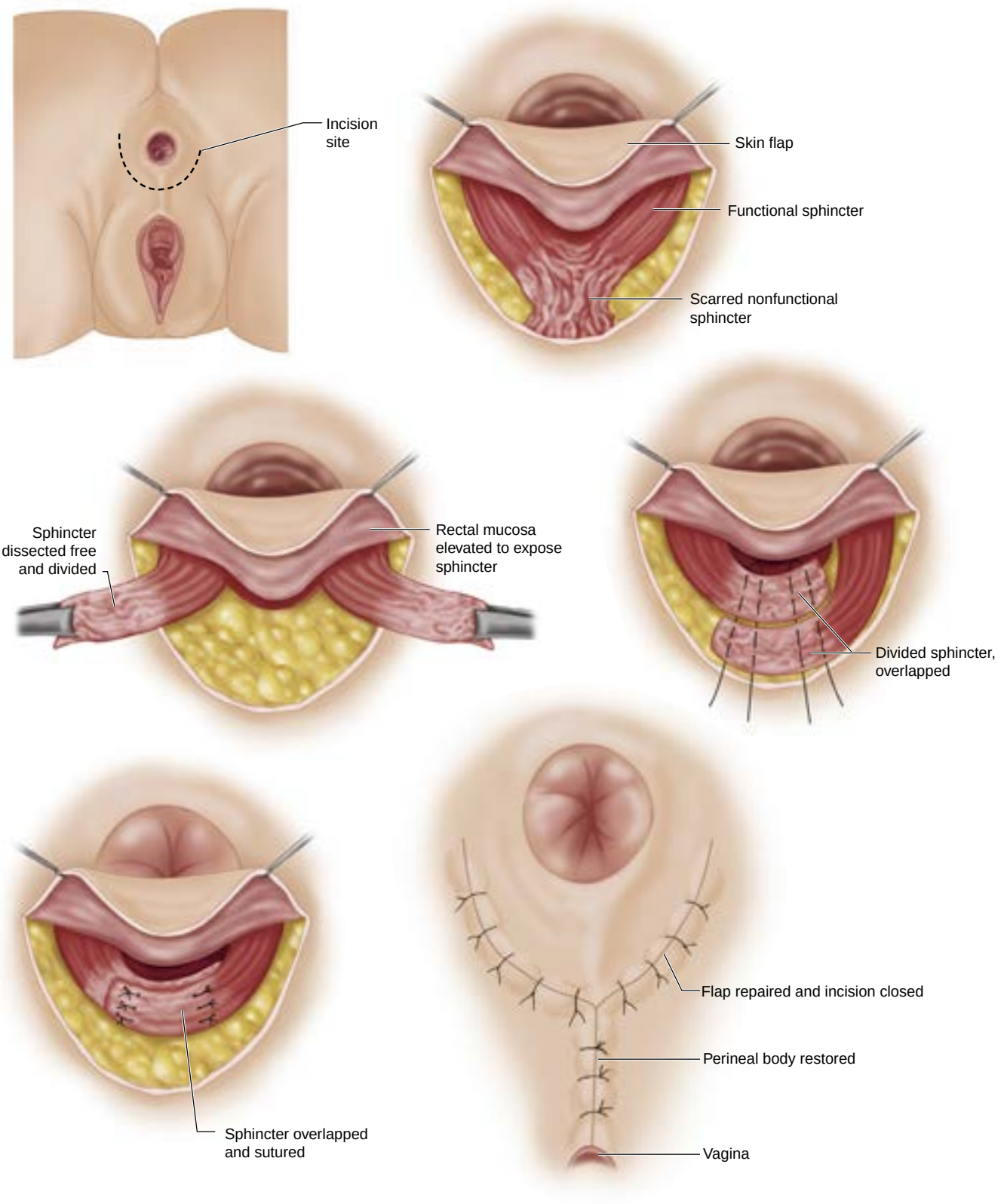


FIG. 4 Overlapping anterior sphincteroplasty. *(From Fleshman JW.* Atlas of Surgical Techniques for Colon, Rectum and Anus. *Philadelphia: Saunders; 2013.)*

products show variable results, and overall evidence for their efficacy is weak. Artificial bowel sphincters provide the best results, however they are associated with high complication rates, with up to 80% of patients requiring explantation or revision within 5 years. Many of these products have been taken off the market in the United States.

Tibial nerve stimulation is a new therapy undergoing evaluation for treatment of FI. Stimulation is delivered with a needle electrode or an adhesive pad. Two randomized controlled trials comparing the therapy to sham neurostimulation have been performed and reported differing results. One trial reported patients undergoing percutaneous therapy to have higher rates of improvement in FI episodes, while the other trial showed similar rates of improvement in both intervention and sham groups. Little is known about the frequency, interval, and intensity of stimulation needed to optimize results of this therapy, but it may be most useful in conjunction with other therapies. Studies regarding this therapy are ongoing.

CONCLUSIONS

Fecal incontinence is a common problem that is often underreported because of its stigma. Evaluation tools include validated scoring systems to quantify symptom severity, anorectal ultrasound, and anorectal physiology testing. Medical management can often provide significant improvement in symptoms. Surgical management depends on the underlying pathophysiology. Current options that have been proven to be most effective at treatment of symptoms include SNS, sphincteroplasty, and diversion.

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Rectovaginal Fistula

Eric G. Weiss, MD, and Emanuela Silva Alvarenga, MD

Rectovaginal fistulas (RVFs) are extremely life altering for women who develop this condition, but thankfully it is not common. Regardless of the low incidence, RVFs are vexing problems both for physicians and patients. Expertise in evaluation and management is often needed yet is rarely available in the communities where the patients live and often requires tertiary referral if a patient is not initially being managed in such a center.

Patients can present with a multitude of signs and symptoms, from minor drainage to flatulence via the vagina to frank stool leaking out of the vagina. One can imagine the psychological impact this has on a women's self-image and relationship with her significant other and impact on work life and quality of life overall.

Most series of repairs are small, single-institution procedures and often are limited in the types of procedures performed. In addition, RVF classification varies, and treatment by procedure type is often linked to the fistula classification or its etiology.

This chapter will focus on a variety of repairs and a stepwise process to determine which repairs may be appropriate for which RVFs in the hopes that the most favorable outcomes and least morbidity can be achieved.

ETIOLOGY AND CLASSIFICATION

There are three main etiologies for RVFs: obstetric injury, cryptoglandular sepsis, and Crohn's disease. Each etiology tends to form the fistula by different means, and the locations, other associated injuries, and treatment options vary as a result of these and other factors. Less common but more difficult to manage are those formed as a complication of radiation therapy or following anastomotic complications related to colorectal surgery with stapled anastomoses that have leaked.

Obstetric injury is the most common etiology, typically resulting from an episiotomy or a third- or fourth-degree tear. These fistulas can occur in the immediate postpartum period or can present several weeks to months later with failure of laceration repairs or episiotomy repairs. These are often associated with anterior external sphincter muscle defects and at times clinical fecal incontinence.

Crohn's disease involving the anal canal and/or rectum can lead to a RVF by poor control of the underlying disease resulting in a full-thickness penetration of the Crohn's disease and fistula into the vagina. Often these are associated with some degree of anal stenosis and other perianal manifestations of the underlying Crohn's disease.

Other etiologies as mentioned earlier have a variety of locations, sizes, and factors associated with them depending on which etiology is responsible for formation of the fistula.

Classification can also be useful in planning repairs. Classification is based on several factors including etiology, location, and underlying conditions. Simple fistulas tend to be low in relation to the sphincter mechanism, caused by obstetric or iatrogenic injury, and smaller than 2.5 cm in diameter. Complex fistulas are larger, located higher in the vagina, and associated with other underlying diseases or mechanisms such as radiation therapy, inflammatory bowel disease, or colorectal or gynecologic cancers (Box 1).

EVALUATION

The clinical evaluation, classification, appropriate workup, and multidisciplinary approach is important and should allow for the most optimal control of symptoms before repair and ultimately the most favorable outcomes following surgical management.

A thorough history is required. The timing of the development of the fistula to the inciting event should be well documented because regardless of the type of repair that is appropriate, it is usually necessary to wait an obligate amount of time from the initial event. Obtaining prior operative reports, delivery reports, treatment notes, and prior diagnostic studies is optimal. Obtaining images and not only reports allows for review with radiology and comparison to any future studies. Documenting the patient's current and prior bowel function, continence level, and sexual function is important.

Physical examination in the office should be performed but may be limited as a result of patient discomfort or pain. Visual examination of the perianal skin, anal verge, and vaginal introitus should be performed in all patients. The condition of the skin, any incisions, any secondary fistulous openings, if the anus is patulous, and any readily

BOX 1 Causes of Rectovaginal Fistulas

Obstetric Injury

Episiotomy, third- and fourth-degree perineal lacerations

Inflammatory Bowel Disease

Crohn's disease

Iatrogenic

Anorectal surgery (fistulotomy)
Vaginal surgery (hysterectomy, rectocele repair)
Abdominal surgery (hysterectomy, low anterior resection, J pouch, procedure for prolapse and hemorrhoids)

Infectious

Cryptoglandular abscess, diverticulitis, tuberculosis

Neoplastic

Anal cancer, rectal cancer, vaginal cancer, cervical cancer

Radiation Induced

External beam radiation, brachytherapy

identifiable drainage or stool should be noted. Next, a digital vaginal and rectal examination should be performed if possible. Determining the quality of the rectal and vaginal tissue and site of the fistula may be possible. Anoscopic examination and vaginal speculum examination may also be possible in the office. If any of the aforementioned physical examinations cannot be performed in the office, then it may be appropriate to perform an examination under anesthesia either in the operating room or in the endoscopy suite. Ultimately knowing the anatomy of the fistula tract and levels and size of the fistula are mandatory in classification and for surgical planning.

Adjunct procedures including flexible sigmoidoscopy or colonoscopy, contrast enemas, pelvic magnetic resonance imaging (MRI), or computed tomography (CT) may all be necessary. Evaluation of the sphincter muscles with endoanal ultrasound may be useful if there is concomitant fecal incontinence. For patients with Crohn's disease, understanding the distribution of disease with magnetic resonance enterography (MRE) or computed tomography enterography (CTE) may also be required, and communicating with their treating physician about their current medical management may be important and may influence their surgical plan, particularly if they are on steroids or biologics.

Once a surgical plan is decided upon, a thorough discussion and informed consent should occur with realistic outcomes and expectations being discussed. Emphasizing the complex nature of these fistulas, the difficulties in some operations and the less than 100% success rates should be fully discussed.

ABDOMINAL APPROACHES

Abdominal approaches are typically used for higher RVFs, those associated with anastomotic etiologies, and those in which local tissue loss of the rectum and vagina are not amenable to local procedures for repair and reconstruction. Often, the rectum as it is at the time of diagnosis is unsuitable for a local repair because of a concomitant stricture or chronic leak or sepsis in addition to the known RVF. Thus, resection and reanastomosis are required. This most commonly results from fistulas caused by anastomotic leaks that initially form a pelvic abscess and drain into the vagina for decompression. Alternatively, mobilizing the rectum during proctectomy can devascularize the posterior vaginal wall, or a portion of the vaginal wall can unfortunately be incorporated into the staple line during stapling, leading to a RVF.

Regardless, once the decision to perform an abdominal approach has been reached, specific considerations for the conduct of the surgery to minimize complications and appropriate discussion and informed consent is necessary to set reasonable expectations. As this is likely reoperative pelvic surgery, timing of abdominal reentry is important. A minimum of 3 months and at times 6 months or more should be the waiting time before attempting a redo-anastomosis with takedown/closure of the fistula. One does not want to get into the situation of a hostile abdomen, multiple enterotomies, or worse, an aborted procedure. Ureteral stent placement should be strongly considered. Liberal use of a diverting ileostomy with appropriate preoperative counseling and stoma marking should be utilized.

Although minimally invasive approaches may be attempted and at times completed, often conversion to laparotomy or an initial plan for laparotomy may be made. As long as there is a well-thought-out plan and specific situations leading to conversion before complications, it is appropriate to approach in this fashion. The approach regardless is to initially either develop adequate working space if minimally invasive or full entrance in the abdomen if via laparotomy. Once that is accomplished, the next step is to get everything out of the pelvis except the colon/rectum heading down to the fistula and anastomosis. Once this is achieved, the next step is to get back into the pelvis. Often this is best approached by going posterior and into the presacral plane, going distal to the anastomosis and fistula, and then coming around laterally and anteriorly with the colon or rectum now only attached to the vagina. Next is separating the fistula, which at times leads to larger defects in the colon, rectum, and/or vagina. Once the fistula is divided, than one needs to get to healthy rectum below that level. Once that is achieved, then one can redivide the rectum distally. This typically requires a small TA type stapler such as a TA-30/45 or Contour stapler. Once stapled and divided, the colon or rectum above the anastomosis or fistula can be brought out of the pelvis. Next, adequate reach for a tension-free colorectal or coloanal is necessary. This may require division of the inferior mesenteric artery and vein, full mobilization of the splenic flexure, and at times more complex maneuvers such as derotation or the creation of an ileal mesenteric window. If technically possible, closure of the vaginal opening should be performed but may not be possible. At times, repairing transvaginally may be necessary as opposed to transabdominally, depending on exposure. Consideration of having gynecology available might help mitigate the difficulties in performing the closure transvaginally. Adequate blood flow can be assessed in traditional ways, but consideration for indocyanine green (ICG) angiography should also be utilized liberally. Once the stapled anastomosis is performed, flexible endoscopy with air leak testing and assessment should be performed. Based on the results of the endoscopy, conduct of the surgery, blood loss, patient stability, and the patient's ability to tolerate an anastomotic leak, a proximal diversion with a loop ileostomy should be considered. Typically, prior radiation therapy, an anastomosis less than 4 cm from the anal verge, or a less than ideal anastomosis should be diverted.

Consideration for omental pedicle interposition should always be considered at this point. If adequate omentum is present, it can be made into a pedicle based on the right or left gastroepiploic vessels and then brought down into the pelvis anterior to the anastomosis and posterior to the vaginal defect/repair to act as a physical separator, keeping the repair and anastomosis separated. There are multiple methods of securing the flap within the pelvis, but often it will stay in place just based on the narrowness of the distal pelvis and interposition within the rectovaginal septum.

PERINEAL APPROACHES

Transanal Fistulotomy

Transanal fistulotomy entails the direct opening of the entire fistula tract. This method is preferably indicated for superficial fistulas and should be performed after the fistula tract is well defined by the

local fibrosis. This is normally promoted by a pretreatment period of draining seton once the local infection has been treated and the tract has matured. In the operating room setting, the seton is removed, and the residual fistula tract is curetted and cut open.

The procedure results in high rates of a long-lasting fecal incontinence, likely caused by a combination of the violation of the anterior anal canal, where sphincter muscle is sparser, and a resulting deforming wound defect.

Despite its theoretical indications, the transanal fistulotomy has fallen out of favor for the management of RVFs.

Endorectal Advancement Flap

The endorectal advancement flap (ERAF) is the most standard treatment for low-lying simple posttraumatic RVFs. It is a compelling approach, especially when there is a concern for fecal incontinence as it does not cause any surgical division of the external sphincter muscle.

Advancement of the anterior rectal wall with the aim to obliterate the internal opening by sliding a flap of healthy rectal wall consisting of mucosa, submucosa, and a circular muscle from proximal to cover the opening and suture it into place was first described by Noble in 1902 and since then has been extensively reported with slight modifications.

Preoperatively, patients undergo bowel preparation with either oral mechanical bowel preparation the night before the surgery or two sodium phosphates enemas the morning of the surgery.

The patient is placed in the jack-knife prone position over a Kraske roll. The buttock is taped widely apart, and the patient is prepped and draped in normal sterile fashion. Exposure can be further optimized by effacing the anus with the use of a Lone-Star retractor. A lighted Hill-Ferguson retractor or a Pratt bivalve anoscope is placed into the anal canal to expose the anterior rectal wall. The fistula tract is identified and assessed by a probe passed from the vaginal side. Using Bovie electrocautery, a U-shaped flap is outlined with its apex sited distally to the location of the fistula. The rectal wall is incised through the mucosa, submucosa, and down to the internal sphincter for a partial-thickness flap. The base of the flap should be two to three times as wide as the apex to ensure adequate blood supply of the flap. Care should be taken to avoid making a hole in the repair. The flap is raised for a distance sufficient to allow tension-free anastomosis, normally 4 to 5 cm. Once the flap is created, the fistula tract is debrided and closed by approximating the fibers of the internal sphincter. Additional mobilization might be required to allow to the edges of the internal muscles to be sutured over the fistula opening. The closure is performed in one or two layers using interrupted 2-0 Vicryl sutures. After hemostasis is reassured, the distal end of the flap containing the fistula is trimmed, and the healthy flap is anastomosed distally (Fig. 1). The vagina side is left open for drainage.

The addition of a biologic graft to reinforce the rectovaginal repair has been described by some surgeons. A manufactured

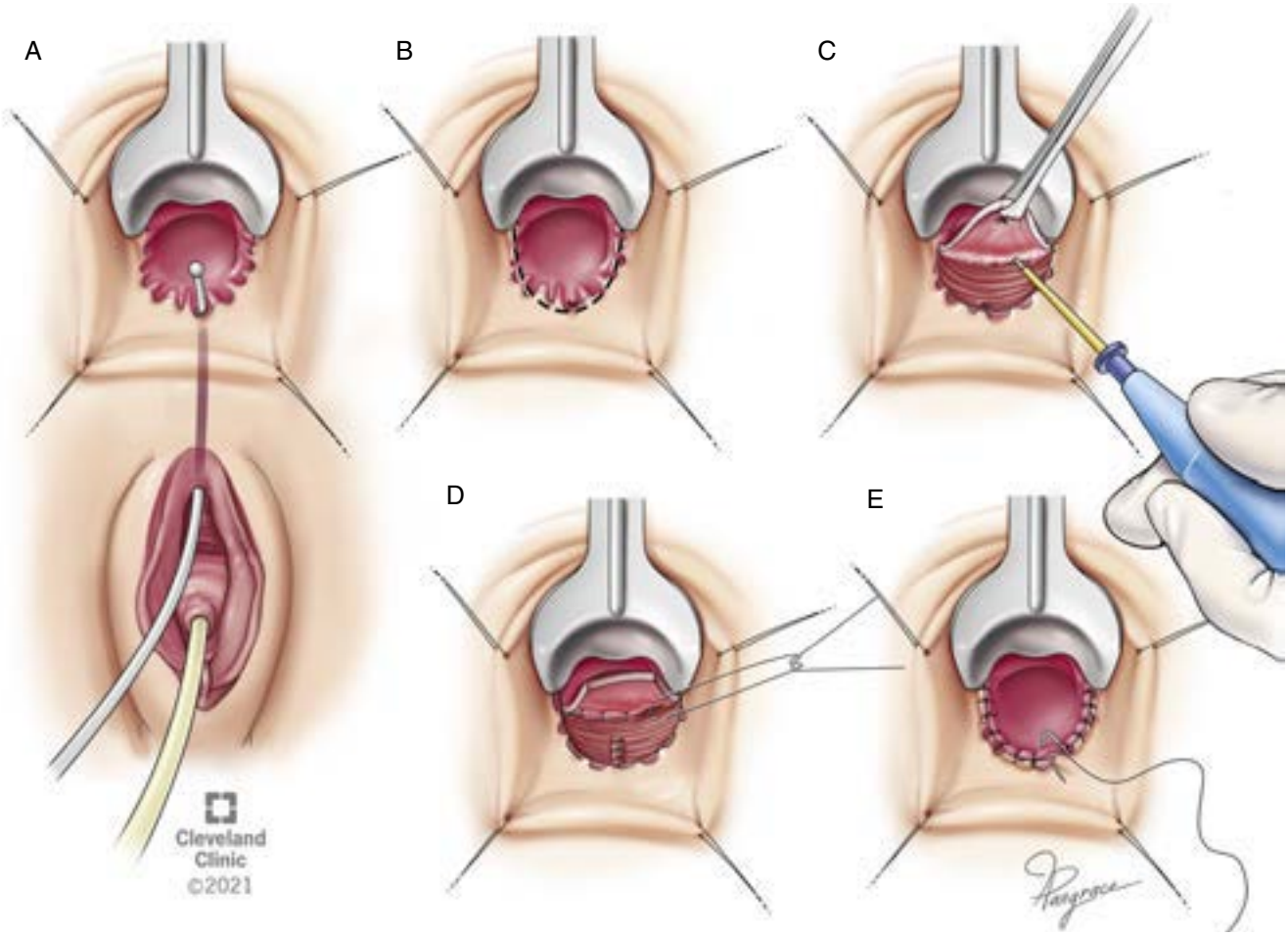


FIG. 1 Endorectal advancement flap. (A) Probe identifies the fistula tract. **(B)** Endorectal advancement flap. **(C)** Depth of the flap containing mucosa, submucosa, and circular muscle. **(D)** Mobilization of the flap without tension. **(E)** Flap sutured in place. (From Cleveland Clinic Center for Medical Art & Photography. Copyright 2021. All Rights Reserved.)

porcine small bowel submucosa is sized accordingly and employed in the rectovaginal space, with the flap sutured over the graft.

The overall success rate for ERAF for RVF is short term. It ranges widely in the literature from 29% to 93%. Most publications are made up of heterogeneous series of varying sizes, with mixed complex and simple fistulas and diverse closure techniques including ERAF alone or in combination with other approaches.

Flap failure is a dreaded complication. The most common cause for flap failure is retraction of the anastomosis, ischemia, and consequent necrosis with dehiscence of the anastomosis leading to flap loss and a potentially larger rectal defect after surgery.

Flap loss within 7 days is considered early failure and has been reported to be up to 6%. Late flap loss/failure rates range from 16% to 37%. Hence, enough flap mobilization for a tension-free anastomosis is paramount. Crohn's disease, complex fistula, and recurrent fistula and prior failed attempts at fistula repair are a risk factor for ERAF failure. Main contraindications to the ERAF include active Crohn's disease, acute anal abscess, and scarred or stenosed anorectum.

If an associated sphincter defect is present and a concomitant sphincter repair is performed, the success rate of the ERAF for RVF is higher and has been found to be as high as 100% in a small series of patients with obstetric low RVFs by Chew et al.

All women with an obstetric-related RVF should undergo evaluation for occult sphincter injury.

Fibrin Glue

The injection of fibrin glue can be performed for low RVFs with an intact rectal sphincter complex. The procedure is performed in the operating room. After the fistula tract is debrided, a fibrin adhesive is injected into the fistula tract until it exits the secondary opening. The theory is that the glue seals the fistula while also promoting fibrous tissue ingrowth and subsequent fistula healing without violating anorectal anatomy. Although this procedure does not threaten continence and causes minimal disruption to tissue planes, reported healing rates less than 60% have been frustrating enough to cause the fibrin glue to have a very limited place in the management of RVFs. The advantage is that potential future repairs are possible (Bhama et al., 2019).

Fistula Plug

The currently available fistula plug is made from lyophilized porcine intestinal submucosa, (Surgisis Biodesign Button; Cook Surgical) which provides a matrix for ingrowth of connective tissue. As for the fibrin glue application, the fistula tract is first curetted, the plug is prepared as per manufacturer recommendations, and with the guidance of a suture tied to the tip of the plug, the plug is passed from the rectum to the vagina until it is snug in the tract. The plug is the then sutured to the rectal mucosa. The excess fistula plug is trimmed flush to the opening at the vaginal side and sutured or not sutured to it; both ways have been described (Fig. 2).

The plug is costly, and there has not been enough experience with this technique. Reported results are extremely variable, with some series reporting an over 75% failure rate.

Like the fistula glue, the fistula plug carries very low complication rates with preservation of sphincter function and no violation of the perineal planes, however it is rarely performed.

TRANSVAGINAL REPAIRS

Transvaginal Approach Vaginal Advancement Flap

This approach is more extensively described in the gynecologic literature. In this instance, a flap is created in the vaginal wall instead.

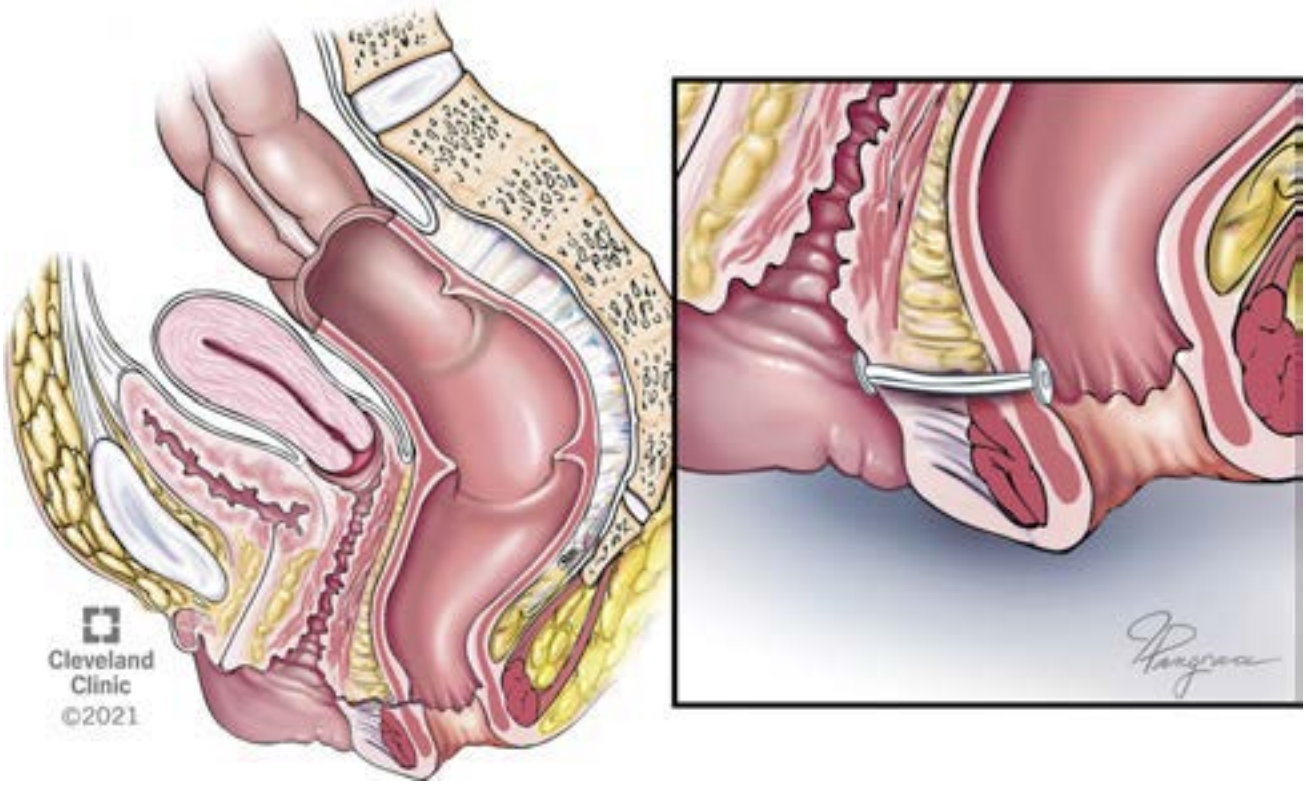


FIG. 2 Fistula plug. Plug placement within the rectum and the vaginal openings. (From Cleveland Clinic Center for Medical Art & Photography. Copyright 2021. All Rights Reserved.)

Supporters of this procedure emphasize optimized access and ease when mobilizing the flap and closing the opening of the fistula from the vaginal aspect compared with the transanal approach. They also claim a better-quality flap with well-vascularized vaginal tissue.

As the rectal advancement flaps, a flap of the vaginal mucosa is raised, the fistula tract is resected, the apex of the flap is trimmed to excise the fistula opening, and it is sutured into position to close the wound. An important technical aspect with this method is that the rectal mucosa still should be repaired. Because the rectal side constitutes the infected, high-pressure side of the fistula, failing to address the rectal mucosa significantly decreases the chances of a successful repair. The rectal wall is typically closed with interrupted absorbable sutures.

Despite published satisfactory success rates and described technical advantages of the approach, the transvaginal repair has been less commonly used than the ERAF. This is perhaps because of the theoretic possibly of increased pressure from the rectal side or an ongoing infection process compromising the vaginal flap.

A transvaginal advancement flap may be a good option when the rectal mucosa is diseased, such as in Crohn's disease, or when an ERAF has previously failed. Small series have reported a transvaginal flap for Crohn's-related RVF, with a success rate up to 93%, with fecal diversion.

Bhome et al. described a flapless transvaginal technique for the repair of primary and recurrent low- and mid-level RVF of varying etiology in which the fistulotomy and the closure of the rectum is performed from the vaginal side followed by closure of the rectovaginal septum and vagina. The authors reported 15 cases of RVF. The healing rate was 67% in a median follow-up of 48 months. Seven patients had fecal diversion. They concluded that the method was a safe, effective, faster, and technically less challenging alternative to ERAFs.

Transperineal Repairs

Most of the transperineal approaches are accomplished by a transverse or circumlinear incision made over the mid portion of the perineal body, dissection of the rectovaginal septum, division of the RVF tract, closure of the fistula openings in the rectum and vagina, and layered closure of the incision. These approaches include the transperineal repair with levatorplasty, ligation of the intersphincteric fistula tract (LIFT), and sphincteroplasty. The episioproctotomy is a transperineal approach in which a fistulotomy is carried out with transection of full-thickness of the perineal body followed by subsequent sphincter repair.

Transperineal Ligation with a LIFT Procedure

The LIFT procedure has been performed for management of transsphincteric fistulas-in-ano with acceptable success rates. More recently, the technique has been incorporated as an alternative for treatment of RVFs. The fistula tract is identified with use of a fistula probe, and a transverse or semi-circumferential incision is performed at the mid-portion of the perineal body. Then the subcutaneous tissue is dissected toward the intersphincteric groove, and the intersphincteric plane is entered and mobilized from the rectal mucosa posteriorly through approximately one-third of the circumference of the anus and rectum. The fistula tract is isolated and completely transected in this plane. The dissection extends in the rectovaginal septum 2 to 3 cm proximal to the fistula. The fistula openings in the mucosa of the rectum and vagina are closed or imbricated with interrupted, absorbable sutures. A bioprosthetic graft can be interposed in the intersphincteric plane and is advocated by some authors. Benefits of this method include its low impact on fecal continence and low complication rates. Sphincteroplasty can be combined if there is an associated sphincter defect. An ERAF can be included depending on the state of the rectal wall (Fig. 3).

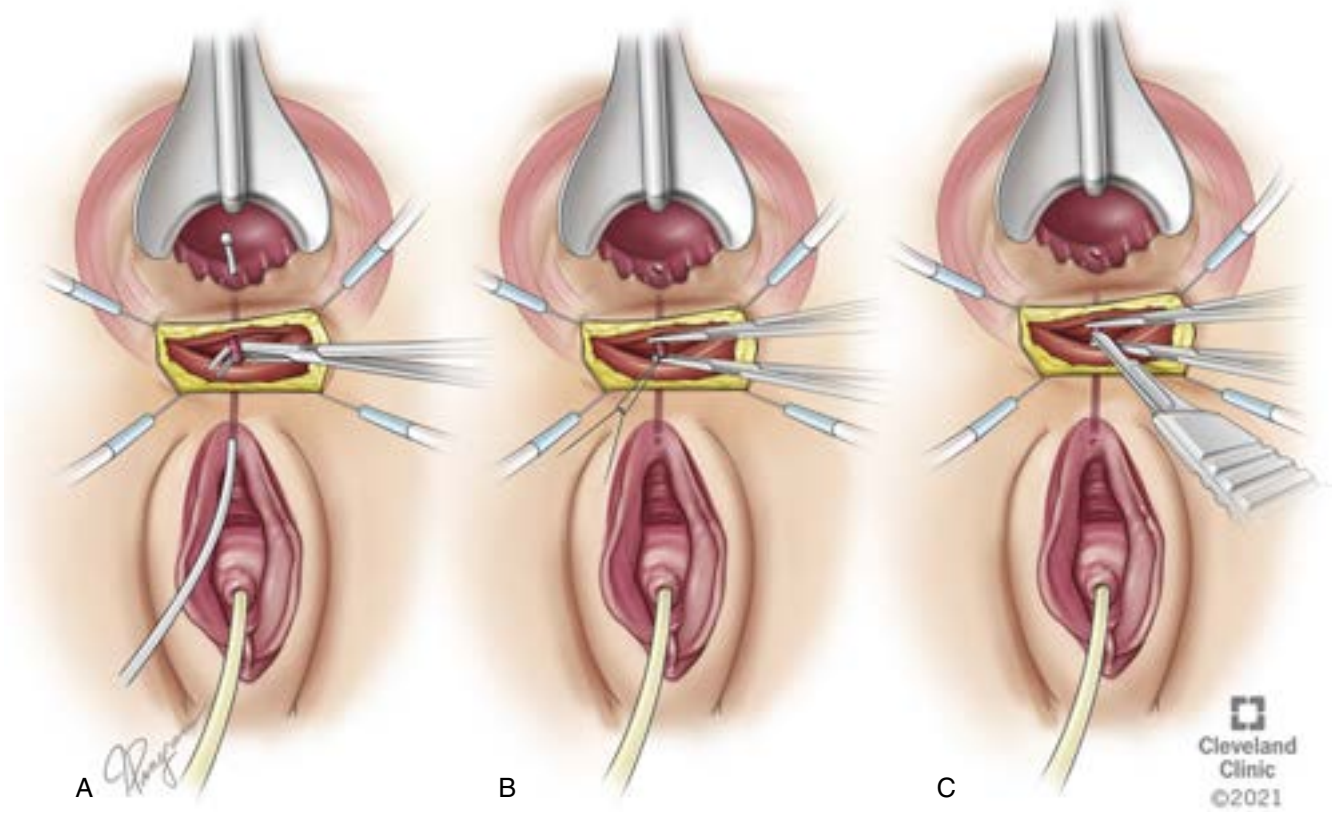


FIG. 3 Ligation of the intersphincteric fistula tract (LIFT). (A) Probe illustrating the rectovaginal fistula tract. **(B)** Closer view of the dissection of the fistula tract at the intersphincteric plane. **(C)** The fistula tract is completely transected in this plane. (From Cleveland Clinic Center for Medical Art & Photography. Copyright 2021. All Rights Reserved.)

There is still no robust experience with LIFT for RVF, with or without bioprosthetic material. Published success rates from a paucity of studies range from 57% to 94%. Ellis et al. published the only series assessing the use of bioprosthetic material added to the LIFT procedure in 27 patients. In this study, an undetermined number of patients underwent concomitant sphincteroplasty. Healing occurred in 81%. Long-term, comparative, randomized controlled studies are needed.

Overlapping Anterior Sphincteroplasty

For patients with RVF who have a palpable sphincter defect and a thin anovaginal septum, an overlapping anterior sphincteroplasty is indicated.

After entering the rectovaginal septum, lateral dissection is undertaken to identify the edges of the external anal sphincter. The scarred edges are grasped with an Allis clamp, and the dissection continues laterally along the external sphincter, until the edges are mobilized enough to come together. To avoid injury to the pudendal nerves bilaterally, care must be taken not to dissect too far laterally. The ends of the external sphincter are then overlapped for 1 to 2 cm and sutured together using a delayed absorbable suture. The incision is then closed in layers, with the medial portion left open for drainage. Patients must avoid straining and hard stools in the postoperative period, which may lead to early failure of the repair.

As described earlier in this chapter, the success rate of the ERAF combined with sphincteroplasty for RVF caused by obstetric injury is higher and has been found to be as high as 100%.

Episioproctotomy

In this technique, the rectum and vagina are separated from one another, the fistula tract is divided, and all tissue between the rectum and vagina is split through the perineal body, converting the fistula into a complete perineal laceration. Next, the vaginal wall is dissected from the perineal body, the rectal mucosa is closed in layers by approximation of the internal and external sphincters, and perineal body reconstruction is performed with or without an interposed muscle between the rectum and vagina with a levatorplasty or sphincteroplasty (Fig. 4). The combined methodology technique is especially suitable to obstetric-related fistulas associated with an extensive sphincteric defect with incontinence as it addresses both issues.

The overall success rate for this technique ranges from 70% to 88% in the literature, with described restoration of continence in 70% to 98% (Khanduja et al.) and significant improvement in both defecatory and sexual function in comparison with ERAF (Hull et al.). The combined interposition of biologic grafts has been described, with a success rate of 80% (Ellis et al.).

The downside of this procedure is that is creates a much larger wound, which can result in a larger fistula with worse incontinence, should the repair fail. Therefore, this procedure should only be performed by or with the assistance of experienced surgeons.

Transperineal Stapled Repair

Lately, a novel procedure utilizing a transperineal stapled transection of the RFV fistula was published in seven patients with RVFs of various etiologies, excluding Crohn's disease and malignancy. The authors performed a concomitant levatorplasty in four patients and sphincteroplasty in two patients. Two patients had a stoma. Their preliminary results reported no recurrence, no complications, and 100% satisfaction rate in a median follow-up of 6 months (range 3–33 months) (Lin et al., 2019).

Interposition Flaps

The gracilis muscle and bulbocavernosus (Martius) flaps are the two most popular pedicled flaps for RVFs. Other flaps have been described but never gained popularity. Those include gluteoplasty with bilateral tongues of the gluteus maximus and Lotus flap, a fasciocutaneous flap that is raised on perforators around the perineum, mostly described in the gynecologic literature.

The interposition of healthy, substantial tissue between the rectum and vagina confers the highest success rates of all transperineal repairs. The bulk added to the rectovaginal septum also increases the distance between the rectum and vagina. The morbidity related to these repairs is not high but includes wound healing complications, pain, dyspareunia, and undesirable cosmesis, particularly with gracilis interposition. Yet for the gracilis muscle interposition, caution is recommended in patients with muscle atrophy, myopathy, or impaired mobility.

These are complex operations, typically performed in tertiary centers by a surgeon with expertise on the technique. Fecal diversion is usually recommended, and most patients had previously undergone fecal diversion because of various prior failed repairs.

Gracilis Muscle Transposition

Gracilis muscle is a resourceful, well-vascularized tissue for perineal reconstruction because of its long length, substantial bulk, and single proximal neurovascular pedicle in most patients. The patient is placed in the Lloyd-Davies position using Allen stirrups or, alternatively, in a frog-leg position with a sterile bump under the knee. The groove between the gracilis muscle and the sartorius muscle is identified in either thigh. Approximately 2 cm above the knee joint, a 4-cm longitudinal incision is made, and the dissection is deepened through the subcutaneous tissue to expose the fascia overlying the tendon of the gracilis muscle. Then fascia is incised, and muscle is mobilized until all perforating vessels are identified. The perforating vessels can be divided and ligated between clamps or with ultrasonic shears or a bipolar cutting instrument. A tunnel under the fascia is created by blunt digital dissection that is gently continued as proximal as possible, with care to stay superficial to the muscle. Next, a second incision is made immediately proximal to the apex of the tunnel, approximately at the mid-medial thigh, immediately posterior to the saphenous vein from 4 to 8 fingerbreadths distal to the anterior superior iliac spine. The fascia is incised, and the muscle is dissected free in a similar fashion. The tendon is subsequently divided distally, and the distal muscle is delivered to the proximal incision.

Another incision is made at a higher level at the top of the thigh. The gracilis muscle is exposed and dissected free to the level of the proximal neurovascular pedicle. Sufficient blood supply is ensured, and sufficient length to reach the perineum is assessed. Following, a tunnel is made from the upper aspect of the upper incision and dissected. The tip of the tendon is exteriorized at the ipsilateral edge of what will become the perineal incision and then securely sutured to the skin. The patient is repositioned in the prone jack-knife position with the thighs fixed. The dissection is initiated with a 5- to 7-cm anterolateral circumanal incision made through the perineal body and deepened into a plane between the subcutaneous and superficial portions of the external anal sphincter and the vagina. Once adequate wide cephalad and lateral mobilization into soft areolar tissue in all directions is accomplished, the edges of the fistula are resected to leave soft and viable tissue for further closure of the fistula. Both the rectal and vaginal sides can be closed directly or with an advancement flap. The muscle is then secured to the apex of the dissection with interrupted Prolene sutures (Fig. 5).

The wound is copiously irrigated. A 15-Fr drain is placed into the bed of the gracilis muscle harvest and secured to the skin using silk suture. A 10-Fr drain is placed through a separate stab incision along the muscle and into the perineal sinus. The perineal incision is closed

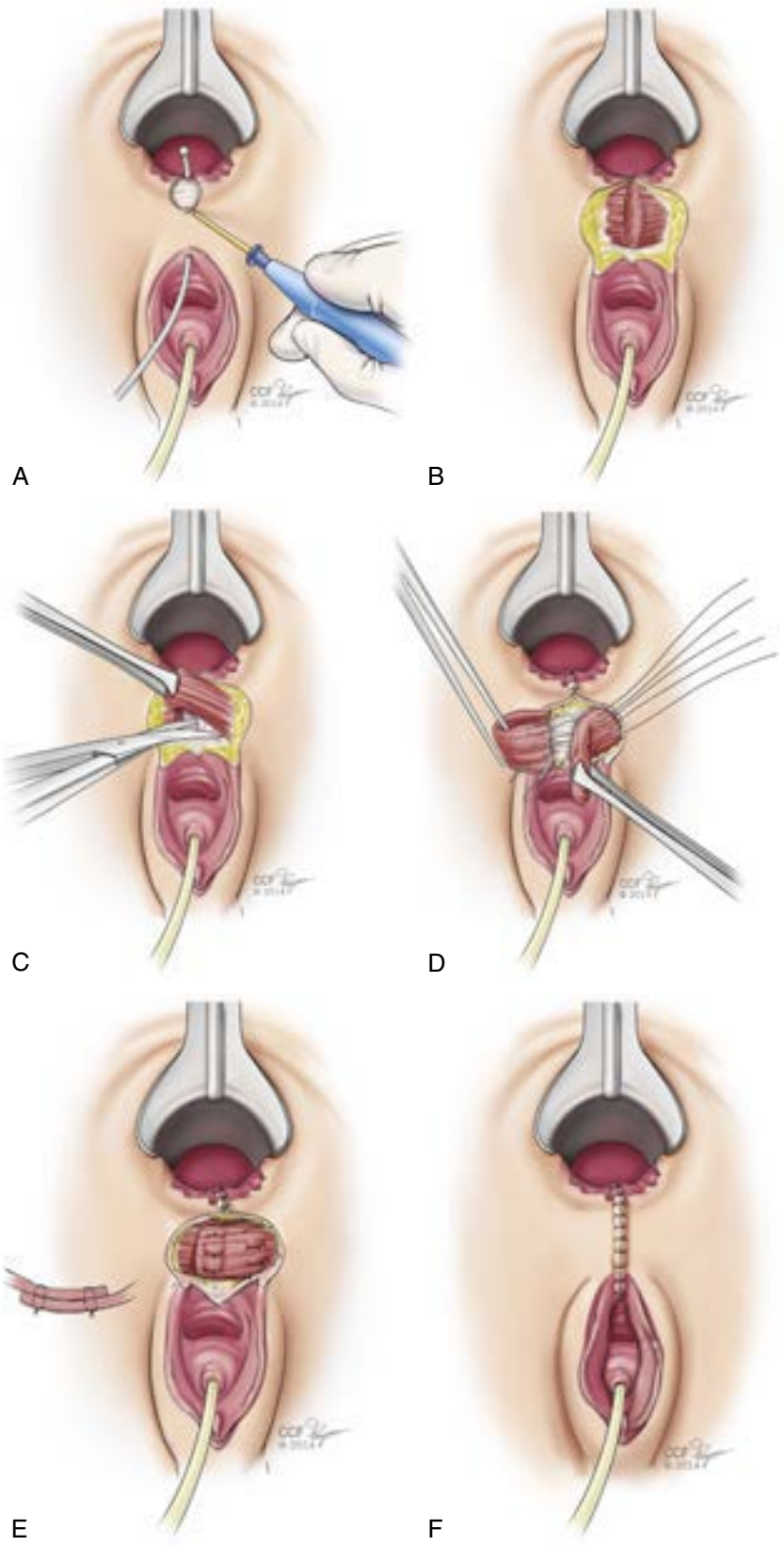


FIG. 4 Episioproctotomy. (A and **B)** Separation of the rectum and vagina with division of the fistula tract including all tissue between the rectum and vagina through the perineal body. **(C–E)** Rectal mucosa closure in layers by approximation of the internal and external sphincters and perineal body reconstruction with sphincteroplasty. **(F)** Perineal closure. (From Cleveland Clinic Center for Medical Art & Photography. Copyright 2021. All Rights Reserved.)

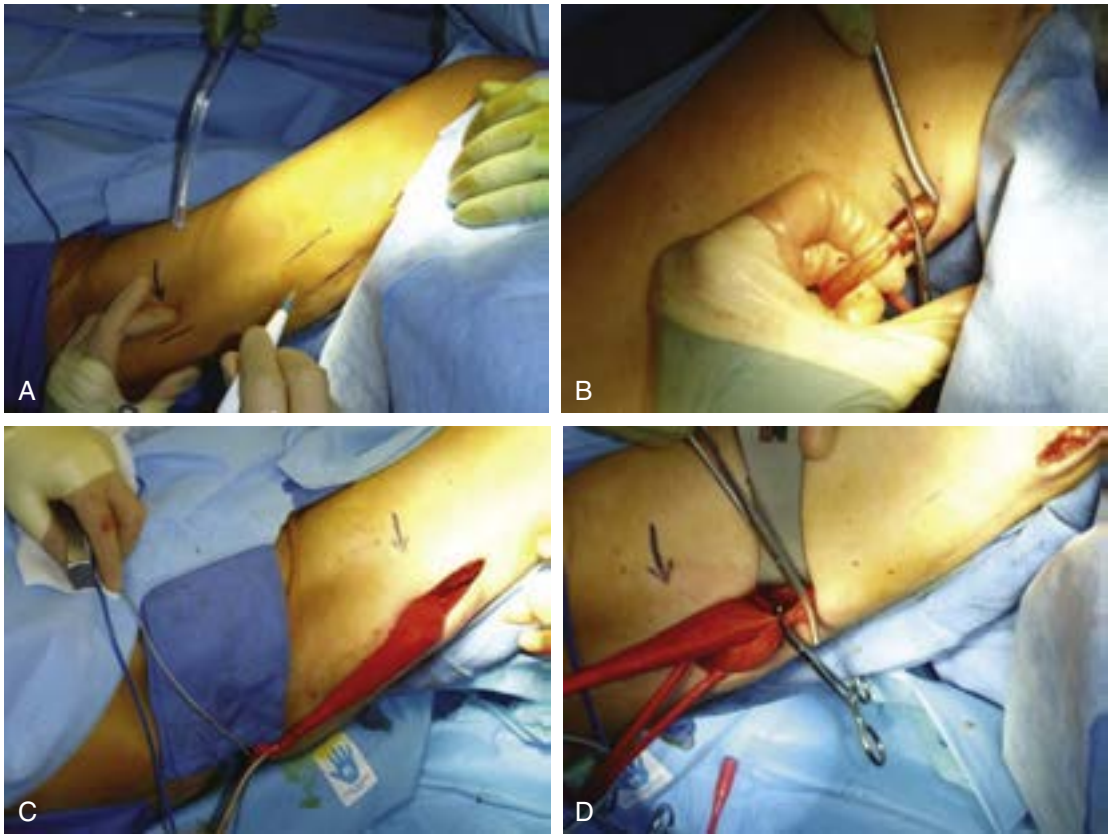


FIG. 5 Gracilis muscle interposition. (A) Thigh incision marking sites. **(B)** Division of the tendon. **(C** and **D)** Mobilization of the gracilis muscle.

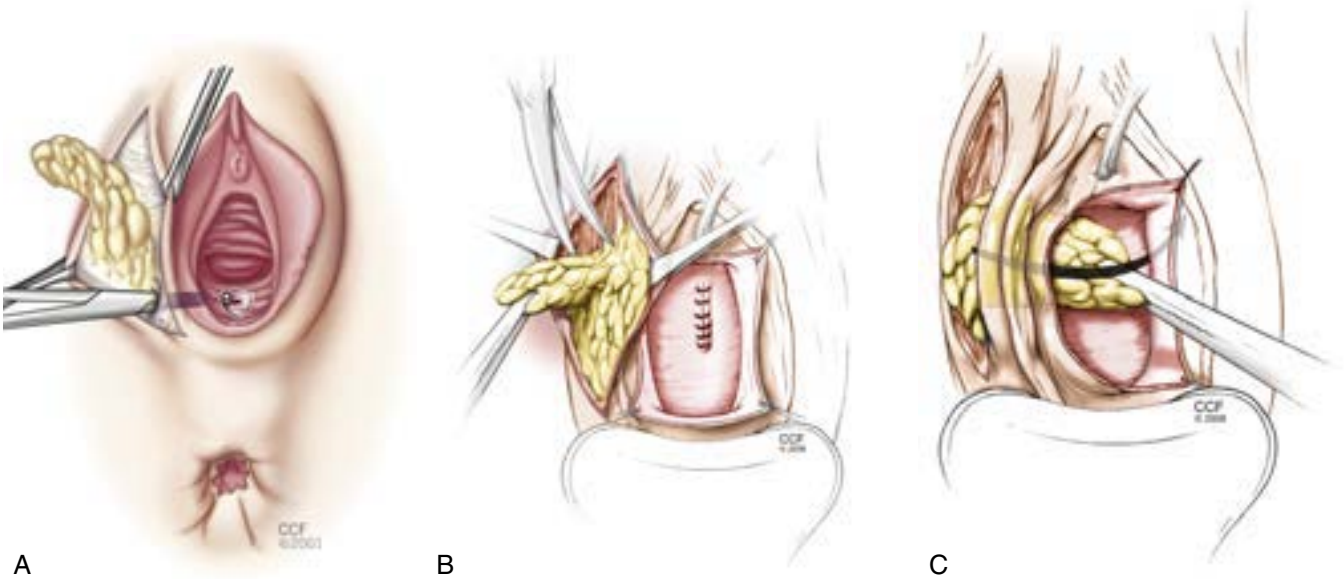


FIG. 6 Martius flap. (A) Subcutaneous tunnel is created up to the rectovaginal septum. **(B)** Mobilization of the labia majora after primary closure of the rectovaginal fistula tract. **(C)** The graft is rotated and placed in the rectovaginal septum. *(From Cleveland Clinic Center for Medical Art & Photography. Copyright 2021. All Rights Reserved.)*

using several layers of 2-0 Vicryl suture. All incisions over the thigh are closed with staples.

Healing is assessed by proctoscopy and a water-soluble contrast enema approximately 3 months after surgery. In the absence of a residual or recurrent fistula on the aforementioned studies, an examination under anesthesia is undertaken with anoscopy and probing. If necessary, additional procedures are performed to obtain complete healing of the fistula. When the fistula is no longer identified, the stoma is closed.

Success rates range between 33% and 100% for RVF repair of all etiologies and between 47% and 92% for RVF repair of obstetric etiology.

Bulbocavernosus (Martius) Flap

Dr. Heinrich Martius first described a flap consisting of a pedicled, bulbocavernosus, muscular fat pad graft from either labia majora based on the perineal branch of the pudendal artery. It has been used for a long time by gynecologists and urologists for treatment of uretherovaginal fistulas and later adopted by colorectal surgeons for the repair of low, complex RVFs.

First, the flap is harvested through a longitudinal incision over the labia, and the bulbocavernous muscle is mobilized from the labia with care not to injure the vascular pedicle. Next, the rectum and vagina are separated through a transperineal incision at the vaginal introitus, the fistula is divided, and both the rectum and vagina are closed primarily. A subcutaneous tunnel is created up to the rectovaginal septum, and the graft is placed into the septum and secured in place with absorbable sutures, ensuring that the vascular pedicle is not twisted. The labia and the perineum incisions are then closed (Fig. 6).

To date of this publication, the largest series published included 23 patients with a reported healing rate of 65% (Pitel et al.). In this series, 70% of patients had a diversion stoma. Success rates from smaller series are 65% to 100% (Kniery et al.).

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Anal Condyloma

Edward P. Hagen, DO, and Raman Menon, MD

OVERVIEW

Condyloma acuminata, commonly known as *anogenital warts,* is one of the most common sexually transmitted diseases in the United States. It is caused by the highly contagious human papilloma virus (HPV), which infects squamous epithelia. HPV is a small, nonenveloped, double-stranded DNA virus from Papovaviridae family. The incubation period ranges from 3 weeks to 8 months. Most infections are transient and are cleared within 2 years.

There are over 120 distinct HPV subtypes, of which approximately 35 types target the anogenital epithelium and have varying malignant potential. High-risk (oncogenic) types are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, and 82. Low-risk (nononcogenic) types are 6, 11, 40, 42, 43, 44, 54, 61, 72, and 81. Ninety percent of condyloma harbor HPV types 6 or 11. HPV types 16, 18, 31, 33, and 35 are occasionally identified in condyloma and are often a coinfection with subtypes 6 or 11. Growth patterns range from focally grouped diminutive warts to large and exophytic carpet-like lesions.

INCIDENCE

An accurate incidence of condyloma acuminata cannot be obtained because the size of the population at risk is unknown and because many cases are likely to be undiagnosed or subclinical. It is estimated that there are 500,000 to 1 million new cases of genital warts annually in the United States. In the United States, 24 million people are currently infected with HPV. Although condyloma affect both genders, recent data reveal that women accounted for 67% of the patient population.

RISK FACTORS

HPV is highly contagious and mostly transmitted through sexual activity. Unprotected vaginal, anal, and oral intercourse along with intercourse at a younger age are risk factors for transmission. Transmission from mother to child during delivery can also occur. Risk factors for development of condyloma include immunosuppression caused by HIV or transplantation, use of injectable drugs, cigarette smoking, and diabetes. Recent data have suggested that African Americans are at increased risk for larger lesions at time of diagnosis, resulting in more frequent need for surgery.

PATHOGENESIS, PRESENTATION, AND DETECTION

HPV invades and infects the basal keratinocytes of the epidermis. The general appearance of condyloma range from small solitary flesh-colored plaques to distinct 1- to 2-mm flesh-colored papules that occur in large clusters (Fig. 1).

The symptoms of infection may vary depending on the number of lesions and their location. The most common sites of occurrence are the perianal skin, anal canal, and genital region. Patients with a small number of warts may be asymptomatic. Other patients, especially those with larger disease burden, may have pruritus, bleeding, burning, tenderness, discharge, or pain. Larger exophytic masses can interfere with defecation, intercourse, or vaginal delivery. Lesions involving the proximal anal canal may also cause stricture.

The lesions are often easily visualized during physical examination of the external anal skin in the office. The extent of involvement should be documented by physical examination and anoscopy, sigmoidoscopy, colposcopy, and/or vaginal speculum examination, as indicated. Application of 5% acetic acid causes the lesions to turn white and can aid with identification. Other lesions may also resemble anal condyloma, and the differential diagnosis

includes benign skin tags, hypertrophic anal papillae, molluscum contagiosum, seborrheic keratoses, hypertrophied sebaceous glands, condylomata lata (secondary syphilis), dysplastic nevi, and anal cancer. A biopsy with histopathologic analysis will confirm the diagnosis.

MANAGEMENT OF ANAL CONDYLOMA

The management of anal condyloma is individualized to the patient and predicated on the size, number, anatomic distribution, and presentation of the lesions. Spontaneous resolution of condyloma has been reported, but most patients require intervention. The goal of treatment is complete destruction of all condyloma, understanding that the underlying viral infection may persist. The choice of medical management, outpatient office treatment, or treatment in the operating room, in our opinion, is based on whether it is an initial outbreak or recurrent disease, the number and distribution of the lesions, and the presence or absence of intraanal lesions (Figs. 2 and 3). There is no evidence to suggest that one treatment is significantly superior to another, and patients should be counseled in advance that recurrence is common and generally occurs within the first few months after treatment. A summary of common treatments is listed in Table 1.



FIG. 1 Anal condyloma.

We have found that managing the initial presentation in the operating room under conscious sedation allows for excellent results. This allows for careful inspection of the perianal skin and anal canal and identification of all lesions with or without the use of counterstaining with acetic acid. Additionally, excision of representative samples from all quadrants with submission for pathologic examination can confirm the putative diagnosis and identify potential patients who may have a high-grade squamous intraepithelial lesion (see further discussion later). Electrocautery fulguration of the remaining condyloma is the mainstay in addressing small to moderate lesions. Use of needle-tip cautery is very useful as it can more precisely target the remaining small condyloma with decreased damage to the surrounding tissue. In this manner, the lesions are fulgurated, first turning white and then forming an eschar that can be removed with a curette. What may appear to be a large carpet of numerous condyloma can be treated in this fashion as the condyloma often have a narrow base, and islands of normal perianal skin can be identified between them. This approach has been shown to be safe and without significant risk of anal stenosis, even with confluent condyloma. One recent small study suggested that argon plasma treatment may be more effective at decreasing relapse in HIV-positive patients, however there can be viable virus in the smoke plumes, which in theory presents a higher risk of transmission to the exposed treatment team.

On rare occasions, one may encounter carpeting of condyloma with a wide base and minimal to no intervening normal perianal skin. In this circumstance, we recommend staging the treatment of the lesions to minimize anal scarring and stenosis. Such patients benefit from treatment in the operating room, where only half the perianal skin is treated and allowed to heal before returning in 3 to 4 weeks to treat the other half.

After clearance of all lesions in the operating room, close office surveillance is critical. Typically, recurrence is limited to a few lesions, which are amenable to topical treatment by the physician in the office or by the patient at home. Trichloroacetic acid (TCA) is a keratolytic and chemically cauterizes the skin. It can be applied very precisely in the office with a small cotton-tipped swab with minimal damage to the surrounding normal skin (see Fig. 2). The most commonly used self-administered topical treatments are imiquimod and podofilox. The best approach to recurrence may be a combination of ablative therapy and topical therapy, with reduced recurrence of condyloma when imiquimod was used as an adjunct to conventional ablation. Recent data suggest that refractory intraanal condyloma in particular may benefit from combined therapy with imiquimod and ablative methods.



FIG. 2 Treatment of anal condyloma before **(A)** and after **(B)** treatment in office with trichloroacetic acid.

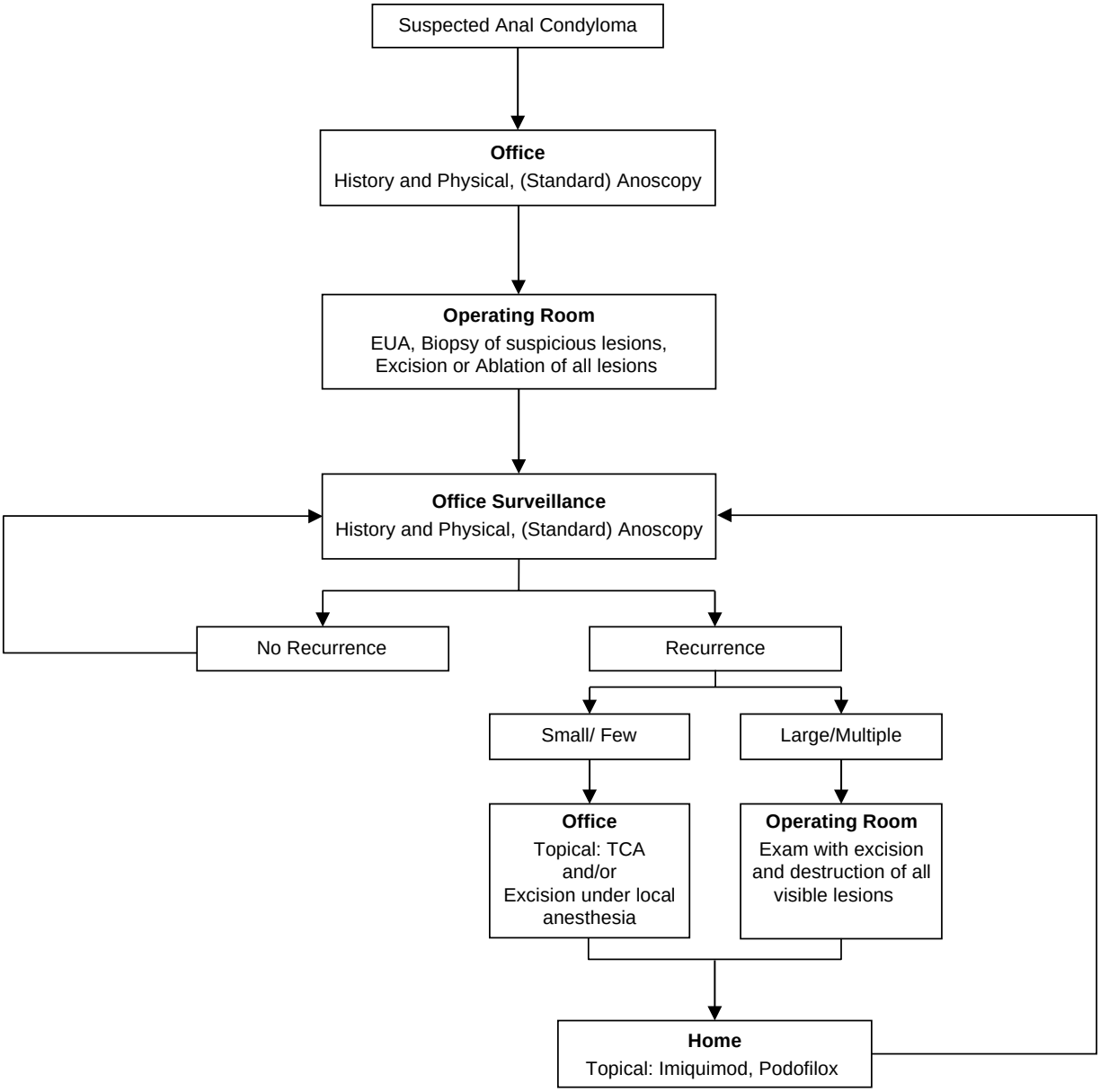


FIG. 3 Treatment algorithm for anal condyloma.

Future treatment may include "therapeutic vaccination" in which a fusion protein antigen of the virus is used to generate an immune response targeting infected cells. This minimizes the risk of attacking healthy tissue while enhancing a CD4/CD8 T-cell response. No vaccine has yet been licensed for therapeutic use at this time, but ongoing investigations are underway.

GIANT CONDYLOMA ACUMINATA

Giant condyloma acuminata (GCA) is a rare, poorly-defined condyloma variant. No formal size criteria has been established, though reports in the literature vary from 1.5 to 30 cm in maximum diameter. It was originally described as lacking malignant potential, however it is now believed that up to 50% of GCA may contain foci of squamous cell carcinoma. The disease is characterized by large, slowly progressive, exophytic, ulcerative, cauliflower-shaped tumors that infiltrate adjacent tissue. It affects men more than women and is associated with immunodeficiency, smoking, and multiple sexual partners.

On clinical examination, one may encounter a palpable tumor mass with bleeding, pain, fistulae, and clinical pruritus. Most practitioners recommend operative management with a wide-local full-thickness excision with 1-cm tumor-free margins. In lesions that involve the anal sphincter complex, abdominoperineal resection may be necessary. Adjuvant treatment with chemotherapy and radiation may also be considered in light of the high risk of recurrence.

ANAL SQUAMOUS INTRAEPITHELIAL LESION

The incidence of squamous intraepithelial lesions is increasing. It has been recognized that these HPV-associated anal dysplastic lesions may be the precursor for anal squamous cell cancer, though the exact timing of transformation is unclear. Risk factors for progression

TABLE 1 Common Treatments for Anal Condyloma

Forms of Treatment	Mechanism of Action	Treatment Instructions	Clearance Rate	Recurrence Rate	Side Effects/ Pregnancy
Imiquimod (Aldara) (Patient-applied)	Induction of pro-inflammatory cytokines	5% cream, applied at bedtime and washed off in the morning three times per week (Monday, Wednesday, Friday) for up to 16 weeks	40%–80%	10%–20%	Irritation, erythema, ulceration, pain, burning, edema, induration Pregnancy: Category C
Podofilox (Condylox) (Patient-applied)	Mitosis interruption	0.5% gel, applied twice daily for 3 consecutive days, followed by 4 days without treatment; not to exceed 4 weeks	65%–70%	20%–35%	Irritation, erythema, ulceration, pain, burning, edema, induration Pregnancy: Category C
Synecatechins (Veregen) (Patient-applied)	Unknown	15% ointment, applied three times per day for up to 16 weeks	55%–60%	5%–10%	Irritation, erythema, ulceration, pain, burning, edema, induration Pregnancy: Category C
5- Fluorouracil (Efudex) (Patient-applied)	Mitosis interruption	5% cream applied daily for up to 10 weeks or 1% cream applied twice a day for 2–6 weeks	50%–75%	25%–50%	Irritation, erythema, ulceration, pain, burning, edema, induration Pregnancy: Category X (contraindicated)
Trichloroacetic acid (Tri-Chlor) (Physician-applied)	Chemical cauterization	80%–90% solution applied to lesions while avoiding uninvolved surrounding skin; may repeat monthly	70%–75%	20%–40%	Irritation, pain, burning Pregnancy: Safe to use
Liquid nitrogen (Physician-applied)	Cryoablation	Apply with applicator whitening the surrounding skin; may repeat monthly	70%–75%	30%	Irritation, edema, necrosis, ulceration, pain Pregnancy: Safe to use
Podophyllin (Podocon-25) (Physician-applied)	Mitosis interruption	25% extract applied to lesions once per week to be washed off by patient 4 hours later for up to six treatments; not to exceed 0.5 mL per application	40%–70%	30%–55%	Irritation, erythema, ulceration, pain, burning, edema, induration; systemic absorption may cause fatal side effects Pregnancy: Category X (contraindicated)
Electrocautery (Physician-applied)	Electrocauterization	Target lesions while minimizing damage to normal skin; repeat as needed	60%–90%	35%	Pain, scarring Smoke plumes may contain viable virus and may pose an infectious risk to healthcare provider Pregnancy: Safe to use
Argon laser (Physician-applied)	Vaporization	Target lesions while minimizing damage to normal skin; repeat as needed	80%	30%–50%	Pain, scarring Smoke plumes have been shown to contain viable virus and pose an infectious risk to healthcare provider Pregnancy: Safe to use
Surgical excision (Physician-applied)	Removal by tangential excision	Target lesions while minimizing damage to normal skin; repeat as needed	60%–90%	40%	Pain, bleeding, scarring Pregnancy: Safe to use

include HIV infection, anoreceptive intercourse, transplantation, and a history of cervical or vulvar neoplasia and lesions with HPV-16.

In patients who are at higher risk for malignant transformation, one may consider performing anal cytology akin to the cervical Pap smear. The terminology used in describing cytologic findings is similar to that of the cervical Pap: atypical squamous cells of undetermined significance (ASC-US) and low-grade (LSIL) or high-grade squamous intraepithelial lesion (HSIL). The finding of HSIL or LSIL from either anal cytology or on biopsy of a condylomatous lesion requires further investigation and workup.

There is controversy on the optimal management and surveillance strategy of patients with HSIL or LSIL. The two general approaches to managing these patients are high-resolution anoscopy (HRA) or expectant management (EM). HRA involves careful inspection of the anal canal with a high-resolution microscope after application of acetic acid (with Lugol's solution counterstaining) to identify other putative dysplastic regions for biopsy or ablation. EM involves frequent office examinations with operative excision of any visible lesions. In a recently published single-institution, retrospective, cohort series, Crawshaw et al. analyzed the outcomes for 424 patients with biopsy-proven LSIL or HSIL who underwent either HRA (220 patients) or EM (204 patients). Only 3 patients progressed to anal squamous cell cancer (1 in the HRA group and 2 in the EM group), with all 3 patients being noncompliant with either treatment or follow-up. Our practice has been to follow the EM pathway for these patients.

HUMAN PAPILLOMAVIRUS VACCINE

Human papillomavirus (HPV) vaccination is an effective method to prevent HPV infection. Three different vaccines are available in United States: a quadrivalent vaccine (HPV4, Gardasil) targeting HPV 6, 11, 16, and 18; a 9-valent vaccine (HPV9, Gardasil 9) targeting HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58; and a bivalent vaccine (HPV2, Cervarix) targeting HPV 16 and 18.

In 2019, the United States Advisory Committee on Immunization Practices (ACIP) combined the recommendations for administering the HPV vaccine series (HPV9, HPV4, or HPV2) to males and females. Their current recommendations are that the vaccine is given routinely at 11 to 12 years of age or until 26 years of age if not started previously. These vaccines can be administered as young as 9 years of age. Catch-up vaccination is also recommended for females 13 to 26 years of age who have not been previously vaccinated, and in 2019 they added males to this recommendation.

No data exist regarding the long-term efficacy of administration of the HPV vaccine in the setting of active or previous HPV infection. Some practitioners advocate vaccinating in this setting as it may confer protection against the other HPV strains to which the patient may not have been exposed. Our practice has been to refer high-risk patients to an infectious disease specialist for further discussion.

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Management of Pilonidal Disease

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INTRODUCTION

Pilonidal disease represents a spectrum of disorders ranging from a simple asymptomatic sinus in the skin up to a large, complex open wound with multiple draining sinuses and infection. It is for this reason that the old nomenclature of *pilonidal cyst* or *pilonidal sinus* should likely be replaced by the more appropriate term *pilonidal disease* (PD). The term *pilonidal* is derived from the roots "pilus" (hair) and "nidus" (nest). PD is believed to be an acquired disease related to trapping of hairs in the natal cleft that leads to local trauma and inflammation. It is common, and although it can affect anyone, it is typically seen in hirsute individuals who have deep natal clefts. Elevated body mass index, poor hygiene, prolonged sitting, and excessive sweating may be additional risk factors. Hair type may be a predictor, with some authors hypothesizing that recently cut short pieces of hair more easily insinuate themselves into the gluteal cleft, and others hypothesizing that hair with barbed ends may more easily become trapped in the gluteal cleft and incite PD.

The typical individual presents with drainage or pain in the area of the gluteal cleft. Patients will often have acute abscesses that require immediate drainage. Definitive surgical management in the face of active infection must be discouraged. Simple abscess drainage may be all that is required or may act as a bridge to definitive surgery. Management with oral antibiotics will fail in the setting of acute abscess, but it may be successful in the inflammatory phase before abscess formation. Diagnosis is based largely on history and physical examination and requires no laboratory or radiographic testing. The presence of midline pits in the sacrococcygeal region coupled with drainage, abscess formation, or an open wound all suggest PD, whereas alternative diagnoses of hidradenitis suppurativa, Crohn's disease, anal fistula, and in rare cases neoplasm should also be considered.

TREATMENT

Treatment options range from simple shaving without surgery to wide local excision and complex flap reconstruction. There are many described methods of treatment. It is the belief of the authors that a surgeon should be familiar with three to four methods of surgical management that address the entire spectrum of disease severity and then work to develop expertise in each of them. It is the disease

severity in fact that should drive the method selected for surgical treatment. Although any method could potentially be used in any situation, it would seem inappropriate to do a complex flap procedure such as a rhomboid flap in the setting of very minor disease. Less-extensive methods will lead to optimal outcomes with lower risk in the setting of mild disease.

Nonoperative Treatment

In selected cases of minor disease, nonoperative treatment consisting of shaving and hygiene measures can be quite successful. Older retrospective studies have shown that patients have more favorable outcomes if shaving is used and surgery is avoided. It should be noted that these data are older and were compiled during the era when wide excision with healing by secondary intention was more common. Laser hair removal has been shown to reduce recurrence of PD in cohort studies, but there are no randomized controlled trials to date to support its use. It may also be reasonable to encourage laser hair removal in the setting of minor disease such as primary treatment. The risk is low, but the cost to the patient may be quite high, and this should be considered. Weight loss and avoidance of prolonged sitting may also help minimize symptomatic PD.

Operative Management

We will focus on several procedures. These techniques can be grouped into basic or simple procedures, intermediate procedures, complex flap procedures, and endoscopic procedures. The literature regarding the success of one procedure over another is mixed and consists mostly of small retrospective cases series, with some randomized controlled trials comparing two or three methods. It is possible to find data supporting the use of any procedure over another; therefore it is critical that a surgeon is familiar with their personal outcomes as they relate to procedural approach. Aftercare by the patient and provider is likely as important as the procedural technique in success. It is imperative that patients keep the operative area clean, perform excellent wound care, and avoid strenuous activity until healing has taken place. Poor wound management and poor decision making will lead to failure.

Principles of Treatment

Several basic principles should be considered when treating pilonidal disease so that optimal outcomes can be achieved, as discussed in the following sections.

Control Sepsis

All acute abscesses must be drained, and any attempt at definitive surgical management in the setting of active infection should be avoided. All PD will be colonized with bacteria, but this is very different from active infection. Primary closure with or without flap reconstruction will fail in the setting of infection and will make future management more difficult.

Do the Least Amount of Work Possible

As stated previously, the anatomy or severity of disease should drive treatment method selection. If the disease is minor, yet the patient requests surgery, a pit-picking procedure (description to follow) plus or minus a small amount of additional excision may be all that is needed. Complex and recurrent disease typically requires a wide excision and flap reconstruction.

Avoid Too Much Excision

The old adage advising excision of all disease down to the post-sacral fascia results in an extremely large and complex wound. This technique should be avoided whenever possible. Excision that is too deep or aggressive has been shown to correlate with disease recurrence/treatment failure.

Unroof All Disease, Debride Granulation Tissue, and Remove Hair

This principle goes part and parcel with the principle of avoiding too much excision. Removal or unroofing of skin overlying active disease may be essential, but do not be tempted to dissect any deeper. It is important, however, to account for all disease. Any hair or debris should be removed, and granulation tissue should be curetted or cauterized. It may be helpful to inject sinuses with methylene blue to ensure that no extensions are missed. Probes may also be used. If the wound is to be closed, adequate irrigation of the wound with saline is encouraged.

Use Off-Midline Excision and Closure

It is essential to attempt to perform an off-midline excision and closure. Wounds located in the midline of the gluteal cleft just do not seem to heal as well as those located elsewhere. Although it may be impossible to keep the entire wound out of the midline, there should be significant effort to minimize the amount of wound in the midline.

Minimize Tension if the Wound Is Closed

Because of the inherent difficulty with wounds located in the region of the gluteal cleft, every effort should be taken to minimize wound morbidity. A "tension-appropriate" closure should be utilized. If this cannot be achieved initially, then tissue undermining or use of a flap should be considered. When flaps are used, it is important to ensure a lack of tension at both the excision site and the donor site. Tension and separation of the operative wound seem to be better tolerated at the donor site because these sites are off the midline.

Change the Anatomy/Flatten the Natal Cleft

It is believed that deep natal cleft anatomy contributes to formation of pilonidal disease; therefore it seems reasonable that any procedure designed to flatten cleft anatomy would lead to lower recurrence rates. Most flap procedures, and certainly the Bascom cleft lift procedure, are designed to do this. The cleft lift procedure in particular combines most if not all of the aforementioned principles into one operation, which has likely contributed to its success. That stated, not all PD requires this to be done.

Never Underestimate the Impact of Postoperative Care

Postoperative management has a significant impact on the ultimate outcome, especially in cases of off-midline closure. Limitations in physical activity, work restrictions, and limitations of weight bearing on the buttock will help minimize wound dehiscence. There are no true prescribed evidence-based recommendations to follow, but clear written instructions should be provided to patients that can easily be followed. These recommendations should be covered in the preoperative discussion as they will sometimes affect a patient's decision to undergo a surgical procedure.

Basic/Simple Procedures

Abscess Drainage

An individual presenting with an acute pilonidal abscess requires only definitive incision and drainage at first. Typically, the abscess "points" to one side of the natal cleft, and this is easily visualized or is palpable. Our recommendation is to incise the abscess cavity just off midline under local anesthetic. It is important to ensure that all loculations are broken up and that all purulence is drained. Initial packing is often employed for hemostasis, but we have not found continued packing to be necessary. Once or twice daily showering with soapy water aids in keeping the wound clean. These wounds will typically close in 1 to 2 weeks, but they can sometimes result in a chronic wound.

Non-Excisional Procedures

Patients with relatively minor disease who wish to avoid an excisional procedure may be candidates for alternate therapies, such as

the injection of phenol or fibrin glue. This procedure begins with removal of hair and debris from the tracts or pits. After administration of local anesthetic, the tracts are injected with phenol to create epithelial destruction and inflammation to encourage tract closure. Alternatively, fibrin glue may be injected to close the tracts. These can be combined with endoscopic techniques to delineate all tracts and thoroughly debride them (discussed later).

Pit-Picking/Simple Bascom Procedure

In cases of mild chronic disease in which the primary complaint is related to midline pits or in cases in which there is a small wound off-midline, this procedure may be considered ideal. It is simple and results in a healed wound rather quickly—usually in 1 to 3 weeks. In most cases, PD shows an affinity for one side of the natal cleft. In cases in which disease is localized purely to the midline in the form of pits, a pit-picking procedure alone is appropriate. In this technique, the central pits are excised using a punch knife of appropriate size (just slightly larger than the pit itself). The knife is inserted to full depth, hair and debris are removed, and the wound is closed primarily. The authors prefer 3-0 Vicryl suture, but any absorbable or permanent suture may be used. This is repeated until all pits are excised. It is not unusual to encounter a bit of bleeding after pit excision, and this can be controlled with needle-tip electrocautery.

In cases in which there is induration off the midline, a true simple Bascom procedure can be performed. Pits are excised as described earlier, and a 2- to 3-cm incision is created just lateral to the indurated area off the midline. A skin and subcutaneous flap is created by dissecting toward the midline pits, ultimately connecting the two areas of dissection. Indurated tissue is excised, the wound is irrigated, and then it is partially closed at the superior and inferior portions leaving the central portion open. A small amount of packing is placed in the open portion of the wound and is removed the next day. Continued packing may be used or omitted per surgeon and patient preference. This technique minimizes excision in the midline and keeps the larger wound in a lateral position, which expedites and simplifies healing (Fig. 1).

Excision With or Without Primary Wound Closure

Many consider the gold standard of surgical management to be simple excision with healing by secondary intention. It is certainly still commonly performed, though many patients prefer to avoid an open wound. Using the principles outlined earlier, the disease should be unroofed ensuring that all hair, debris, and granulation tissue is removed, curetted, or cauterized. Every attempt should be made to minimize the tissue excised and to keep the majority of the wound off the midline. If possible, a simple primary closure can be performed, though the authors' experience is that this often fails. Alternatively, the wound may be left open to heal by secondary intention, and the skin edges may be marsupialized.

This procedure rarely results in a complex wound if patients are appropriately selected. If careful and meticulous wound care is employed postoperatively, the rate of success is reasonably high with this technique—again in appropriately selected individuals. Patients with extensive and destructive disease should not be managed this way as management results in a large and complex wound that rarely heals. Complete healing in the best of cases takes weeks to months. Some have reported the use of negative pressure dressings in this setting, but management of these devices in this location is often challenging. This option may be appropriate with larger wounds if resources are available.

Intermediate Procedures

These procedures involve the excision or unroofing of disease in the midline (or just off the midline) followed by subcutaneous flap mobilization and tension-appropriate closure with or without the use of a closed-suction drain. They are designed to alter the cleft anatomy while minimizing the amount of excision. They also employ an off-midline closure. Patients with mild to moderate disease are ideal for these techniques. Those with extensive or destructive disease are not likely suitable for this type of management. Disease that is very close to or abuts the anal verge may also present a challenge if considering this type of management.

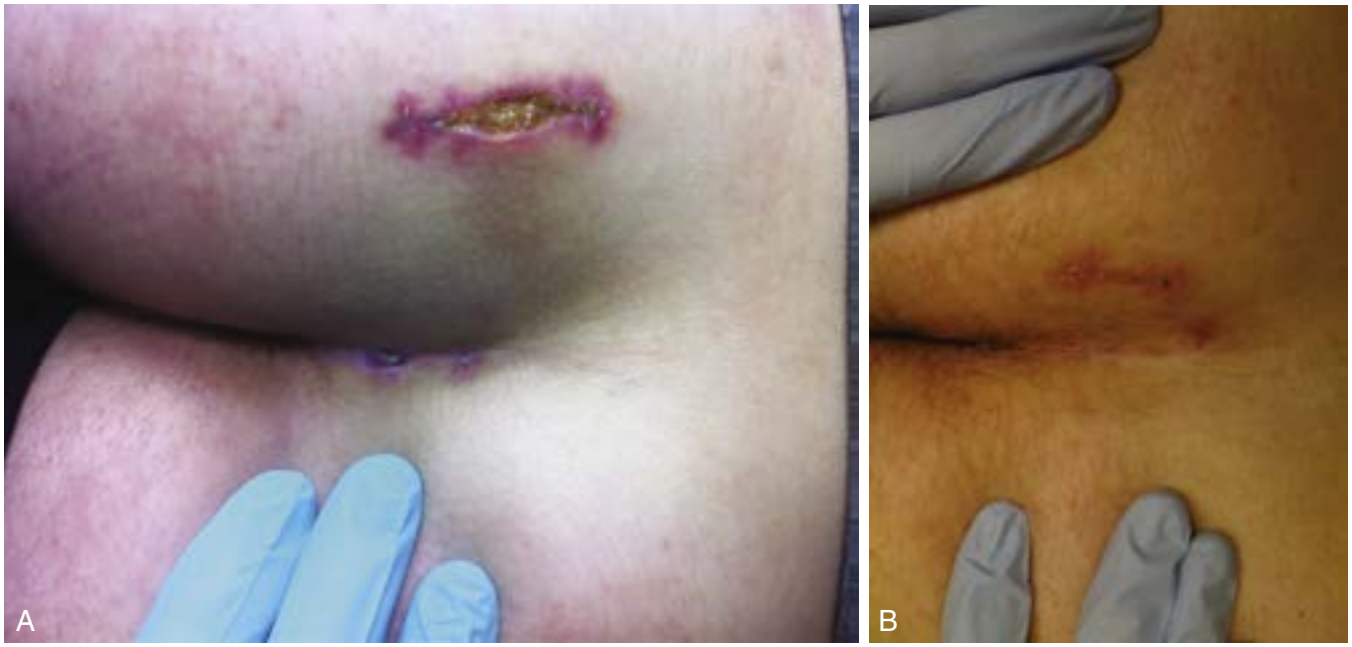


FIG. 1 Two cases treated with the simple Bascom approach (lateral excision and midline pit excision or pit picking). (A) Patient in the early stages of healing. **(B)** Patient near completely healed. *(Courtesy Eric Johnson, MD.)*

Karydakis Flap

Initially, the affected tissue in the midline is excised, which results in an elliptical defect in the natal cleft. A skin flap with a beveled edge is then created and mobilized such that it will reach across midline to facilitate a tension-appropriate primary closure. The wound is closed in layers to obliterate as much dead space as possible. Superficial wounds do not require drainage, but deeper wounds may require employment of a closed-suction drain. Development of seroma places the repair at risk. If a drain is used, the authors leave it in place for a minimum of 3 days and require that the output be 20 mL or less per day for 2 consecutive days. This is a simple procedure to perform and results in some flattening of the natal cleft as well as a closure off the midline (Fig. 2).

Cleft Lift Procedure

This is a simple yet creative procedure originally popularized by the late Dr. John Bascom. It employs all the aforementioned principles and is suitable for most patients who are encountered. Preoperative marking of the patient in the prone position in the operating room is essential to correct performance of this procedure. This is the preferred procedure of the authors for patients with mild to moderate PD. Before a chlorhexidine prep is performed, the "safe-zone" is marked with indelible marker by pressing the gluteal tissue together in the midline. The mark is drawn where the tissue from each side touches in the midline. The buttocks are then taped apart revealing a "wishbone"-shaped mark. This establishes a "safe zone" beyond which no further dissection should be performed. This also ensures a tension-appropriate closure. An additional elliptical/scimitar-shaped mark is placed over the area with more significant disease after skin preparation. This marks the skin that will be excised. The inferior portion of this mark is scimitar-shaped to ensure appropriate closure near the anal verge. After instillation of epinephrine containing local anesthetic, the skin of the diseased area outlined by the elliptical mark is excised. Take care not to excise much if any subcutaneous fat. This will invariably expose some sinus tracts, hair, and granulation, which should all be removed, curetted, or cauterized. A skin/subcutaneous flap, about the thickness of a mastectomy flap, is created by dissecting toward the opposite side safe-zone boundary. Use of skin hooks facilitates this dissection. When the flap is raised inferiorly (near the scimitar), the dissection should be slightly deeper, providing additional thickness to this portion of the flap. Scar tissue in the midline is then released by dividing it into small squares. The flap is mobilized across the midline, and the wound is closed in layers, taking care to obliterate as much dead space as possible. In the majority of cases, a closed-suction drain will not be necessary, though when used it should be managed as described earlier. This procedure results in flattening of the natal cleft with an off-midline closure and is easy to perform (Fig. 3).

Complex Procedures

These procedures consist of a wide excision of severely diseased tissue followed by mobilization of a lipocutaneous flap from an adjacent donor site that is utilized for closure of the complex wound. They will almost always require closed-suction drainage. These procedures are ideal for patients who present with complex, destructive, and recurrent disease. The advantage of these techniques is that they bring thick and healthy tissue into the midline to fill and close large defects. They also flatten the natal cleft, potentially leading to lower recurrence rates. Disadvantages include the time and skill required to perform the procedures as well as the complexity of wounds that result from flap failure. Fortunately, complete loss or dehiscence of a flap is a relatively rare complication if patients are appropriately selected.

Rhomboid Flap

This is a more complex procedure that is quite useful in the setting of complicated PD. The patient is again positioned in the prone position, and a chlorhexidine skin prep is performed. We do administer intravenous antibiotics to cover skin flora. A diamond-shaped area of skin is excised, encompassing all disease. This is typically carried down to the post-sacral fascia, though a more conservative excision may be performed based on the amount of disease present. It is helpful to orient the original diamond- or rhombus-shaped excision just slightly counterclockwise. This ensures that the inferior tip of the rhombus is not located adjacent to the anus, which is the most likely area of postoperative wound separation. This technique is referred to as a *modified rhomboid* or *Limberg flap.* The flap is then mobilized from the donor site, typically the right buttock. The thickness of the flap should be identical to the thickness of the tissue excised from the midline. The flap should be handled gently throughout the case. It is created by incising laterally from the right lateral tip of the rhombus onto the right buttock and then inferiorly (Fig. 4). One must ensure preservation of a thick and wide pedicle to ensure adequate blood

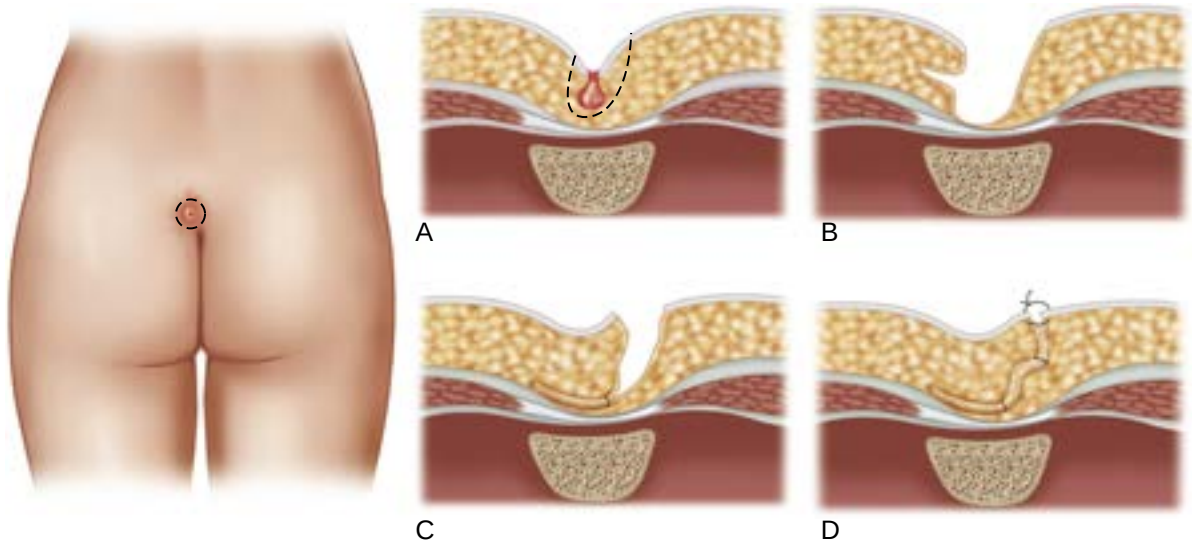


FIG. 2 Karydakis flap procedure. (A) Midline pits are excised. **(B)** Skin flap from one side is raised. **(C)** Skin flap is secured down to the underlying tissue so that the wound is moved off the midline **(D)**.



FIG. 3 Bascom cleft lift procedure. (A) The "safe zone" is marked by pressing the gluteal tissue together in the midline and marking where the skin of each side touches the midline. **(B)** Scimitar-shaped area of diseased skin is excised, curving away from the anal verge and favoring one side of the safe zone. **(C)** Skin flap from the opposite side of the safe zone is raised. **(D)** Skin flap is secured to the underlying tissue, moving the wound off the midline. **(E)** Completely healed wound. *(Courtesy Eric Johnson, MD.)*

supply. It is also wise to mobilize some of the tissue above the flap on the right buttock to minimize tension at the donor site closure portion of the repair.

After adequate flap harvest, it is rotated in a counterclockwise direction to cover the midline. The closed-suction drain should be placed, typically from the right side superiorly, and the flap is then secured to the mid-portion of the wound with a 2-0 absorbable suture. This will often require the help of an assistant. At this point, it is not unusual to feel just a bit unsure of one's ability to close this large wound. Do not worry; it will close. The wound is then closed in layers with absorbable suture. The authors close the skin with a 4-0 monofilament absorbable suture and then cover the wound with surgical skin glue. The drain is managed as referenced earlier (see Fig. 4).

It is imperative to ensure that the patient does not engage in strenuous activity for 4 to 6 weeks after this procedure. This wound is always closed under some tension and is at risk for dehiscence during this period. It is not unusual to develop one or two small areas of wound separation that may drain in the first 1 to 2 weeks after surgery. This is not a serious complication, but it will require some minor wound care for 2 to 4 weeks. These areas almost always close. If they fail to close by 12 weeks postoperatively, we do not hesitate to return the patient to the operating room for minor debridement and primary closure of these areas, which has been uniformly successful (Fig. 5).

Special Situations

In some patients, the extent of disease extends far enough up onto the lower back that it may be impossible to harvest a flap large enough to close the entire wound. We have encountered this several times and have a standard approach that we take in this setting. The key is to excise the portion of the wound involving the natal cleft and nothing more. The portion of the wound above the cleft can be debrided and treated like any open wound. It will heal because it is not in the low midline, as long as one has source control in the natal cleft. The rhomboid flap can be created in the standard fashion, rotated into place, and left with a free edge superiorly (Fig. 6). A negative pressure wound dressing is an excellent adjunct in this setting and will assist with rapid healing.

Although we will not go into an extensive description, the V-Y flap technique is useful in the setting of failed flap repairs. This method allows mobilization of a large amount of tissue into the midline to close large defects. This is the only setting in which we use this technique, as the rhomboid flap is extremely effective as a primary complex technique. When performing these complex flap repairs, patient selection is imperative. It is unwise to embark on an attempt in a patient who is a tobacco user or an uncontrolled diabetic. Those with collagen vascular disorders or documented problems with wound healing should be approached with caution. In terms of procedural timing, we will attempt definitive surgery after abscess drainage when there is no visual evidence of ongoing acute inflammation or infection. If a definitive procedure fails, we wait as long as possible before a salvage procedure—no sooner than 12 weeks (early and rare) and typically between 6 and 12 months. It is important to allow a "failed" procedure time to heal, as they often will.

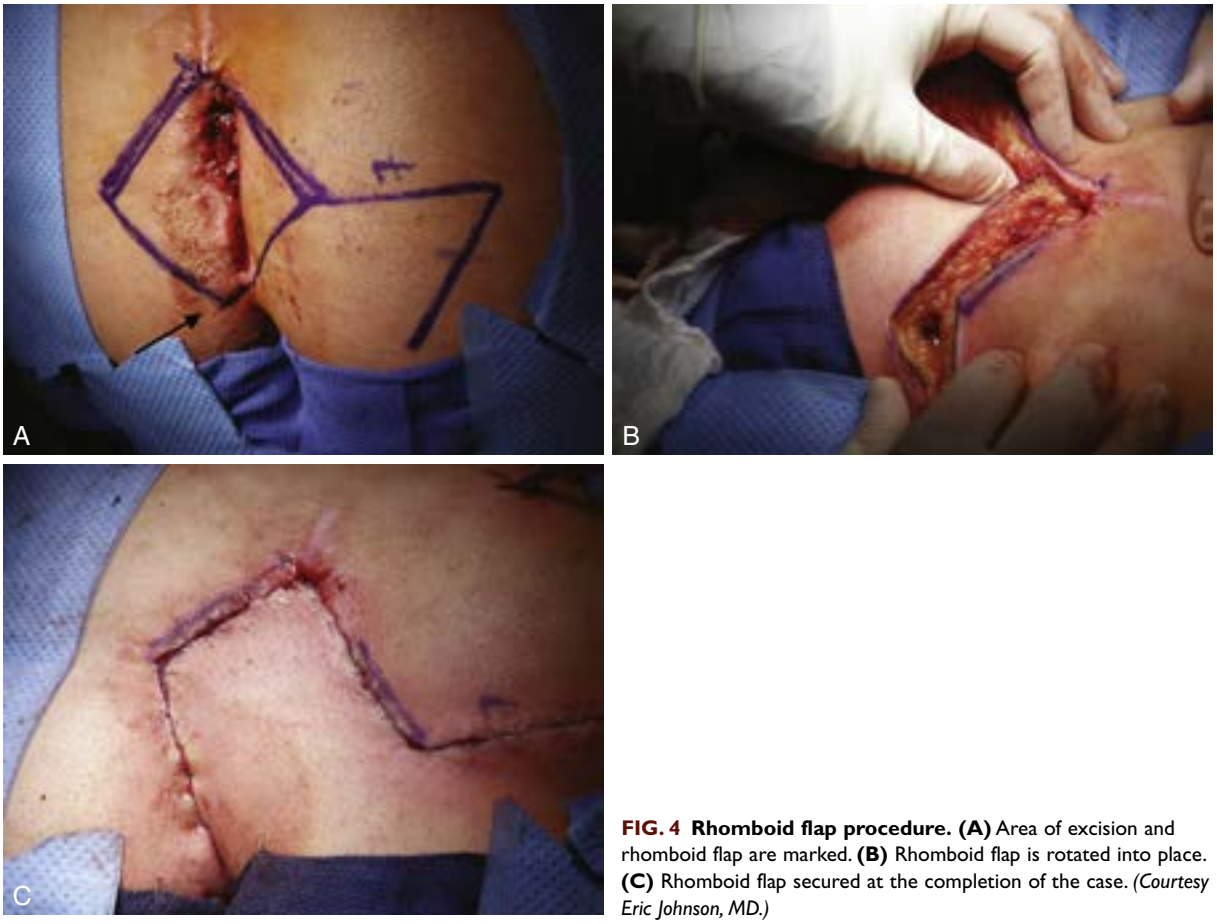


FIG. 4 **Rhomboid flap procedure. (A)** Area of excision and rhomboid flap are marked. **(B)** Rhomboid flap is rotated into place. **(C)** Rhomboid flap secured at the completion of the case. *(Courtesy Eric Johnson, MD.)*



FIG. 5 Patients treated with a rhomboid flap may develop small areas of wound separation during the healing process. These occur commonly and tend to drain for a short time before healing. *(Courtesy Eric Johnson, MD.)*



FIG. 6 Patient who was treated with a rhomboid flap but had disease that extended for a fair distance cephalad. The cephalad portion of the disease was debrided/unroofed and left open. The wound was treated with a negative pressure device and healed without incident. *(Courtesy Eric Johnson, MD.)*

Endoscopic Procedures

Because of the size and morbidity of the wound that is often created using the aforementioned procedures, there is a growing interest in minimally invasive or endoscopic techniques. Using techniques first used to treat perianal fistulae, video-assisted ablation of pilonidal sinus (VAAPS) was developed in 2013. In this procedure, a fistuloscope is used to cannulate and explore all pilonidal openings and their associated internal tracts. Endoscopic forceps are used to remove any hair and debris. Electrocautery is then used to ablate the sinus tracts. Finally, an endobrush or curette is used to remove any remaining debris or granulation tissue. This procedure has also been combined with phenol instillation in the tracts to sclerose the remaining epithelium, destroy any necrotic debris, and promote healing of the sinus. The external openings are left open to drain, and a light dressing is applied. This procedure can be done under local anesthesia with minimal patient discomfort. Early results have been encouraging, with reported healing rates over 90%.

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Pneumatosis Intestinalis and the Importance for the Surgeon

Joseph Kim, MD, Ahmed Chatila, MD, Muhammad Hammami, MD, and Eric Goldberg, MD

INTRODUCTION

Pneumatosis intestinalis (PI) refers to the presence of gas-filled or air-filled cysts in the bowel wall. The clinical significance can range from an incidental radiologic finding with an excellent prognosis to manifestation of an underlying intraabdominal catastrophe requiring emergent surgical intervention. Distinguishing benign etiologies from underlying surgical emergencies is crucial and requires a strong understanding of etiologic associations and clinical presentations.

BENIGN CAUSES OF PNEUMATOSIS INTESTINALIS

There are a variety of theories on the pathogenesis of PI. The mechanical theory postulates that PI results from dissection of air through the mucosal or serosal surface of the bowel wall. The bacterial theory postulates that luminal bacteria gain access intramurally and produce gas. Each one of these theories likely has merit with certain etiologic associations. For example, mechanical theory can explain the association of PI with pulmonary conditions such as chronic obstructive pulmonary disease (COPD) or mechanical ventilation where ruptured air blebs can track along the mesenteric root into the bowel wall. The bacterial theory better explains the association of PI with gastrointestinal motility disturbances such as those seen with intestinal pseudo-obstruction or scleroderma or with patients with mucosal disruption such as inflammatory bowel disease. Etiologic associations of PI are outlined in Table 1.

Although most patients with PI are asymptomatic, some can present with symptoms including abdominal pain, obstruction, bleeding, or symptoms caused by the underlying disorder associated with PI. Location of the PI also affects the types of symptoms patients will experience. PI involving the small intestine more often presents with abdominal pain, distention, and vomiting, whereas colonic PI presents with diarrhea or hematochezia. In the absence of complications, the physical examination is typically unremarkable but may demonstrate abdominal distention or a palpable mass on abdominal or digital rectal examination.

PNEUMATOSIS INTESTINALIS RESULTING FROM AN INTRAABDOMINAL EMERGENCY

When PI results from an underlying abdominal catastrophe such as necrotizing enterocolitis (infants), bowel ischemia, or bowel perforation, the symptoms of the underlying surgical emergency dominate the clinical presentation. Signs and symptoms suggesting a surgical emergency include severe abdominal pain, pain out of proportion to the physical examination, fever, vomiting, presence of peritoneal signs such as rebound tenderness, and changes in vital signs such as hypotension, tachycardia, tachypnea, and hypoxia. Patients with an underlying intraabdominal emergency will typically require hemodynamic support in an intensive care unit setting.

IMAGING FINDINGS

PI is not a disease but rather a radiographic finding. It can be discovered on imaging performed for evaluation of abdominal complaints or incidentally discovered on imaging performed for nonrelated issues. Imaging not only helps with establishing a diagnosis of PI, but also with assessing the severity of disease, diagnosing associated complications, and making decisions regarding appropriate therapy.

X-ray

Findings include intramural gas (linear, curvilinear, or circular in appearance) or pneumoperitoneum. However, up to one-third of abdominal plain films fail to diagnose PI.

Computed Tomography

Computed tomography (CT) remains the most sensitive imaging modality in the identification of PI. Findings include intramural gas

TABLE 1 Etiologic Associations of Pneumatosis Intestinalis

Life-Threatening Causes	Pulmonary	Intestinal	Immunologic Conditions	Medications	Infections
Toxic megacolon	Asthma	Inflammatory bowel disease	AIDS	Corticosteroids	Tuberculosis
Mesenteric vascular disease	Chronic obstructive pulmonary disorders	Intestinal pseudo-obstruction	Rheumatoid arthritis	Chemotherapy	COVID-19
Ingestion of corrosive agents	Cystic fibrosis	Peptic ulcers	Scleroderma	Lactulose	*Clostridium difficile*
Trauma	Mechanical ventilation	Pyloric stenosis	Lymphoproliferative disorders		HIV
Necrotizing enterocolitis		Endoscopic procedures	GVHD		Cytomegalovirus
Intestinal ischemia/infarction			Solid-organ transplantation		*Tropheryma whipplei*
Bowel perforation					

AIDS, Acquired immunodeficiency syndrome; *GVHD,* graft-versus-host disease; *HIV,* human immunodeficiency virus.

(Figs. 1 and 2) appearing as either cystic collections of air that are adjacent to the bowel, air collections running parallel with the wall of the bowel, or linear collections of air without characteristic luminal air-fluid levels.

Additionally, CT allows for identification of associated findings that may indicate an underlying surgical urgency or emergency. These include bowel wall thickening, mucosal enhancement, bowel dilation, soft tissue stranding, and the presence of portal venous gas. The presence of portal venous gas is typically an ominous finding and is suggestive of mesenteric ischemia.

Ultrasound

Findings of PI on ultrasound imaging typically include air trapped within the intestinal wall, high-amplitude gas echoes accompanied by shadowing, lack of motion of air over time in the bowel wall, and lack of motion of air with compression.

Magnetic Resonance Imaging

PI is typically seen as circumferential collections of air near or within the bowel wall. Magnetic resonance imaging (MRI) is typically not the diagnostic modality used for the detection of pneumatosis, but physicians should be familiar with its appearance on MRI.

Laboratory Findings

Laboratory findings are instrumental in determining the management needed for PI. Although laboratory findings may be normal or nonspecific, a handful of "red-flag" laboratory values must be considered when evaluating whether PI has resulted from an underlying intraabdominal emergency. Elevations in serum lactate ≥2.0 mmol/L, marked leukocytosis with a predominance of immature white blood cells, elevated hematocrit suggestive of hemoconcentration, amylase > 200 U/L, or a bicarbonate level <20 ml/L can be suggestive of mesenteric ischemia or bowel infarct, which can help guide physicians toward the need for surgical intervention. The strongest predictor of pathologic disease and poor outcomes in PI remains a serum lactate ≥2.0 mmol/L.

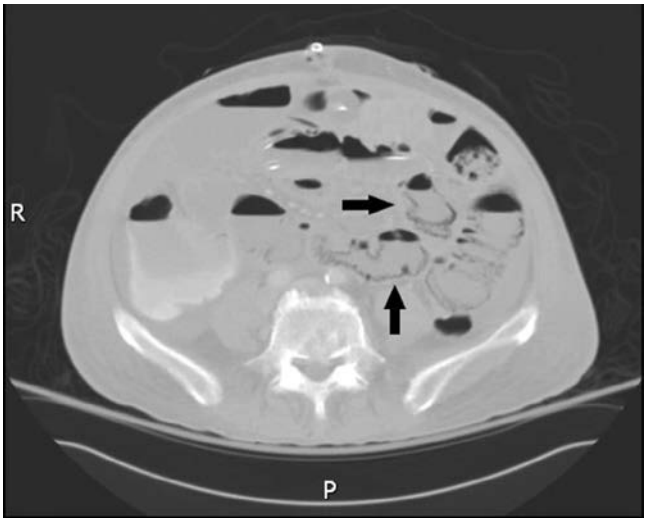


FIG. 1 CT scan of the abdomen demonstrating pneumatosis intestinalis of the small bowel. *Arrows* point to pneumatosis.

Endoscopic Findings

PI can be seen incidentally on both colonoscopy and sigmoidoscopy. The endoscopic appearance resembles submucosal blebs that can vary in size from several millimeters to centimeters in size. They have a pale/bluish appearance and on biopsy can rapidly deflate with an accompanied audible hiss. Diagnosis can be confirmed formally with endoscopic ultrasound, which will demonstrate the air-filled blebs.

Distinguishing Benign from Pathologic Pneumatosis Intestinalis

The management of PI from medical causes (see Table 1) is strikingly different from the management of PI from an underlying intraabdominal catastrophe such as mesenteric ischemia or intestinal perforation. When PI results from an underlying intraabdominal



FIG. 2 CT scan demonstrating portal venous gas.

catastrophe, the prognosis is extremely poor without immediate surgical intervention. Therefore, the most important step in the evaluation is determining whether there is a surgical emergency. As discussed earlier in the chapter, signs and symptoms suggestive of a surgical emergency include fever, pain out of proportion to physical examination, peritoneal signs, and hemodynamic changes such as tachycardia, hypotension, and orthostasis. Laboratory values that are red flags include leukocytosis, hemoconcentration, metabolic acidosis, and lactic acidosis. Most surgical emergencies will be readily evident on CT imaging of the abdomen. If PI is associated with portal venous gas, strong consideration should be given to surgical exploration.

A retrospective study by DuBose et al. on 500 patients with PI showed that a lactate level ≥2.0 mmol/L, hypotension, and/or vasopressor use were highly predictive of PI from mesenteric ischemia. In addition, a prospective study by Ferrada et al. on 127 patients with PI indicated that a lactate level ≥2.0 mmol/L, elevated INR, decreased hemoglobin, and peritonitis were predictive of PI from transmural ischemia. In Ferrada's study, the presence of small bowel involvement, ascites, or adynamic ileus was also associated with PI from transmural ischemia. Recently, a five-factor score ranging from 0 to 11 (low-risk 0–4, intermediate-risk 5–6, high-risk 7–8, and very high-risk 9+) has been proposed for predicting PI from transmural ischemia. The score is based on the presence of small bowel PI, age ≥70 years, heart rate ≥110 beats per minute, lactate ≥2 mmol/L, and neutrophil-lymphocyte ratio ≥10. In a validation cohort, low-risk patients for surgical causes of PI had an observed rate of 0.0% for transmural ischemia, and very-high-risk patients had an observed rate of 82.4%.

Medical Management of Benign Pneumatosis Intestinalis

Patients with PI without evidence of mesenteric ischemia or other intraabdominal emergencies do not require exploratory laparotomy and can be managed medically. However, there is no consensus regarding the best treatment. Expectant management with serial radiographs, abdominal examinations, empiric antibiotics, elemental diet, and oxygen therapy are commonly employed.

The underlying etiologic association of PI should be treated in all patients. This includes removal of offending medications, treatment of inflammatory bowel disease, eradication of intestinal infections, and treatment of pulmonary disease.

Antibiotic therapy typically consists of metronidazole 500 mg orally three times daily until PI clinically and radiographically resolves or for up to 3 months. It is theorized that antibiotics can alleviate symptoms by reducing the amount of gas produced by bacteria. Alternatives to metronidazole include ampicillin, tetracycline, or rifaximin.

An elemental diet has been proposed for symptomatic PI. It is theorized that an elemental diet can decrease production of gas by colonic flora as it is totally absorbed in the small intestine. Other mechanisms of action include alteration of intestinal flora.

Inhalational oxygen and hyperbaric oxygen therapy are effective for patients with moderate symptoms. Although the mechanism of action has not been fully elucidated, it is theorized that high concentrations of O_2 reduce the partial pressure of non-oxygen gases in the venous system and promote diffusion of these gases out of the bowel wall. In addition, oxygen may act as a toxin to anaerobic bacteria in the gut.

Endoscopic puncture, sclerotherapy, or surgical resection can be considered in patients who remain symptomatic with bleeding or obstruction from large blebs of intramural air.

Serial imaging should be conducted every 1 to 3 months until PI resolution is documented. Recurrence of PI is not uncommon and likely results from persistence of predisposing factors (see Table 10).

SURGICAL MANAGEMENT OF PATHOLOGIC PNEUMATOSIS INTESTINALIS

Patients deemed to have PI from transmural ischemia require emergent exploratory laparotomy. Surgical exploration is strongly recommended for these patients presenting with a lactate ≥2 mmol/L, peritonitis, or with hemodynamic changes. Careful clinical correlation with a low threshold for emergent exploratory laparotomy should be considered in those PI patients with small bowel involvement, adynamic ileus, or portal venous gas. Several key considerations are paramount to optimal outcome once the decision has been taken for surgical exploration, as discussed in the following sections.

Constant Communication with the Anesthesiologist

If the patient is in shock, anesthesia can result in a further insult. Ensuring that further vasodilation is kept at a minimum can help maintain adequate perfusion.

Resuscitation to Euvolemia

Hypovolemia increases the chances of further bowel necrosis and renal failure. On the other hand, hypervolemia results in further bowel swelling. Therefore, goal-directed resuscitation using methods such as arterial-line waveform analysis or echocardiography are advisable to maintain strict euvolemia.

How Much to Resect

Patients with transmural ischemia are usually in a state of shock. Minimizing blood loss and operative time is imperative. Consideration should be given to resecting only the areas of necrosis, leaving the patient in discontinuity, if necessary, to allow for better resuscitation.

Avoiding or Delaying an Anastomosis

Unless the cause of ischemia is clearly mechanical and can be relieved in the operating room, consideration should be given that the bowel might be in continued ischemia, which is disastrous for an anastomosis. In this case, the anastomosis would likely fail and place the patient at risk for a second source of intraabdominal sepsis.

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Management of Rectal Cancer

Gregory K. Low, MD, and Matthew Mutch, MD

BACKGROUND

The rectum is the distalmost aspect of the large intestine and measures 12 to 15 cm in length. From a surgical standpoint, it extends from the anus at the anorectal ring to the confluence of the taeniae coli at the rectosigmoid junction. Within the pelvis, it is bordered laterally by the pelvic sidewall, posteriorly by the sacrum, and anteriorly by the prostate gland in men and the vagina in women. From an oncologic standpoint, rectal cancer typically refers to tumors within the rectum located at or below the peritoneal reflection.

Current data show that there are approximately 150,000 cases of colorectal cancer per year in the United States. Of these, approximately 45,000 are newly diagnosed rectal cancers. There are approximately 50,000 colorectal cancer related deaths per year, making it the third most common cause of cancer-related death in women and the second most common cause of cancer-related death in men. Overall, the incidence of colon and rectal cancer has been decreasing since the adoption of routine screening. For patients under than age of 50, however, the incidence of both colon and rectal cancer is on the rise, with a rate of 2% to 4% per year. Young-onset colon and rectal cancers are more likely to be left-sided and higher-stage cancers at the time of diagnosis. Therefore special attention should be given to this patient group when they present with symptoms.

Rectal cancer poses a unique challenge to surgeons because of the bony confines of the pelvis and its proximity to other vital structures, which influences the margins of resection. Additionally, there have been many recent changes and evolving practices within the realm of radiation oncology and medical oncology. Overall, the management of rectal cancer is a complex topic that should be approached in a multidisciplinary fashion to give patients the best opportunity for favorable outcomes.

CLINICAL EVALUATION AND CLINICAL STAGING

The most common clinical presentation of rectal cancer is a change in bowel habits. Other presentations include bleeding, iron deficiency anemia, change in stool caliber, presence of a palpable mass, tenesmus, and rectal pain. Tenesmus and rectal pain are late findings and are often indicative of locally invasive lesions. Left untreated, rectal tumors may cause obstruction or perforation, which may significantly complicate management.

The diagnosis of rectal adenocarcinoma is typically secured by biopsy during endoscopy. A complete colonoscopy is preferred if the lesion can be traversed given the 3% to 5% risk of synchronous tumors. In-office evaluation should include a thorough personal history, family history, and a complete physical examination. Anorectal examination should specifically note the tumor's location relative to the anal verge, the sphincter complex, and orientation within the rectum. Rigid proctoscopy (as opposed to flexible endoscopy) is the preferred method for assessment of distance from the anal verge when tumors are not palpable on examination. On rigid proctoscopy, tumors within 12 to 15 cm of the anal verge are considered rectal cancers; on flexible endoscopy, tumors located at or below the third fold are considered rectal cancers. Although not diagnostic, carcinoembryonic antigen (CEA) levels are useful for the purpose of prognosis and posttreatment surveillance, so they should be obtained following a rectal cancer diagnosis.

Rectal cancer staging utilizes the Tumor, Node, Metastasis (TNM) staging system from the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC), which is currently in its eighth edition. Locoregional staging was historically completed using endorectal ultrasound (EUS), however its use is limited in the setting of bulky disease and posterior tumors. Additionally, EUS is highly operator dependent and does not allow complete evaluation of lymph nodes. More recently, magnetic resonance imaging (MRI) has become the preferred method for locoregional staging. High-resolution, T2-weighted, thin-cut images allow for accurate evaluation of depth of invasion, locoregional lymph nodes, and involvement of the circumferential resection margin.

Regional nodes for rectal cancer include those within the mesorectum and internal iliac drainage pathways. Nodal involvement of the inguinal, external iliac, common iliac, or aortocaval chains is considered metastatic disease. On MRI, both the size and morphology of the nodes are evaluated to aid in identification of clinically positive nodes (Fig. 1). Factors associated with an increased risk of nodal involvement include short axis greater than 9 mm, round shape, irregular borders, and heterogeneous signal intensity.

A key component of locoregional staging is accurate assessment of the circumferential resection margin (CRM), which is the radial margin of the mesorectum removed during total mesorectal excision. On imaging, the presence of a threatened CRM (tumor within 1 mm) is highly predictive of positive radial margins at the time of surgical resection, which translates into poor disease-free survival and overall survival.

Up to 20% of those with colorectal cancer will present with metastatic disease at the time of diagnosis. The most common sites of metastatic disease include the lymph nodes, liver, and lung. Distant metastatic disease should be evaluated with computed tomography (CT) of the chest and abdomen. If there is concern for potential liver metastasis, MRI of the abdomen may be obtained. Similarly, positron emission tomography (PET) is not considered part of the standard

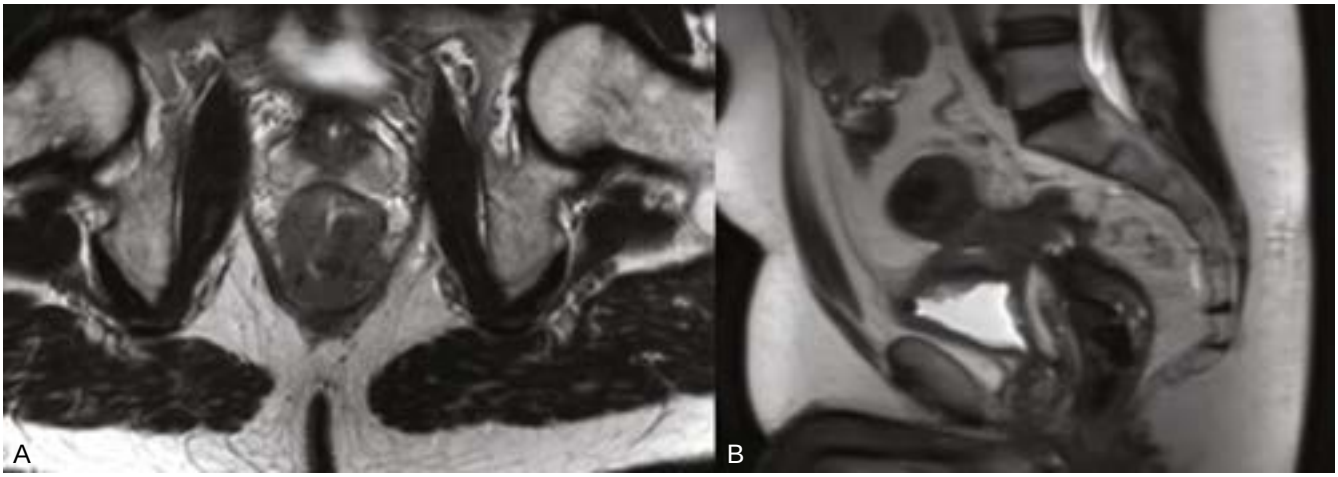


FIG. 1 (A) T3 tumor involving the superior margin of the internal anal sphincter on axial view. (B) T4 upper rectal tumor involving the bladder on sagittal view.

staging workup, but it may be considered in the setting of nondiagnostic CT or to confirm the presence of solitary metastasis before an attempt at surgical resection.

NEOADJUVANT THERAPY

Historically, proctectomy alone in the setting of rectal cancer was associated with 5-year local recurrence rates as high as 30%. Several sentinel clinical trials have transformed the management of locally advanced rectal cancer. The Swedish rectal cancer trial was one of the first studies to demonstrate the benefit of neoadjuvant short-course radiotherapy. However, this trial was criticized because of the lack of standardization of the surgical technique. The Dutch Colorectal Cancer Group addressed this issue by focusing on the concept of the total mesorectal excision. With the standardization of surgical resection, they demonstrated a significant decrease in the local recurrence rate associated with neoadjuvant short-course radiotherapy. Finally, the German Rectal Cancer Group demonstrated that chemoradiotherapy was best in the neoadjuvant setting given issues with significant toxicity and patient tolerance when given after surgery. Until recently, short-course radiotherapy was not widely accepted in the United States. The Polish trial and Trans-Tasman Radiation Oncology Group trial evaluated short-course radiation therapy versus conventional chemoradiotherapy and found no significant differences in local recurrence, disease-free survival, overall survival, or late grade 3 or 4 toxicity.

Current indications for neoadjuvant therapy include clinical T3, T4, or node-positive disease. Although it is occasionally discussed that neoadjuvant treatment can be considered in the setting of distal T2 disease in hopes of converting a planned abdominoperineal resection (APR) to a low anterior resection (LAR), this concept is not well supported and not currently recommended by clinical guidelines.

Traditionally, neoadjuvant therapy is given as long-course chemoradiotherapy consisting of 1.8 to 2 Gy/day for 25 fractions and a fluoropyrimidine for radiosensitization. Following long-course radiotherapy, proctectomy is typically delayed for 6 to 10 weeks (8 weeks preferred) to allow for ongoing tumor response. Longer wait times have been associated with increased pathologic complete response rates.

Short-course radiotherapy is typically given as 5 Gy/day over 5 consecutive days. Short-course radiotherapy is not a new concept and is commonly utilized in Europe. In recent years, it has garnered more attention and use in the United States given its reduced toxicity, shorter treatment time, and lower cost with no difference in pelvic control, overall survival, or disease-free survival. As opposed to long-course radiotherapy, surgery can be performed within 7 to 10 days after completion of short-course radiotherapy. Although immediate surgery does have certain benefits, recent trials have demonstrated a lower risk of complications for those undergoing delayed proctectomy (5–12 weeks) versus immediate proctectomy (less than 10 days).

Neoadjuvant therapy has greatly improved our ability to provide local control of rectal cancers, but it has not improved survival. Current local recurrent rates for stage II and III rectal cancer treated with neoadjuvant therapy followed by surgery can be as low as 4%, but the risk of distant recurrence remains 25% or greater. In attempts to improve survival and decrease the risk of distant failure, the concept of total neoadjuvant therapy (TNT) was developed. TNT involves administration of radiotherapy and all scheduled systemic chemotherapy in the preoperative period, with the goal of treating micrometastatic disease as soon as possible rather than up to 4 months after initiation of therapy. Radiotherapy may be given in short- or long-course format, and chemotherapy (typically the oxaliplatin-based FOLFOX regimen) can be given as induction (before radiation) or consolidation (after radiation). Current National Comprehensive Cancer Network guidelines recommend TNT for T4 lesions, T3 lesions with threatened margins, and those patients that are medically inoperable. Additionally, TNT may also be considered in T3 lesions, even in the absence of threatened margins and for T1–T2 lesions with positive nodes. TNT has been shown to result in higher pathologic complete response rates compared with chemoradiotherapy alone, and patients are more likely to complete planned treatment without dose reductions compared with postoperative chemotherapy. Whether these benefits translate into improved survival is a topic of ongoing investigation, but there are early data to suggest that TNT followed by surgery may result in improved survival compared with conventional chemoradiotherapy followed by surgery and adjuvant chemotherapy. In addition, a pathologic complete response after completion of TNT opens the door for an organ preservation/watch-and-wait strategy.

MANAGEMENT OF TUMOR-RELATED COMPLICATIONS

Some patients, especially those with locally advanced tumors, may present with complications related to tumor growth before or during neoadjuvant treatment. Tumor-related complications may include large bowel obstruction, bleeding, and perforation, all of which have serious consequences for patients' overall outcomes.

For patients presenting with large bowel obstruction, preoperative fecal diversion should be performed followed by neoadjuvant therapy. Diverting colostomy creation is often preferred as opposed to ileostomy as it avoids problems with dehydration and the risk of a

closed-loop obstruction in the setting of a competent ileocecal valve. Ideally, the stoma should be created distal to the eventual proximal resection margin to minimize complications to the proximal colon, which will be used to make an eventual colorectal anastomosis. Endoscopic stent placement is generally not recommended within the rectum as it results in pain and tenesmus. Partial or near obstructions may resolve with rapid initiation of radiotherapy, but patients should be closely observed for an initial worsening in their symptoms, which would require operative intervention.

Perforation of rectal tumors may result in abscess and/or fistula formation within the pelvis, perineum, or perianal regions. For contained perforations, fecal diversion and drainage of any abscess is necessary before initiating neoadjuvant therapy. Patients with free perforations or who are unstable present significant challenges. Ideally, the patient can be managed with drainage, either abdominally or transperineally, and fecal diversion. Rarely is resection required or recommended as obtaining an R0 resection will be difficult. At the time of radical resection, the perforation cavity and fistula track should be excised given the high likelihood of tumor spillage. Often this will require an abdominal perineal resection, and there may be need for tissue transfer to reconstruct the pelvic floor.

Hemorrhage from a rectal tumor is ideally managed with rapid initiation of radiotherapy as this is effective in over 90% of cases. When this is not feasible, endoscopic management, angiography, and topical treatments should be considered in an attempt to avoid emergency resection.

RADICAL RESECTION

Despite many recent advances in the realm of rectal cancer, radical resection remains the cornerstone of treatment. Radical resection includes resection of the rectum and the associated mesorectum, which contains the blood supply and lymphatics supplying the rectum. The goal of radical resection is to achieve negative distal and radial margins and restore gastrointestinal continuity with preservation of sphincter complex when possible. The gold standard technique for proctectomy was defined by Bill Heald in 1982 and is known as total mesorectal excision (TME). TME involves sharp dissection within the avascular plane between the visceral and parietal layers of the endopelvic fascia, resulting in a complete excision of the involved mesorectum and lessening the likelihood of autonomic nerve injury. As part of standard pathologic assessment, the quality of the mesorectal excision should be graded and reported. The quality of TME is graded as complete (intact mesorectal fascia), near complete (small, <5-mm defects in mesorectal fascia), and incomplete defects (>1 cm or exposure of muscularis propria).

Preoperatively, patients should receive mechanical bowel preparation in additional to oral antibiotics. This combination eliminates the stool burden from the colon and has been shown to reduce the risk of surgical wound infection compared with mechanical bowel preparation alone. If a stoma is planned, preoperative site marking should be performed to ensure a satisfactory location away from large skin folds, scars, or hernias. On the day of surgery, all patients should receive deep vein prophylaxis and intravenous antibiotics for surgical site prophylaxis.

The choice among an open, laparoscopic, or robotic approach is largely up to surgeon and patient preference as there have been no definitive studies that demonstrate significant differences in oncologic outcomes. Compared with open proctectomy, the laparoscopic technique is associated with improved short-term outcomes including less pain, lower rates of ileus, shorter length of stay, and less blood loss. Robotic proctectomy has rapidly increased in utilization in recent years, caused in part by the benefits of three-dimensional visualization and instrument articulation within the pelvis compared with a straight laparoscopic approach. Robotic proctectomy is associated with a lower conversion rate compared with laparoscopic proctectomy, but it is associated with longer operative times and higher costs.

The extent of resection during proctectomy for rectal cancer depends on its location within the rectum, relation to the sphincter complex, and involvement of additional pelvic structures (Fig. 2). For upper rectal cancers undergoing LAR, a distal margin of 5 cm is preferred. For low rectal tumors in which sphincter preservation is being attempted, a margin of 1 cm is acceptable provided that the entire mesorectum has been resected (Figs. 3 to 6).

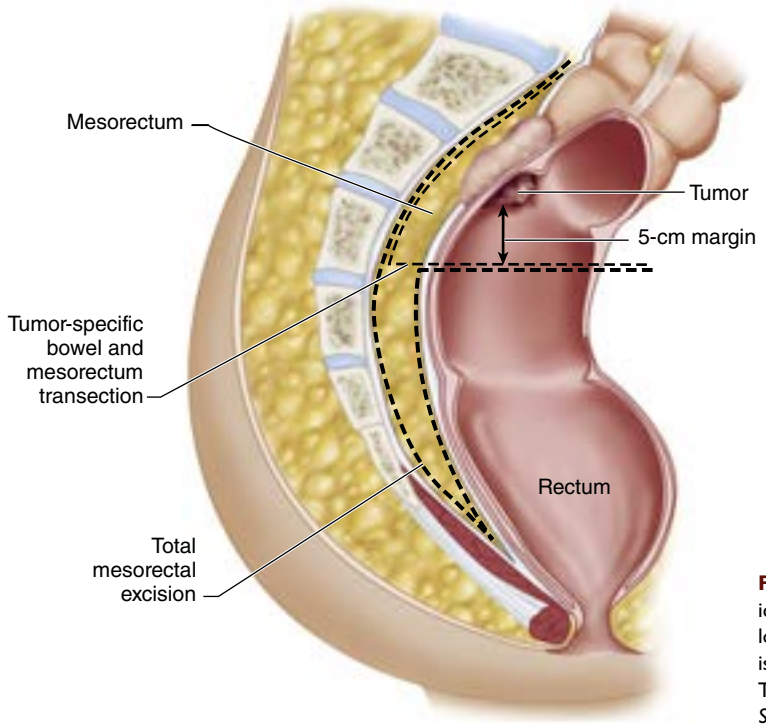


FIG. 2 For upper rectal tumors, tumor-specific mesorectal excision is appropriate. For mid to low rectal cancers, complete mesorectal excision is required. (*From Fleshman, et al.* Atlas of Surgical Techniques for Colon, Rectum and Anus. *Philadelphia: Saunders; 2013*)

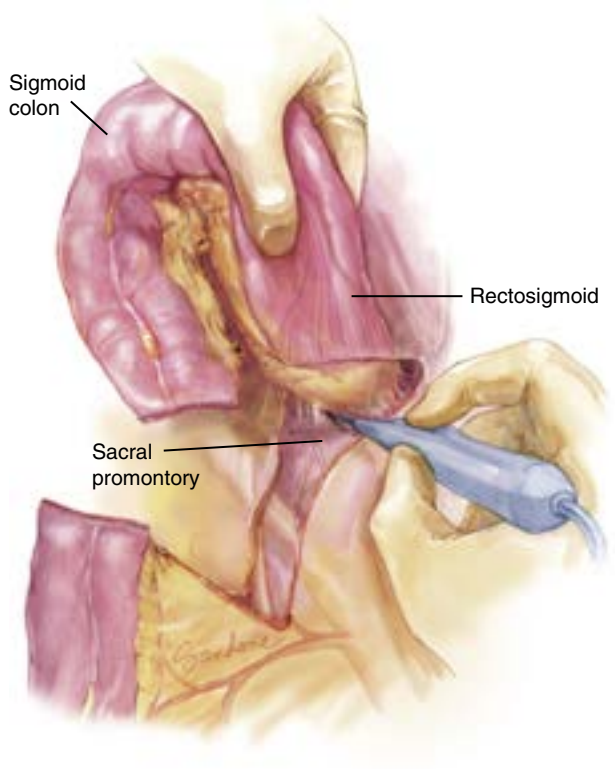


FIG. 3 Total mesorectal excision is initiated at the sacral promontory. The plane between the presacral fascia and fascia propria is identified with gentle traction. *(Courtesy Corinne Sandone. From Cameron J, Sandone C.* Atlas of Gastrointestinal Surgery, *vol 2. 2nd ed. Shelton, CT: People's Medical Publishing; 2014.)*

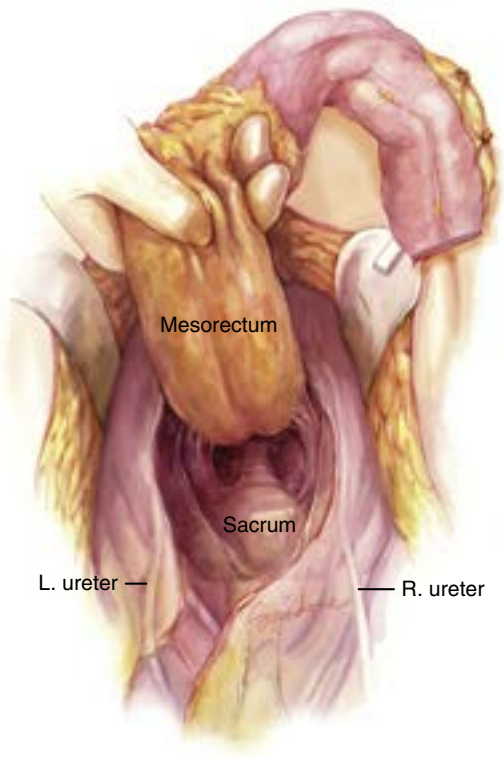


FIG. 4 Dissect posteriorly along the areolar tissue to identify the correct total mesorectal plane. *(Courtesy Corinne Sandone. From Cameron J, Sandone C.* Atlas of Gastrointestinal Surgery, *vol 2. 2nd ed. Shelton, CT: People's Medical Publishing; 2014.)*

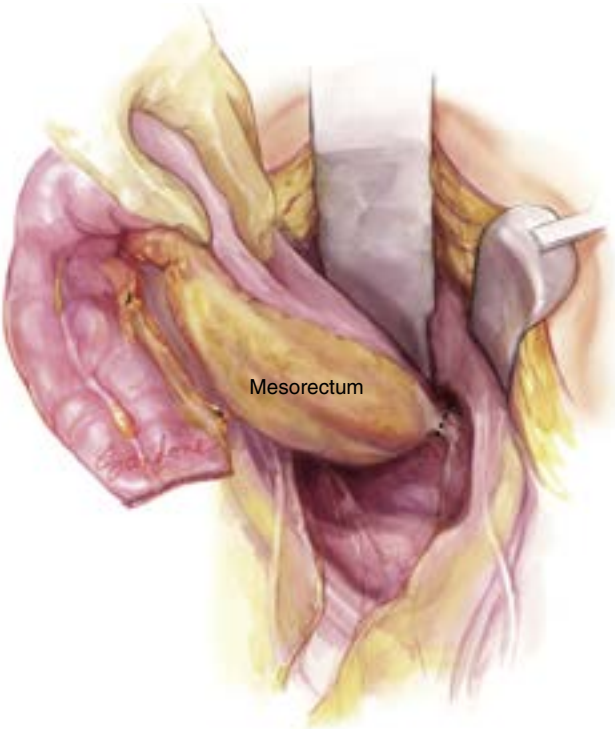


FIG. 5 Extend the dissection laterally along the pelvic sidewall. Avoid injury to side wall structures and inferior hypogastric plexus. *(Courtesy Corinne Sandone. From Cameron J, Sandone C.* Atlas of Gastrointestinal Surgery, *vol 2. 2nd ed. Shelton, CT: People's Medical Publishing; 2014.)*



FIG. 6 Use traction and countertraction to facilitate division of the anterior peritoneal reflection. *(Courtesy Corinne Sandone. From Cameron J, Sandone C.* Atlas of Gastrointestinal Surgery, *vol 2. 2nd ed. Shelton, CT: People's Medical Publishing; 2014.)*

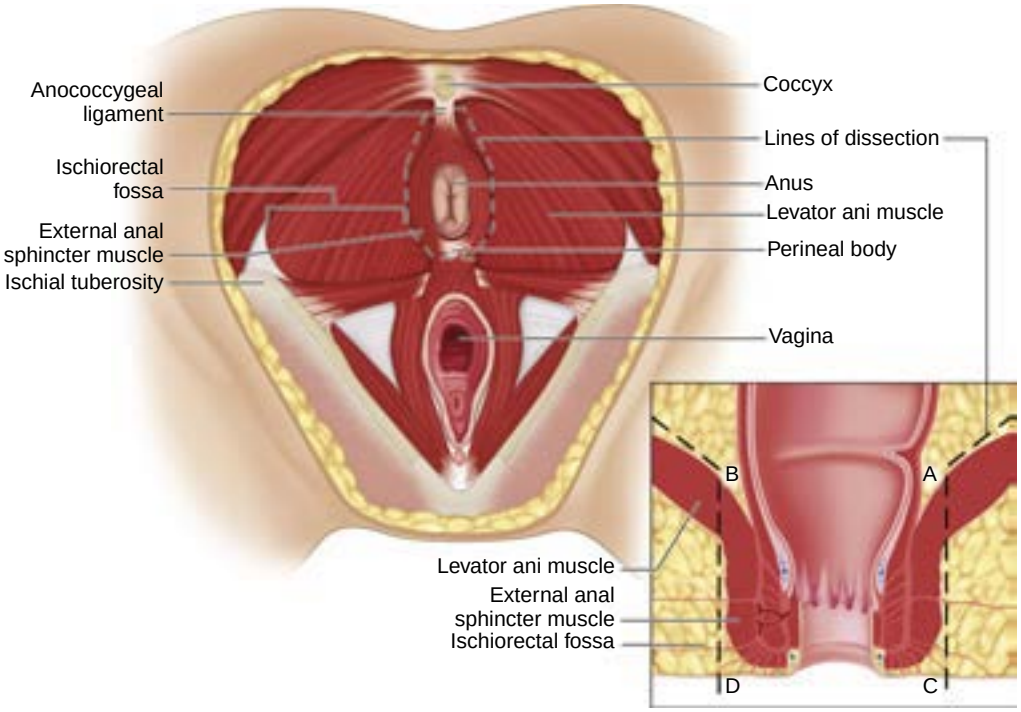


FIG. 7 Pelvic floor anatomy encountered during abdominoperineal resection. The anus, sphincter complex, and portion of the levator ani muscle are divided. The tip of the coccyx can be used as a guide to access the posterior pelvic space and guide the dissection. *(From Fleshman, et al.* Atlas of Surgical Techniques for Colon, Rectum, and Anus. *Philadelphia: Saunders; 2013).*

APR is required when tumors involve the sphincter complex or in those with a locally advanced low rectal tumor that is prohibitive of achieving an adequate distal margin (Fig. 7). For patients with poor preoperative bowel function, fecal incontinence, or chronic diarrhea, an end colostomy/Hartmann resection should be considered. Multivisceral resection refers to removal of the rectum in addition to other pelvic organs including the bladder, prostate, vagina, pelvic floor, and/or sacrum. Soft tissue coverage in the form of rotational or free flaps are often necessary following APR and pelvic exenteration given the large tissue defects in a radiated field.

Regardless of approach, the inferior mesenteric artery (IMA) may be divided either near its origin (high ligation) or just distal to the left colic artery at the origin of the superior rectal artery (low tie). High ligation is necessary in the setting of bulky adenopathy in the IMA chain and to help improve reach for a low anastomosis. The inferior mesenteric vein should be ligated at the ligament of Treitz to allow complete splenic flexure mobilization and improve reach into the pelvis.

Restoration of gastrointestinal continuity is most commonly accomplished using an end-to-end, stapled anastomosis. In appropriately selected patients with an ultra-low rectal cancer, a handsewn coloanal anastomosis may be performed to achieve sphincter preservation. Other options for anastomotic construction include the colonic J-pouch or an end-to-side colorectal anastomosis. In theory, these configurations improve the capacity of the residual rectum and improve function, however most studies demonstrated early improvement in function, but after 2 years there appeared to be no significant differences in long-term outcomes.

Temporary fecal diversion is frequently required during radical resection. In general, it should be performed in patients with a low anastomosis (less than 5 cm), those who received neoadjuvant radiotherapy, those who are immunosuppressed, and in the presence of a positive intraoperative leak test. Diverting stoma creation reduces the rate of clinical anastomotic leak, reduces the rate of reoperation, and increases the rate of salvage of the colorectal anastomosis if a leak does occur. Loop ileostomy is the most common type of diverting stoma created following radical resection given the simplicity of the subsequent reversal operation compared with reversal of an end colostomy. Diverting stoma reversal is typically performed 8 to 12 weeks following radical resection, but this timeline should be modified for patient-specific factors such as the need for adjuvant treatment. Before reversal, patients should undergo a water-soluble contrast enema to evaluate the integrity of the anastomosis.

Complications of proctectomy may range from minor to major, and they potentially have devastating consequences. Anastomotic leak is one of the most feared complications and, after low anterior resection, occurs in 5% to 25% of cases. For stable patients with a contained leak, simple percutaneous drainage may be feasible, but for unstable patients or those with an uncontained leak, reoperation is typically required. Suture repair, drainage, and fecal diversion may be adequate for small anterior defects in stable patients. For larger defects, those with poor tissue quality, or in the face of hemodynamic instability, takedown of the anastomosis and creation of an end stoma may be required.

During TME, pelvic bleeding can arise from the presacral plexus or the pelvic side wall. Presacral bleeding occurs as a result of injury to the presacral venous plexus, while pelvic side wall bleeding often originates from branches of the internal iliac vessels. Depending on the severity, presacral bleeding may by managed with electrocautery or direct pressure, but in the face of massive bleeding, pelvic packing is the most appropriate next step. Muscle fragment welding with a 2-cm area of rectus abdominus muscle or metallic thumbtacks may also be utilized. There are also several commercially available hemostatic agents that can be used such as Floseal or a Denver patch. Ureteral injury can also occur, especially in the setting of locally advanced tumors, and this typically requires reconstruction or reimplantation into the bladder depending on the character and location of the injury. Inadvertent injury to the superior hypogastric plexus during inferior mesenteric artery ligation may result in retrograde ejaculation, while injury to the hypogastric nerves or inferior hypogastric plexus during TME may result in erectile dysfunction and urinary dysfunction.

LOCAL EXCISION

Local excision for rectal cancer avoids the morbidity of proctectomy and may be considered in favorable lesions (Box 1). To be considered for local excision, lesions should be T0 or T1, be less than 3 cm

BOX 1 Criteria for Local Excision of Rectal Neoplasia

Tumor Characteristics

- T0 or T1
- <3 cm in diameter
- <30% lumen circumference
- Mobile on examination
- cN0 on staging imaging

Histopathologic Criteria

- Well to moderately differentiated
- No lymphovascular invasion
- No perineural invasion
- Negative margins after excision



FIG. 8 Full-thickness local excision of rectal neoplasia. *(Courtesy Andrew Russ, MD, and Mark Casillas, MD.)*

in diameter, involve less than 30% of the lumen circumference, be mobile, be amenable to resection with negative margins (3 mm), have no evidence of lymph node disease on cross-sectional imaging, and have favorable histologic features (well-differentiated, no perineural or lymphovascular invasion).

There are various techniques available for local excision depending on the tumor characteristics, location, and surgeon experience. Transanal excision is the simplest of these techniques and may be considered for easily accessible distal lesions. Transanal endoscopic microsurgery (TEM) and transanal minimal invasive surgery (TAMIS) are newer techniques that offer improved visualization and the ability to reach more proximal lesions (Fig. 8). Data show that TEM and TAMIS result in less specimen fragmentation, a lower risk of positive margins, and lower local recurrence compared with transanal excision.

Following local excision, the specimen should be thoroughly reviewed by an experienced pathologist to confirm the margin status and depth of invasion. If there is evidence of deep T1 or T2 disease, high-risk features, or positive margins after local excision, patients should be offered radical resection given the risk of nodal disease.

NONOPERATIVE MANAGEMENT

Following administration of neoadjuvant therapy, some patients will have a complete pathologic response. Following neoadjuvant long-course chemoradiotherapy, this occurs in 10% to 20% of patients. With the increasing usage of TNT has come the realization that up to 50% of patients will have an initial complete clinical response. These patients are candidates for an organ preservation strategy that involves intensive surveillance with MRI, endoscopy, and digital rectal examination. At 2 years, up to 30% of patients will experience local regrowth, and they should be offered radical resection. To date, data demonstrate that regrowth tends to occur luminally as opposed to within regional nodes or as distant metastatic disease. Although national guidelines have slowly started to include watch and wait as an acceptable management strategy in select patients, additional randomized studies are ongoing, and generally it should only be performed in select centers where adequate support and experience are available.

MANAGEMENT OF METASTATIC DISEASE

For the 10% to 20% of patients who present with metastatic disease, multidisciplinary input is essential. Systemic chemotherapy is the mainstay of treatment and should be initiated without delay. For those with isolated liver or lung metastases, resection with curative intent is feasible and is associated with a 5-year disease-specific survival up to 20%. The order of resection or decision to perform a simultaneous resection should be individualized based on the patient's symptoms, overall health, and complexity of planned operations. Outside of an attempt at surgery with curative intent, radical resection should not be performed on asymptomatic primary tumors. However, in the setting of highly symptomatic lesions, radical resection may be required.

POSTOPERATIVE MANAGEMENT/ SURVEILLANCE

For stage II and III patients who received neoadjuvant chemoradiotherapy but not systemic chemotherapy, an oxaliplatin-based regimen should be initiated within 8 weeks of radical resection. In the event a patient underwent upfront surgery for what was thought to be a stage I tumor, postoperative radiation may be administered for high-risk stage II or III disease. Following total neoadjuvant therapy; additional systemic chemotherapy is not generally required.

Following successful surgical management of rectal cancer and completion of all adjuvant treatment, patients undergo surveillance, which is based on the final pathologic stage. Rectal cancer may reoccur luminally at an anastomosis, within the pelvis, in lymph nodes, or as metastatic disease, typically to the liver or lungs. Overall, recurrence rates are higher for rectal cancer than for colon cancer, with local recurrence occurring in 4% to 22% of cases. Early detection is key as it allows for potential salvage or curative surgical procedures.

Most surveillance guidelines focus on the first 5 years after surgical resection as 80% of all recurrences will occur within 3 years of surgery, and 95% will occur within 5 years. Those with stage I disease should receive a colonoscopy at 1 year postoperatively, with no need

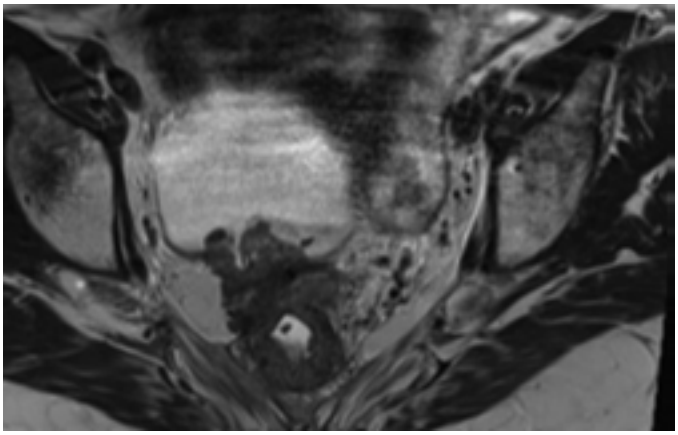


FIG. 9 T2-weighted MRI demonstrating local recurrence after low anterior resection with tumor involvement of the vagina and bladder, which was managed with pelvic exenteration.

for CEA or additional surveillance imaging. For stage II, III, and IV, patients should have a history and physical examination and CEA level every 3 to 6 months for 2 years, then every 6 months for a total of 5 years. CT of the chest, abdomen, and pelvis should be obtained yearly for 5 years, except in the setting of stage IV disease, which warrants imaging every 6 months for the first 2 years and then yearly, for a total of 5 years. All stages should have a surveillance colonoscopy performed at 1 year. For the select patients who undergo local excision, proctoscopy and MRI of the pelvis should be performed every 3 to 6 months for 2 years, followed by every 6 months for a total of 5 years.

Should local recurrence be identified, management is a complex topic that necessitates a multidisciplinary approach (Fig. 9). Treatment options may include additional chemotherapy, radiotherapy, and/or surgical resection depending on the site, extent of disease, and prior treatments. It is imperative to exclude additional distant metastatic disease, so repeat staging with PET/CT should be considered. Upfront treatment with additional chemotherapy is common, especially in the setting of extensive disease. If no prior radiotherapy was given, it should be administered preoperatively, and re-irradiation may be considered in select circumstances. Metastatic disease to the lung or liver may be resected with curative intent when feasible. Surgical resection of local recurrence often requires multivisceral resection, so careful assessment of the patient's expected postoperative function is imperative.

Suggested Readings

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Management of Tumors of the Anal Region

Emilie C. Barnes, MD, and Jose G. Guillem, MD

OVERVIEW AND ANATOMY

The surgical anal canal extends from the anal verge proximally to the upper part of the anorectal ring and typically measures about 4 cm in length (Fig. 1). Histologically, the canal can be divided into three different zones. The zone proximal to the dentate line is composed of columnar and cuboidal cells that are similar to those in the nearby rectal mucosa. The area around the level of the dentate line and valves of Morgagni is known as the *anal transition zone* (ATZ) and is composed of transitional epithelium. The most distal zone is made up of squamous epithelium. The anal margin, located at the intersphincteric groove, is a mucocutaneous junction with non-keratinized squamous epithelium proximally and keratinized squamous epithelium distally that contains hair follicles, apocrine glands, and sweat glands.

The blood supply and lymphatic drainage vary depending on the location within the anal canal. The proximal anal canal is supplied by the superior rectal artery. Venous drainage occurs via the superior and middle rectal veins, and lymphatic drainage occurs via the mesorectal, internal iliac, and inferior mesenteric lymph nodes. In contrast, the distal anal canal (below the dentate line) is supplied by the inferior rectal branch of the pudendal artery, and venous drainage occurs via the inferior hemorrhoidal vessels that drain to the internal iliac veins. Lymphatic drainage occurs via the inguinal lymph nodes. This distinction between the proximal and distal anal canal is important when considering locoregional spread of anal neoplasms.

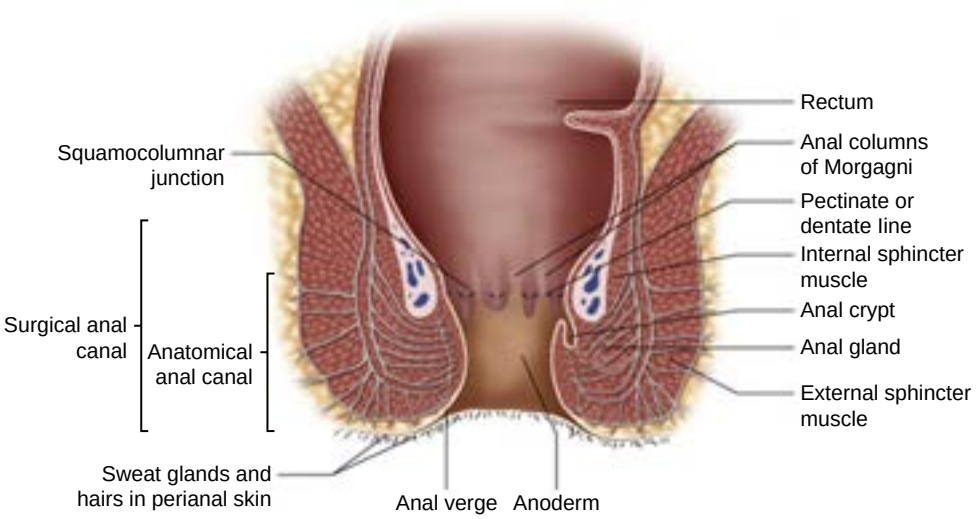


FIG. 1 Anatomy of the anal canal. *(From Steele SR, et al. The ASCRS Textbook of Colon and Rectal Surgery. 3rd ed. Springer; 2016.)*

Although the diagnosis of anal cancer remains rare, the incidence is on the rise and now accounts for about 0.5% of all cancer diagnoses in the United States and roughly 3% of all gastrointestinal malignancies. The vast majority (85%) are of squamous cell histology, followed by adenocarcinoma (5%–10%) in addition to rare lesions such as melanoma, mesenchymal tumors, neuroendocrine tumors (NETs), and lymphoma. Patients often present with rectal bleeding and pain, which can sometimes be confused for benign anal conditions, such as hemorrhoids. Others have no symptoms, and the diagnosis is made incidentally. HPV infection is highly associated with the development of anal cancer, and up to 90% of anal cancers are attributed to this infection. Other major risk factors include older age, smoking, and immunocompromised states, particularly patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) or transplant patients.

SQUAMOUS NEOPLASMS

Human Papilloma Virus and Anal Squamous Neoplasia

Human papilloma virus (HPV) is the most common sexually transmitted infection in the United States. Although there are over 100 subtypes, subtypes 16 and 18 have a strong relationship with the development of anal squamous cell carcinoma (SCC). The Centers for Disease Control and Prevention (CDC) estimates that these two subtypes of HPV account for up to 79% of all anal cancers. The quadrivalent HPV vaccine, which targets subtypes 6, 11, 16, and 18, has been shown to be efficacious in reducing rates of anal intraepithelial neoplasia and the subsequent development of cancer. However, uptake of the vaccine in the United States has been suboptimal. Currently, the CDC recommends routine vaccination for children beginning at age 11 and for all patients up to the age of 26 who have not been previously vaccinated.

Condyloma Acuminatum (Anal Warts)

Condyloma acuminatum, also known as *anal warts,* occurs secondary to HPV infection, most commonly subtypes 6 and 11 (Fig. 2). Other factors that increase the risk of development, larger size, and recurrence after treatment include smoking and immunocompromised states such as HIV. Lesions can present in a variety of ways, including single, multiple, flat, dome-shaped, cauliflower-shaped, skin-colored, erythematous, hypopigmented, or hyperpigmented. Location can also be within the anal canal or on the perianal skin. Evaluation of these lesions should include a complete anogenital examination, including anoscopy and referral to gynecology for vaginal examination with a Papanicolaou (Pap) smear in females.

Although it is estimated that up to one-third of anogenital warts will regress on their own within 4 months of detection, recurrence rates are high, therefore treatment should be offered to all patients. Options include topical therapies such as imiquimod cream, podophyllotoxin, and sinecatechins, with clearance rates ranging from 35% to 75%. Other treatment options include application of trichloroacetic acid (TCA) to cryotherapy and surgical fulguration/excision. Recurrence rates for all of the aforementioned treatments remain high at about 20% to 40% and are likely attributed to persistent HPV infection.

Buschke-Lowenstein Tumor (Verrucous Carcinoma)

The Buschke-Lowenstein tumor, also known as *verrucous carcinoma* or *giant condyloma acuminatum,* is a rare, slow-growing SCC that lacks basement membrane invasion (Fig. 3). As a result, it tends to spread laterally and rarely metastasizes. This tumor presents as an exophytic, fungating, cauliflower-type mass that is strongly associated with HPV (particularly subtypes 6 and 11). The standard of care involves wide local excision and potentially abdominoperineal resection (APR) for more extensive disease. Even with aggressive surgical management, recurrence rates are high (up to 70%), and malignant transformation occurs in up to 50% of cases.

Anal Intraepithelial Neoplasia

Anal intraepithelial neoplasia (AIN) is a premalignant lesion for anal SCC characterized by cellular and nuclear abnormalities of the squamous epithelial cells without extension into the basement membrane. In more recent years, the terminology surrounding AIN has evolved to a two-tier system of *low-grade squamous intraepithelial lesions* (LSILs) and *high-grade squamous intraepithelial lesions* (HSILs). AIN I, which involves replacement of the lower third of the epithelium with abnormal cells, is now considered LSIL. What was formerly described as AIN II/III and involved replacement of greater than one third of the epithelium now corresponds to HSIL. The use of the term *Bowen disease,* which is synonymous with *AIN III* or *SCC in situ,* is no longer encouraged. In addition to HPV infection, major



FIG. 2 Condyloma acuminatum. *(From Fazio V, Church J, et al.* Current Therapy in Colon and Rectal Surgery. 3rd ed. Philadelphia: Elsevier).



FIG. 3 Buschke-Lowenstein tumor. (From Fazio V, Church J, et al. *Current Therapy in Colon and Rectal Surgery. 3rd ed. Philadelphia: Elsevier).*

risk factors for the development of LSIL/HSIL, and eventually SCC, include HIV-positive status, men who have sex with men (MSM), women with a history of cervical dysplasia, and cigarette smoking.

Although the prevention of cervical cancer with screening for precancerous lesions has proven to be effective, it is less clear if the same principles apply to anal carcinoma. There is currently no data to support screening in the general population, however, screening with anal Pap tests may be beneficial in high-risk patients, such as those that are HIV positive, MSM, and females with a history of cervical dysplasia. Unfortunately, there is no current conclusive data to support the use of anal cytology to identify patients at risk for dysplasia, resulting in a reduction in rates of anal cancer, therefore the decision to perform screening anal Pap tests should be a shared decision between patients and providers.

Diagnosis

Most patients with anal squamous intraepithelial lesions are asymptomatic, and diagnosis is made either incidentally or as part of a surveillance program. If symptomatic, the most common symptoms include rectal bleeding, perianal pruritis or irritation, and tenesmus. Diagnosis typically is initially based on cytology and is obtained via anal Pap smear. The Bethesda classification system classifies cells as *atypical squamous cells of undetermined significance* (ACUS), LSIL, HSIL or atypical squamous cells cannot exclude HSIL. Immunohistochemical stains, such a p16, can be used to help differentiate HSIL from other mimics. Abnormal anal cytology should be followed by direct anal examination and tissue biopsy. This can be accomplished with either traditional anoscopy or high-resolution anoscopy (HRA).

Although in some patients LSIL or HSIL regresses without treatment, in others it progresses to malignancy. Patients with HIV are at the highest risk of progressing from LSIL to HSIL. In fact, in patients with HIV, the rate of progression from HSIL to SCC ranges from 8.6% to 19.6%.

Management

All patients with evidence of anal dysplasia should be followed clinically at regular intervals with a history and physical examination. The frequency of these examinations and the addition of HRA is debated and is also dependent on patient risk factors, most importantly HIV status, and provider training with HRA. For patients with LSILs who are HIV negative, examinations can be performed every 6 to 12 months. However, HIV-positive patients with LSILs should be examined more frequently, on the order of every 3 to 6 months.

Local therapy, which includes topical or ablative treatments, is indicated for HSILs and can also be considered in patients with LSILs, given the small but real risk of progression to invasive cancer. Topical options include imiquimod, 5-fluorouracil (5-FU), and trichloroacetic acid (TCA). Imiquimod is an immune modulator that can be directly applied to the anal canal by the patient or provider. One randomized trial in HIV-positive MSM who received either placebo or imiquimod demonstrated 43% resolution or downgrading of their dysplasia with a 61% sustained response at 36 months. Use of this medication is somewhat limited by side effects that include irritation, burning, and erosions. Similar results have been seen with topical 5-FU, with response rates up to 57% (39% with complete response). However, recurrence rates remain high at around 50%. Finally, although it is well tolerated by patients, TCA has been reported to have response rates up to 72%, but with recurrence occurring in about 20% of cases.

Options for local ablative therapy include radiofrequency ablation (RFA), infrared coagulation, and electrocautery. Studies on RFA and infrared coagulation are limited to a small number of retrospective studies that have shown response rates up to 64% (either complete resolution or downgrading of dysplasia) but dramatic recurrence rates, up to 91% in HIV-positive MSM at 17 months. Data on the outcomes regarding infrared coagulation are also limited, but one single-center retrospective study reported an up to 82% treatment response in HIV-positive patients. Recurrence rates have been difficult to estimate because of the number of patients lost to follow-up. Finally, electrocautery ablation has been shown to have initial clearance rates as high as 80%, but recurrence was also extremely common (up to 61%). Surgical excision remains an option for recalcitrant lesions but is challenging with larger lesions and resultant large defects that may require local flaps that may lead to stenosis and/or seepage.

In patients with HSIL who are treated with local topical or ablative therapy, surveillance involves regular follow-up with a complete history and physical examination with the addition of HRA being provider-dependent. Patients with persistent dysplasia or who are HIV-positive should be examined every 3 to 6 months, and those without evidence of persistent dysplasia and who are HIV negative can be seen annually. The ANCHOR study is a randomized controlled clinical trial comparing topical or ablative treatment with active monitoring in preventing anal cancer in HIV-positive patients with evidence of HSIL. As of October 2021, the study was halted after researchers found that treating HSIL lesions significantly reduced chances of progression to anal cancer. Although official results have yet to be published, this randomized controlled trial will hopefully provide the information needed to establish definitive treatment and surveillance strategies for HIV-positive patients with anal intraepithelial lesions.

Squamous Cell Carcinoma

Diagnosis

SCC accounts for the vast majority of anal neoplasms (up to 85%) (Fig. 4). Although many patients are asymptomatic, about 45% present with anorectal bleeding. Unfortunately, this is often attributed to hemorrhoids, which leads to a delay in diagnosis. Other symptoms include anorectal pain, inguinal pain, tenesmus, and change in bowel habits, particularly narrowing of stool caliber. About one-half of patients are found to have localized, node-negative disease at the time of diagnosis, while another one-third of patients are found to be node positive. The remaining 10% to 15% present with evidence of distant metastases.

Initial evaluation should involve a thorough history including evaluation of baseline anal sphincter continence, prior radiation, and assessment of risk factors such as MSM, anal receptive intercourse, and immunosuppression. If HIV status is unknown, this should be included in addition to basic laboratory studies. Physical examination should include a thorough examination of the perianal skin, examination of the inguinofemoral region for adenopathy, digital rectal examination, and anoscopy. Specific attention should be paid to the sphincter tone, size of the mass, and any evidence of fixation to



FIG. 4 Anal squamous cell carcinoma: fungating mass at the anal verge.

surrounding structures, such as the vagina, prostate, coccyx, or pelvic sidewall. Males should undergo a scrotal and penile examination, while females should be referred to gynecology for a cervical examination with Pap smear given the association with other anogenital malignancies. All patients should also be examined for evidence of inguinal lymphadenopathy. Given the risk of a synchronous colorectal neoplasm, a colonoscopy should also be performed.

Staging

Staging of anal SCC is according to the TNM classification system. All patients should undergo radiologic staging with computed tomography (CT) of the chest, abdomen, and pelvis. Magnetic resonance imaging (MRI) of the pelvis is also often obtained for evaluation of the extent of locoregional disease but is not required for staging. More recently, positron emission tomography (PET)/CT has been utilized as an additional imaging modality for assistance with staging as well as for radiation planning. A biopsy with fine-needle aspiration should be performed on any concerning inguinal lymphadenopathy based on examination or imaging.

Treatment

Historically, anal SCC was treated surgically with APR. In 1974, Nigro et al. published the initial case series in which neoadjuvant chemoradiotherapy (5-FU, mitomycin C, and 30 Gy of radiation) was administered before APR. They found that many of the surgical specimens had no evidence of residual disease on final pathology. This realization led to a significant paradigm shift from upfront surgical management to the current standard of care of chemoradiotherapy (CRT).

The current standard of care involves a regimen of mitomycin C and 5-FU or mitomycin C and capecitabine administered concurrently with radiation. A multifield technique is used to administer a minimum radiation dose of 45 Gy over a 5-week period. Additional boosts of radiation are given for lesions greater than T1 or with positive lymph nodes for a maximum dose of 59 Gy. 5-FU is given on days 1 to 4 and from days 29 to 32. Mitomycin C is given on days 1 and 29. Alternatively, capecitabine can be substituted for 5-FU and given 5 days per week for 4 to 6 weeks. The most common side effects of chemoradiation include gastrointestinal side effects such as nausea, diarrhea, bowel incontinence, and abdominal pain, urinary symptoms such as frequency, urinary incontinence, and dysuria, and sexual side effects.

National Comprehensive Cancer Network (NCCN) guidelines recommend that patients should be examined 8 to 12 weeks after the completion of CRT. This should include a digital rectal examination, anoscopy, and palpation of the inguinal lymph nodes. Persistent disease without evidence of progression can be followed clinically with serial examinations every 4 weeks for up to 6 months as tumor regression can continue for up to 6 months after completion of CRT. Repeat biopsy is indicated for any evidence of disease progression or persistent disease at 6 months.

Local excision is reserved for the management of anal cancer in two specific scenarios. First is for the treatment of superficially invasive anal canal cancer, which is defined as anal cancer with ≤3 mm basement membrane invasion and a maximal horizontal spread ≤7 mm. Additionally, local excision with 1-cm margins is indicated for T1N0, well-differentiated perianal SCC.

Posttreatment Surveillance

Patients found to have complete response after CRT should undergo digital rectal examination, anoscopy, and palpation of inguinal lymph nodes every 3 to 6 months for 5 years. Patients who were found to have T3/T4 disease or nodal involvement at the time of diagnosis or required salvage APR should also undergo CT of the chest/abdomen/pelvis yearly for the first 3 years.

Treatment of Recurrent or Persistent Disease

After the completion of CRT, up to 10% to 30% of patients have evidence of persistent disease or develop locoregional recurrence. Predictors of persistent or recurrent disease include higher T and N stages at original presentation, HIV-positive status, and inability to complete a full course of CRT. For disease that is localized to the anal canal and/or perineum, salvage APR is indicated. For patients undergoing salvage APR, 5-year overall survival has been reported to be 25% to 60% compared with a 3-year overall survival of 5% for patients who are unable to undergo a salvage APR. Unfortunately, given the effects of prior CRT, patients who undergo salvage APR are at higher risk of developing issues with wound healing and often benefit from reconstructive tissue flaps such as vertical rectus abdominis myocutaneous (VRAM), gracilis, or gluteus flaps.

Metastatic Disease

About 10% to 15% of patients with anal SCC are found to have evidence of distant metastases at the time of diagnosis. Most common locations include the liver, lungs, extrapelvic lymph nodes, peritoneum, bones, and brain. Chemotherapy remains the mainstay of therapy, despite fairly limited data supporting its use. Traditionally the most common regimen was a combination of cisplatin and 5-FU, which boasted response rates around 60%. However, more recently, a randomized controlled trial (InterAAct) was published that specifically compared the traditional regimen of cisplatin and 5-FU to carboplatin and paclitaxel in patients with locally recurrent inoperable or metastatic disease. Although no difference was seen with regard to objective response rate (ORR), reduced toxicity was seen in the cohort receiving carboplatin plus paclitaxel as well as a trend toward longer survival. In the setting of metastatic disease that is refractory to chemotherapy, some small studies examining PD-1/PD-L1 inhibitors have shown response rates up to 24%.

COLUMNAR NEOPLASMS

Adenocarcinoma

Anal adenocarcinoma is rare and accounts for only about 5% to 10% of all anal cancer diagnoses. This form of adenocarcinoma typically arises from two locations: the columnar epithelium of the upper anal canal and from the anal canal glands. The upper anal canal type can often be difficult to differentiate from low rectal adenocarcinoma. The anal canal gland type tends to be associated with chronic anal fistula tracts that are more commonly seen in patients with Crohn's disease. Initial workup and staging includes laboratory tests (including CEA level), colonoscopy, CT of the chest/abdomen/pelvis to evaluate for metastatic disease, and MRI of the pelvis to evaluate locoregional spread. Given the rarity of this diagnosis, there are no randomized controlled trials to help establish the standard of care. Instead, the NCCN guidelines recommend applying the same treatment algorithm that it is used for rectal adenocarcinoma. Although local excision can be considered for well-differentiated T1N0 tumors, most require neoadjuvant chemoradiation followed by an APR. However, with the advent of organ preservation approaches, anal adenocarcinoma may be amenable to preoperative chemoradiotherapy and a possible "watch and wait" approach in the case of a complete clinical response.

Paget's Disease

Perianal Paget's disease is an intraepithelial adenocarcinoma of the perianal skin (Fig. 5). Presentation is frequently nonspecific and can often be mistaken for other skin conditions like eczema or dermatitis. Skin involvement is limited to the apocrine gland–bearing areas and is typically characterized by well-circumscribed erythematous or leukoplakic plaques or as macules with either hyperpigmentation or hypopigmentation. Patients frequently complain of pruritis and, less commonly, bleeding and ulceration. Diagnosis is confirmed with biopsy of the involved skin, which demonstrates intraepithelial



FIG. 5 Perianal Paget's disease.

carcinoma. The classic histologic finding is Paget cells, which are glandular epithelial cells with abundant clear cytoplasm.

Paget's disease can simply represent a primary malignancy of the apocrine glands versus a synchronous or metachronous lesion from another site as there is a high association with rectal, anal, and bladder adenocarcinoma. In fact, up to 70% to 80% of perianal Paget's disease is thought to arise secondary to invasive malignancy from the anus, rectum, or colon. Patients with a new diagnosis of Paget's disease should undergo a thorough history and physical examination as well as colonoscopy. In patients with primary perianal Paget's disease, the standard of care is wide local excision with a 1-cm margin. If Paget's disease is found in association with a locally invasive anorectal adenocarcinoma, neoadjuvant chemoradiation followed by APR is an option.

MELANOMA

Anal melanoma accounts for 1% of all anorectal malignancies and 0.4% to 1.6% of all melanomas. Symptoms are often subtle and nonspecific, most commonly including rectal bleeding, pain, obstruction, and tenesmus in larger lesions. Prognosis of anal melanoma is poor because of the frequently delayed presentation of these patients in combination with the development of early distant metastases. The preferred treatment involves surgical resection, either wide local excision or APR, depending on the extent of sphincter involvement. However, this has not shown to improve median survival, which has been reported as less than 2 years.

NEUROENDOCRINE AND MESENCHYMAL TUMORS

NETs make up about 1% of all anal canal tumors. Most NETs in this location are nonfunctional. Another rare type of anal canal tumor includes mesenchymal tumors, which include smooth muscle tumors and gastrointestinal stromal tumors. Treatment for these tumors typically involves local excision alone, but it may require radical resection if the tumors are large or locally advanced.

MALIGNANT LYMPHOMA

Although rare, both Hodgkin's and non-Hodgkin's lymphoma of the anal canal have been reported. The most common type is high-grade B-cell lymphoma. Like many of the other anal tumors previously discussed, anal lymphoma is associated with immunocompromised states and is more commonly seen in patients with HIV. Treatment is not typically surgical and instead involves chemoradiation.

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Cystic Disease of the Liver

Lucas W. Thornblade, MD, MPH, and Yuman Fong, MD

INTRODUCTION

Cysts of the liver are a common phenomenon and occur in approximately 5% to 20% of adults. They are sporadic and largely not associated with familial syndromes. Most cysts of the liver are simple and benign, however a minority of liver cysts and cystic lesions harbor either active malignancy or malignant potential (Table 1). The challenge presented to the liver surgeon is differentiating cysts that are very likely benign (and therefore appropriate for observation or no surveillance at all) from cysts with features of potential malignancy that are better suited to resection. Although most liver cysts are diagnosed incidentally, a minority of cysts cause compressive or mass-effect symptoms, particularly when they become large or bleed, either spontaneously or as a result of trauma. Less commonly, cysts can rupture into the peritoneal cavity, cause biliary compression, become infected, or sustain torsion. Control of masslike, infectious, or hemorrhage-related symptoms are indications for treating cysts of the liver aside from their malignant potential. Cysts or abscesses of the liver from infectious or parasitic causes are beyond the scope of this chapter, however echinococcal cysts and amebic abscesses of the liver must be thoroughly ruled out by patient history, imaging features, and serology testing when appropriate. This chapter reviews (1) imaging characteristics of liver cysts, (2) types of common and uncommon cysts and cystic lesions of the liver, (3) special considerations when working up hepatic cysts, and (4) surgical and nonsurgical approaches to management of hepatic cysts.

Imaging Characteristics

Benign liver cysts are simple, round, fluid-filled cavities that are found within the liver parenchyma and exhibit a single layer of cuboidal epithelialized lining of the cyst wall. They do not communicate with the biliary tree. Simple cysts can be a few millimeters in size or grow to contain several liters of clear simple fluid. Benign liver cysts are slightly more common in the right lobe of the liver and have a slight female predominance. Large and symptomatic simple liver cysts, however, are much more commonly found in females.

Ultrasound is the least expensive and therefore a common first modality for assessment of liver cysts. Ultrasound of liver cysts demonstrates anechoic or hypoechoic features that are consistent with a round, unilocular, fluid-filled structure complemented by posterior acoustic enhancement. On CT scan, benign cysts appear hypodense with Hounsfield unit measurements close to that of water. The walls of benign cysts do not enhance with intravenous contrast and are quite thin. On MRI, the feature of a cystic lesion in the T2 sequence is high attenuation (i.e., bright), and this easily distinguishes the cyst from solid lesions. Cysts are T1 hypoattenuating. The added benefit of MRI in evaluating cysts of the liver is the increased detail provided to differentiate cyst contents as simple fluid from hemorrhage products, protein, and mucin. MRI can also provide detail on features such as subtle mural nodules or projections. Figure 1 presents an example of a large benign cyst on CT and ultrasound imaging.

Benign cysts are round, therefore asymmetry or even ovoid shapes are worrisome features. Benign cysts may have lobulated borders if the cyst wall folds around fixed portal pedicle structures as they grow. The wall of a benign cyst, regardless of the imaging modality, is nearly imperceptible. The absence of additional features adds confidence to the diagnosis of a benign cyst. Specifically, cysts that lack features of wall thickening, wall nodularity, papillary features, septations, or other masses are very likely to be simple and benign cysts. Clinical characteristics must complement the imaging of liver cysts to differentiate them from abscesses and tumors with areas of liquified necrosis. Hemorrhage into a cyst can result in areas of increased density or even the appearance of septation. Calcifications are a feature of echinococcal cysts. Figure 2 demonstrates the compressive effect of a large cyst on surrounding parenchyma resulting in focal biliary dilation.

Types of Cystic Liver Lesions

Benign liver cysts are common. However, the differential diagnosis for non-simple cysts is broad and demands thoughtful consideration.

Mucinous Cystic Neoplasm and Mucinous Cystadenocarcinoma

Mucinous cystic neoplasms (previously *cystadenoma*) are a class of rare cystic lesions found in the liver that are histologically similar to pancreatic mucinous cystadenoma. Morphologically, these cysts have a biliary-type glandular lining with projections and cryptlike invaginations. Their glandular tissue is surrounded by dense fibrous (mesenchymal) tissue described as ovarian-type stroma. Radiographically, mucinous cystic neoplasms appear as complex cysts with thickened and irregular (or even nodular) walls. Ultrasound features include internal echoes. The contents of mucinous cystic neoplasm may be bloody or chocolate colored. Mucinous cystic neoplasms of the liver have malignant potential as they can develop atypia or dysplasia. Over a prolonged period (perhaps >10 years), an estimated 2% to 15% of mucinous cystic neoplasms will degenerate into malignancy known as *mucinous cystadenocarcinoma.* These occur in older adults and have metastatic potential. Mucinous cystadenocarcinomas are overall rare but should definitively be resected along with all mucinous cysts exhibiting worrisome features. Mucinous cystic neoplasms that do not appear to contain malignancy can be

TABLE 1 Types of Cystic Lesions of the Liver and Their Characteristics

Cyst Type	Characteristics	Proposed Treatments
Simple cyst	Round, thin wall, simple fluid	None, observe, sclerotherapy, fenestration
Mucinous cystic neoplasm	Complex cyst, thickened irregular wall, ovarian-type stroma	Observe, enucleation, resection
Mucinous cystadenocarcinoma	Like mucinous cystic neoplasm, may form masses	Resection
Ciliated hepatic foregut cyst	Four-layered cyst, commonly within segments 4A/B	Observe, enucleation
Cystic subtypes of primary liver cancer and metastasis	Complex solid and cystic mass of the liver	Resection
Traumatic cysts	Occur in areas of disrupted liver parenchyma, may develop as a biloma	Observation
Pseudocysts of the liver	Occur as a consequence of adjacent pancreatitis	None
Intraductal papillary mucinous neoplasm of the bile duct (IPMN-B)	Mucin-containing cystic dilations of the bile duct with associated papillary mass, intermittent jaundice	Resection
Polycystic liver disease	Autosomal dominant, ≥20 cysts	Observe, fenestration, transplantation

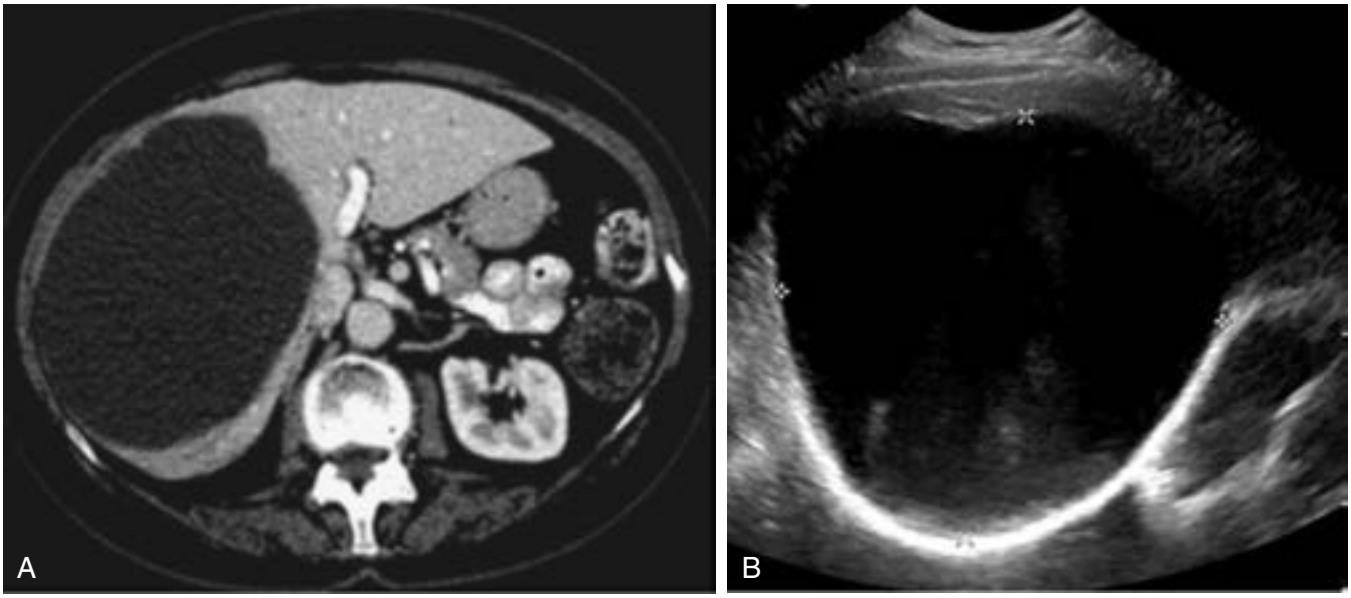


FIG. 1 Simple cyst with homogenous appearance and no wall nodularity on CT **(A),** verified to be a simple cyst by ultrasound **(B).**

enucleated and do not require resection with a margin of normal liver parenchyma. Which patients to take for enucleation, however, remains controversial. In patients who are high risk for liver surgery, observation of mucinous cystic neoplasms is appropriate.

Intraductal Papillary Mucinous Neoplasm of the Bile Duct

The entity known as *intraductal papillary mucinous neoplasm of the bile duct* (IPMN-B) is a mucin-producing solid neoplasm that arises within the liver and has direct communication with the bile ducts. It has only recently been described as it was previously believed to be a papillary subtype of cholangiocarcinoma. Because of its secretion of mucin, like IPMNs of the pancreas, the lesion will appear as a cystic lesion on imaging. The intraductal solid component is made up of frondlike papillary projections that grow along the mucosal surface of the duct. These frondlike projections produce mucin that fills the duct. IPMN-B invariably presents with proximal biliary dilation, though jaundice may be intermittent. Although sampling of these lesions may be low yield, endoscopic retrograde cholangiopancreatography (ERCP) provides diagnostic clarity. Like IMPNs of the pancreas, many IPMN-Bs contain cancer or will degenerate into cancer, therefore resection is recommended. The prognosis for these patients is generally considered favorable compared with cholangiocarcinoma.

Ciliated Hepatic Foregut Cyst

Only a few cases of ciliated hepatic foregut cysts are described each year. These lesions are solitary and histologically have four layers: a

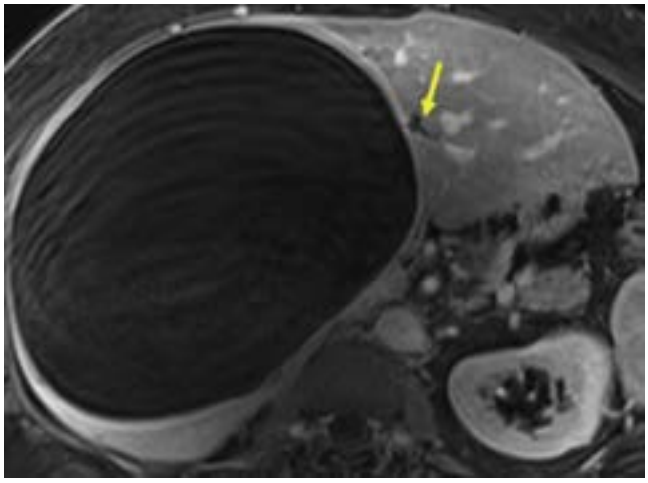


FIG. 2 Very large cysts can cause compression of adjacent structures, including bile ducts *(arrow)*.

ciliated and pseudostratified columnar epithelium, a subepithelial connective tissue layer, a smooth muscle wall, and a tough fibrous capsule. These may present at any age but can cause pain or jaundice. Ciliated hepatic foregut cysts often occur within segments 4A/4B and may abut the gallbladder. They are largely benign; therefore if ciliated hepatic foregut cysts are treated surgically, enucleation is appropriate. Only rarely, squamous cell carcinoma is described within large ciliated hepatic foregut cysts.

Cystic Malignancy

Both primary and secondary malignancies of the liver may present with cystic components. Therefore, one should not deduce that cystic lesions exhibiting any solid component or associated masses are benign. For example, there are cystic subtypes of hepatocellular carcinoma, cystic primary liver sarcoma, cystic metastatic neuroendocrine tumors, and cystic colorectal liver metastases. As with the workup for solid liver lesions, the finding of a cystic mass of the liver warrants a careful history and physical, dedicated liver imaging, tumor markers, consideration of a workup for primary tumor site (e.g., colonoscopy, upper endoscopy), and a biopsy in the case of any diagnostic uncertainty. Intrahepatic ductal dilation associated with a cyst is a sign suggestive of underlying malignancy. Rate of growth can be helpful in elucidating an appropriate level of concern in indeterminate lesions. Because CA 19-9 is expressed by normal biliary epithelium, elevation of this tumor marker may not differentiate cancerous and non-cancerous cystic liver lesions.

Hepatic Pseudocysts and Traumatic Cysts

As a result of severe pancreatitis, inflammation along the hepatoduodenal ligament can cause cystic transformation of these structures resulting in the appearance of cysts within the liver. Like pancreatic pseudocysts, they do not have an epithelial lining. With resolution of pancreatitis, these lesions should resolve and do not require surgical drainage or other intervention unless they become infected. Trauma to the liver can also result in cystic degeneration of tissue over time. Parenchymal disruption may lead to hematomas, which over time coalesce into fluid-filled spaces within the parenchyma or beneath the Glisson capsule. Like other benign cystic structures of the liver, they do not warrant further intervention unless symptomatic. Posttraumatic cysts of the liver may also communicate with the bile duct and therefore should be considered a biloma. Percutaneous drainage of bilomas should be avoided because of the risk of ongoing bile leak. Bilomas may require endoscopic biliary decompression to resolve.

TABLE 2 Mayo Clinic Classifications of Polycystic Liver Disease

Type	Symptoms	Portal Vein or Hepatic Vein Occlusion of Preserved Sector	Area of Relatively Normal Liver Parenchyma
A	Absent/Mild	Absent	
B	Moderate/Severe	Absent	≥2 sectors
C	Moderate/Severe	Absent	≥1 sector
D	Moderate/Severe	Present	<1 sector

Polycystic Liver Disease

Some patients with polycystic kidney disease will also develop polycystic liver disease, and the development of concomitant liver cysts increases with increasing age. By 60 years of age, at least half of patients with polycystic kidney disease will have also developed cystic proliferation in the liver (Table 2). A less common condition is autosomal dominant polycystic liver disease (ADPLD), which is defined as ≥20 cysts of the liver. This occurs in a heritable pattern, typically as a result of mutations in the *PRKCSH* gene that encodes for hepatocystin; mutations in the *SEC63* gene; or loss-of-function mutations in the *ALG8*, *GANAB,* or *SEC61B* genes, which effect polycystin-1 biogenesis. The number of affected alleles determines the extent of cystic degeneration, therefore there is disease heterogeneity. Patients with ADPLD can also develop cerebral aneurysms. Patients with ADPLD do not have concomitant kidney cysts but, whether heritable or otherwise, they may develop hundreds of cysts in the liver that increase in size over time. Because of their multiplicity, cyst resection is often not beneficial to these patients. When liver parenchyma is replaced by a large volume of cysts, synthetic function of the liver is preserved, but patients can develop infections and biliary obstruction and may require numerous endoscopic procedures. Some patients with hepatomegaly will be considered for liver transplantation.

The Mayo Clinic classifications for polycystic liver disease quantify symptoms, extent of normal liver parenchymal preservation, and the status of vascular inflow and outflow (see Fig. 2). This can be used to guide whether patients should be observed, treated with limited resection, or referred for transplantation. Some patients benefit from the use of long-acting octreotide in polycystic liver disease.

Special Considerations

Biliary Cysts

Biliary cysts, elsewhere described as *choledochal cysts,* are saccular or fusiform dilations of the intrahepatic or extrahepatic bile ducts. Biliary cysts alone may be asymptomatic, but all carry an increased risk of cholangiocarcinoma. Based on the location of the cyst and the age of the patient, resection is commonly recommended to prevent degeneration into carcinoma. The proximity to the hepatic parenchyma, biliary bifurcation, or ampulla of Vater will determine whether the patient may require a resection of the extrahepatic bile duct alone or along with liver resection and/or pancreaticoduodenectomy. Characterization of biliary cysts is best facilitated by magnetic resonance cholangiopancreatography (MRCP), and this modality should be employed if there is any diagnostic uncertainty or if lesions are difficult to distinguish from primary liver cysts. Patients with biliary cysts that are considered low risk or who are not surgical candidates may be best followed with serial MRCP. Type V biliary cysts, also known as *Caroli's disease,* can present with diffuse cystic degeneration of the biliary tree.

Extrahepatic Cysts

Occasionally, cysts of the adrenal gland, kidney, or bowel mesentery may be difficult to distinguish from the liver parenchyma. For cases in which imaging modalities are insufficient to differentiate the organ of origin, surgical exploration may be indicated to distinguish and/or treat these larger and sometimes symptomatic cysts.

Cystic Lesions Associated With Infection or Parasites

Any hypodense or fluid-filled lesion of the liver should be viewed with the possibility that the lesion is caused by infection or parasites. Although a thorough review of infectious or parasitic liver abscesses is beyond the scope of this chapter, here we review important considerations in differentiating these lesions from the more common non-infectious liver cysts. A pyogenic liver abscess may result from hematogenous seeding of liver parenchyma with bacteria from elsewhere in the body (e.g., resulting from bacterial endocarditis or diverticulitis). Pyogenic abscesses appear to have a thickened area of rim enhancement and should be easily distinguished from benign liver cysts on intravenous contrast-enhanced CT scan. A history of fever, leukocytosis, abdominal pain, and evidence of an extrahepatic infection will further solidify the diagnosis. Pyogenic abscesses are managed by intravenous antibiotics and commonly benefit from image-guided percutaneous drainage. Liver abscesses that are refractory to antibiotics and percutaneous drainage may require surgical drainage.

Amebic liver abscesses occur as a result of infection from *Entamoeba histolytica,* a protozoa found in tropical areas. It affects males much more commonly than females (10:1) and can present with fever, abdominal pain, and colitis. Serum antibodies are highly sensitive for distinguishing amebic abscesses from pyogenic liver abscesses. Amebic liver abscesses contain a brown fluid that is described as "liver paste." Antibacterial treatment with metronidazole is the principal therapy, and aspiration or surgery may only be required in a minority of treatment-refractory cases.

Echinococcal cysts (also known as *hydatid cysts*) are caused by the larvae of *Echinococcus granulosus,* which is a subtype of tapeworm parasite. This parasite's definitive host is typically dogs and other small carnivorous animals. Infection of humans is uncommon in the United States and is usually seen only in patients who have traveled or lived in South America, Africa, or Asia. Affected humans develop larval cysts most commonly within the liver but also in the lung, spleen, brain, and elsewhere. Echinococcal cysts are spherical and may exhibit septations. The cyst is described as a three-layered structure with an inner germinal layer, a laminated layer, and an outer pericyst layer. Echinococcal cysts classically contain "daughter cysts" within the primary cyst or at the periphery and may also be calcified. Small larval capsules within the cyst are seen on imaging as hydatid "sand." Patients with echinococcal infection may be asymptomatic for many years, though in advanced stages they can present with fatigue, cholestasis, pain, or liver failure. Serology can be used to confirm the diagnosis. Treatment is founded by antihelminthic medications (e.g., albendazole) and may also include surgery or the puncture, aspiration, injection, and reaspiration (PAIR) procedure.

Treatment Considerations

Indications for treatment of liver cysts pertain to the underlying risk of malignancy and symptoms attributable to the cyst or cysts. As stated earlier, lesions with solid components or high-risk features that are concerning for underlying malignancy should be considered for resection with a negative parenchymal margin. When resecting a cystic lesion that may contain malignancy, great care should be taken

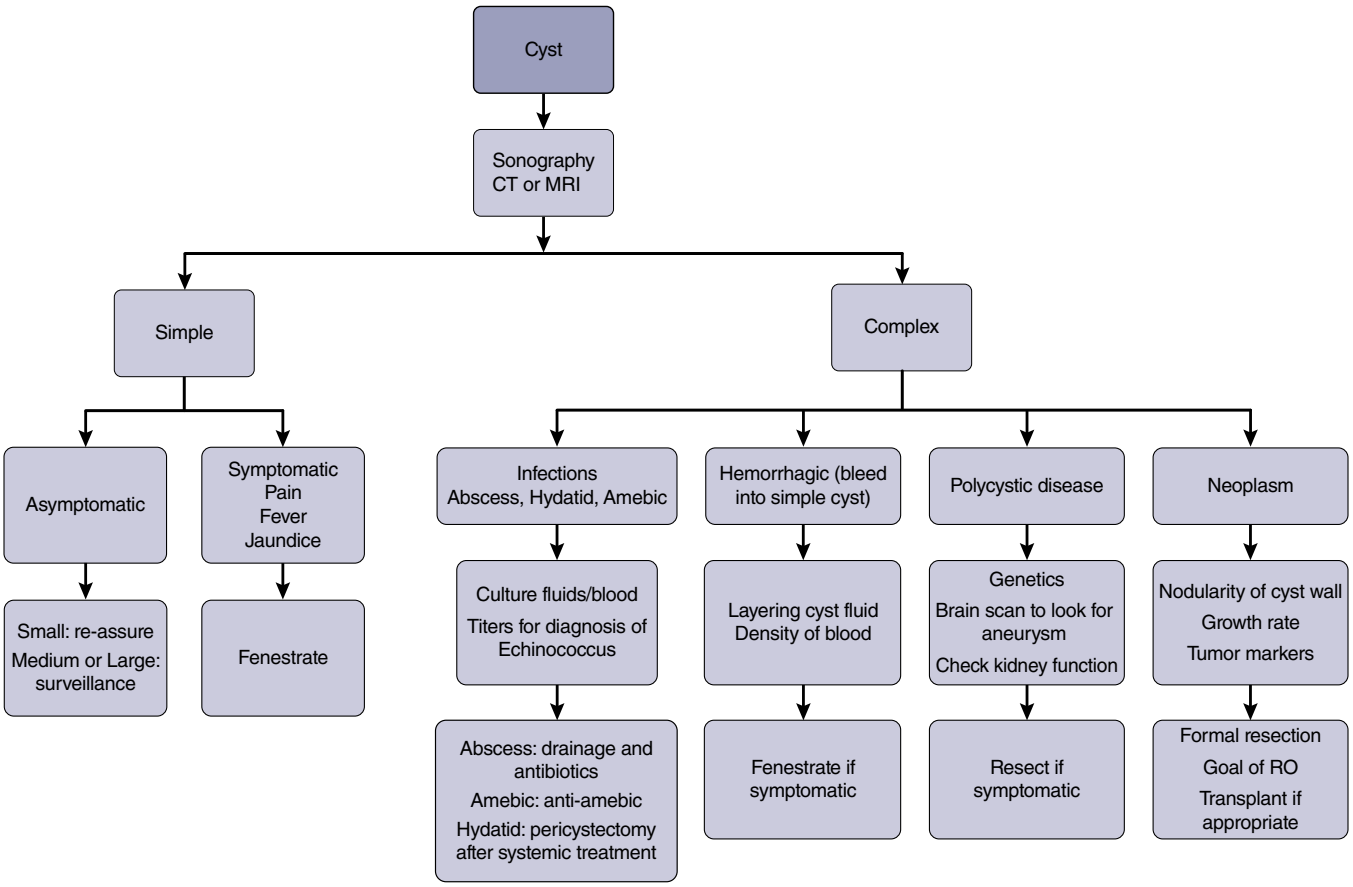


FIG. 3 Flowchart of treatment decisions in managing patients with liver cysts.

to avoid rupture of the cyst because this may cause seeding of the peritoneal cavity with malignant cells and inadvertent dissemination of the cancer.

Although greater than 90% of liver cysts are asymptomatic, large cysts may present with symptoms such as abdominal pain or discomfort, nausea, early satiety, or other compressive symptoms on the stomach and bowel. A sudden increase in abdominal pain may be attributable to hemorrhage within the cyst. Although a patient may have abdominal pain or other digestive symptoms as well as a large liver cyst, the liver cyst may not necessarily be the cause of symptoms as there remains a broad differential diagnosis for abdominal pain. Although typically not indicated, a diagnostic aspiration may be employed to discern whether symptoms improve with a reduction in cyst volume.

Options for treatment of liver cysts include simple aspiration, aspiration with injection of sclerosant, surgical cyst fenestration, enucleation, or resection. The advantage of sclerotherapy is the potential to destroy the epithelial lining and therefore prevent fluid reaccumulation. Before injection of sclerosant, a puncture and test aspiration should be performed to allow space for injection and to confirm that the cyst does not communicate with the biliary tree, which is a contraindication to the use of sclerosant. Agents employed include tetracycline, ethanol, minocycline, and hypertonic saline. Contrast may also be injected to study the cyst anatomy. Up to 90% of small- and medium-size cysts may be successfully treated with sclerotherapy via the PAIR approach.

For large cysts that demand treatment and are not amenable to sclerotherapy, surgical cyst fenestration can provide a durable outcome. This may be performed via a minimally invasive approach and spare a major incision. The goal of this procedure is to unroof the cavity by removing the atrophied parenchyma and capsule overlying the cyst while sparing the vascular structures and bile ducts deep to it. Once laparoscopic or robotic exposure to the cyst is secured, the surgeon begins by aspirating the fluid and evacuating the space. Then the thin roof of tissue may be resected with either a vessel sealer or if thicker, a stapler. Unless there are neoplastic features, the deep cyst wall does not need to be enucleated but can be ablated with cautery or argon beam. Before completing the operation, ensure that any leaking biliary radicles are controlled with suture ligature. A pedicled omental flap may be used to fill the space. Drains should be reserved only if there is concern of infection or bile leakage.

When lesions such as mucinous cystic neoplasms are selected for enucleation, the surgeon should develop the plane between the cyst pseudocapsule and surrounding liver parenchyma. Along this plane, the hepatic veins and bile ducts may be compressed, so care must be taken to avoid disrupting them. Figure 3 presents a simple flowchart of treatment decisions for liver cysts.

CONCLUSION

Most liver cysts are incidental, asymptomatic, and benign and therefore warrant no treatment. In working up a patient with cystic lesions of the liver, bacterial and parasitic infections should be ruled out by history and laboratory tests. Liver cysts should also be differentiated from biliary cysts, which demand a different treatment approach. Cysts displaying asymmetry, nodules, complex architecture, or associated masses should be evaluated for primary malignancy of the liver or metastatic disease. Suspicious cystic liver lesions should be biopsied or simply resected, and mucinous cystic neoplasms of the liver may be enucleated to prevent malignant transformation. In large cysts that are symptomatic, sclerotherapy via PAIR or surgical cyst fenestration can be considered.

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Management of Echinococcal Cyst Disease of the Liver

Miral Sadaria Grandhi, MD, and Henry A. Pitt, MD

Echinococcal cyst disease of the liver, also termed *hepatic cystic echinococcosis* or *hydatid cyst disease,* is a zoonosis caused by the canine tapeworm of the genus *Echinococcus*. The disease is endemic in the Mediterranean, Africa, the Middle East, South America, Asia, and parts of Europe in areas where sheep farming is predominant. Dogs (including wolves, foxes, and coyotes) are the primary host for this intestinal tapeworm, and sheep are the major intermediate host. Deer, elk, caribou, yaks, goats, camels, and other livestock also can carry the larval form. Humans become incidental intermediate hosts, and in the United States hepatic echinococcosis is encountered most often either in immigrants or in Americans who have traveled to endemic areas. The combination of immigration and tourism has made hepatic echinococcosis a worldwide disease that may present many years after exposure. Antiparasitic chemotherapy with mebendazole or albendazole alone is not as effective as these agents combined with surgery. Percutaneous aspiration is another treatment option. However, this chapter will focus on the surgical approaches for the management of echinococcal disease of the liver.

PATHOLOGY AND CLASSIFICATION

Echinococcal infections are divided into two distinct subtypes, *cystic* and *alveolar*. Cystic echinococcus is the predominant form. Hepatic hydatid disease is generally caused by fecal-oral transmission of the larval form of the dog tapeworm *Echinococcus granulosus*. Ova are shed in the feces of intermediate hosts (sheep, goats, or other herbivores), inadvertently ingested in contaminated food, and then penetrate the intestinal wall, entering the portal circulation. Once

in the circulation, embryos can infect any tissue, such as the liver (55%–80% of reported cases), lungs (10% to 40% of human cases), brain, or bones. In the liver, *E. granulosus* has a two-layer cyst wall: an inner active cyst wall that consists of a single cell germinal layer, where the echinococcal scolices and daughter cysts develop, and an outer thicker acellular layer (Fig. 1). This outer, reactive fibrous layer is called the *pericyst* and is calcified in approximately 50% of patients.

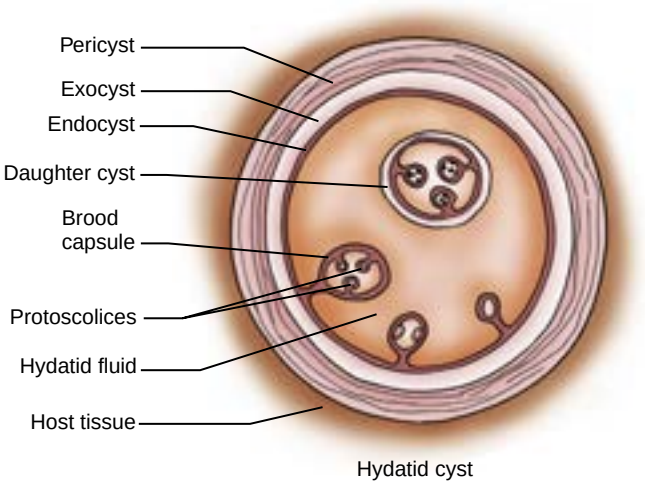


FIG. 1 Structure of echinococcal cyst showing pericyst, exocyst, endocyst, and protoscolices.

Budding of the inner germinal layer within the cyst is termed *daughter cysts* or *hydatid sand.* In approximately one-third of patients, cyst expansion may result in rupture into the biliary tree, erosion through the diaphragm into the pleural cavity, or, rarely, rupture into the peritoneum. On the other hand, mature cysts may become inactive, asymptomatic, further calcified, and be associated with negative serology results.

Alveolar echinococcal infections are caused by *Echinococcus multilocularis,* more commonly found in elk or caribou. *E. multilocularis* is much less common in North America than *E. granulosus* and is mainly endemic to central Europe, Russia, Turkey, China, and Japan. *E. multilocularis* has a high affinity for the liver (99% of cases), causing a hepatic infiltrate, which is a more "tumorlike" form of the disease. Alveolar echinococcosis is fatal in the absence of appropriate treatment, with 5-year mortality approaching 70% and 10-year mortality reaching 94% in untreated patients.

Classification of echinococcal cyst disease of the liver has changed over the past 20 years. In the early 1980s, Gharbi published an ultrasound classification of hepatic echinococcal cysts that divides the cysts into five types (I to V) based on the morphologic imaging appearance. However, in 1995, the World Health Organization Informal Working Groups on Echinococcosis (WHO-IWGE) put forth a standardized classification system that was updated again in 2003 to characterize cysts that incorporate both the functional status of the parasite (active, transitional, or inactive) and the ultrasonographic appearance of the cysts (Table 1, Fig. 2). The WHO-IWGE classification has aided in the selection of optimal therapy and has since been applied to other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Resembling the TNM staging classification, the WHO-IWGE also developed a PNM classification system to standardize disease diagnosis and treatment strategies for alveolar echinococcal infections. *P* refers to the size and

TABLE 1 World Health Organization Informal Working Groups on Echinococcosis Classification of Hepatic Echinococcal Cysts

Cyst Type (Gharbi)	Status	Ultrasound Features	Remarks	Treatment Approach
CL (none)	Active	Unilocular, anechoic Usually round Cyst wall *not* visible	Early, not fertile Needs diagnostic tests	Needs diagnosis
CE 1 (type I)	Active	Unilocular, anechoic Round or oval Cyst wall *visible* Hydatid sand *(snowflake)*	Usually fertile *Pathognomonic*	<5 cm–ABZ >5 cm–PAIR + ABZ
CE 2 (type III)	Active	Multivesicular, septated Round or oval Cyst wall *visible* Rosette, *honeycomb-like*	Usually fertile *Pathognomonic*	PT or surgery + ABZ
CE 3 (type II)	Transitional	Detached floating membrane Less round, complex mass *Water lily sign*	Starting to degenerate *Pathognomonic*	PT, PAIR, or surgery + ABZ
CE 4 (type IV)	Inactive	Heterogenous, hypoechoic degenerating membrane No daughter cyst *Ball of wool*	Most not fertile Needs diagnostic tests	Surgery + ABZ, or watch and wait
CE 5 (type V)	Inactive	Thick, calcified wall Arch-shaped *Cone-shaped shadow*	Most not fertile *Highly suggestive* Needs diagnostic confirmation	Surgery + ABZ, or watch and wait

ABZ, Albendazole; *CE,* cystic echinococcosis; *CL,* cystic lesion; *PAIR,* puncture, aspiration, injection, and reaspiration; *PT,* percutaneous therapy.

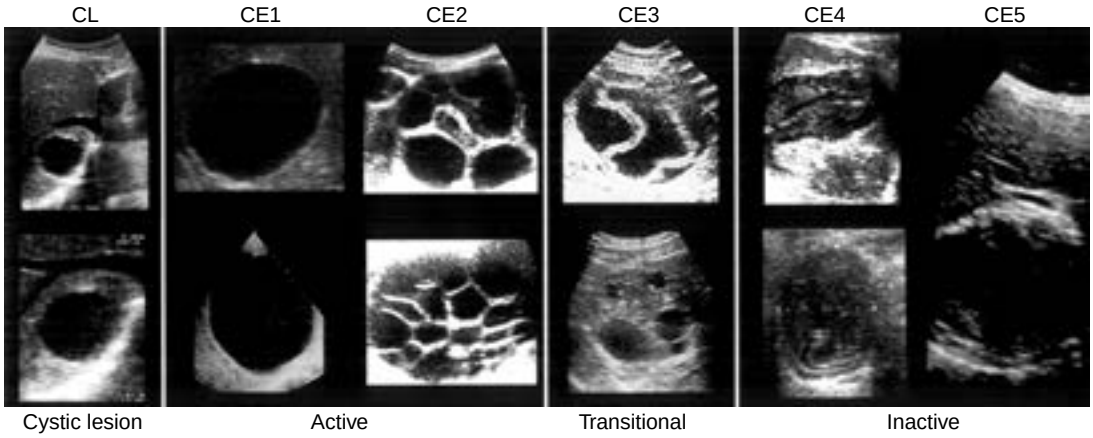


FIG. 2 World Health Organization Informal Working Group on Echinococcosis classification of hepatic echinococcal cysts. *CE,* cystic echinococcosis; *CL,* cystic lesion. *(From Goldman L, Schafer A.* Goldman Cecil Medicine. *24th ed. Philadelphia: Elsevier; 2009.)*

location of the parasite within the liver; *N* indicates involvement of neighboring organs; and *M* evaluates the absence (M0) or presence (M1) of distant metastases.

PRESENTATION AND DIAGNOSIS

Patients with echinococcal cyst disease of the liver can have a widely varied presentation that ranges from an extended asymptomatic period to rupture of the cyst into the peritoneal cavity with an acute abdomen and anaphylactic shock. Most patients, however, have uncomplicated disease that may be asymptomatic or present with right upper quadrant pain, fullness from cyst expansion, hepatomegaly, or fever. Obstructive jaundice, cholangitis, and productive cough from rupture into the pleural cavity and the lung are less common presenting symptoms. With the increase in abdominal imaging studies, incidental discovery of a cyst before symptom development is another common presentation. The diagnosis of this disease is centered on clinical findings, imaging, and serology and is confirmed with either demonstration of protoscoleces on direct microscopy or changes in ultrasound appearance that are pathognomonic for cystic echinococcosis.

Laboratory Tests

Evaluation may include various laboratory tests to help establish the diagnosis, including routine complete blood count (CBC) with differential demonstrating eosinophilia in approximately 40% of patients, liver function tests (LFTs) revealing normal or mildly elevated alkaline phosphatase or transaminases, and serum antigen testing. Enzyme-linked immunosorbent assay (ELISA) has a sensitivity of 85% to 89% and has replaced all other traditional immunodiagnostic methods such as the Casoni intradermal test, complement fixation test, indirect hemagglutination test, indirect immunofluorescence antibody test, immunoelectrophoresis, and latex agglutination test. Confirmatory testing can be performed for *E. granulosus* by either immunoblotting or ELISA techniques as well as testing for antigen 5 and antigen B on the hydatid cyst fluid. For alveolar disease, the Em2 antigen has a 99% specificity for *E. multilocular*. Em16 and Em18 were antigens developed to differentiate between active and inactive lesions.

Imaging

Ultrasound and CT are the most widely used imaging modalities for diagnosis of liver cysts, including echinococcal disease of the liver. These studies show position, size, number of cysts, proximity to vascular structures, and evidence of extrahepatic cysts. The WHO-IWGE classification system, which characterizes the cysts based on ultrasound appearance, has standardized cyst description and attempted to facilitate the use of ultrasound as the primary diagnostic tool (see Table 1 and Fig. 2). Because of its low cost and its specificity of 90%, ultrasound is the preferred first-line imaging study worldwide. Classic findings for hydatid cysts are thick unilocular or multilocular walls (often with calcifications) and daughter cysts.

When compared with ultrasound, CT may offer more detailed information about the location and depth of the cyst as well as the relationship to the vasculature, which is useful for operative planning (Fig. 3A). MRI also can be utilized to demonstrate cyst characteristics, their relation to vascular and biliary structures, and liquid areas within the cyst matrix with T2-weighted imaging sequences. Magnetic resonance cholangiopancreatography (MRCP) offers further detail of the biliary tree and can delineate cystobiliary fistulae or associated abscesses in complicated cysts. Hydatid cysts also must be differentiated from simple congenital cysts, amebic abscesses, and cystadenomas. Positron emission tomography (PET) can be performed to detect metastatic lesions as well as demonstrate active areas of infection for alveolar echinococcus. However, lack of uptake on PET does not rule out the presence of infection, but it may suggest that the inflammation is being suppressed.

Because communication with the biliary tract occurs in up to 25% of cases of hydatid cysts, endoscopic retrograde cholangiopancreatography (ERCP) may be useful in the workup, especially in patients presenting with cholangitis or jaundice. ERCP delineates biliary anatomy, shows communication between the cysts and bile ducts, and can be used to drain the biliary tree before surgery (Fig. 3B). Routine use of ERCP is controversial but may be helpful to completely define the bile duct anatomy and visualize any clinically silent connections between the bile ducts and the cysts. When operative treatment for hydatid disease is undertaken, intraoperative ultrasound of the liver also should be considered to confirm the relationship of bile ducts and vasculature to the cyst.

TREATMENT

The principles of treatment of echinococcal cyst disease of the liver include early intervention to prevent secondary complications, eradication of the parasite, and prevention of disease recurrence with minimization of morbidity and mortality. Although most cysts are

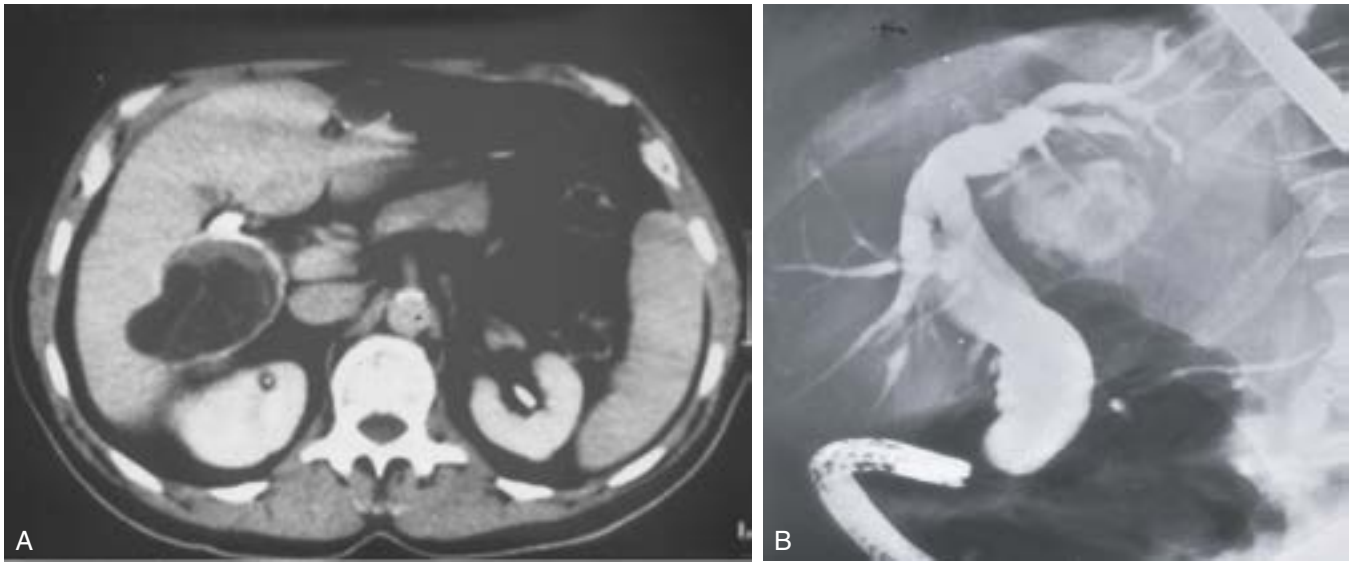


FIG. 3 **(A)** CT scan shows a calcified cyst near the gallbladder fossa. **(B)** Endoscopic retrograde cholangiopancreatography scan shows a cyst with biliary communication and an abnormally dilated biliary tree.

TABLE 2 Treatment Option Pros, Cons, and Outcomes

	Pros	Cons	Outcomes
Medical therapy	Noninvasive	Higher recurrence rates	Recurrence 70%–80%
PAIR	Nonsurgical option for high-risk patients	Lower risk of major and minor morbidity than with surgery (8% and 13% for PAIR, 25% and 33% for surgery)	Recurrence ~10%
Open cyst evacuation	Definitive treatment option, lower risk procedure than pericystectomy	Invasive, potential for spillage, 5% risk of major morbidity	Recurrence ~20%
Minimally invasive cyst evacuation	Decreased length of stay, shorter operating room time, quicker recovery	Pneumoperitoneum with increased risk of spillage and contamination, limited manipulation, difficulty aspirating thick cyst contents	Recurrence ~20%
Pericystectomy	Decreased risk of spillage and recurrence	Invasive, 20% risk of major morbidity including bile leak and bleeding	Recurrence ~10%
Liver resection/ transplantation	Low risk of recurrence, minimizes risk of ischemic hepatic tissue	Most invasive option; increased operative times and length of stay, postoperative morbidity around 40%	Recurrence ~10%

PAIR, Puncture, aspiration, injection, and reaspiration.

asymptomatic, complications such as cholangitis, anaphylaxis from cyst rupture, and pulmonary infection do occur and necessitate complete therapy. Protection of the patient against spillage of scolices and management of any complications that develop are imperative. Surgery remains the predominant therapeutic modality, but systemic chemotherapy; puncture, aspiration, injection, and reaspiration (PAIR); other percutaneous interventions; and watchful waiting also play a role in hydatid cyst management (Table 2). Factors such as the patient's health, cyst characteristics, and the presence of complicated disease all contribute to the decision over which treatment is most appropriate for each individual patient. The optimal or "best" treatment option for this disease has yet to be identified, and clinical trials comparing all available modalities do not exist. Therefore, available medical and surgical expertise and equipment, patient compliance, and the presence of recognized or national treatment centers should be weighed in the decision-making process.

Medical Management

Systemic chemotherapy with antihelminthic drugs (benzimidazoles) is the mainstay of medical treatment for echinococcal disease of the liver. Albendazole (400 mg orally twice daily for patients 60 kg or greater; 10 to 15 mg/kg/day divided twice daily for patients less than 60 kg, with 800 mg/day maximum daily dose) is the drug of choice because it is readily absorbed from the gut, metabolized in the liver to its active form, and concentrated better in cystic fluid when compared with mebendazole. Formal assessment of the optimal treatment dose and regimen has not been performed, and recommendations

vary from continuous treatment for 3 to 6 months with monotherapy to immediate discontinuation after surgery. These agents are not indicated for the treatment of inactive or calcified cysts, except in complicated lesions. Monitoring of leukocyte counts and LFTs are essential because side effects include neutropenia, hepatotoxicity, nausea, and alopecia. More recent data suggest that albendazole combined with the antiparasitic drug praziquantel (a synthetic isoquinoline-pyrazine derivative, 25 mg/kg/day orally in varying regimens) is more effective than albendazole alone. When used without other therapeutic modalities, the success rate of monotherapy with these drugs is approximately 30%; thus it is only recommended in specific smaller (<5 cm) liver cysts (WHO cystic echinococcosis type 1 [CE1]). Therefore additional percutaneous or surgical therapy should be used in conjunction with medical treatment (see Table 1). When combined with surgery, albendazole has been shown to both reduce the number of viable cysts at the time of surgery and decrease disease recurrence.

Percutaneous Therapy

Percutaneous treatment of hepatic cystic echinococcosis has become increasingly acceptable in recent years for carefully selected patients. Therapy can consist of either PAIR aimed at destroying the germinal cyst layer or needle decompression and catheter drainage with the goal of evacuating the entire endocyst. Catheter drainage is generally reserved for giant (>10 cm) unilocular cysts. In this procedure, the catheter is left in place until the daily output is less than 10 mL per day. Current consensus guidelines recommend PAIR for patients who are at high-risk or patients who refuse surgery, fail medical management alone, have infected cysts, or experience recurrence after surgery. Cysts that are greater than 5 cm and classified as CE1, CE2, or CE3 are most amenable to primary treatment with PAIR plus a benzimidazole. PAIR is contraindicated in patients with biliary fistulae, complicated cysts, and inaccessible or high-risk locations (superficial) and in those with CE4 or CE5, inactive, or calcified cysts. Symptomatic pregnant women and children older than 3 years of age should be evaluated with care, and individual treatment decisions should be made regarding the use of PAIR.

The PAIR procedure consists of percutaneous puncture and aspiration of the cyst with ultrasound guidance followed by injection or instillation of an indwelling scolicidal solution for 10 to 30 minutes, and then reaspiration of the agent and final irrigation with 0.9% saline solution. Protoscolicides typically used include either hypertonic 20% saline or absolute alcohol. The goal is to reduce the size and volume of the cyst, detach the inner germinal layer from the pericyst with the scolicidal agent, thicken the cyst wall, and eventually solidify the cyst. To prevent spillage of protoscoleces and improve efficacy of the therapy, albendazole should be administered before PAIR and for up to 1 month after the procedure. Whether preprocedural albendazole should be started a few hours or up to 1 week before PAIR is unclear. However, data have shown that combined treatment of PAIR plus albendazole is superior to either alone.

More than 4000 PAIR interventions have been performed over the past 20 years, proving the safety of the procedure. A 2003 meta-analysis compared PAIR plus albendazole or mebendazole with surgical therapy and found that PAIR and chemotherapy had a higher cure rate, less recurrence, fewer complications, and decreased length of stay. However, the surgical group was a historic control of mixed cases performed before 2001, and more than half of the patients did not receive any antihelminthic drug therapy, the standard of care, which makes interpretation of the results difficult. Although PAIR and percutaneous drainage have been proven to be relatively safe, better data on the various therapies will be required before the optimal treatment of hepatic hydatid cysts can be fully determined.

Operative Therapy

Surgical management of echinococcal cyst disease of the liver was the only treatment option before the 1980s and has long been the primary therapeutic modality. Indications for surgery include large CE2 to CE3 cysts with multiple daughter cysts; superficial singular cysts at risk for spontaneous or traumatic rupture; infected cysts or those with biliary communication, particularly when percutaneous therapy is not available or possible; and cysts with a mass effect on adjacent vital organs. Evaluation of cyst type, size, location, presence or absence of complications, and patient factors (comorbidities, compliance) should be considered when choosing surgical intervention versus other therapies. Operative management is generally contraindicated in patients who are unfit for surgery or those with inactive asymptomatic cysts, poorly located cysts, and very small cysts. The tenets of treatment with surgery remain to completely inactivate the scolices, eliminate the parasite and viable cyst contents, prevent recurrence or spillage of cyst contents, manage the cyst cavity, and prevent untoward morbidity and mortality.

A variety of surgical techniques exists, including open and laparoscopic cyst evacuation, pericystectomy, liver resection, and transplantation. Proper preoperative evaluation of the location of bile ducts and vascular structures with ultrasound, CT, or MRI should be obtained. If a biliary communication is suspected, preprocedural ERCP should be performed. The use of intraoperative ultrasound also is helpful in identifying and avoiding key structures. These operative therapies all should be used in conjunction with a benzimidazole (administered for at least 1 day before surgery and for up to 1 month after surgery, if viable scolices are present) to decrease the risks of residual or recurrent disease.

The surgical treatment can be categorized as *conservative* or *radical* based on the extent of the operation. The conservative approach involves partial or subtotal resection of the cyst, resecting the endocyst, and leaving the pericyst behind. The residual cavity is generally dealt with by securing an omental pedicle flap into the cavity. The radical approach is aimed at removing the entire cyst, including the pericyst, which can be performed as a pericystectomy, a segmental or lobar liver resection, or liver transplantation in rare scenarios. Although the radical approach has a decreased risk of recurrence, an increased risk of morbidity is present with this approach because of the more aggressive nature of the surgical intervention.

Scolecoidal Agents

Inactivation of protoscolices and prevention of their spillage during surgery with scolecoidal agents is strongly recommended. In the past, considerable controversy existed over the use and type of scolecoidal agents. Formalin, cetrimide, and chlorhexidine all have been used, but the safety and efficacy of these agents have not been established. The WHO recommends 20% hypertonic saline solution that should be in contact with the germinal layer of the cyst for at least 15 minutes before intervention. Hypertonic saline solution and other agents should be avoided in patients with cystobiliary fistulas because of the risk of chemically induced sclerosing cholangitis if the agent enters the biliary tract. Care should be taken to prevent the development of hypernatremia, another potential side effect of hypertonic saline solution that is seen with overuse. Peritoneal contents can be protected with protoscolicide-soaked surgical sponges. In addition, preevacuation injection of hypertonic saline solution into the cyst should be avoided because intracyst pressure is already high and may increase the likelihood of protoscolex spillage. A meticulous surgical technique is warranted rather than overreliance on scolecoidal agents. If spillage does occur, the peritoneum should be washed with hypertonic saline, and patients should be treated with albendazole (3–6 months) and a brief course of praziquantel (7 days).

Open Cyst Evacuation

As one of the safest surgical approaches, open evacuation of hydatid cysts is considered a conservative surgical therapy and is most suitable for peripherally located cysts on or near the surface of the liver. When anterior, an abdominal approach is best, whereas cysts in segments VI and VII are more amenable to a lateral flank approach. Figure 4A depicts evacuation of the cyst contents via aspiration; subsequent injection of a scolecoidal agent is optional at the time. Note that the field is lined with hypertonic saline solution–soaked

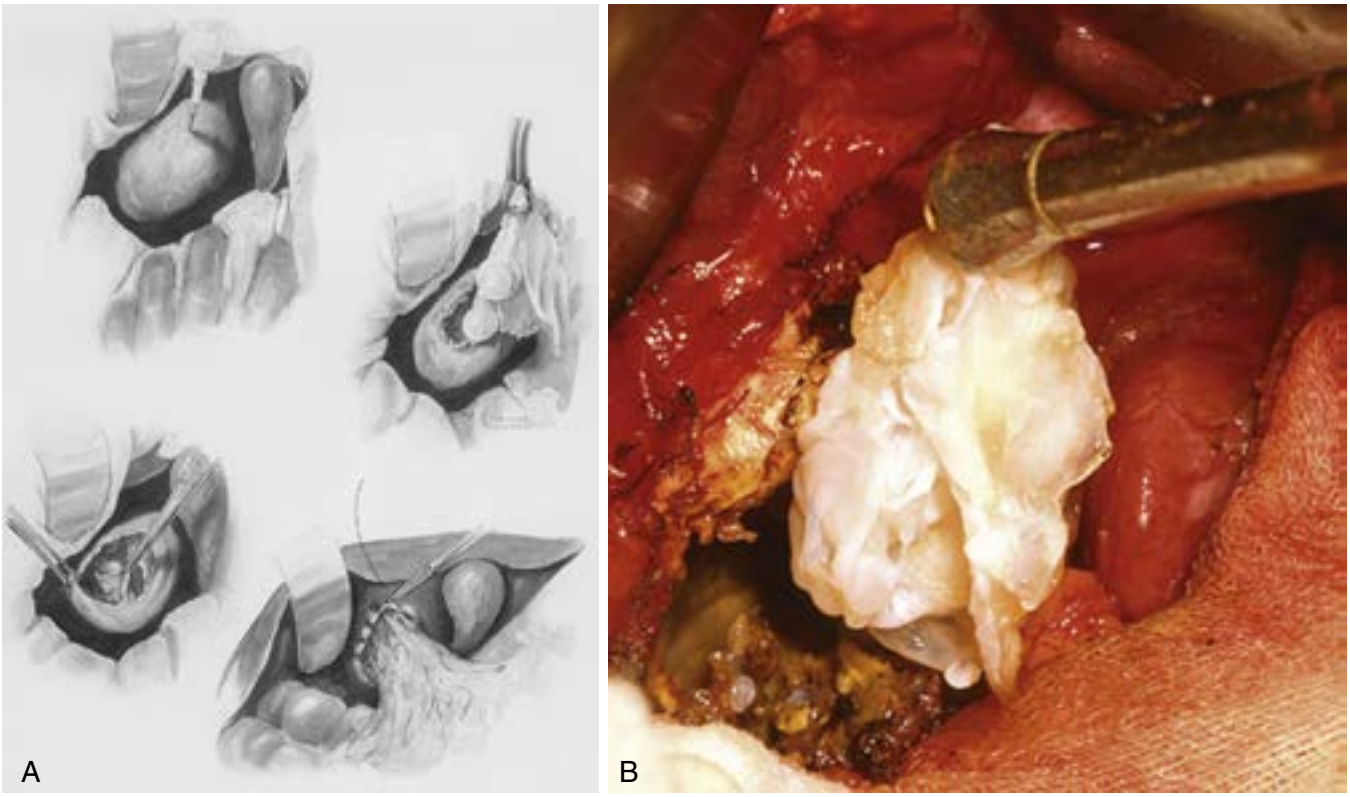


FIG. 4 **(A)** Open cyst evacuation shows cyst aspiration *(top left),* suction removal of daughter cysts *(top right),* resection of the active cyst lining *(bottom left),* and omental packing with suture tacking *(bottom right).* **(B)** Operative picture shows the daughter cysts. *(From Cameron JL, Sandone C.* Atlas of Surgery: Gallbladder and Biliary Tract, the Liver Portosystemic Shunts, the Pancreas. *Philadelphia: BC Decker; 1990.)*

gauze in the event of spillage. The cyst cavity is then opened, and the contents are aspirated with a large suction device with high negative pressure (Fig. 4B). Removal of daughter cysts, resection of the active cyst lining, and meticulous clearance of any remaining debris can be performed once the cyst is completely opened. The cyst may then be irrigated with a scolecoidal agent, as described previously, and packed with omentum.

However, if the cyst fluid is bile stained or communication with the bile ducts was shown on preoperative ERCP, intracavity scolecoidal agents should be avoided. Simple closure of any biliary connection should be performed with absorbable sutures, and the cyst cavity should be filled with omentum. If the cystobiliary fistula cannot be easily closed, external drainage with a closed-suction drain may be warranted. A cystobiliary fistula also should be suspected in large cysts (>7.5 cm) for which the incidence is as high as 80%, prompting a search for biliary communication. The application of diluted hydrogen peroxide into the cyst cavity can help identify any small biliary communication.

Minimally Invasive Cyst Evacuation

A minimally invasive approach to echinococcal liver disease uses the same principles as open surgery. Several reports have shown that carefully selected patients with peripherally located hepatic hydatid cysts may be safely managed with laparoscopic cyst evacuation. Anterior cysts without thick calcified walls and those in segments VI and VII (with a right lateral approach) are particularly amenable to this approach. One laparoscopic technique uses an 11-mm trocar placed just above the cyst, through which 10% povidone-iodine–soaked sponges are placed to act as a scolecoidal agent. The cyst is then punctured with a 14-gauge needle and aspirated, causing the endocyst to shrink away from the wall and rest at the bottom of the cyst. The 11-mm trocar is then upsized to 18-mm so the germinal membrane can be aspirated. The laparoscope is then inserted directly into the cyst to identify any remaining daughter cysts or biliary fistulae, and the cyst cavity is irrigated with 20% hypertonic saline solution. Excision of the cyst wall followed by omentoplasty or closed-suction drainage is then performed to complete the procedure.

Advantages to the laparoscopic approach include reduced hospital stay, decreased hospital cost, and earlier return to productive activity. With laparoscopy, short operative times (less than 90 minutes) and low complication rates also have been reported. In properly selected patients with uncomplicated cysts, conversion to an open procedure should occur in less than 5% of cases. Although no large case series, retrospective studies, or prospective studies exist regarding a robotic approach to hydatid cysts, one study from Italy consisting of 15 patients undergoing major hepatectomy, partial hepatectomy, and cyst-pericystectomies demonstrated that a robotic approach to hydatid cysts is safe and effective with shorter postoperative stay, quick return to daily activity, and absence of surgical site recurrence.

Despite improved visualization, these minimally invasive approaches have not gained widespread acceptance because of the relative inability to avoid or control peritoneal spillage in the setting of high intraabdominal pressures from the pneumoperitoneum (a limited area for manipulation) and difficulty aspirating thick cyst contents. Techniques to minimize spillage of cyst contents include insertion of iodine-soaked sponges as described, fixing the cyst to the abdominal wall, lavage with scolicidal agents, and creation of a scolicidal pool around the liver by operating in the reverse Trendelenburg position. Whatever approach is used, oral albendazole both before and after surgery is still indicated. In addition to simple drainage, laparoscopic partial cystectomy and even total pericystectomy also have been described.

Pericystectomy

Pericystectomy involves complete resection of the cyst wall either closed, without entering the cyst cavity itself, or open, by sterilizing

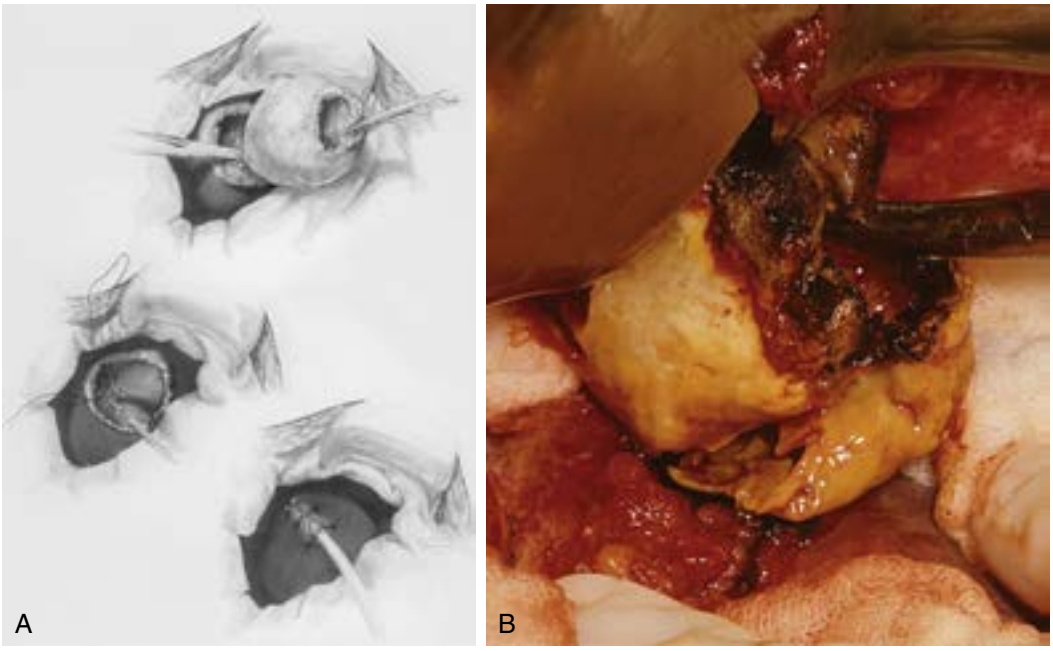


FIG. 5 **(A)** Pericystectomy depicting removal of the calcified pericyst *(top)*, suture closure of a communicating bile duct *(middle),* and (optional) closure of the cavity over a drain *(bottom).* **(B)** Operative picture shows cyst removal. *(From Cameron JL, Sandone C. Atlas of* Surgery: Gallbladder and Biliary Tract, the Liver Portasystemic Shunts, the Pancreas. *Philadelphia: BC Decker; 1990.)*

the contents with protoscolicidal agents, evacuating the cyst tissue, and then removing the pericyst tissue (Fig. 5A). This procedure can be performed with electrocautery or a dissector, either along a plane outside the pericyst or along the cyst wall itself. When dissecting around the cyst, some authors advocate use of a cleavage plane between the inner layer of the host's reaction toward the parasite and the outer layer, or adventitia, which limits damage to the liver parenchyma and allows safer removal (Fig. 5B). Similar to cyst evacuation, pericystectomy is best performed on cysts along the periphery of the liver.

The advantage of this procedure over simple cyst drainage is a decreased risk of cyst content spillage into the peritoneal cavity when performed as a closed pericystectomy, which avoids potential anaphylaxis and decreases the risk of recurrence. Complete removal of the adventitia and elimination of the need for scolecoidal agents can be achieved with a closed procedure. The disadvantages of pericystectomy are an increased risk of bleeding or damage to bile ducts in proximity to the cyst wall because of the need for hepatic parenchymal transection. When encountered, vascular and biliary structures can be controlled with clips or sutures as illustrated in Figure 5A, and the cavity can be closed over a drain.

In a study comparing closed cyst resection with pericystectomy versus open cyst resection, closed cyst resection was demonstrated to have 0% recurrence rate at 5 and 10 years versus 18% and 27% recurrence in the open cyst resection group, respectively. However, the closed cyst resection group had a high rate of major morbidity at 19% compared with the open resection group at 5%. Despite the higher risk of morbidity, pericystectomy is preferred to cyst evacuation because of a lower risk of secondary echinococcosis from protoscolex dissemination. However, the conservative approach of cyst evacuation is well suited for endemic areas, where operations are performed by nonspecialty-trained general surgeons and resources are limited.

Liver Resection/Transplantation

Another "radical" surgical approach to the management of hepatic echinococcal cyst disease is liver resection, which can range from nonanatomic wedge resection to formal hemihepatectomy. Although formal liver resection for benign disease may seem excessive, hepatic resection is now very safe, especially when performed by surgeons and centers with expertise in liver surgery. Multiple indications for liver resection exist, including complicated cysts with large biliary fistulae and small peripheral cysts where the cut surface of the liver is less with resection than with pericystectomy. Liver resection also should be considered for multiple cysts within proximity to one another or major structures, such as portal or hepatic veins or bile ducts, or when the resection would be relatively safe as seen with cysts confined to the left lateral segments II or III. Patients with recurrent disease who have failed more conservative management also are candidates for liver resection. Formal resection of the liver should be initiated only if complete excision of all cysts is possible. In one study, operative time, length of stay, postoperative morbidity, and cyst recurrence were shown to be increased in patients treated with liver resection compared with pericystectomy. However, resection avoids pedunculated ischemic hepatic tissue, which can be seen with pericystectomy.

Perhaps the most radical of surgical management options, liver transplantation, is rarely indicated in the treatment of hepatic hydatid disease not amenable to alternative therapies. As opposed to *E. granulosus,* which tends to form solitary cysts, *E. multilocularis* can produce a more complicated form of the disease with multiple cysts known as *alveolar echinococcosis.* These cysts can result in fulminant liver failure from sclerosing cholangitis, Budd-Chiari syndrome, or biliary sclerosis. In such unusual cases, orthotropic liver transplantation may be indicated.

SUMMARY

Uncomplicated Disease

Patients with uncomplicated echinococcal cyst disease of the liver typically are asymptomatic with incidental cyst discovery on imaging or at abdominal surgery for other reasons. However, they may present with right upper quadrant pain without fever, chills,

jaundice, or cough. A complete history and physical examination should be performed, laboratory tests including LFTs and serology should be sent, and the WHO-IWGE type should be determined with ultrasound imaging or other available studies. For patients with CE1, CE2, or CE3 (Gharbi types I, III, or II, respectively) cysts, particularly if they are anterior, peripheral, unilocular, less than 5 cm, and not heavily calcified, PAIR or minimally invasive cyst evacuation should be considered depending on local expertise (Table 3). Alternatively, uncomplicated cases with CE4 or CE5 (Gharbi types IV or V) cysts that are posterior, central, greater than three in number, large (>5 cm), or calcified should undergo open evacuation or resection when surgery is indicated. The WHO guidelines further suggest that in uncomplicated CE4 or CE5 cysts proven to be inactive, a watch and wait approach may be undertaken with long-term ultrasound imaging follow-up, especially if local surgical expertise is not available. The decision to perform cyst evacuation, pericystectomy, or liver resection should be individualized based on patient and cyst characteristics and surgeon experience.

Complicated Disease

Patients with complicated hepatic hydatid cysts can be secondarily infected or have biliary obstruction, cystobiliary fistula, or rupture into the biliary tree, peritoneal cavity, or pleural cavity. Secondary bacterial infection generally results from biliary communication and should be treated with appropriate systemic antibiotics and adequate cyst drainage. In carefully selected patients, percutaneous drainage may be needed before definitive surgical treatment. In the 5% to 15% of patients with hydatid cysts on imaging who present with jaundice or cholangitis, ERCP is indicated to both evaluate potential fistulae between the cyst and biliary tree and to drain the biliary system with a stent. A sphincterotomy alone may not provide adequate treatment.

Once drainage is sufficient and cholangitis has resolved, open cyst evacuation should be performed and the biliary fistulae closed as described previously. Cyst diameter greater than 7.5 cm is a risk factor for a biliary-cyst communication, even in asymptomatic patients, with an 80% likelihood of a fistula being present at surgery.

TABLE 3 Treatment Option Summary

PAIR or Minimally Invasive Evacuation	Open Evacuation or Liver Resection
UNCOMPLICATED CASES	
CE1, CE2, CE3 cysts (Gharbi I, III, II)	CE4 or CE5 cysts (Gharbi IV or V)
Anterior location	Posterior or central location
Small size (<5 cm)	Large size (>5 cm)
Few number (1–3 cysts)	Multiple (>3 cysts)
Minimal or no calcification	Heavy calcification
COMPLICATED CASES	
Infected cysts meeting previous criteria	Infected cysts meeting previous criteria Biliary or pulmonary communication Peritoneal rupture

Albendazole or mebendazole should be used in conjunction with all treatments.

CE, Cystic echinococosis; *PAIR,* puncture, aspiration, injection, and reaspiration.

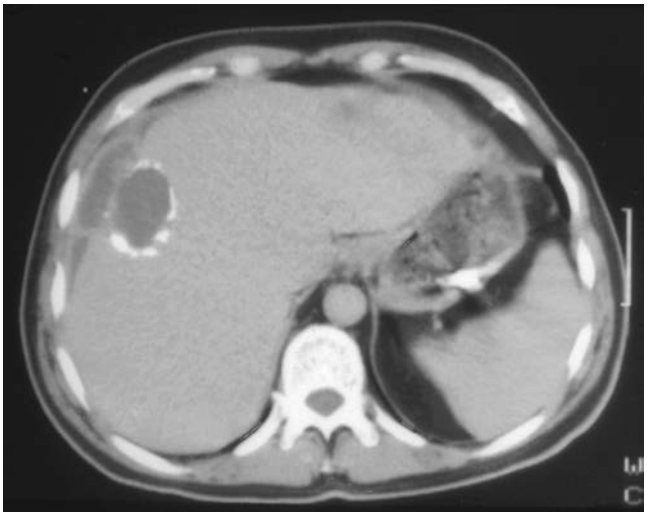


FIG. 6 CT scan shows rupture of a hepatic cyst through the diaphragm into the pleural space.

Therefore, one should be prepared to deal with a biliary fistula in the operating room in patients with large cysts. A concomitant cholecystectomy and intraoperative cholangiogram to ensure complete cyst debris clearance from the bile ducts also may be required. In rare instances, a biliary-intestinal anastomosis or liver resection may be needed to fully treat cystobiliary fistulas.

Complicated disease also occurs occasionally when hydatid hepatic cysts rupture into the peritoneum or through the diaphragm into the pleura and lung (Fig. 6), which can result in widespread disseminated disease. Free rupture of a cyst into the peritoneal cavity presents with peritonitis, shock, and/or anaphylaxis. Treatment of the allergic reaction and surgical evacuation are necessary. In these situations, an open surgical approach is recommended to thoroughly control the spread of disease throughout the abdomen. Supportive and intensive therapy also is usually required for the care of these patients. On the other side of the diaphragm, the workup for patients with pulmonary complications includes imaging, serology, and bronchoscopy when bronchocystic fistulae are suspected. Benzimidazoles alone can be used for small, uncomplicated lung cysts. However, surgical management for these patients often includes evacuation of cysts from both the liver and the pleural spaces. Open cyst evacuation with closure of the diaphragm and drainage are indicated but should be as conservative as possible. For extended pulmonary involvement, severe suppuration, or other complications, pulmonary resection also may be required. In the chest, as in the abdomen, care must be taken to prevent spillage of cyst contents to avoid recurrent infection or anaphylaxis.

RESULTS

Morbidity and Mortality

Advances in the management of patients with echinococcal cyst disease of the liver have decreased the morbidity and mortality of the disease in recent years. In a 2003 meta-analysis of patients with all types of disease (uncomplicated and complicated) that compared 769 patients who underwent PAIR with 952 who had surgical intervention, minor and major morbidity rates for each modality were 8% and 13%, respectively, for PAIR as opposed to 25% and 33%, respectively, for surgery. The overall mortality rate reported in the same study was 0.1% for PAIR and 0.7% for surgery, demonstrating the relative safety of both approaches. Another study of nearly 3000 patients undergoing percutaneous drainage reported complication rates to be 0.05%

for anaphylaxis leading to death, 0.38% for major complications (such as death, secondary echinococcal disease from contamination, sclerosis), and 1.27% for recurrence. Thus, in patients with uncomplicated hydatid cysts who undergo elective percutaneous or laparoscopic drainage procedures, open evacuation, pericystectomy, wedge resection, or left lateral sectionectomy, mortality should be very low, with morbidity rates ranging from 15% to 20%.

A recent retrospective analysis of patients undergoing surgical treatment of hepatic echinococcal infection reported 0% mortality and 47% morbidity for resection procedures, but only a 17% morbidity rate for cyst evacuation. Not surprisingly, less invasive techniques were associated with reduced hospital stay and cost. In patients with complicated disease who undergo open evacuation, pericystectomy, or resection, morbidity is in the range of 40% to 50%, and mortality should be less than 5% (reports range from 0.5% to 4%). The presence of sepsis, peritoneal rupture, underlying comorbid disease, and malnutrition all are factors that increase mortality.

Long-Term Outcomes

Overall, the long-term cure rate for appropriately and adequately treated patients with echinococcal hepatic cysts is excellent and ranges from 90% to 95%. Medical treatment with benzimidazoles alone should only be used in patients who are otherwise not candidates for percutaneous or surgical therapy because recurrence rates are approximately 70% to 80%. Therefore, when possible, medical therapy should be used in combination with a drainage or resection procedure. In uncomplicated cases, open surgical, minimally invasive surgical, and percutaneous drainage techniques all have low recurrence rates around 10%. Because of the endemic nature of this disease and potential for reinfestation, long-term follow-up is necessary with serologic tests and imaging studies.

WHO guidelines recommend follow-up visits including ultrasound imaging and laboratory tests (CBC and LFTs) every 3 to 6 months initially, and then yearly once the situation is stable. Serologic tests also can be followed. Although a persistence of raised or a further increase in antibody levels may indicate residual or recurrent disease, these findings may occur even with full, adequate treatment. Currently, new antigens show promise for posttreatment monitoring. Patients with echinococcal cysts complicated by infection, cholangitis, pleural extension, or peritoneal rupture have unique problems. If the complication such as cholangitis can be treated before definitive cyst treatment, the long-term outcomes are comparable to those of uncomplicated echinococcosis. However, patients with rupture into the pleural cavity or the peritoneum may have a recurrence rate as high as 25%.

Suggested Readings

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Management of Liver Hemangioma

Victor M. Zaydfudim, MD, MPH, and Reid B. Adams, MD

OVERVIEW

Liver hemangiomata are the most common benign liver tumors, with a 2% to 20% overall prevalence in the general population. Similar to other benign and frequently asymptomatic findings, the incidental diagnosis of hemangiomas has increased considerably with more frequent use of cross-sectional imaging. Hemangiomata are more common in women (5:1 predominance), multifocal in up to a third of patients, and can be present in combination with other benign liver tumors. The vast majority of hepatic hemangiomata are asymptomatic, will remain asymptomatic regardless of size, and do not require operative management or surveillance. In most cases, the diagnosis is unequivocally achieved by imaging findings and expert image interpretation. If operative treatment is pursued, either enucleation or parenchymal resection are reasonable options based on the location and the extent of the hemangioma.

Pathogenesis and Clinical Presentation

Pathogenesis of liver hemangioma is not clearly understood. Similar to hemangiomata of other sites, these vascular malformations are congenital and enlarge by vascular ectasia rather than angiogenesis. Hemangiomata are structurally surrounded by a pseudocapsule, with growth of this benign liver tumor results in volumetric expansion and compression of the surrounding tissue by the expanding hemangioma and its pseudocapsule (Fig. 1). This expanding, but not invasive, growth compresses the neighboring vascular and biliary structures, displacing them. As a result, surrounding vascular and biliary structures are typically not directly involved by the hemangioma. Hemangiomata are multifocal in 10% to 30% of patients and are present in approximately 10% to 20% of patients with other benign liver tumors (hepatic adenoma and/or focal nodular hyperplasia). The pathophysiology of hemangioma growth is not completely understood. In some, growth is associated with a higher estrogen state, such as puberty, estrogen replacement therapy, or pregnancy; however, causality between a higher estrogen state and hemangioma growth has not been established. Asymptomatic growth of hemangiomata, sometimes to very large sizes, can occur in the elderly. Interestingly, a decrease in the size of a known hemangioma, at times with complete involution, has been observed in many patients with chronic liver disease including both fibrosis and cirrhosis.

The vast majority of hemangiomata are asymptomatic. These blood-filled benign liver tumors have the consistency of a soft, spongelike sac that compresses with pressure. When present, the most commonly reported symptoms are abdominal pain, discomfort, fullness, early satiety, and nausea/vomiting. A common postulate to explain symptoms in patients with hepatic hemangiomata is linked to the distention and stretch of Glisson's capsule. The theory is plausible because Glisson's capsule is innervated; however the majority of patients with capsular involvement by hemangiomata are not symptomatic. Furthermore, symptoms are frequently absent in patients with hepatic malignancies that invade and distort Glisson's capsule. The term *giant* is frequently used; however, this term is misleading and lacks clinical significance. The cutoff for *giant* classification has increased from 5 cm (20 to 30 years ago) to over 10 cm currently. Despite their large size, most hemangiomata are asymptomatic. Rarely, very large hepatic hemangiomata can cause clinical biliary obstruction, hepatic venous compression (which can lead to Budd-Chiari syndrome), or hemangioma thrombocytopenia syndrome (Kasabach-Merritt syndrome).

As hemangiomas are most frequently asymptomatic, the majority are identified incidentally during diagnostic imaging for either a separate problem (e.g., trauma evaluation, nephrolithiasis) or during clinical evaluation of epigastric or right upper quadrant pain. The key feature for management of a hemangioma is establishment of the correct diagnosis. In most cases, the diagnosis is established by ultrasonography or cross-sectional diagnostic imaging; rarely the diagnosis can be challenging and requires more invasive measures. In even more rare scenarios (commonly sclerosed hepatic hemangioma), preoperative diagnosis is not established, and resection is pursued for a postoperative diagnosis of hepatic hemangioma. The diagnosis of *atypical hemangioma* should raise suspicion and likely stimulate additional imaging review or investigation.

Overall, four principles should be considered in the management of patients with hemangioma: (1) the majority of patients with hemangiomata, regardless of size, are asymptomatic and do not require intervention; (2) a broad differential diagnosis (including gastroesophageal reflux, peptic ulcer disease, gallstone disease) should be considered in patients who present with epigastric/right upper quadrant complaints and imaging demonstrating hepatic hemangioma; (3) when resection is considered, both minimally invasive and open techniques can be pursued, however minimally invasive approaches should not expand indications for treatment; and (4) operative treatment of hepatic hemangioma does not improve underlying symptoms in approximately 30% to 50% of selected patients.

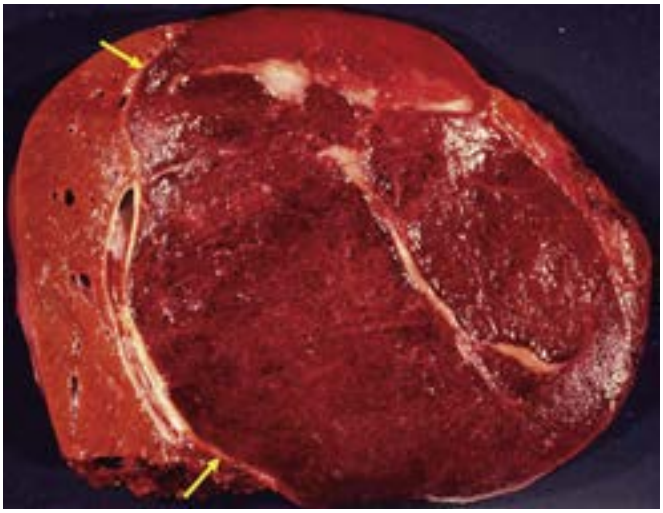


FIG. 1 Hemangioma with surrounding pseudocapsule *(arrows)*.

Diagnosis

Ultrasonography is diagnostic in many patients with hepatic hemangiomata and is particularly accurate in patients with small hemangiomata (<3 cm). Most smaller hemangiomata are composed of vascular ectatic architecture without cavernous features, and ultrasound imaging demonstrates a homogenous, hyperechoic, well-circumscribed liver lesion without posterior acoustic shadowing (Fig. 2A). These small hepatic hemangiomata can be challenging to classify with single-phase computed tomography (CT), therefore, in the appropriate clinical setting (e.g., a healthy patient without known chronic liver disease or malignancy), diagnostic ultrasound rather than further escalation of cross-sectional imaging can easily establish the correct diagnosis at minimal cost. Contrast-enhanced ultrasound (CEUS) can highlight vascular enhancement typical for hemangiomata (Fig. 2B) and can avoid escalation to cross-sectional imaging. It can also be used in instances in which contrast cross-sectional imaging is either nondiagnostic or cannot be technically performed.

Traditional multiphase (triple-phase) CT imaging is diagnostic for the vast majority of patients with hepatic hemangiomata. The CT



FIG. 2 **(A)** Ultrasound shows numerous small, hyperechoic, well-circumscribed liver lesions without posterior acoustic shadowing, consistent with multifocal hemangiomata (*arrows* highlight three lesions). **(B)** Contrast-enhanced ultrasonography *(CEUS)* shows differential timing of contrast uptake with intense uptake by some hemangiomata *(yellow arrows)* and slower more nodular uptake by another *(red arrow)* during early arterial-phase contrast injection. Contrast uptake is homogeneous during portal venous phase and there is contrast retention during the delayed phase (**B** courtesy Dr. Rachita Khot).

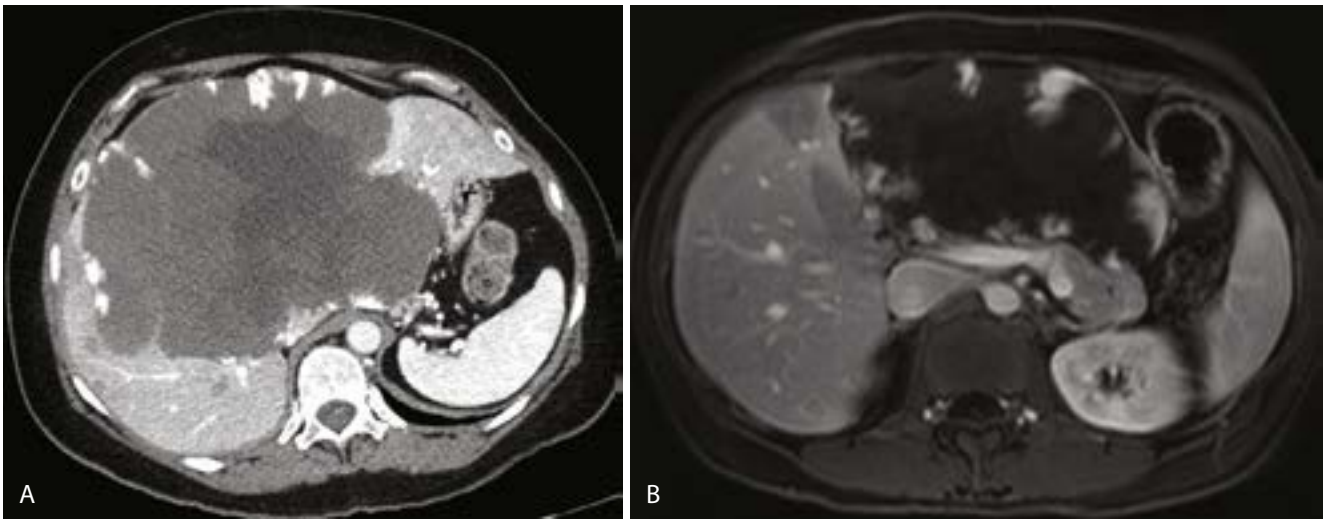


FIG. 3 Typical peripheral nodular contrast enhancement patterns for hemangioma as visualized with CT arterial phase **(A)** and MR post-gadolinium **(B).**

criteria for diagnosis of hemangiomata are: (1) a well-defined and relatively hypointense liver lesion during the precontrast phase, (2) early discontinuous nodular peripheral enhancement of the lesion during the arterial phase (Fig. 3A), and (3) progressive centripetal contrast enhancement with opacification of the lesion during the venous phase. CT imaging characteristics can vary between patients, with differing hemangiomata sizes and internal characteristics of lesions. Atypical enhancement patterns can be present in both small and large hepatic hemangiomata. Small hemangiomata frequently enhance too rapidly to demonstrate nodular filling, while larger hemangiomata demonstrate variable opacification dependent on the size of the lesion and internal architecture.

When ultrasound and/or CT demonstrate atypical features, MRI with vascular (rather than hepatobiliary) contrast can help secure the diagnosis. The overall accuracy of MRI in establishing the diagnosis of hemangiomata is very high, with a sensitivity of approximately 90% and a specificity approaching 100%. MRI diagnostic criteria include lesions that (1) are hypointense relative to normal liver parenchyma on T1-weighted images, (2) are hyperintense relative to normal liver on T2-weighted images, (3) are hyperintense relative to background liver parenchyma on diffusion-weighted imaging secondary to T2 shine-through, and (4) demonstrate discontinuous peripheral nodular enhancement with delayed centripetal filling on T1-weighted sequences after gadolinium administration (Fig. 3B). In rare circumstances, the diagnosis cannot be established using noninvasive diagnostic imaging. In these exceptional cases, percutaneous biopsy or resection can be pursued. There is ample evidence that biopsy of hemangiomata can be performed safely.

Treatment

The most difficult decision, besides confirming the diagnosis, is deciding whether treatment is warranted. In most patients (>90%), irrespective of size, no therapy is indicated or necessary. Treatment is not indicated in women of childbearing age; there is no need for cessation or adjustment in oral contraceptives, modification of pregnancy planning, or modification of activity level. Similarly, surveillance in asymptomatic patients with a hemangioma is not warranted. From a technical perspective, the ability to resect the hemangioma via a minimally invasive technique (laparoscopic or robotic) should not expand the indications for resection.

Rarely, after judicious diagnostic evaluation and patient selection, operative treatment is required. Treatment can be considered for a narrow range of specific indications: (1) severe persistent symptoms in the absence of other potential etiologies, (2) intraparenchymal or intraperitoneal hemorrhage (exceedingly rare; can be associated with hemangioma thrombocytopenia syndrome), (3) biliary or hepatic venous obstruction, or (4) diagnostic uncertainty and inability to exclude malignancy. The first three of these indications are typically associated with massive hemangiomas.

Operative management of hepatic hemangiomas can be performed using one of two technical approaches: enucleation or parenchymal resection. As is typical for any liver resection, the principles of liver surgery including liver mobilization to facilitate exposure, inflow control, and low central venous pressure anesthesia are paramount. Cell salvage can be used to allow for autotransfusion of shed blood.

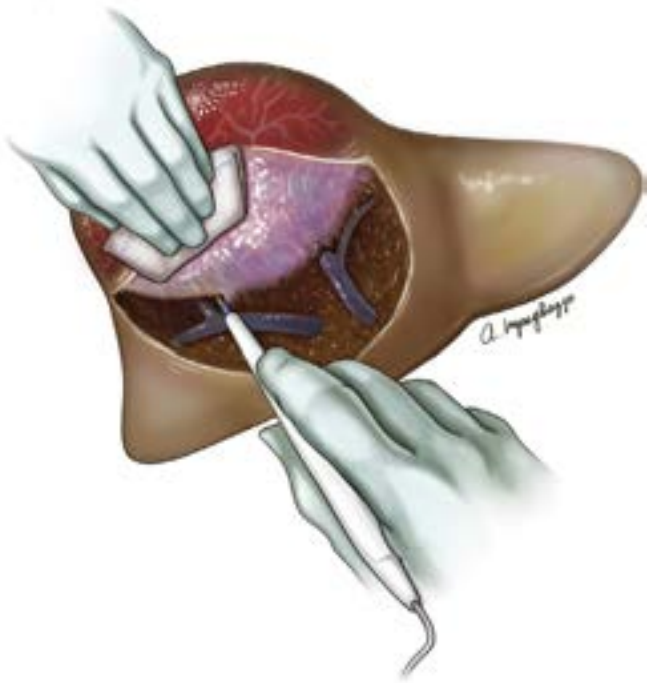


FIG. 4 Enucleation of hepatic hemangioma can be performed following the pseudocapsular dissection plane. Inflow occlusion can help facilitate visualization and dissection of the tumor from the abutting vascular and biliary structures. *(Printed with permission from Anita Impagliazzo.)*

Typically, hemangiomata are surrounded by a pseudocapsule, with resultant compression rather than invasion of adjoining vascular and biliary structures. This feature makes enucleation of hemangiomata technically feasible. Enucleation is particularly attractive as it allows for use of the natural peritumoral dissection plane for the resection, while preserving functional hepatic parenchyma. Many series describe enucleation as the dominant resection strategy. Glisson's capsule is incised next to the tumor to access the plane between the hemangioma pseudocapsule and normal parenchyma. The plane is subsequently further developed with either electrocautery or a clamp (Fig. 4). More sophisticated parenchymal transection devices are not typically required during open enucleation of hemangiomata as retraction of the hemangioma and gentle pressure along the pseudocapsule facilitates separation of the tumor from compressed parenchyma. Vascular structures crossing the resection plane are ligated and divided. Once the dominant artery that supplies the hemangioma is divided, the tumor further decompresses, and dissection typically becomes less challenging; sometimes it is possible to ligate this feeding vessel early during the course of dissection. Large vascular and biliary structures (e.g., anterior or posterior branches of the portal vein or bile duct, the middle hepatic vein) are typically displaced, rather than involved, and can be preserved. If required for visualization, judicious inflow control helps visualize the transection plane as well as the crossing and displaced vascular and biliary structures. Enucleation is technically feasible for many sublobar tumors; lobar hemangiomata are more frequently managed with anatomic resection.

Particularly large hemangiomata, those involving the majority of the liver lobe (or larger), are better suited for anatomic resection. Ipsilateral ligation of the hepatic artery facilitates decompression of the hemangioma. In extenuating cases with massive hemangiomata in which access and control of the hepatic hilum is perceived to be potentially treacherous, preoperative lobar arterial embolization of the affected side (typically performed on the day before resection or the morning of resection) can facilitate hepatic mobilization and hilar dissection and control. Ligation of the hepatic artery supplying the tumor allows one to compress the hemangioma, similar to



FIG. 5 Ruptured hemangioma in a patient with cirrhosis. Initial CT imaging with hemoperitoneum, enhancement adjacent to liver lesion with internal complexity during arterial phase **(A)** and progressive centripetal contrast progression during portal venous phase **(B).** Angiography re-demonstrated a hypervascular tumor **(C),** and bland transarterial embolization with 150- to 250-micron polyvinyl alcohol particles arrested hemorrhage **(D).** Given the atypical presentation in a patient with cirrhosis, a biopsy was performed to confirm the diagnosis of hemangioma.

squeezing a sponge, decompressing it and making liver mobilization and resection easier. This is an especially helpful maneuver for massive hemangiomata that fill a substantial space within the peritoneal cavity. Smaller hemangiomata also can be resected using either anatomic hepatectomy or non-anatomic hepatectomy. Partial hepatectomy, rather than enucleation, is more likely to be used in deeper subcapsular hemangiomas, when indication for resection is frequently diagnostic equipoise.

Minimally invasive operative approaches can be used depending on surgeon and institutional expertise. Both laparoscopic and robotic platforms have been used to perform enucleations and anatomic resections. The use of a minimally invasive approach, however, should not expand indications for resection. Placement of trocars and positioning depends on the location of the hemangioma and whether a laparoscopic or robotic approach is used. Similar to the open operation, inflow control, low central venous pressure, identification of tumor pseudocapsule, and dissection along the pseudocapsule plane with ligation of intervening branches are used in minimally invasive enucleation of hemangiomata.

RUPTURED HEMANGIOMATA, KASABACH-MERRITT SYNDROME, AND BUDD-CHIARI SYNDROME

The vast majority of hemangiomata do not rupture, regardless of tumor size or activity level of the patient. Very rare cases of tumor rupture present with typical symptoms including abdominal pain, hemoperitoneum, and hemodynamic instability. Judicious blood product–directed resuscitation and transarterial embolization (Fig. 5) can be rapidly performed to arrest hemorrhage. Exploration with packing is rarely required with the exception of urgent management in a remote location without ability to rapidly transfer the patient. Rupture of hepatic adenoma or hepatocellular carcinoma (rather than a hemangioma) should be excluded as these are considerably more frequent causes of hemoperitoneum resulting from a ruptured liver tumor.

Kasabach-Merritt hemangioma thrombocytopenia syndrome is similarly very rare. A high index of suspicion in patients with large hemangiomas and thrombocytopenia can prevent emergent management of disseminated intravascular coagulation in patients with

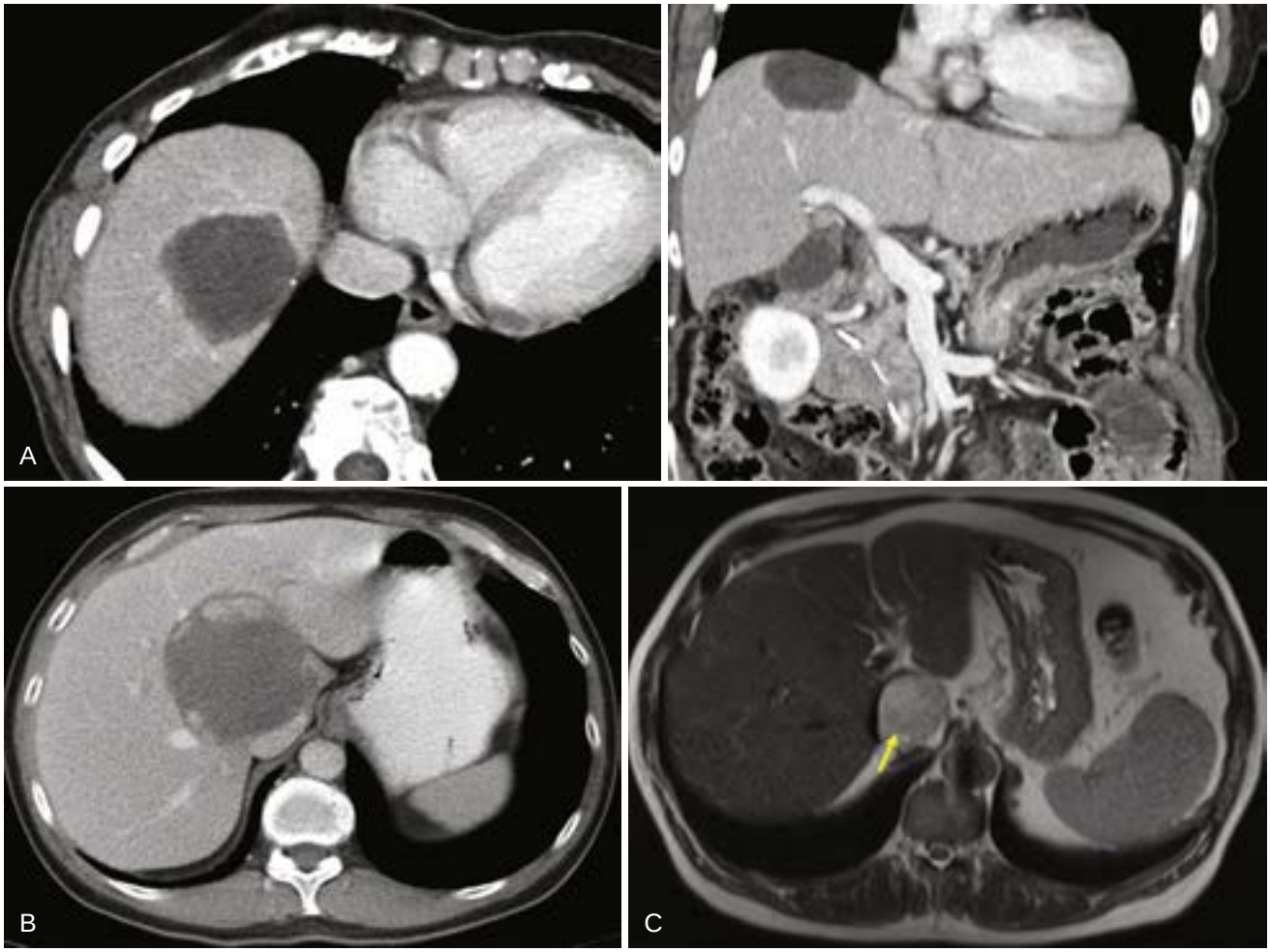


FIG. 6 Establishing the correct diagnosis is critical in the management of liver hemangiomata. Sclerosed or hyalinized hemangiomata are particularly challenging to diagnose prospectively with imaging; either biopsy or resection are pursued in situations with diagnostic equipoise. **(A)** An atypical pattern of enhancement without the typical vascular pattern during either CT or MRI resulted in resection in this patient with a sclerosed hemangioma. **(B)** In patients with a personal history of malignancy, new or growing liver lesions should raise suspicion for metastasis, as in this patient with a metastatic gastrointestinal stromal tumor (lesion with peripheral nodular enhancement). **(C)** Thorough diagnostic evaluation, including consideration for percutaneous or endovascular biopsy, should be undertaken in patients with atypical imaging findings, as in this patient referred for sarcoma with an evaluation diagnostic for a hemangioma.

end-stage hematologic disarray. Resection, if technically permissible, is the preferred treatment strategy in patients with hemangioma thrombocytopenia syndrome. Thromboelastography or rotational thromboelastometry can help manage perioperative coagulopathy; the coagulopathy resolves after removal of the hemangioma. In a very rare patient with a truly unresectable hemangioma in conjunction with hemangioma thrombocytopenia syndrome, transhepatic embolization with adjunct glucocorticoids, propranolol, and cytotoxic therapy has been reported to achieve resolution of the coagulopathy.

Obstruction of hepatic venous outflow with resultant Budd-Chiari pathophysiology is an extremely rare manifestation of hepatic hemangioma. In case reports, this exceedingly rare manifestation of a hemangioma has been addressed with liver resection (if lobar hepatic outflow can be preserved) or, in even fewer cases, transplantation. Case reports of endovascular stenting have been described without medium- or long-term outcome data.

MASQUERADING LESIONS

Establishing the correct diagnosis is arguably the most critical aspect in management of liver hemangiomata. Appropriate clinical suspicion is imperative in cases of diagnostic equipoise. The term *atypical hemangioma* is nonspecific and should be avoided. As hemangiomata typically decrease in size and involute in patients with cirrhosis, small hypervascular lesions in this patient population are most commonly either regenerative nodules or hepatocellular carcinoma. Conversely, small hemangiomata can mimic hepatocellular carcinoma in patients with non-cirrhotic liver disease. In patients at risk for hepatic adenoma, particularly patients with nonalcoholic fatty liver disease, *atypical hemangioma* must be differentiated from *adenoma*. Sclerosed, thrombosed, or hyalinized hemangiomata can mimic a variety of primary and metastatic hepatic malignancies and can be a particular diagnostic challenge (Fig. 6A). Review of prior imaging with establishment of the diagnosis using retrospective comparison to historic imaging is the most reliable noninvasive diagnostic method. Any imaging features of capsular retraction or internal complexity (with atypical characteristics) should be concerning for possible malignancy. A personal history of malignancy with new or growing atypical liver lesions should be concerning for metastatic disease rather than a hemangioma (Fig. 6B).

Questions of diagnostic equipoise can be resolved with appropriate consideration of the patient's presentation history, review of prior imaging, and pursuit of repeat dedicated imaging. If diagnostic imaging remains inconclusive and concern for a worrisome lesion persists (Fig. 6C), either biopsy or resection should be pursued.

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MANAGEMENT OF BENIGN LIVER TUMORS

Richard D. Schulick, MD, MBA, and Ana Gleisner, MD, PhD

Benign liver neoplasms occur in up to 20% of the population and include cystic lesions (simple cysts and mucinous cystic neoplasms [MCNs]) and solid lesions (hemangiomas, adenomas, and focal nodular hyperplasia [FNH]). Most lesions are incidentally discovered during imaging for other indications. When symptomatic, these lesions are associated with abdominal pain and, more rarely, symptoms related to compression of the upper gastrointestinal tract. Symptoms are often vague, and a causal relationship with the liver lesion can be difficult to establish. Surgical resection of benign lesions is typically indicated if symptoms interfere with daily living and after other conditions commonly associated with abdominal pain, such as biliary colic and peptic ulcer disease, have been excluded. Surgical resection is also indicated based on the risk of rupture and hemorrhage (adenomas) and/or the risk of malignant transformation (adenomas and MCNs). Surgeons should be familiar with the clinical workup, imaging features, and indications for intervention for these benign liver neoplasms.

RADIOGRAPHIC EVALUATION OF LIVER LESIONS

The use of abdominal imaging has increased more than twenty-fold in the past four decades, resulting in the increased identification of incidental liver lesions. The vast majority of these lesions are benign, particularly when found in younger patients. With advances in axial imaging technology, most benign lesions may be definitively diagnosed with imaging alone; tissue diagnosis is rarely required. However, because benign liver lesions differ in their potential for malignant transformation and risk of bleeding, making the correct diagnosis is critical to inform the need for surgical intervention. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are the most commonly used modalities to image liver lesions. Although US has the advantages of ease of use, short duration, and absence of ionizing radiation, it has limited specificity to diagnose liver lesions, especially in the presence of steatosis or fibrosis. For these reasons, imaging with CT or MRI is typically required to diagnose benign liver lesions. For accurate diagnosis of liver lesions, intravenous contrast is necessary, with three distinct phases of enhancement: the early hepatic arterial phase, portal venous phase, and delayed hepatic venous phase. In general, MRI has a higher sensitivity and specificity compared with CT for liver lesions and is often used if CT findings are equivocal. Table 1 summarizes common radiographic findings of benign liver lesions using these three modalities. Among solid lesions, hemangiomas, adenomas, and FNH are hypervascular, showing contrast enhancement in the arterial phase.

BENIGN LIVER CYSTS

Pathogenesis

Simple liver cysts are predominately congenital in nature, arising from aberrant bile ducts that lack communication with the biliary tree for drainage. Accumulation of serous, nonbilious fluid creates a spherical, nonseptated cyst lined by a single layer of cuboidal or columnar biliary epithelium with a surrounding fibrous stroma.

TABLE 1 Comparison of Imaging Findings for the Five Most Commonly Encountered Benign Liver Lesions

Lesion	US	CT	MRI
Simple cyst	Round, through-transmission, generally lacks septations Heterogeneity seen with hemorrhage	Well circumscribed, homogenous, hypoattenuated Limited contrast enhancement	Well circumscribed, homogenous T1: hypointense T2: very hyperintense Limited contrast enhancement
Biliary cystadenoma	Round, anechoic, thick cyst wall, internal septations May have mural and septal nodules	Well circumscribed, isoattenuated noncontrast Mural and nodular enhancement with contrast	Well circumscribed, heterogenous T1: hypointense T2: hyperintense Mural and nodular enhancement with contrast
Hemangioma	Homogenous, hyperechoic, posterior acoustic enhancement Blood flow rarely observed	Well circumscribed, homogenous Asymmetric peripheral pools of enhancement in arterial phase Centripetal enhancement and washout delayed phase	Well circumscribed, homogenous T1: hypointense T2: very hyperintense Gadolinium enhancement pattern similar to CT
Adenoma	Well-circumscribed, heterogeneous, variable echogenicity	Isoattenuated noncontrast Hyperattenuated arterial phase, loss of contrast enhancement delayed phases (return to isoattenuation) Heterogeneous if necrosis or hemorrhage Hyperattenuated signal if active hemorrhage	T1: isointense to hyperintense T2: isointense to hyperintense Gadolinium enhancement pattern similar to CT Eovist not retained in delayed, hepatobiliary phase Fat saturation sequences demonstrate intracellular fat
Focal nodular hyperplasia	Variable echogenicity, central scar rarely observed Unreliable modality for diagnosis	Isoattenuated or hypoattenuated noncontrast Hyperattenuated arterial phase, central scar remains enhanced during venous phase Loss of contrast enhancement in delayed phases (return to isoattenuation)	T1: hypointense T2: hyperintense with hyperintense central scar Gadolinium enhancement pattern similar to CT Eovist retention in delayed, hepatobiliary phase

Simple liver cysts are usually small (<3 cm in diameter) and remain stable in size, although growth may be observed because of continued production of serous fluid. Simple cysts are rarely symptomatic and nearly universally benign.

Presentation

Simple liver cysts occur in approximately 18% of the population. They are most often observed in adults and are usually discovered incidentally. There is a slight female predominance (1.5:1), and although cysts may occur throughout the liver, they are found more often in the right lobe. Simple liver cysts are asymptomatic in the vast majority of cases. Occasionally, larger cysts are associated with pain, shortness of breath, early satiety, nausea, or vomiting. Complications such as infection, hemorrhage, or biliary obstruction caused by compression or rupture are rare. Liver function tests are usually within normal limits. Occasionally, large cysts might be palpable on physical examination. A self-limiting bleed into a simple cyst is more common in patients on anticoagulation, and it typically causes acute upper abdominal pain that spontaneously resolves over hours to days. Polycystic liver disease is discussed in a separate chapter.

Imaging

In the majority of cases, US alone may be used to establish the diagnosis of a simple cyst, which appears as a circular or oval anechoic lesion with clearly defined smooth borders, posterior acoustic enhancement, minimal septations, and absence of internal vascularity. Fluid layering, heterogeneity, and internal echoes mimicking septations may indicate cyst hemorrhage, whereas debris within the cyst fluid can be associated with infection or a prior bleed. The presence of internal septations or a thickened, irregular cyst wall with mural nodules and papillary projections or calcifications is concerning for MCN, which is associated with an increased risk of malignant transformation that requires surgical resection. In certain cases, CT or MRI may be necessary to confirm the diagnosis of a simple cyst. On CT, simple cysts appear as well-circumscribed, homogeneous, hypoattenuated lesions that do not enhance with contrast injection (Fig. 1A). On MRI, simple cysts are hypointense with T1-weighted imaging and hyperintense with T2-weighted imaging (Fig. 1B). Similar to CT findings, cysts lack contrast enhancement and appear as well circumscribed and homogeneous on MRI.

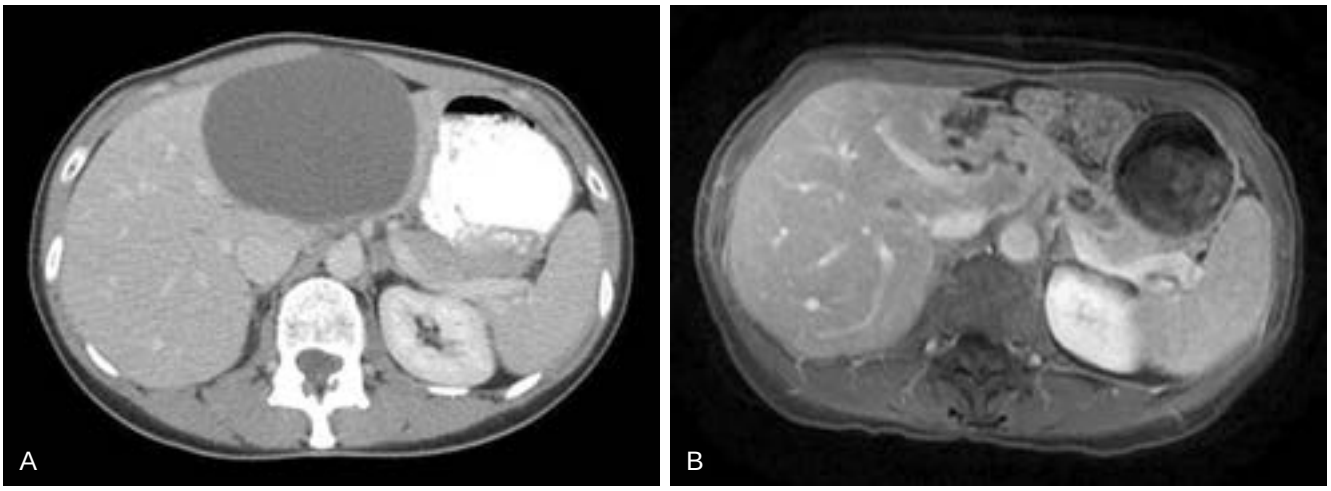


FIG. 1 **(A)** Axial CT scan demonstrating a simple liver cyst in the left lobe of the liver in a 54-year-old woman. **(B)** Axial T1-weighted MRI scan after cyst fenestration shows minimal hypointense, residual fluid in the cyst cavity.

Management

Asymptomatic simple cysts require no treatment or follow-up imaging. For patients with symptoms, surgical fenestration is the treatment of choice. Percutaneous aspiration with injection of sclerosing agents (sclerotherapy) is associated with rare but severe complications and thus is best reserved for patients with a high surgical risk. Cyst aspiration is associated with a high rate of recurrence and is rarely indicated as definitive therapy for symptomatic cases in which the patient is unable to undergo other treatment modalities. Because it typically takes several days for cyst fluid to reaccumulate, however, cyst aspiration may be used as a diagnostic maneuver to determine whether symptoms are attributable to the cyst. In case there is diagnosis uncertainty (e.g., imaging features suspicious for MCN), follow-up imaging or surgical intervention may be necessary.

With surgical fenestration, part of the cyst wall is resected to establish a permanent communication between the cyst and the peritoneal cavity for drainage. Fenestration should be performed with a minimally invasive approach (laparoscopic or robotic) when possible. The minimally invasive approach is associated with reduced hospital stay, decreased postoperative pain, and reduced blood loss compared with an open procedure. An energy device (e.g., harmonic scalpel) or surgical stapler is commonly used to cut through the cyst wall and liver tissue to minimize the likelihood of postoperative bleeding. In open operations, the resection margin can instead be oversewn with a running locked suture. The resected cyst wall is sent for pathologic evaluation to rule out a neoplasm. A mobilized omental flap can be placed into the opened cyst to reduce the risk of recurrence, which is caused by other tissue walling off the opened cyst (e.g., diaphragm). Complete cyst wall resection is rarely indicated and is reserved for instances when there is a high suspicion for MCN. Complete resection can generally be performed with either a wedge or segmental resection. Recurrence rates are comparable between fenestration and complete resection, both between 5% and 15%. Morbidity for surgical fenestration or resection is approximately 15%, and mortality is less than 1%. Main complications include postoperative ascites, bile leak, hematoma, and surgical site infection. For patients with high surgical risk, sclerotherapy can be used to destroy the biliary epithelial lining of the cyst wall, which is the source of fluid production. A catheter is placed into the cyst cavity under US guidance, and contrast is injected to evaluate for communication with the biliary tree, which is a contraindication to sclerotherapy. Sclerosing agents (ethanol, minocycline hydrochloride, or ethanolamine oleate) are injected into the cyst cavity and aspirated after 2 to 4 hours. Sclerotherapy is associated with a lower morbidity and mortality rate, but the recurrence rate is 20% within the first year. Postprocedural pain is common, though self-limiting. Additional contraindications to sclerotherapy include intracystic bleeding and fistula to the gastrointestinal tract or peritoneum.

MUCINOUS CYSTIC NEOPLASM

Pathogenesis

MCNs, previously referred to as *biliary cystadenomas,* are cystic neoplasms of the biliary ductular system that may occur throughout the biliary tree, including both intrahepatic and extrahepatic locations. MCNs typically present as a solitary, multilocular mass with fluid contents. Histologically, MCNs are lined by biliary-type mucus-secreting cuboidal or columnar epithelium, supported by a mesenchymal stroma-resembling ovarian tissue and surrounded by a less cellular layer of collagen. Unlike biliary intraductal papillary mucinous neoplasms, no papillary projections are found in MCNs. Malignant transformation or the presence of an invasive carcinoma (previously referred to as *cystadenocarcinoma*) has been described in approximately 15% of cases.

Presentation

MCNs typically occur as a single cystic mass, predominately in adult women (90%). The majority of these tumors are identified incidentally, although some patients may present with abdominal pain or distention. Cyst rupture and hemorrhage are rare complications.

Imaging

On US, MCNs are multilocular anechoic lesions with a thick wall. Intracystic debris are frequently observed. Mural and septal nodules may be associated with malignant transformation. On CT, MCNs have low attenuation but, unlike simple cysts, the walls are thickened and/or nodular and show enhancement on contrast injection. Similar cyst wall findings are also seen on MRI (Fig. 2). The degree of T1 signal intensity in the cyst fluid indicates the degree of protein and debris. Magnetic resonance cholangiopancreatography (MRCP) may identify a communication between the cyst and the biliary tree. Although mural nodules are more commonly seen in patients with malignant transformation, the diagnosis of invasive carcinoma cannot be reliably made on imaging findings.

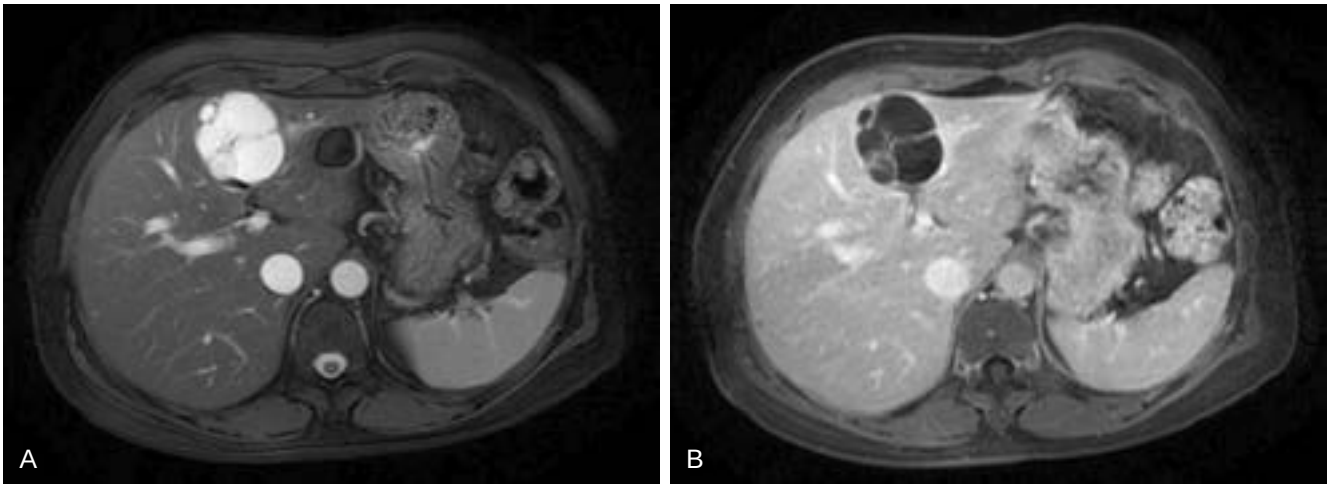


FIG. 2 **(A)** Axial T2-weighted MRI demonstrating a cystadenoma in the left lobe of the liver in a 57-year-old woman. **(B)** Axial T1-weighted imaging of the same lesion reveals a hypoattenuated, septated mass with clear borders.

Management

MCNs should be completely resected with negative margins because of the risk of malignant transformation within the cyst. Aspiration and fenestration are not recommended as the definitive treatment because premalignant or malignant tissue is left behind. In addition, aspiration is associated with high recurrence rates (80%–90%). For intrahepatic disease, technical factors including cyst location and size should determine the type and extent of liver resection. Peripheral lesions should be managed with partial liver resection. For more central lesions near major vessels, enucleation is an acceptable alternative if formal resection is not possible. In extremely rare cases, orthotropic liver transplant can be used in the treatment of MCN.

HEPATIC HEMANGIOMA

Pathogenesis

Hepatic hemangiomas are the most common benign liver lesion, occurring in 5% to 20% of the population. They are congenital malformations comprising blood-filled cavernous spaces lined by a single layer of endothelial cells and separated by fibrous tissue. They are round, well-encapsulated, and may contain thrombi or calcifications. Hemangiomas have no potential for malignant transformation and, in contrast with adenomas, have an extremely low risk of spontaneous hemorrhage or rupture. Most hemangiomas exhibit either slow growth or no growth over time. Although hemangiomas have no estrogen receptors, estrogen exposure may result in higher rates of enlargement with no increase in risk of rupture.

Presentation

Hemangiomas occur predominately in women 20 to 50 years of age. Most patients present with a single lesion, with only 10% of patients presenting with multifocal disease. The majority of cases are incidentally found, with lesions ranging from several millimeters to several centimeters in diameter. Lesions greater than 10 cm are referred to as *giant hemangiomas.* Symptoms are rarely present and include abdominal pain and early satiety resulting from compression of the upper gastrointestinal tract. Giant hemangiomas in children may also result in a consumptive process called *Kasabach-Merritt syndrome,* characterized by thrombocytopenia, hypofibrinogenemia, elevated fibrin degradation products, and coagulopathy.

Imaging

On US imaging, hemangiomas appear as well-demarcated, homogeneous, hyperechoic lesions with posterior acoustic enhancement. On cross-sectional imaging, hemangiomas appear as well-circumscribed lesions with peripheral nodular enhancement in the early phase followed by a progressive centripetal enhancement and washout on delayed phases (Fig. 3B). These lesions are hypointense on T1-weighted MRI and markedly hyperintense on T2-weighted MRI (Fig. 3A).

Management

Asymptomatic patients with small lesions for which the diagnosis of hemangioma is clear on imaging do not need any additional follow-up. For larger lesions (i.e., >5 cm) and/or diagnostic uncertainty, follow-up imaging is recommended in 3 to 6 months. Significant growth or presence of significant symptoms are indications for surgical treatment. In the exceedingly rare situation when the patient presents with rupture or hemorrhage, surgery is indicated. However, preoperative hepatic arterial embolization is typically done before resection to control bleeding. Embolization may also be done before resection of giant hemangiomas to mitigate intraoperative bleeding and for symptomatic patients who are not candidates for surgery. Hemangiomas can be resected through enucleation or liver resection based on the size and location of the lesion, preferably with minimally invasive approaches, if technically feasible. Enucleation is possible because hemangiomas have a large pseudocapsule that can be separated from the liver parenchyma as crossing vascular structures are controlled. Mortality for resection of hemangioma is low (<1%). Enucleation is associated with lower risk of postoperative complications compared with liver resection.

HEPATIC ADENOMA

Pathogenesis

Hepatic adenomas are encapsulated tumors composed of large plates of adenoma cells that are larger than hepatocytes and contain glycogen and lipids. Grossly, they appear as soft, tan lesions perfused by peripheral arteries on their outer surface, sometimes with central necrosis or hemorrhage, and they generally occur in patients with a normal liver, although steatosis and steatohepatitis are risk factors. Other risk factors include estrogen exposure such as those in oral contraceptives, anabolic steroids, and types I and III glycogen storage diseases. Adenomas may be categorized into three distinct subtypes: hepatocyte

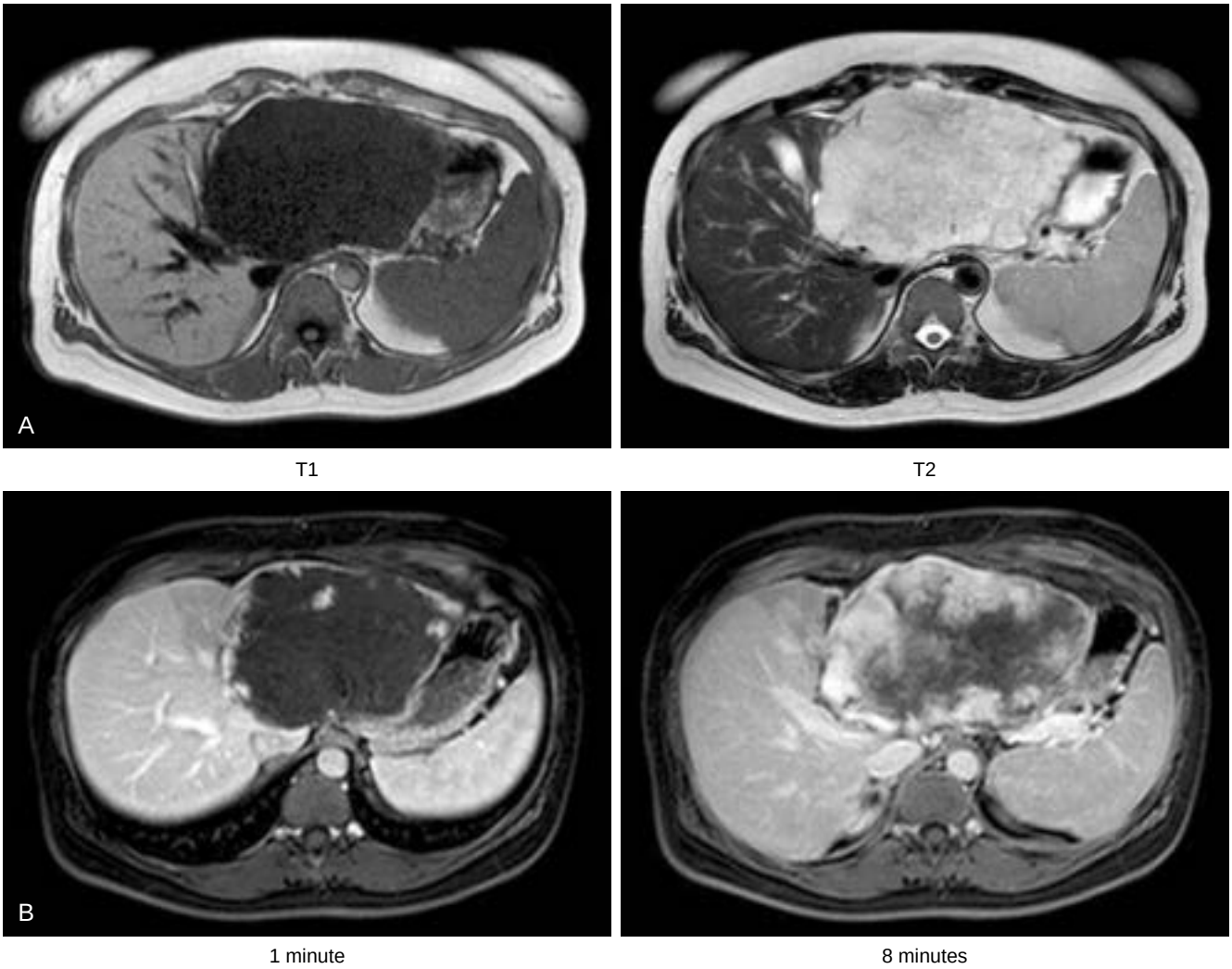


FIG. 3 **(A)** Hemangiomas appear hypointense on T1-weighted MRI and hyperintense on T2-weighted images, as shown by this large left hepatic lobe mass in a 51-year-old woman. **(B)** MRI demonstrates centripetal contrast enhancement over time, which is pathognomonic for hemangioma.

nuclear factor (HNF)-1 alpha–inactivated adenoma, inflammatory adenoma, and beta-catenin activated adenoma, although not all adenomas can be classified within these categories. The HNF1-alpha–inactivated subtype comprises 30% to 50% of adenomas and is characterized by diffuse steatosis and lack of inflammatory infiltrates. Inflammatory adenomas account for up to 50% of cases and are characterized by lymphocytic infiltrates, sinusoidal dilation and hemorrhage, and abnormal activation of the JAK/STAT pathway. Inflammatory adenomas are associated with obesity-induced nonalcoholic steatohepatitis. Adenomas with beta-catenin activation are observed less often, in approximately 10% of cases, but they are the most common subtype in men and are associated with androgen use. These lesions exhibit greater cellular atypia in addition to pseudoglandular formation. Hepatic adenomas are at risk for malignant transformation, mainly among those with beta-catenin activation. Because of the lack of a capsule, there is also risk of spontaneous bleeding and rupture with life-threatening intraabdominal hemorrhage. Bleeding is especially common with inflammatory adenomas.

Presentation

Adenomas can present as single or multiple simultaneous lesions and can range from a few millimeters to greater than 10 cm in diameter. The presence of 10 or more adenomas is referred to as *adenomatosis*. Adenomas occur most often in women 20 to 40 years of age and less commonly in men. Most adenomas are incidentally found during abdominal imaging for other indications. However, some patients present with acute-onset right upper quadrant or epigastric pain secondary to spontaneous hemorrhage, which can be self-limiting or, more rarely, associated with hypovolemic shock and hemoperitoneum. Other symptoms include sporadic abdominal pain, early satiety, and, very rarely, jaundice resulting from biliary obstruction.

Imaging

Adenomas appear as well-demarcated, heterogeneous masses with variable echogenicity on US imaging. Because the appearance is nonspecific, additional imaging is recommended. On CT, adenomas are isodense relative to the surrounding liver parenchyma. On MRI, adenomas appear isointense to hyperintense on both T1-and T2-weighted sequences (Fig. 4B). Multiphasic enhancement with contrast will show adenomas to enhance during the early arterial phase, which disappears in the later phases. Depending on the degree of necrosis or hemorrhage, adenomas may have heterogenous attenuation (Fig. 4A). Gadoxetic acid contrast can help distinguish FNH from adenoma as this contrast will be retained during the late (hepatobiliary) phase in FNHs but not typically in adenomas, with the exception of inflammatory adenomas.

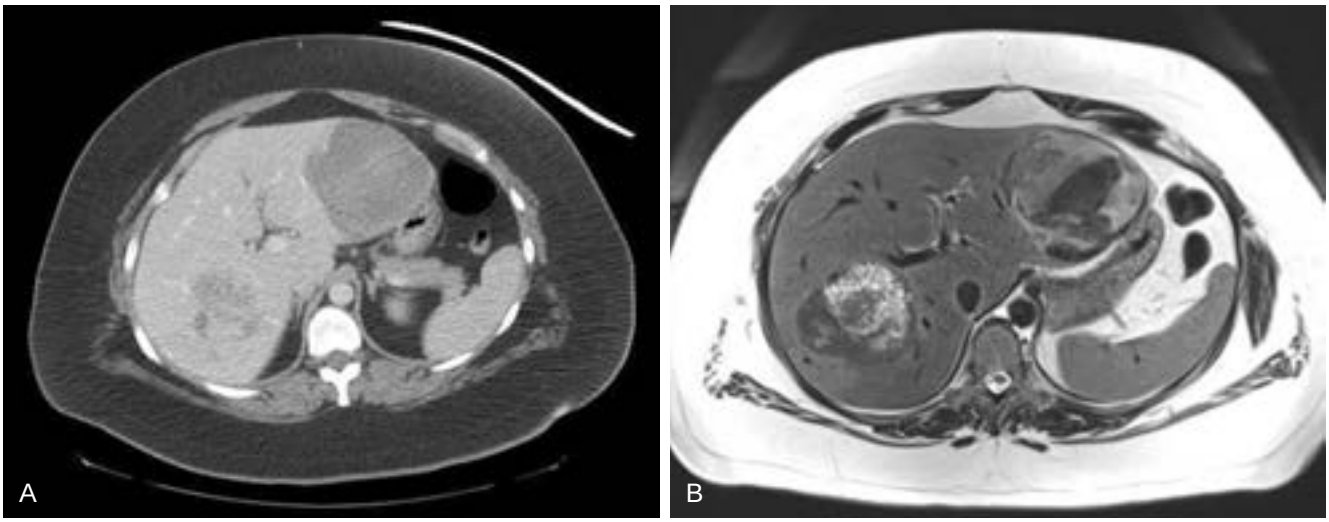


FIG. 4 **(A)** Axial CT scan of a 21-year-old woman with two large adenomas with foci of hemorrhage. **(B)** Axial T2-weighted image of the same lesions shows a mixed-intensity signal that correlates with regions of hemorrhage.

Management

Resection of the adenoma is recommended for patients with symptoms and those at risk of bleeding and/or malignant transformation. Because of the high risk of malignant transformation, all men with adenomas should be considered for surgical resection, regardless of the size of the lesion. For an adenoma less than 5 cm in diameter in a female patient, the initial management strategy is cessation of estrogen or anabolic steroids if present. Obese patients with fatty liver disease should be counseled on lifestyle modifications for weight loss. The main goal with risk mitigation is to avoid further growth. Although regression of the adenoma is possible, disappearance is unlikely, thus long-term surveillance is indicated. Pregnant women are at risk of hormone-induced growth and rupture. Therefore, closer follow-up should be performed in these patients (monthly as opposed to 6–12 months). For women in whom the adenoma continues to grow or becomes symptomatic or for adenomas greater than 5 cm, surgical resection is recommended. Transarterial embolization may be used before surgery to reduce the size of the lesion and is the treatment of choice for bleeding control in cases of acute rupture. After the bleeding is controlled, the patient is referred for surgical resection, except in the rare cases in which there is no residual lesion on follow-up MRI. Embolization and thermal ablation can also be used as definitive treatment of adenoma, but experience with these modalities is limited. Surgical resection is typically accomplished through liver resection, although enucleation can also be used. Resection should be parenchymal-sparing and done minimally invasively when possible, based on the location and size of the lesion. For patients with multiple adenomas or unresectable lesions, close surveillance with MRI is recommended. Growth or worrisome changes on MRI of any specific lesion is an indication to resect that single lesion. For patients who present with acute hemorrhage from a ruptured adenoma for which embolization fails or is not an option, emergent laparotomy is indicated. Liver packing and inflow control with Pringle's maneuver are used for bleeding control. Resection may be performed at the same operation, but patients with acidosis, coagulopathy, or hypothermia may require resuscitation before the definitive operation.

FOCAL NODULAR HYPERPLASIA

Pathogenesis

FNH is thought to be a hyperplastic lesion of the hepatocytes surrounding a congenital arteriovenous malformation and thus not a true neoplasm. Histologically, FNH is characterized by proliferation of mature hepatocytes and bile ducts in a stellate pattern often surrounding a central scar composed of fibrous tissue and malformed vessels. In FNH, the beta-catenin pathway is activated but, unlike in other beta-catenin–activated lesions (adenoma, hepatocellular carcinoma), activating mutations of *CTNNB1* are not observed. FNH shows a characteristic maplike pattern on immunohistochemical staining for glutamine synthetase. Although the presence of this immunohistochemical pattern can help differentiate FNH from other lesions, its differentiation from diffuse glutamine synthetase staining, characteristic of other beta-catering activated tumors, can be difficult in small biopsy specimens. These lesions have no malignant potential and an extremely low risk of bleeding.

Presentation

FNH is the second most common benign liver lesion after hemangioma and occurs most often in reproductive-age women 20 to 50 years of age. These lesions are typically incidental. When symptomatic, vague right upper quadrant or epigastric pain are the most common symptom. FNH usually presents as a single lesion, although multiple lesions may be observed in rare cases and are sometimes associated with a syndrome of vascular malformations.

Imaging

US is an unreliable modality for the diagnosis of FNH. Contrast-enhanced CT and MRI are the standard of care for diagnosing FNH. On noncontrast CT images, FNH will appear isoattenuated or hypoattenuated relative to the surrounding liver parenchyma, and in some cases a hypoattenuated central scar is visible. On T1-weighted MRI, FNH appears hypointense throughout, while on T2-weighted sequences, FNH is hypointense with a hyperintense central scar (Fig. 5A). After contrast injection, FNH will have enhancement in the early, arterial phase (Fig. 5B), which disappears in the venous phase. If a central scar is present, it will remain enhanced in the venous phase. In the absence of a central scar, these findings overlap with those of adenoma and fibrolamellar carcinoma. Retention of gadoxetic acid on delayed hepatobiliary phase in FNH may be helpful in distinguishing it from adenoma. However, retention of gadoxetic acid on delayed hepatobiliary phase can also be seen in inflammatory adenomas.

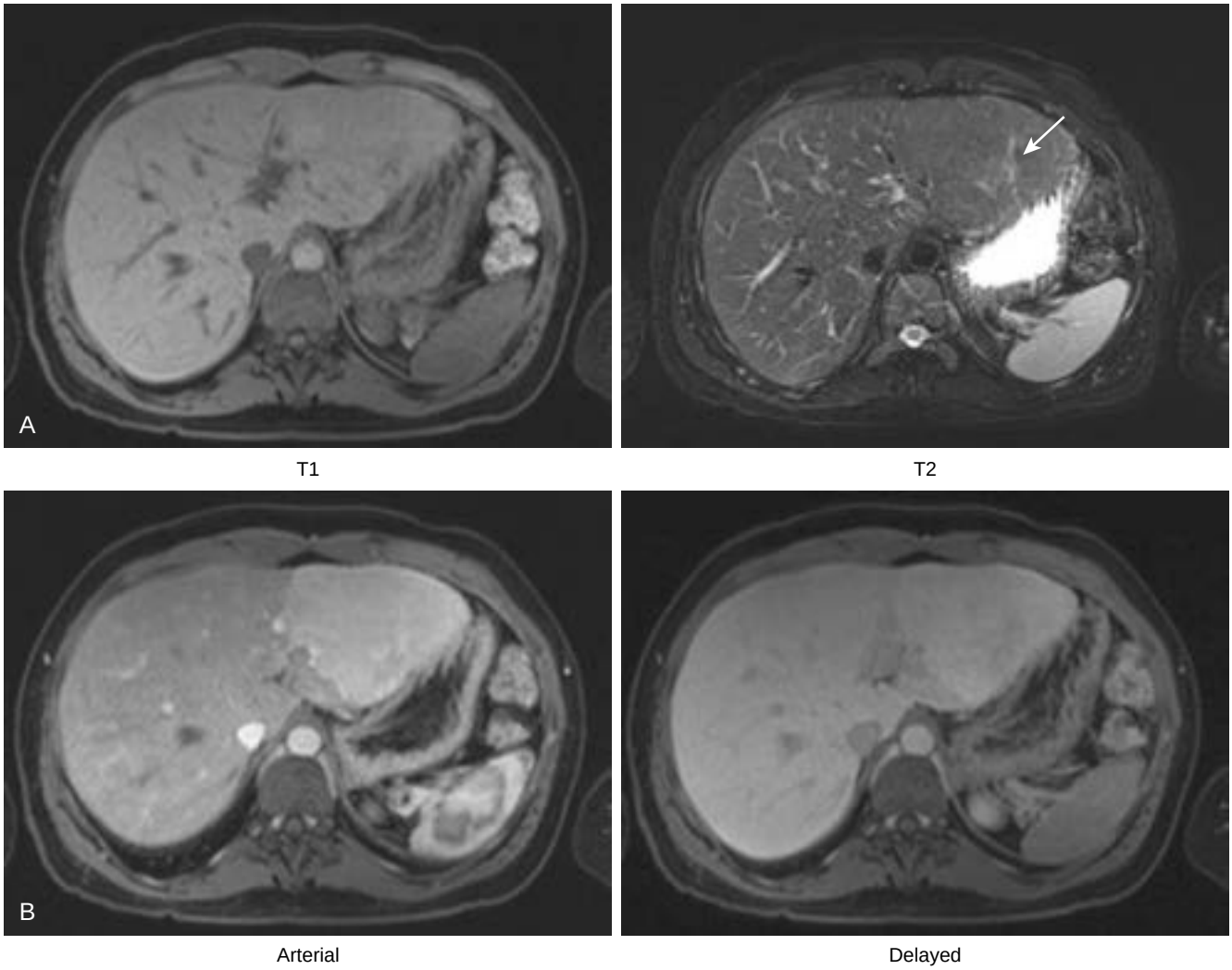


FIG. 5 **(A)** Focal nodular hyperplasia *(FNH)* appears hypointense throughout on T1-weighted MRI, whereas on T2-weighted sequences FNH is hypointense with a hyperintense central scar *(white arrow)*. **(B)** FNH displays early arterial enhancement with rapid washout. During the venous phase, FNH is isointense, while the central scar remains enhanced.

Management

Surgical resection is indicated in the presence of significant symptoms. In addition, surgery may be necessary when the lesion cannot be differentiated from an adenoma or fibrolamellar carcinoma. In the absence of a central scar, a biopsy may be helpful to establish the diagnosis. However, because the typical maplike staining for glutamine synthetase is not always seen on biopsy, the diagnosis of adenoma may be impossible to rule out without resection. In these situations, management will be dictated by the possible risk of bleeding and/or malignant transformation in case the lesion turns out to be an adenoma. When resection of FNH is recommended, minimally invasive approaches are favored. The lesion can be resected with either enucleation or liver resection, based on the size and location of the lesion.

SUMMARY

There has been a substantial increase in the frequency of incidentally discovered liver lesions because of the increased use of axial imaging. The majority of these lesions are benign and include simple cysts, MCNs, hemangiomas, adenomas, and FNH. Management is dictated by the presence of symptoms and the risk of complications, which include bleeding and malignant transformation. Risk of malignant transformation is seen in MCNs and adenoma, therefore, surgical resection is recommended for all patients when MCN is suspected. When the suspicion is low (i.e., presence of internal septations in the absence of wall enhancement/thickening), surveillance is an acceptable alternative to surgery. Adenomas >5 cm in women or of any size in men should be resected. Smaller adenomas in women should be followed long-term with imaging to monitor growth while addressing risk factors (e.g., estrogen and anabolic steroid exposure, obesity). In addition to malignant transformation, adenomas >5 cm are at risk of spontaneous bleeding, which could result in rupture with life-threatening hemoperitoneum. Finally, surgery may be indicated if the diagnosis cannot be confirmed with imaging with or without a core biopsy. This is more commonly seen in patients with hypervascular lesions with imaging features that are common to both FNHs and adenomas. This is especially true in trying to differentiate an FNH with no central scar from an inflammatory adenoma because the retention of gadoxetic acid in the hepatobiliary phase of the MRI, characteristic of FNHs, has also been described in inflammatory adenomas. Moreover, the maplike staining for glutamine synthetase, pathognomonic for FNH, sometimes is not seen on core biopsy because of sampling limitations. When surgical resection is recommended for benign liver lesions, enucleation is preferred in most cases if technically feasible, except in benign liver cysts,

when fenestration is possible, and when there is a risk of malignancy (e.g., MCNs and fast-growing adenomas). The minimally invasive approach should be used when technically possible, and the risk of perioperative complications is typically low. Because establishing a causal relationship between symptoms and the liver lesion is often difficult, patients whose surgical resection is recommended based on the presence of symptoms alone should be counseled on the possibility that symptoms may not improve after surgery. The ability of surgeons to diagnose and appropriately manage benign liver lesions has taken on greater importance given the increased frequency of incidentally identified liver lesions, a current trend that is likely to continue in the future.

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Management of Malignant Liver Tumors

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Malignant tumors of the liver are grouped into two categories: primary and metastatic. The most common primary malignant tumors of the liver include hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). In the Western world, metastatic liver tumors such as colorectal, pancreatic, gastric, and neuroendocrine are significantly more common than primary liver tumors. Colorectal metastases are among the most frequent indications for liver resection.

Surgical resection is the mainstay of treatment for hepatic malignancies. Appropriate patient selection requires evaluation of overall health status, oncologic appropriateness, and resectability of the disease. A lesion is considered resectable if negative margins can be obtained while leaving an adequate amount of functional liver parenchyma with intact hepatic arterial and portal venous inflow, hepatic venous outflow, and biliary drainage. In patients without underlying liver disease or extensive exposure to systemic chemotherapy, this typically requires two contiguous segments of remaining liver parenchyma. If this cannot be achieved, other local (ablation, external beam radiation) or regional (tumor embolization, hepatic artery infusion pump) therapies are frequently possible.

Thermal tumor ablation has evolved significantly over time and is most frequently accomplished with microwave ablation (MWA), which can be performed percutaneously, laparoscopically, or during an open operation. Traditionally, radiofrequency ablation (RFA) and cryoablation were commonly employed, but MWA is more efficient and efficacious. Nonthermal ablation with irreversible electroporation (IRE) is a newer option for tumors adjacent to major vessels or critical structures that could be potentially damaged by thermal ablation. IRE uses short-duration, high-voltage pulses to create defects in the lipid bilayer that ultimately results in cell death. This avoids the heat-sink effect associated with loss of thermal energy when used in close proximity to major blood vessels. In addition to surgical resection and ablation, external beam radiation—either conformal or stereotactic—is an option for local therapy. Tumor embolization can be achieved with a variety of intraarterial therapies, including hepatic arterial bland embolization (HAE), transarterial chemoembolization (TACE), or radioembolization with yttrium-90.

PRIMARY LIVER TUMORS

Hepatocellular Carcinoma

HCC is the most common primary malignant liver tumor worldwide. Although the incidence is highest in Asia and sub-Saharan Africa, the incidence in the United States is rising. Risk factors include cirrhosis and chronic liver disease from any cause, including viral hepatitis, alcohol use, and fatty liver disease. Patients with hepatitis C disease typically develop HCC in the setting of long-standing cirrhosis, but those with hepatitis B may develop HCC without antecedent cirrhosis. A less common subtype, known as fibrolamellar HCC, often occurs in younger patients and those without preexisting liver disease or cirrhosis. In the setting of chronic liver disease, CT and MRI are typically diagnostic for HCC and biopsy is not indicated unless additional tissue is needed for molecular analysis to guide systemic therapy. Imaging findings include homogenous hyperenhancement in the arterial phase with portal venous washout. The Liver Imaging Reporting and Data System (LI-RADS) standardizes terminology and serves as a classification system to characterize liver lesions in patients with chronic liver disease at risk for HCC. A LI-RADS 5 lesion is diagnostic of HCC.

In most cases, HCC must be managed in parallel with chronic liver disease. In addition to the American Joint Committee on Cancer (AJCC) staging system, the Barcelona Clinic Liver Cancer (BCLC) and Okuda staging systems are frequently used. These alternative staging systems also incorporate the extent of chronic liver disease. Staging workup includes a thorough history and physical exam, thorough investigation for extent of chronic liver disease and portal hypertension, laboratory studies including alpha-fetoprotein (AFP) (CA 19-9 and CEA should be included if the diagnosis is unclear), chest CT, and abdominal CT or MRI. Bone scans should be considered selectively. The most common sites of metastatic spread include the lung, peritoneum, bone, spleen, adrenal gland, and brain.

In appropriately selected patients, liver transplantation addresses both the underlying liver disease and the malignancy and therefore is the treatment of choice in patients with advanced cirrhosis and relatively limited HCC. It also addresses the "field defect" present

in a cirrhotic liver and mitigates the risk of new HCC formation by removing the entire diseased liver. Transplantation is limited by organ availability and transplant-associated risks, including organ rejection and complications of immunosuppression. Several other treatment modalities are often employed either as definitive therapy or as a bridge to transplantation.

Surgical resection of HCC is an excellent option in patients with limited underlying liver disease and/or those with tumors beyond criteria for transplant. The presence and degree of hepatic fibrosis/cirrhosis correlates with the risk of posthepatectomy liver failure and long-term survival. Major hepatectomy is generally only an option for patients without underlying cirrhosis or cirrhosis classified as Child-Pugh A (Table 1) with no evidence of portal hypertension. Perioperative mortality in these patients is less than 5% but increases significantly in patients with Child-Pugh B or C cirrhosis, or portal hypertension. A detailed discussion comparing resection and transplantation is available in a separate chapter.

In patients who are medically fit for an operation, resection is only indicated if negative margins can be achieved. Ideally, anatomic resections of portal territories including sectionectomy, segmentectomy, and subsegmentectomy should be performed because HCC tends to spread along portal venous tributaries. Anatomic resection is associated with improved recurrence-free survival and overall survival in patients with HCC. Although bulky portal adenopathy is often present in the setting of chronic liver disease, formal portal lymphadenectomy is typically not necessary. Presently, there are no good options for adjuvant systemic therapy in resected HCC.

If a patient is not fit for surgery, ablation is often an excellent option for local tumor control. Based on multiple randomized trials, thermal ablation of small (<2–3 cm) HCC has long-term outcomes similar to surgical resection with less morbidity and mortality. However, these data should be interpreted with caution as these trials had small sample sizes and were not designed as noninferiority trials. Furthermore, they were primarily conducted in Asian populations with much higher incidence of hepatitis B compared with Western populations.

Intra-arterial embolization (bland HAE, TACE, or radioembolization with yttrium-90) is reserved for patients who are not candidates for potentially curative therapy with transplantation, resection, or ablation. Embolization is often employed as a bridge to transplantation or before attempted ablation of larger tumors measuring 3 to 5 cm. Although transplantation and surgical resection are typically contraindicated in patients with extrahepatic metastasis, other liver-directed therapies may be considered in the setting of liver-dominant disease. Systemic therapy should be considered in patients with more extensive extrahepatic disease. In recent years, systemic options for HCC have increased. The multikinase inhibitors sorafenib and lenvatinib, as well as the anti PD-1 agent nivolumab, are options in the first-line setting. Regorafenib, cabozantinib, ramucirumab, and nivolumab/pembrolizumab are available second-line treatment options.

TABLE 1 Child-Turcotte-Pugh Score*

Measure	1 Point	2 Points	3 Points
Total bilirubin, mg/dL	<2	2–3	>3
Serum albumin, g/L	>35	28–35	<28
PT/INR	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grades I–II (suppressed with medication)	Grades III–IV (refractory)

PT/INR, Prothrombin time/international normalized ratio.

*The score uses five clinical measures: class A, 5–6 points; class B, 7–9 points; class C, 10–15 points.

Intrahepatic Cholangiocarcinoma

ICC is the second most common primary malignant liver tumor and accounts for 10% to 20% of cases. Biliary tract cancers arise from cholangiocytes and can be classified into four types: ICC, hilar cholangiocarcinoma, distal cholangiocarcinoma, and gallbladder cancer. Risk factors for cholangiocarcinoma include sclerosing cholangitis (8%–20% lifetime risk), choledochal cysts (3%–28% lifetime risk), and cirrhosis. There are three gross subtypes of ICC, which include mass forming, periductal infiltrating, and intraductal. The periductal infiltrating type is most common and associated with the worst prognosis.

Staging workup includes thorough history and physical exam, laboratory studies including CA 19-9 (as well as AFP and CEA if the diagnosis is in question), chest CT, and abdominal pelvic CT or MRI. Easily resectable tumors are often resected without a biopsy, but in cases where a neoadjuvant therapy approach is under consideration, a biopsy is necessary. Diagnostic laparoscopy is often helpful to evaluate for occult peritoneal metastasis at the time of planned resection to avoid unnecessary laparotomy, particularly in patients with large tumor or significantly elevated CA 19-9.

Surgical resection with negative margins is the only curative option. Approximately one-third of patients will have nodal metastasis to the porta hepatitis at the time of resection, and formal portal lymphadenectomy is necessary for all patients with suspected biliary tract cancer. This is in contrast to HCC, where portal lymphadenectomy is rarely indicated. Five-year survival after surgical resection is approximately 40% to 60%. Adjuvant chemotherapy is recommended for most patients, even in the setting of early-stage disease. Adjuvant radiation may provide additional locoregional control for patients with positive margins, involved lymph nodes, or inadequate lymphadenectomy.

METASTATIC LIVER TUMORS

Colorectal Liver Metastasis

Colorectal cancer is the third most frequent malignancy with approximately 150,000 new cases diagnosed annually in the United States. Half of all patients diagnosed with colorectal cancer will develop liver metastasis, either at the time of initial diagnosis (synchronous) or months and even years after initial diagnosis (metachronous). Consequently, colorectal liver metastases (CRLM) are far more common than primary liver tumors.

Surgical resection, when feasible, is the best curative option in patients with CRLM. The goal is to remove all disease with microscopically negative margins. Whenever feasible, parenchymal-sparing resection is preferred as this is associated with less morbidity and increased options for salvage in the event of recurrence. In the case of bilateral CRLM, formal hepatic lobectomy can be combined with parenchymal-sparing resection, as well as thermal ablation to treat all sites of disease. The extent of resection that can be performed at the time of a single operation is dictated by the volume of anticipated future liver remnant (FLR) and patient comorbidities. Many of these patients have been treated with chemotherapy before liver resection, with resultant chemotherapy-associated liver injury. This must be considered when calculating the volume of FLR and planning resection. If the anticipated FLR is less than 30% in a patient treated with chemotherapy (or 20% in a patient with a healthy liver), a

two-stage resection is generally recommended, typically with portal vein embolization (PVE) between stages. An alternative to two-stage hepatectomy is associating liver partition and portal vein ligation (ALPPS), which may increase resection rates with comparable surgical margins, complications, and short-term morbidity.

In patients with synchronous CRLM, the primary tumor and liver metastasis can be resected at the same time or in staged operations. Sequencing will also include a period of systemic therapy. In general, extensive hepatectomy in combination with complex colorectal resection, for example, those requiring extensive pelvic resection or low rectal anastomosis, are best avoided. Several factors are considered in sequencing these operations. If the primary tumor is symptomatic with evidence of bleeding or obstruction, it should be addressed first. If the primary tumor is asymptomatic, a "liver first" approach is favored by many centers. In patients with rectal cancer, short- or long-course radiation will also be necessary, and this must be carefully sequenced with systemic therapy and planned surgical resection.

Unlike primary liver tumors, limited extrahepatic metastasis is not necessarily a contraindication to hepatic metastasectomy if the extrahepatic disease can be treated completely. This reflects the excellent response rates to systemic therapy in patients with colorectal cancer. Preoperative chemotherapy is typically administered to assess tumor response and to address potential micrometastatic disease not visible on imaging. A large randomized, controlled trial of perioperative chemotherapy for CRLM demonstrated improved progression-free survival compared with patients who underwent resection alone. However, prolonged chemotherapy can be associated with significant liver injury. Specifically, irinotecan-based regimens are associated with steatohepatitis, and oxaliplatin-based regiments are associated with sinusoidal congestion. "Disappearing" liver metastases are an additional consideration because they will eventually recur in up to 80% of patients if not resected. Careful coordination among members of the multidisciplinary team is necessary to determine sequencing of all therapy. In general, preoperative systemic therapy should be limited to 4 to 6 cycles or 2 to 3 months. In the case of unresectable disease, additional locoregional therapies including ablation, transarterial embolization, and placement of a hepatic artery infusion pump can be considered. Hepatic artery infusion pumps may also be utilized to convert from unresectable to resectable disease and as adjuvant therapy following resection.

Prognostic factors for patients who undergo curative-intent resection include the disease-free interval between diagnosis of the primary tumor and hepatic metastasis, size of the largest hepatic tumor, presence of extrahepatic metastasis, mutation status (e.g., RAS, BRAF), and nodal status of the primary tumor. Five-year overall and disease-free survival range from 30% to 60% and 20% to 40%, respectively.

PREOPERATIVE EVALUATION

Patients should undergo preoperative optimization and risk stratification tailored to their comorbidities and performance status. Liver function is assessed with evaluation of total bilirubin, prothrombin time, albumin, presence of ascites, and history of encephalopathy. The Child-Pugh scoring system (see Table 1) is associated with perioperative mortality rates of 5%, 30%, and 80% in patients with class A, B, and C cirrhosis, respectively. Thrombocytopenia (platelets <100,000 mm^3), splenomegaly, and esophageal varices are indicative of portal hypertension, which is associated with prohibitive rates of perioperative mortality after hepatectomy.

The location of the liver lesions and their relationship to major vascular and biliary structures are determined by high-quality, contrast-enhanced CT scan or MRI. The volume of the FLR is calculated to estimate the risk of posthepatectomy liver failure. In the absence of underlying hepatic dysfunction, an FLR of 20% of the standardized total liver volume is typically sufficient. Patients with some degree of liver dysfunction, such as those who have been treated with cytotoxic chemotherapy, should have an FLR of at least 30%, and patients with cirrhosis need an FLR of at least 40%. Volumetry is calculated with three-dimensional CT scan or MRI. The volume of nonfunctional liver (parenchyma that is either nonperfused or replaced by tumor) is subtracted from the total liver volume, which is especially important for patients with large lesions. Alternatively, the estimated liver volume can be calculated from the patient's body weight or body surface area (i.e., total liver volume in $cm^3 = -794.41 = 1267.28 \times$ body surface area in m^2). Patients with insufficient FLR should undergo PVE of the branches of the segments planned for resection to induce hypertrophy of the contralateral liver. Volumetry is repeated about 4 weeks after PVE and in a few more weeks if the minimal recommended FLR has not been achieved. ALPPS, an alternative to two-stage hepatectomy, was first described in 2011. This consists of a short interval two-stage resection with the first stage typically involving right portal vein ligation and parenchymal transection. This induces rapid contralateral hypertrophy, with the goal of completing the second stage during the same hospitalization in 1 or 2 weeks. This approach is only recommended in highly experienced centers because morbidity and mortality can be high.

TECHNICAL CONSIDERATIONS

Liver resections are classified into anatomic and nonanatomic. Anatomic resections include segmentectomy, sectionectomy, hemihepatectomy, and trisectionectomy. Small peripheral lesions are usually amenable to parenchymal-sparing nonanatomic resections. Larger or more centrally located lesions often require anatomic resection. This can be performed though an open or minimally invasive approach.

Positioning, Incision, and Exposure

Patients are placed in the supine position with arms extended at 90 degrees. Intravenous fluids are restricted until the parenchymal transection is complete to decrease blood loss from hepatic veins. Central venous cannulation is often unnecessary but should be considered in patients with extensive comorbidities, especially if major hepatectomy is planned. If measured, a central venous pressure less than 5 cm H_2O is recommended. Once the parenchymal transection is complete, intravascular volume is restored to achieve euvolemia.

In an open technique, a right subcostal incision with an upper midline extension provides adequate exposure for most cases. Alternative incisions include a midline, inverted "L" (Makuuchi's incision) or bilateral subcostal with midline extension (Mercedes Benz incision). If necessary, the xiphoid is removed to facilitate visualization of the suprahepatic inferior vena cava (IVC). The peritoneal cavity is explored for extrahepatic metastasis. The round ligament is divided and the falciform is dissected along the anterior surface of the liver up to the hepatic venous outflow. The gastrohepatic ligament is opened to expose the caudate lobe with care not to injure an accessory or replaced left hepatic artery. Intraoperative ultrasound is performed to identify all lesions, including any that may have been occult on preoperative imaging. Furthermore, ultrasound is used to define tumor relationship with vascular and biliary structures and define the resection plane.

Inflow and Outflow and Outflow Control

For major hepatic resections, hepatic and portal venous inflow can be dissected and controlled in the hilum of the liver, intraparenchymally, or through small hepatotomies (Fig. 1). The latter approach should be avoided if the tumor is within 2 cm of the hilum. Inflow control before parenchymal resection will result in a vascular demarcation line that will guide the correct transection plane. It is our practice to divide the inflow structures in the hepatic hilum using a vascular stapler or sutures. After inflow has been controlled, the hepatic venous outflow is controlled. This can also be done extrahepatically, which is our preference whenever feasible, or within the parenchyma during the transection.

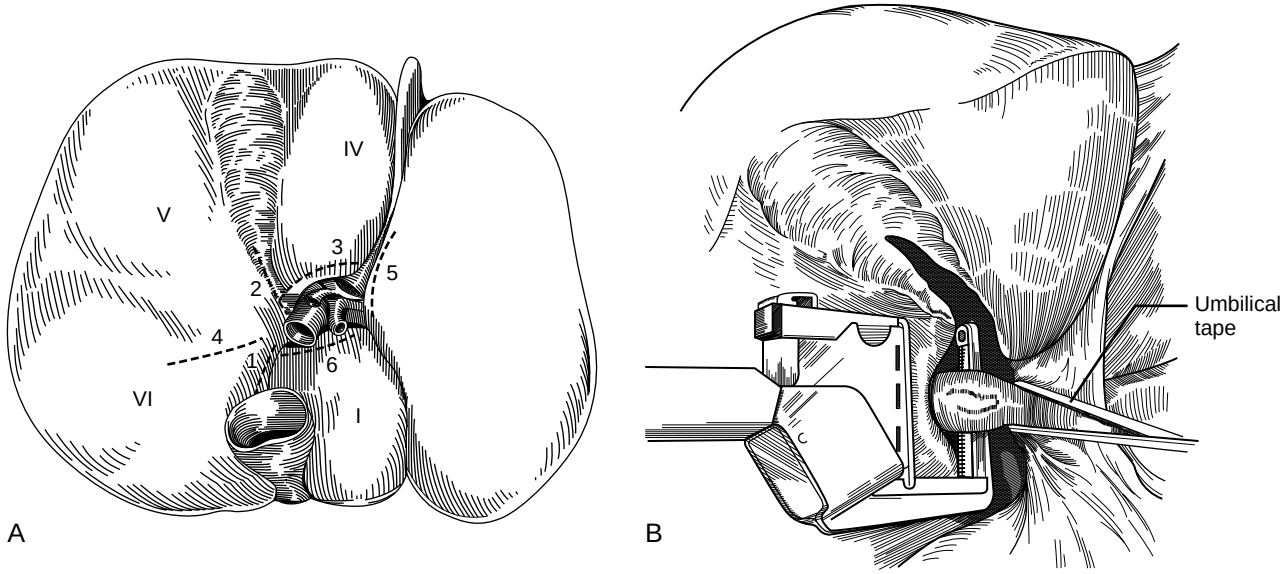


FIG. 1 **(A)** For the right portal pedicle to be accessed, hepatotomies are made in the gallbladder fossa *(2)* and in the caudate process *(1)*. The pedicle is encircled with a renal pedicle clamp, and a vessel loop is passed around it. The vessel loop is used to retract the main portal vein/left portal vein to the left as a TA stapler is passed and fired **(B)** to divide the right portal pedicle. *(From Fong Y, Blumgart LH. Useful stapling techniques in liver surgery.* J Am Coll Surg. *1997;185:93.)*

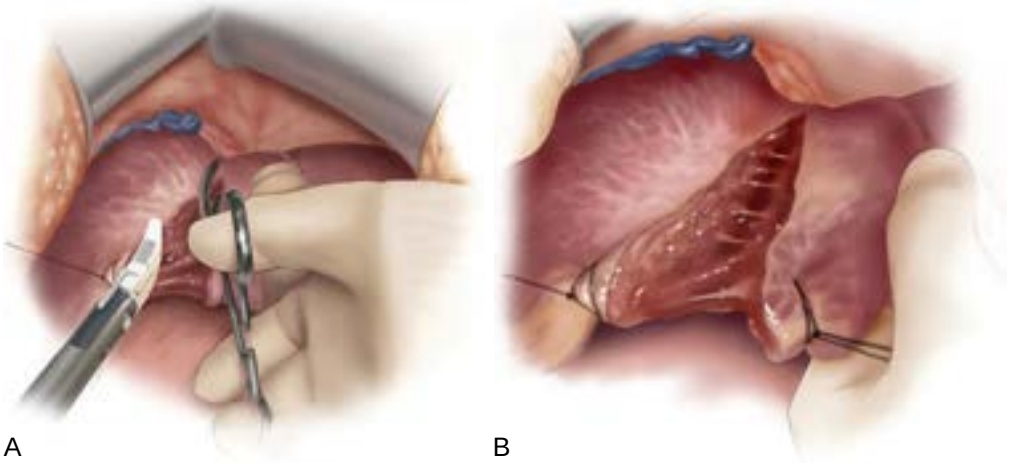


FIG. 2 **(A)** For division of the liver parenchyma, two stay sutures are placed for traction. The parenchyma is sequentially crush-clamped with a Kelly clamp; this demonstrates various size pedicles and veins. Those <5 mm are sealed and divided with the LigaSure device. **(B)** If the structure is >5 mm, the endovascular stapler, clips, and ties are used. *(From Patrlj L, Tuorto S, Fong Y. Combined blunt-clamp dissection and LigaSure ligation for hepatic parenchyma dissection: postcoagulation technique.* J Am Coll Surg. *2010;210:39.)*

We also generally apply umbilical tape with a Rummel tourniquet to the porta hepatitis, which can be tightened in the event a Pringle's maneuver is needed to control bleeding from the contralateral inflow structures.

Parenchymal Transection

Multiple tools and techniques are available for parenchymal transection. There are no compelling data to support one method over another and thus is left to the discretion, expertise, and comfort of the surgeon. A simple and frequently employed technique is the crush-clamp method in which the liver parenchyma is gently "crushed" with a Kelly clamp exposing branches of portal pedicles and hepatic veins that can be controlled with a combination of energy devices (Fig. 2), clips, ties, and firings of a vascular stapler. An alternative method is the two-surgeon technique, in which one surgeon dissects with the Cavitron Ultrasonic Surgical Aspirator (CUSA) and the other surgeon divides the vasculature and provides exposure. Regardless of technique, small vessels less than 3 mm can be divided with electrocautery, medium vessels are controlled with titanium clips, and larger vessels greater than 5 mm are divided with suture or a vascular stapler. Caution should be given to overuse of linear staplers in the absence of meticulous parenchymal dissection as this technique can lead to inadvertent biliary or vascular injury, especially in the setting of significant bleeding and poor exposure.

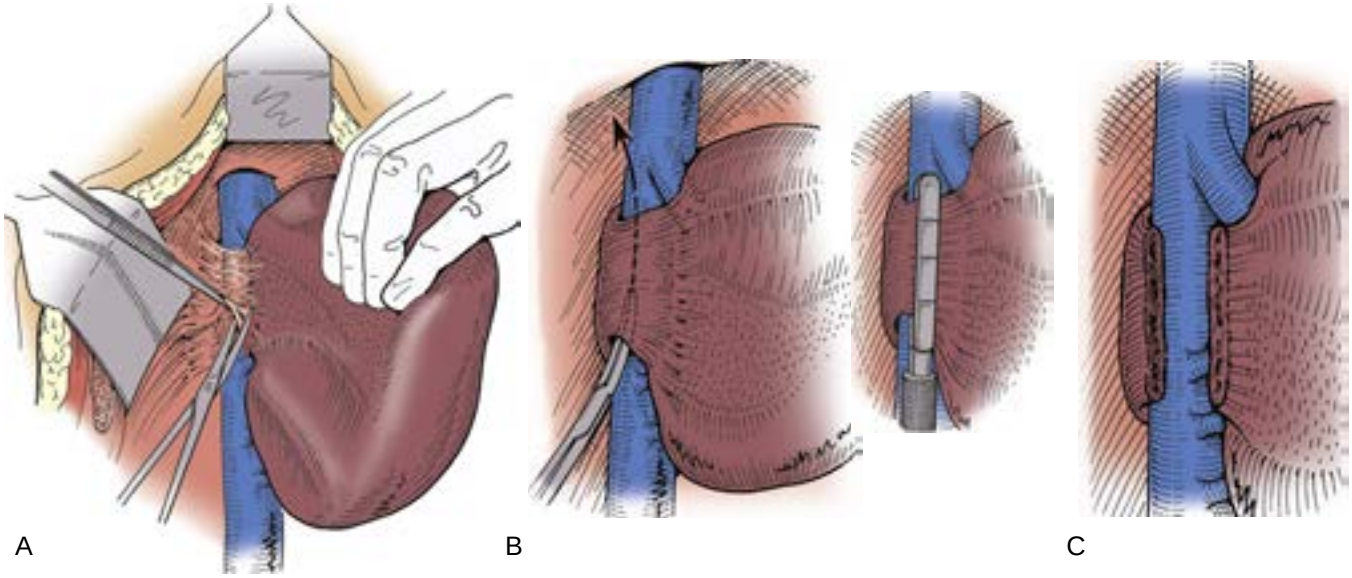


FIG. 3 **(A)** Division of the inferior vena cava ligament. **(B)** This ligament may contain liver parenchyma and/or a short hepatic vein and is therefore most safely transected with a stapler. **(C)** Transection will allow exposure and control of the right hepatic vein. *(From Blumgart LH, editor.* Surgery of the liver, biliary tract, and pancreas. 4th ed. *Philadelphia: Elsevier; 2007: I 354.)*

HEPATECTOMY

Right Hepatic Lobectomy

If a right hepatectomy is planned, further dissection of the falciform ligament is carried up to expose the hepatic venous outflow, particularly the right hepatic vein. The right coronary and triangular ligaments are divided, exposing the bare area of the liver. The right liver is mobilized and rotated to the patient's left. The short hepatic veins draining directly into the retrohepatic IVC are controlled with a combination of clips, ties, and firings of a vascular stapler for any larger branches. The retrocaval ligament (Makuuchi's ligament) is identified and transected with a vascular stapler (Fig. 3). Further dissection between the liver and the IVC will isolate the right hepatic vein, which is encircled with a vessel loop.

Attention is turned to the hilum, where the right hepatic artery and right portal vein are dissected and divided. A clear line of demarcation should be visible. The right hepatic vein, which was previously controlled with a vessel loop, is divided with a vascular stapler (Fig. 4). The transection plane follows the area of vascular demarcation. The right hepatic duct can be divided with a stapler or between ties.

For large right-sided tumors, an anterior approach can be used in which the parenchyma is divided before liver mobilization. Inflow control is obtained, and the parenchyma is transected until the anterior surface of the IVC is exposed. The right hepatic vein and short hepatic veins are identified and ligated. The hanging maneuver, elevation of the liver by an umbilical tape passed between the anterior surface of the IVC and the liver, can facilitate an anterior approach. The space between the right and middle hepatic veins is dissected, and a long clamp is gently passed along the anterior surface of the vena cava to emerge between the right and middle hepatic veins. An umbilical tape is then passed behind the liver and used to gently elevate the liver, serving as a guide to the transection plane.

Right Trisectionectomy

This includes extension of the right parenchymal transection to include segment IV. The initial hepatic mobilization is as described for a right hepatectomy. The transection plane is along the falciform ligament, from the groove separating the middle and left hepatic veins cranially to the right side of the umbilical fissure caudally, directed toward the medial aspect of the right hilar plate while avoiding the confluence of the left and right hepatic ducts. Inflow to segment IV is controlled during the transection, as is the middle hepatic vein as the surgeon follows the transection caudally.

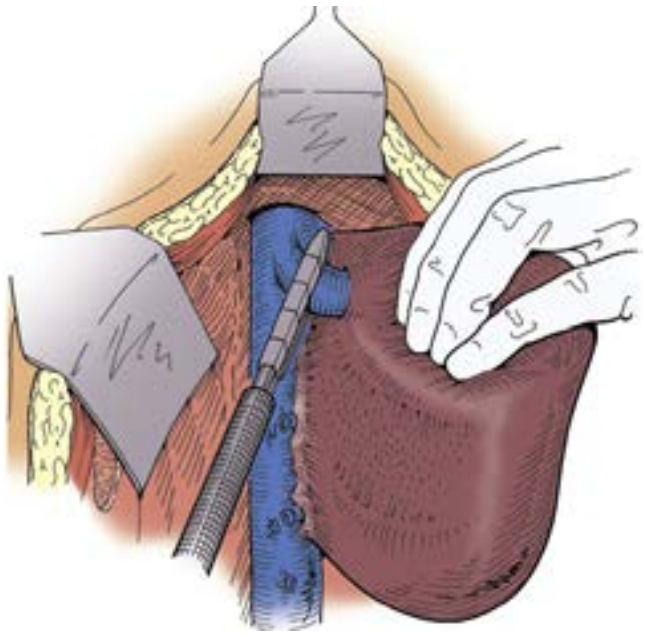


FIG. 4 Division of the right hepatic vein. With the liver retracted to the left, the right hepatic vein may be rapidly and safely divided using an Endo GIA stapler (Covidien) with a vascular load. *(From Blumgart LH, editor.* Surgery of the liver, biliary tract, and pancreas. 4th ed. *Philadelphia: Elsevier; 2007:364.)*

Left Hepatic Lobectomy

For a left hepatectomy, the triangular ligament is divided, exposing the IVC and left hepatic vein. The round ligament is elevated and the parenchymal bridge between segments II and IVB is divided, exposing the left hilum at the base of the umbilical fissure. The left hepatic artery, portal vein, and hepatic duct are ligated individually. The left lateral segment is rotated to the patient's right and the gastrohepatic ligament is divided. Exposure of the left hepatic vein is facilitated by dividing the ligamentum venosum at its insertion. The common trunk of the middle and left hepatic veins is encircled. Depending on the location of the pathology and the anatomy of the venous outflow, the middle and left hepatic vein may be divided together as a common trunk or the middle hepatic vein may be spared. The outflow can usually be divided extrahepatically with a vascular stapler before proceeding with the parenchymal transection. If this is not feasible, the left hepatic vein can be divided intraparenchymally. The liver parenchyma is transected along the line of vascular demarcation. If oncologically feasible, the transection plane should run horizontally, approximately 1 cm above the hilum, from the area of transection of the left hilar plate to the left side of the gallbladder fossa, thus avoiding transection of an aberrant right anterior or posterior duct, and then turning vertical, parallel to Cantle's line.

Left Trisectionectomy

When indicated, the right anterior section (segments V and VIII) may be transected along with the left hemiliver. The initial steps are the same as for a left hepatectomy. The main challenge is to define the transection plane, which is horizontal, extending from the right of the gallbladder fossa and anterior to the right hepatic vein toward the base of segment IV without injuring the inflow to the posterior sector. The right anterior pedicle is identified and ligated as the parenchymal transection approaches the hilum.

Suggested Readings

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Hepatic Malignancy: Resection Versus Transplantation

Sharon R. Weeks, MD, and Shane E. Ottmann, MD

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor in the liver and the fifth most common cause of malignancy worldwide. It develops most commonly in the setting of hepatic injury or chronic liver disease. Prevalence of HCC is higher in populations and geographic regions with higher rates of hepatitis infection; the highest HCC rates are seen in Asia and sub-Saharan Africa. Worldwide, the most common risk factor for HCC is hepatitis B virus infection or carrier status, whereas in the United States, hepatitis C is the most critical risk factor. Although the rates of many cancers in the United States have been decreasing over the last decade, the incidence of HCC and resultant mortality have been on the rise. HCC remains the third most common indication for transplant in the United States, comprising 14% of liver transplants performed in 2019.

The prognosis for HCC is poor if left untreated, with a 5-year overall survival of less than 10% and a median survival less than 6 months. For patients with a resectable tumor without underlying liver disease, resection is the treatment of choice. However, as the majority of patients with HCC have concomitant chronic liver disease, resection options can be limited due to concern for postoperative liver failure from inadequate remnant volume. Although transplantation for well-selected HCC patients has excellent outcomes and should be the treatment of choice in patients with decompensated cirrhosis, the limited donor pool prevents widespread application of this treatment modality for all patients. The patient with a resectable HCC in the setting of well-compensated cirrhosis presents a treatment dilemma: who should be resected and who would be better served with transplant? The answer for any given patient depends on local resources, including the availability of transplant, severity of underlying liver disease, and the technical resectability of the tumor, while weighing the risks associated with remnant liver recurrence and dropout on the transplant waitlist from tumor progression. Finally, while surgical intervention is the mainstay of treatment for HCC, many patients present at advanced stages that are not amenable to resection or do not meet criteria for transplant. For these patients, multiple locoregional therapies have been developed in the last few decades, including ablation, embolization, and radiation therapy; these interventions can be used as monotherapy or as a bridge to surgical therapy.

PATIENT EVALUATION

Risk factors for development of HCC include hepatitis B and C, alcohol consumption, genetic hemochromatosis, nonalcoholic fatty liver disease (NAFLD), primary biliary cirrhosis, alpha-1 antitrypsin deficiency, and other causes of cirrhosis. Patients with HCC are typically asymptomatic until advanced stages of the disease. When patients do have symptoms, they are typically due to mass effect of the tumor and may include abdominal pain, early satiety, weight loss, or a palpable mass. As cirrhosis is present in more than 90% of patients with HCC, cirrhotic symptomatology may be present, including weakness, fatigue, jaundice, pruritis, and hepatic encephalopathy. Patients may also manifest features of liver decompensation such as ascites

or variceal bleeding. Finally, liver decompensating events may result from tumor extension into the hepatic or portal veins.

Ideally, patients at high risk for HCC are followed via a surveillance protocol with ultrasound and alpha fetoprotein (AFP). The National Comprehensive Cancer Network (NCCN) recommends surveillance ultrasound every 6 months in all patients with chronic hepatitis B (including those without cirrhosis) as well as patients with cirrhosis due to any cause. Cross-sectional imaging with multiphasic CT or MRI is a more sensitive but less cost-effective approach to HCC screening; these modalities may be used as alternatives to ultrasound if visualization is poor. Unfortunately, adherence to these recommendations is low and patients often present at advanced stages of disease. Whether identified on surveillance, incidental, or for cause imaging, the diagnosis of HCC can typically be made radiographically without need for liver biopsy. Abdominal multiphasic CT or MRI with contrast should be performed to confirm the diagnosis and the extent of tumor burden. All patients with diagnosis of HCC warrant oncologic staging; NCCN guidelines recommend evaluation for distant metastases with chest CT and complete imaging of the abdomen and pelvis if not previously performed. The most common sites of metastasis are lungs, bone, and lymph nodes; less common sites include adrenal and peritoneal metastases. Consequently, selective use of bone scan in patients with skeletal symptoms may be considered. Laboratory evaluation should include hepatitis panel, bilirubin, transaminases, alkaline phosphatase, coagulation factors, basic chemistry and blood counts, and AFP if not previously performed.

The differential diagnosis for a presumed HCC on imaging includes cholangiocarcinoma, metastases, and benign liver masses, but typically imaging is diagnostic, particularly in high-risk patients. Patients at high risk for HCC are also at risk for intrahepatic cholangiocarcinoma and combined HCC-cholangiocarcinoma; these diagnoses should be considered in patients without sufficiently diagnostic imaging characteristics and in those with elevated CA 19-9 or carcinoembryonic antigen (CEA). In these patients or in other cases of diagnostic dilemma, such as patients with concern for metastasis or those with a low risk history, biopsy is warranted to confirm the diagnosis and guide treatment decisions.

Once diagnosis is confirmed, further treatment is guided by underlying liver function, resectability of tumor, and availability of treatment modalities, including transplantation.

ASSESSMENT OF LIVER FUNCTION

Of primary concern for choosing a treatment course is determination of the patient's underlying liver function. Multiple schemas have been developed for this purpose, the most well-known of which are the Child-Pugh classification (shown in Table 1) and the Model for End-Stage Liver Disease (MELD) score. Both predict mortality in cirrhotic patients, including postoperative mortality. Child class C cirrhotic patients, with up to 80% risk of mortality after surgery, are not generally considered candidates for nontransplant surgery. The MELD score, most recently modified to include sodium, includes bilirubin, international normalized ratio, and creatinine, and is used for prioritization of patients on the liver transplant waitlist. It has also been shown to predict 30-day mortality after surgery, with a 1% increase in mortality per MELD point in patients with MELD scores less than 20 and an additional 2% increase per MELD point greater than 20.

In recent years, other scoring systems have been evaluated as predictors of mortality in cirrhotic patients. The Mayo postoperative mortality risk calculator attempts to provide more specific results for a patient given their comorbidities; it calculates probability of mortality using age, American Society of Anesthesiologists (ASA) score, bilirubin, creatinine, International Normalized Ratio (INR), and the etiology of cirrhosis. This calculator provides predicted mortality at 7, 30, and 90 days postoperatively as well as at 1 and 5 years. Recently, use of the hepatic venous pressure gradient (HVPG) has been used to predict 1-year mortality in cirrhotic patients undergoing elective surgery. HVPG values higher than 16 mm Hg have been shown to be independently associated with higher mortality, and values greater than 20 mm Hg were associated with a very high risk of death, up to 44%. Notably, HVPG values <10 mm Hg have been shown to be protective against postoperative decompensating liver events.

In evaluating the specific question of the risk of postresection liver failure in patients with HCC, the albumin-bilirubin (ALBI) grade was found to effectively predict outcomes and importantly does not rely on the subjective scoring of the Child-Pugh classification. The ALBI grade performed as well as the Child-Pugh classification in predicting mortality in cirrhotic patients with HCC. Three grades, corresponding to three separate prognostic groups, were identified: ALBI grade I (score ≤−2.60), grade II (score >−2.60 to ≤−1.39), and grade III (>−1.39). The three grades also predicted 1-year survival after hepatic resection, with rates of 100%, 81.9%, and 62.9%, respectively.

The most commonly used staging classification for HCC that incorporates both tumor characteristics as well as underlying liver function is the Barcelona Clinic Liver Cancer (BCLC) staging system (Fig. 1). It classifies patients based on Child-Pugh classification and performance status, in addition to tumor size, nodal and metastatic disease, and local invasion characteristics. It also provides recommended treatment modalities for patients based on these characteristics. Studies of its prognostication outcomes have been mixed, with some evidence that it outperforms many models (including the American Joint Committee on Cancer [AJCC] TNM staging system) but underperformed in other settings. Importantly, several studies have shown that treatment outside Barcelona guidelines can be effective, and surgical resection has potential beyond the limited scope detailed in BCLC guidelines.

TABLE 1 Child-Pugh Classification

	1 point	2 points	3 points
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dL)	<2	2–3	>3
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Slight	Moderate
Encephalopathy	None	1–2	3–4

Child-Pugh classification is calculated by summing the points per parameter. Class A = 5–6; Class B = 7–9; Class C = 10–15.

RESECTION FOR HEPATOCELLULAR CARCINOMA

Surgical resection remains the mainstay of treatment for HCC patients without underlying liver disease. Additionally, in many areas where access to transplantation is low, it remains standard therapy for HCC patients with well-compensated cirrhosis without evidence of portal hypertension. Well-selected patients in this group have an overall 5-year survival as high as 60% to 70%. However, recurrence rates in the remnant liver are quite high, with most large studies reporting only 25% to 45% disease-free survival at 5 years. Furthermore, as many patients present with advanced disease, only 20% to 30% present as initially resectable on surgical evaluation.

Careful preoperative evaluation of these patients to determine candidacy for resection is critical. Imaging studies can determine resectability in regard to location, vascular involvement, and absence of distant metastases. Volumetrics, using CT, MRI, or scintigraphy, can be obtained to estimate the size of the remnant liver; 20% to 30% is considered adequate for a healthy liver. Larger remnants, 30% for the steatotic or chronic hepatitis liver and 40% for the cirrhotic liver,

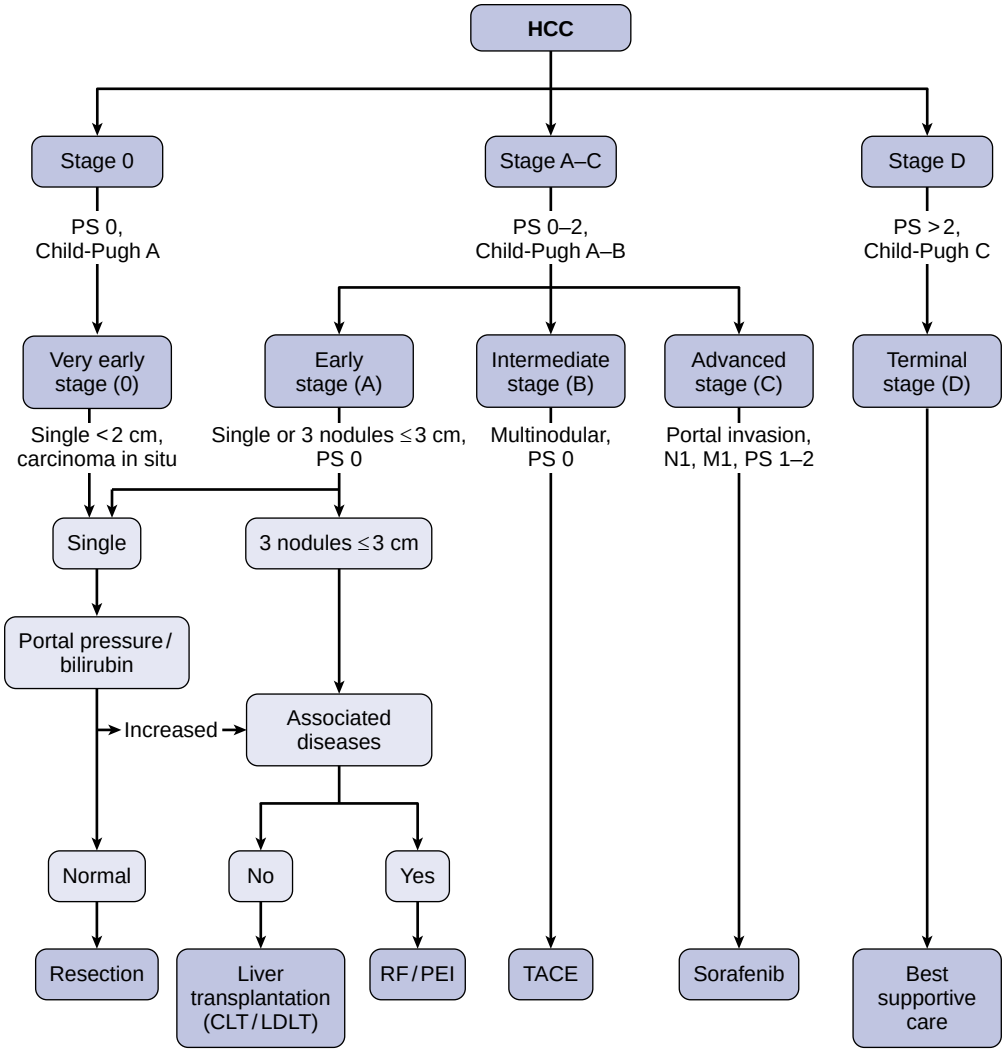


FIG. 1 **Barcelona Clinic Liver Cancer staging system for hepatocellular carcinoma.** *(From Khorsandi SE, Heaton N. Contemporary strategies in the management of hepatocellular carcinoma.* HPB Surg. *2012;2012:154056.)*

are recommended for the diseased liver. Preoperative assessment of liver function is also critical to prevent postoperative liver failure and decompensating liver events. Patients with Child class A cirrhosis, no evidence of portal hypertension, and well-preserved synthetic liver function can be considered as resection candidates. Patients without evidence of portal hypertension include those with HVPG <10, normal platelet count, normal appearing spleen, and lack of ascites and esophageal varices. In these patients, however, the risk of recurrence in the liver remnant and time at risk (with respect to patient age and other comorbidities) must be considered. Risk factors independently associated with tumor recurrence include tumor size greater than 5 cm and vascular invasion. Most studies have failed to identify a significant benefit to recommend anatomic over nonanatomic resection in preventing recurrence or mortality. Some have advocated for anatomic resection based on the theoretical risk of intrahepatic metastases via portal vein tributaries, but this recommendation has not yet been supported by evidence of improved outcomes. Regardless of planned approach, intraoperative ultrasound should be used liberally to best define the tumor burden intraoperatively and ensure an oncologically sound resection margin. It is the most sensitive imaging modality for identifying intrahepatic metastases and tumor margins, and it may clarify or expand on findings from preoperative imaging.

In patients in whom the remnant liver volume is of concern, portal vein embolization and the two-staged associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure are available modalities to facilitate resection. Preoperative portal vein embolization utilizes any of a number of embolization agents injected in percutaneous fashion via a transjugular or transhepatic approach to obliterate the portal blood flow to the ipsilateral side of the liver as the tumor (Fig. 2). This insult elicits hypertrophy of the contralateral side to augment volume of the future liver remnant and is performed 2 to 8 weeks in advance of a planned hepatic resection. Repeat imaging before surgery can determine effectiveness of the procedure. In a large clinical series of 358 patients, median regeneration of the future liver remnant was 50.3% at a median of 32 days postprocedure. Harnessing similar pathophysiology, the ALPPS procedure has been developed to accelerate hypertrophy of the liver remnant. The first stage involves operative portal vein ligation and in situ parenchymal transection of the resection plane. The second stage, at postoperative week one or two, involves completion of the resection and removal of the specimen. Published studies report liver remnant growth of 40% to 160% in only 6 to 9 days, a period in which significant tumor progression is less likely than the longer regenerative time period needed for portal vein embolization. Currently, ALPPS remains

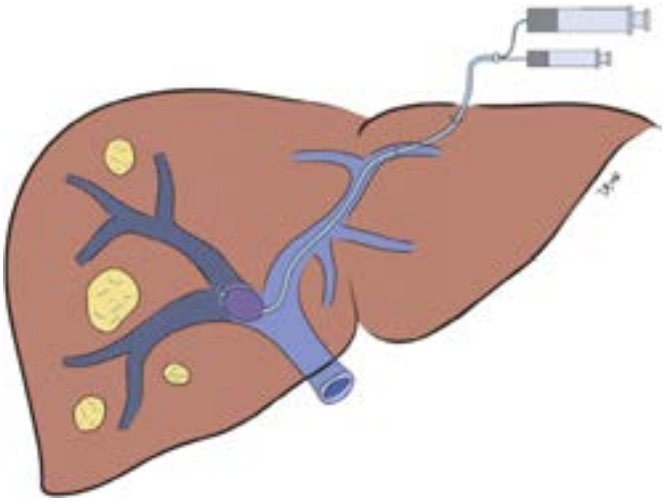


FIG. 2 Portal vein embolization. Right portal vein embolization from the contralateral approach. *(From Jarnagin: Blumgart's* Surgery of the Liver, Biliary Tract and Pancreas, 6th ed. *Elsevier; 2017.)*

limited to high-volume centers due to concerns regarding high rates of morbidity and mortality. However, a recent randomized trial showed higher resection rates for the ALPPS group compared with patients undergoing two-stage hepatectomy with portal vein embolization. Additionally, the vast majority of patients who fail to reach a sufficient future liver remnant with embolization were able to be rescued with ALPPS. With these improved outcomes and increasing experience with the procedure, ALPPS may play a larger role as a treatment modality in the future for patients with an insufficient future liver remnant.

LIVER TRANSPLANTATION IN HEPATOCELLULAR CARCINOMA

Excellent data exist to support transplantation of patients with cirrhosis and HCC tumors with early stage HCC; 5-year survival rates after transplant exceed 70%. The Milan criteria were developed in 1996 and remain the most commonly used and accepted criteria for listing of liver transplant candidates with HCC. Patients meet Milan criteria if they have a single nodule ≤5 cm or up to three nodules, each ≤3 cm; additionally, they must be free of macroscopic vascular invasion or distant disease. Overall survival after transplantation within Milan criteria is over 75% at 5 years. In the decades following Milan, the criteria received criticism for being unnecessarily narrow and excluding patients who would benefit from transplant. Multiple other extended criteria were proposed, with the University of California San Francisco (UCSF) criteria being the most commonly utilized. Patients qualify by UCSF parameters if they have a single nodule ≤6.5 cm or up to three nodules, each ≤4.5 cm, with a total tumor diameter ≤8 cm. Five-year overall survival using these criteria is 70% to 80%; conversely, transplantation outside these criteria was quite poor with less than 50% 1-year survival.

In patients with cirrhosis, multiple studies have shown clear benefits in disease-free and overall survival in those undergoing transplantation compared with resection. In a retrospective study of 1765 patients with HCC and concomitant cirrhosis who met Milan criteria, patients undergoing transplantation had significantly improved survival at 5 (74% vs. 53%) and 10 years (54% vs. 22%), as well as increased disease-free survival (72% vs 30% at 5 years; 53% vs 12% at 10 years) compared with transplant eligible patients who underwent liver resection. However, in the same large series, only about 10% of patients presenting with HCC and cirrhosis were eligible for transplant based on Milan criteria.

Given the threat to life from malignancy not captured by the degree of liver dysfunction, HCC patients in the United States who fall within the Milan criteria are given exception points on the liver transplant waitlist after a 6-month waiting period that correlates with the region's mean MELD at transplant. Thus, while transplantation is the most oncologically sound treatment for patients with HCC, drastically reducing the risk of recurrence compared with resection, the choice to proceed with transplant must be weighed against the risk of tumor progression on the waitlist. Living donor liver transplantation, which has been growing in safety and availability through the United States, may prove to reduce this risk. Some studies have shown that living donor liver transplantation significantly decreases risk of death from time of listing due to lower dropout rates.

FUTURE DIRECTIONS

Adjunctive and palliative treatments for HCC patients who are not resection or transplant candidates at presentation deserve special mention. These include transarterial chemoembolization, radiofrequency ablation, and other local therapies; they may serve as adjuvant or palliative therapy, as well as a bridge to definitive therapy. Ablative therapies for recurrences limited to the liver have also shown promising results. The long-term outcomes of these treatments and their use as a bridge to transplant or resection remain to be well defined, but these modalities are becoming more widespread, and indications are expanding.

Resection is the mainstay of therapy for cholangiocarcinoma, but the majority of patients are deemed unresectable at presentation. The Mayo protocol for unresectable cholangiocarcinoma treated with preoperative chemoradiotherapy followed by transplantation reported impressive results with a 5-year survival rate of 82%. These results have been questioned as many patients included in the study were found to be without viable tumor in the hepatectomy specimen. Multiinstitutional studies using similar protocols showed improved outcome for transplant over resection for hilar cholangiocarcinoma. Transplantation for cholangiocarcinoma remains controversial and is an area for further investigation.

SUMMARY

Any discussion of resection versus transplantation for HCC must include the degree of liver disfunction, tumor stage, availability of transplant, potential of recurrence in the remnant, and magnitude of the liver resection required to render the patient disease free. Retrospective analysis of resection versus transplantation is difficult to generalize given the obvious selection bias; patients who undergo resection are more likely to have less severe liver disease and patients without liver disease rarely undergo transplantation. These studies also necessarily exclude those patients on the waitlist who did not receive a transplant due to tumor progression. Although definitive data are lacking, most studies and observational experience support improved disease-free and overall survival in patients undergoing transplantation compared with resection. Over the past 30 years, there have been substantial advances in operative techniques of both liver transplantation and complex hepatic surgery, leading to improved selection and survival in both groups. There is little debate that resection can benefit many with isolated liver disease regardless of tumor size in a noncirrhotic patient. Liver resection offers the additional advantage of typically being immediately available and not dependent on the organ donor population. Similarly, HCC patients with liver failure and obvious decompensation clearly benefit from transplant provided there is a route to transplantation and the tumor is within acceptable criteria. The patient with well-compensated cirrhosis and early-stage tumors within transplantable criteria presents a treatment challenge; the risk of delayed intervention while awaiting a suitable organ must be weighed against the inferior survival and disease-free survival rates seen after hepatic resection. When these patients present early enough to fall within transplantable criteria,

we believe they should be referred to a transplant program to discuss the options of resection versus transplant. Important considerations for all HCC patients include the risk of disease progression while on the transplant waitlist, options for living donor liver transplant, risk of HCC recurrence in the remnant liver, liver failure following hepatectomy, and liver transplant outcomes in the modern era.

Suggested Readings

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Management of Colorectal Liver Metastases

Jordan M. Cloyd, MD, and Timothy M. Pawlik, MD, MPH, PhD

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer-related deaths throughout the world with up to 50% of patients developing colorectal liver metastases (CRLM) during the course of their disease. For patients with CRLM, surgical resection provides the only opportunity for potentially curative therapy. Although improvements in modern systemic chemotherapy have expanded the number of patients eligible for curative-intent surgery, advances in operative techniques and perioperative care have simultaneously improved the outcomes following liver surgery. Given the therapeutic complexity, the management of CRLM requires expert multidisciplinary care by an experienced oncology team. This chapter provides an overview of contemporary management of CRLM with an emphasis on surgical approaches.

EVALUATION

The diagnosis of CRLM is usually based on cross-sectional imaging obtained during the staging evaluation of patients recently diagnosed with CRC or during surveillance of patients with a history of treated CRC. A thorough history and physical examination, an elevated carcinoembryonic antigen (CEA) level, and characteristic imaging of a liver lesion are generally sufficient to make a diagnosis of CRLM. When necessary, the diagnosis may be confirmed via percutaneous image-guided biopsy. Surgical planning for CRLM requires high-quality imaging. On contrast-enhanced multidetector computed tomography (CT), CRLMs typically appear as hypoattenuating lesions best visualized on portal venous phases. Arterial phase images can be helpful to distinguish metastases from benign vascular lesions, to clarify vascular anatomy for operative planning, and/or if placement of a hepatic arterial infusion pump is being considered. Although CT is advantageous given its widespread availability and ease of use, magnetic resonance imaging (MRI) provides enhanced sensitivity of smaller tumors and better characterization of indeterminate lesions (Fig. 1).

An evaluation of candidacy for liver resection involves a comprehensive assessment along three domains: physical, oncologic, and technical. First, patients must be healthy enough and have appropriate functional status to undergo major liver surgery. For patients with prohibitive comorbidities or poor performance status, nonoperative therapies should be considered. Oncologic resectability refers to the selection of patients for surgery based on underlying tumor biology. Relevant factors may include the number or size of metastases, the presence of extrahepatic disease, the disease-free interval for metachronous tumors, tumor mutation status, and/or the response to neoadjuvant therapy. Technical resectability refers to the ability to perform a margin-negative resection while preserving an appropriate future liver remnant (FLR). In general, the minimum FLR must consist of at least two contiguous segments with intact vascular inflow, outflow, and biliary drainage. In addition, the estimated FLR volume should be calculated using liver volumetry to minimize the risk of posthepatectomy liver failure (PHLF). Although patients with normal hepatic function can safely tolerate resection with a planned FLR size of >20%, individuals with compromised liver function (obesity, receipt of chemotherapy for greater than 12 weeks, diabetes mellitus) should have an FLR >30%, and those with fibrosis/cirrhosis require an FLR >40% to 50% of total liver volume.

ROLE OF CHEMOTHERAPY

A major contributor to improved survival among patients with advanced CRC, and a driving factor in expanding the role of surgery for CRLM, has been the advent of improved systemic therapies. Contemporary first-line chemotherapy for metastatic CRC primarily consists of fluorouracil-based regimens containing oxaliplatin and/or irinotecan, namely FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), XELOX (capecitabine and oxaliplatin), or FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan). Biologic agents, such as bevacizumab or cetuximab, can be added to increase response rates. The choice of regimen largely depends on the patient's performance status, prior receipt of chemotherapy, and the presence of RAS or BRAF mutations. Tumors with evidence of mismatch repair deficiency are more likely to respond to immunotherapy.

For patients with resectable CRLM, neoadjuvant therapy is controversial. In the European Organisation for Research and Treatment of Cancer (EORTC) intergroup 40983 trial, patients with resectable CRLM were randomized to either upfront surgical resection or perioperative FOLFOX chemotherapy. Neoadjuvant therapy led to a 9% absolute improvement in progression-free survival but no difference in overall survival (OS) (Fig. 2). Therefore, neoadjuvant chemotherapy continues to be used selectively for patients with high-risk features or unclear resectability. However, prolonged chemotherapy may lead to chemotherapy-associated liver injury (CALI). Specifically, irinotecan-based treatment

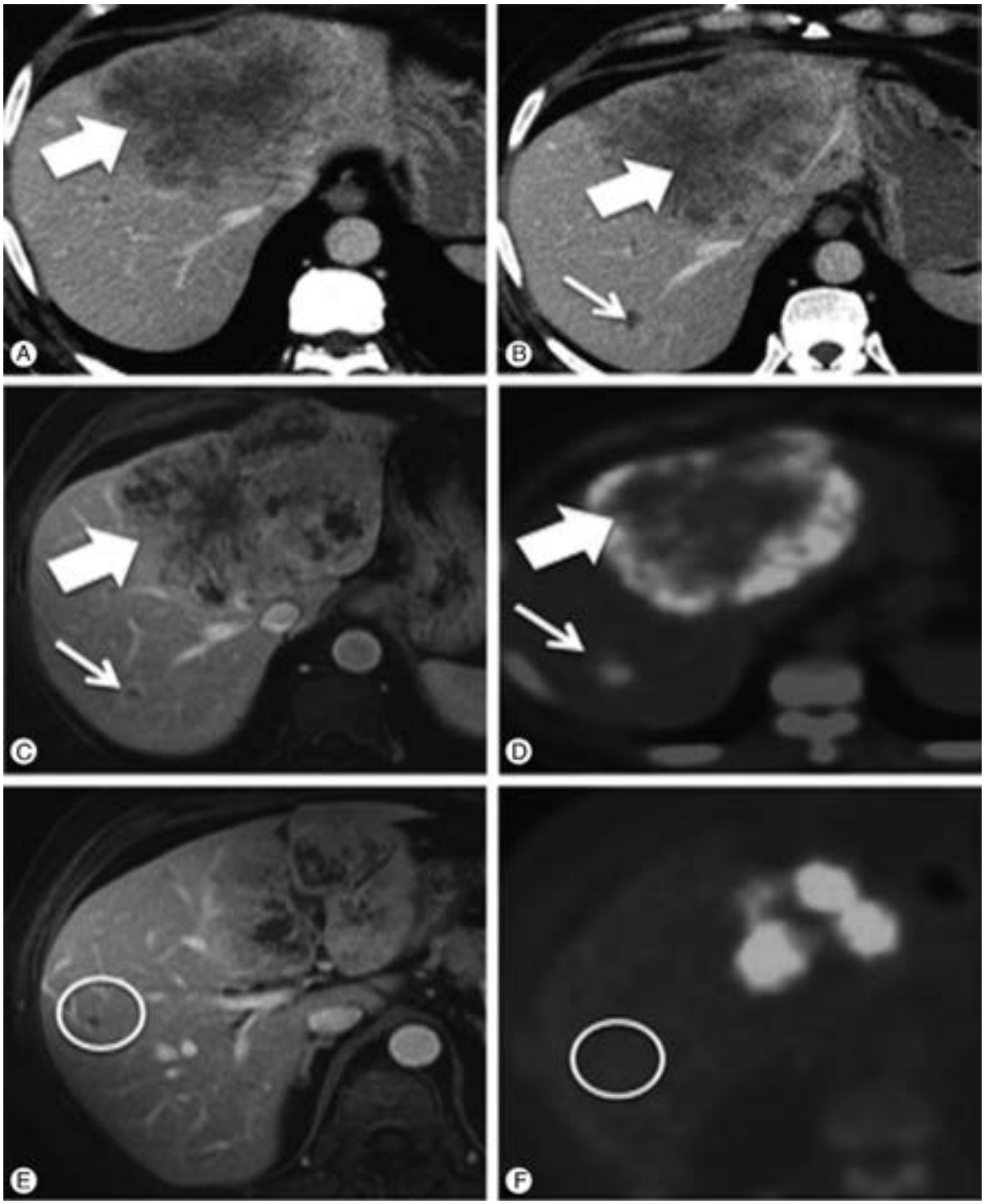


FIG. 1 Imaging of colorectal liver metastases. **(A)** Portal venous phase contrast-enhanced liver CT: necrotic mass, with fibrous enhancement centered on segments 2–4 *(arrow)*. **(B)** A second hypodense lesion on CT scan is visible in segment 7 *(thin arrow)*. **(C)** MRI shows peripheral enhancement of both lesions *(arrows)*. **(D)** Both lesions are hypermetabolic on PET-CT *(arrows)*. **(E)** Discovery of an additional lesion on portal venous phase contrast enhanced MRI *(circle)*. **(F)** This third lesion was not seen on CT or PET-CT *(circle)*. *(From Rahnemai-Azar A, Dillhoff M, Schmidt C, Pawlik T. Colorectal Liver Metastases. In:* Hepatobiliary and Pancreatic Surgery: A Companion to Specialist Surgical Practice, *6, 104–120.)*

is associated with steatohepatitis, whereas oxaliplatin-based chemotherapy is associated with sinusoidal congestion (Fig. 3). In general, if preoperative chemotherapy is used, the duration should be limited to 4 to 6 cycles (i.e., 2–3 months). In addition, neoadjuvant chemotherapy may lead to disappearing liver metastases, especially for small (<2 cm), centrally located tumors. If not surgically resected, these lesions will recur in up to 50% to 80% of patients.

Similarly, the role of adjuvant chemotherapy following resection of CRLM also remains controversial. Given that data from randomized controlled trials have produced mixed results, adjuvant chemotherapy is most often used selectively in patients with

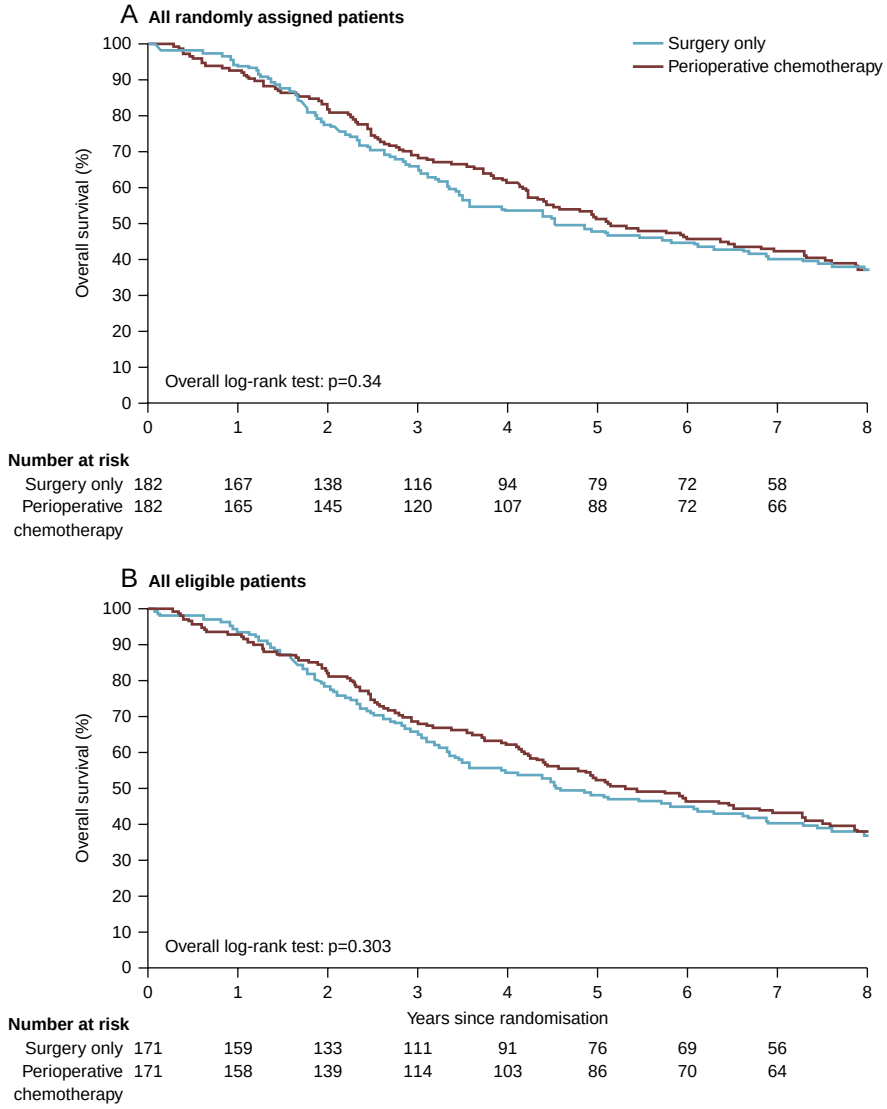


FIG. 2 Long-term overall survival of patients with resectable colorectal liver metastases randomized to perioperative chemotherapy versus upfront surgery in the EORTC 40983 trial. All randomly assigned patients **(A)** and all eligible patients **(B)**. *(From Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial.* Lancet Oncol. *2013;14(12):1208–1215.)*

high-risk disease (e.g., number of tumors, margin status, initial CEA level, etc.). Several nomograms or clinical risk scores have been developed to aid in prognostication and use of adjuvant therapy however, the use of these tools in the real-world clinical setting has been variable.

SURGICAL RESECTION

Surgical Technique

While there are several different techniques to divide the liver parenchyma, the universal goal of resection for CRLM is complete resection of all metastases with microscopic negative margins. A comprehensive understanding of liver anatomy is mandatory when performing hepatic resection of CRLM, as is adept use of intraoperative ultrasound for identifying all tumors, guiding planned surgical margins, and targeting intraoperative ablation (Fig. 4). Given its importance to perioperative and oncologic outcomes, strategies to minimize operative blood loss are paramount. A low central venous pressure (CVP) maintained by an experienced anesthesiologist is one of the most important steps. Although numerous parenchymal transection techniques are available, with none consistently demonstrating superiority over others, excessive use of staplers should be avoided given the potential for compromising margins and/or inadvertent injury to biliovascular pedicles. Intermittent hepatoduodenal ligament clamping (i.e., Pringle's maneuver) can help minimize blood loss. Enhanced recovery after surgery protocols can reduce postoperative length of stay and morbidity after liver surgery.

Margin Status

Although an R0 resection consists of surgical margins >1 mm, the optimal margin width at the time of liver resection for CRLM remains controversial. In a seminal study, R1 margin status was associated with worse OS following liver resection for CRLM, but greater margin widths were not associated with improved outcomes (Fig. 5). Other studies have demonstrated that wider margins >1 mm are not advantageous; however, even submillimeter margin widths have been associated with improved OS compared with microscopically positive margins. Increasing evidence suggests that margin status may be more reflective of a biological effect. For example, patients with RAS mutations are more likely to have positive margins, and the prognostic significance of R1 margin status is lessened among patients who respond to neoadjuvant therapy. Therefore the objective of any resection for CRLM should remain a microscopically negative margin ≥1 mm, yet the direct association between margin

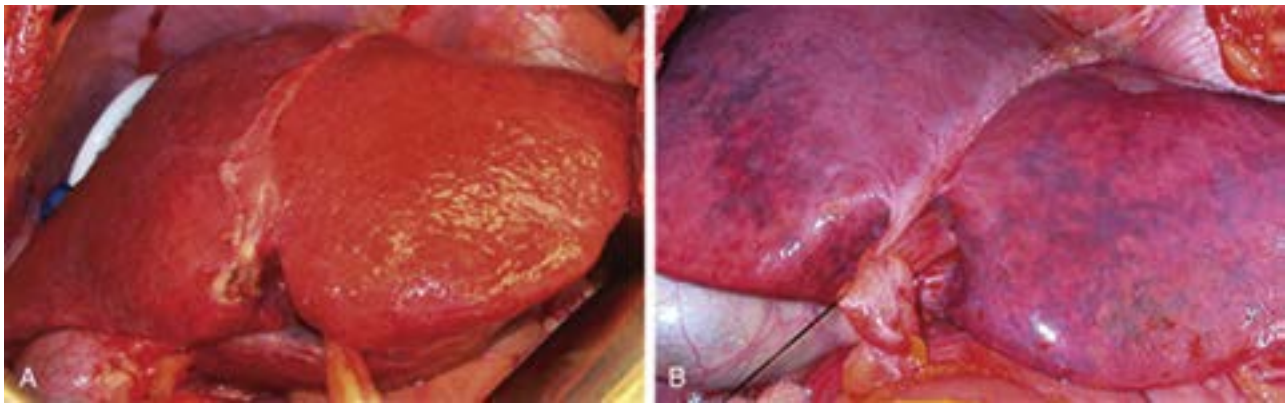


FIG. 3 Chemotherapy-associated liver injury. **(A)** Intraoperative gross photograph of a fatty liver. Note the hepatomegaly, yellow appearance, and rounded edges. **(B)** Intraoperative photograph of a liver with sinusoidal obstructive syndrome. Note the patchy blue mottled appearance. *(From Srinevas K. Reddy S, Geller D. Hepatic steatosis, steatohepatitis, and chemotherapy-related liver injury. In:* Blumgart's Surgery of the Liver, Biliary Tract and Pancreas, *Philadelphia: Elsevier; 2007)..*

status and patient outcomes is likely influenced by a myriad of clinical and biological factors.

Parenchymal-Sparing Techniques

A parenchymal-sparing approach is increasingly advocated in the surgical management of CRLM. The goals of parenchymal-sparing hepatectomy (PSH) are to achieve the oncologic principles of margin-negative resection while preserving maximal uninvolved liver parenchyma. PSH not only leads to improved perioperative outcomes and reduced incidence of PHLF, but the preservation of normal liver is also associated with improved odds of salvageability in the case of liver recurrence. Although some anatomic resections, such as segmentectomy or sectionectomy, can be considered parenchymal-sparing approaches, PSHs are more commonly nonanatomic resections, occasionally termed wedge resections. An example of a PSH might be several nonanatomic resections of superficial tumors in the right liver instead of a formal right hepatectomy.

Minimally Invasive Approaches

While minimally invasive approaches to liver surgery have had slower widespread adoption than in other areas of surgery, minimally invasive liver resection (MILR) is now considered an acceptable approach to the management of CRLM by experienced surgeons. Numerous retrospective and institutional studies have demonstrated its safety and appropriate oncologic outcomes. More recently, the OSLO-COMET trial randomized patients with resectable CRLM to either open or laparoscopic PSH. In this study, patients who underwent MILR experienced improved perioperative outcomes with no differences in margin status or long-term outcomes. Increasingly, robotic surgery is employed to extend the benefits of MILR to patients with CRLM, and robotic approaches appear to result in similar short- and long-term outcomes compared with laparoscopic liver surgery. Several society guidelines have recommended MILR as the standard of care for metastases in favorable locations (e.g., left lateral sectionectomy, nonanatomic resections in anterosuperior segments), and MILR is increasingly used at experienced centers for major hepatectomy.

LOCOREGIONAL THERAPIES

Ablation

For oligometastatic disease that is not amenable to resection, thermal ablation is an alternative locoregional therapy for select patients (Fig. 6). For small tumors, thermal ablation is a potentially curative-intent treatment with only marginally increased local recurrence rates compared with resection when performed by experienced providers. Intraoperative ablation can also be used at the time of surgical resection to address multifocal or bilateral disease in a parenchymal-sparing approach, especially for central tumors that would otherwise have required a hemihepatectomy. Cryoablation and radiofrequency ablation (RFA) are less commonly used now in place of microwave ablation (MWA), which offers advantages in thermal spread and efficiency of use. Ideal metastases are <3 cm that are separate from major blood vessels and other vital structures. Ablation can generally be performed open, laparoscopic, or percutaneous.

Hepatic Artery Infusion Therapy

The primary rationale for hepatic artery infusion (HAI) therapy is that liver metastases derive their blood supply predominantly from the hepatic artery, while normal hepatocytes are primarily supplied by portal venous blood. HAI therapy involves delivering chemotherapy directly to the liver via a catheter surgically placed into the gastroduodenal artery and connected to a subcutaneous port that can be accessed percutaneously. HAI therapy is generally well tolerated, although hepatic artery thrombosis, biliary toxicity, incomplete perfusion of the liver, and toxicity from inadvertent perfusion to the stomach or duodenum can occur. In general, the primary tumor should be resected and there should be minimal or no extrahepatic disease. Floxuridine (FUDR) is the most commonly utilized drug for HAI therapy and is especially ideal given its short half-life and high hepatic extraction.

There are two current indications for HAI therapy: unresectable CRLM and adjuvant therapy following resection of CRLM. For patients with initially unresectable CRLM, the use of HAI therapy, with or without simultaneous systemic chemotherapy, has been shown to increase response rates compared with systemic therapy alone in some studies. A limitation of the current evidence is that most trials of HAI therapy were not compared with patients receiving contemporary multiagent chemotherapy with biologic agents. Although further randomized controlled trials are needed, HAI therapy can be considered for patients with isolated unresectable CRLM to increase the odds of successfully downstaging to surgical resection. Similarly, a few randomized controlled trials, primary performed at a single high-volume institution, have suggested improved outcomes with adjuvant HAI therapy typically combined with systemic therapy versus systemic chemotherapy alone following resection of CRLM. Given the single institution nature of this evidence, the potential toxicity associated with HAI therapy, challenges

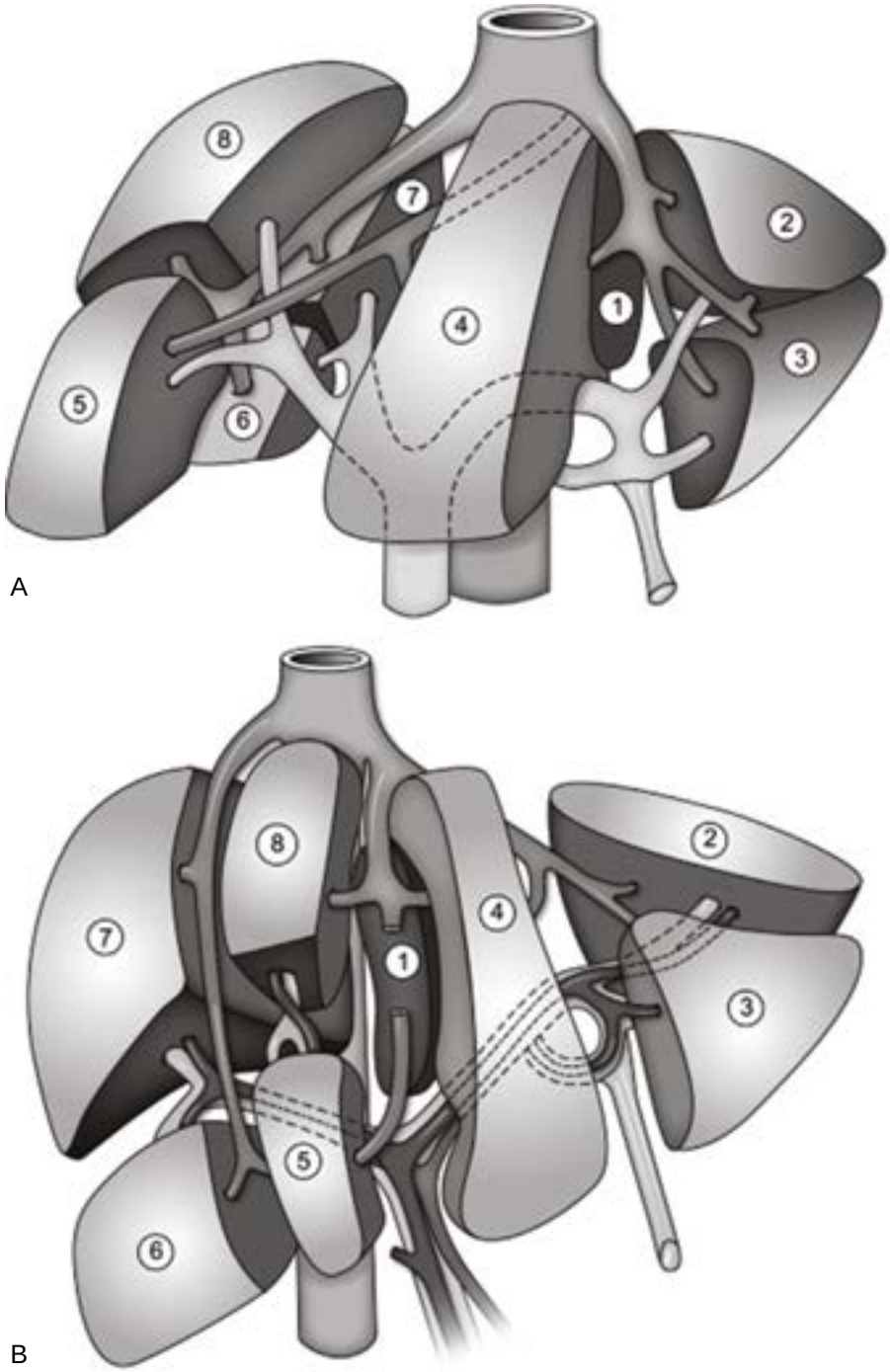


FIG. 4 Functional division of the liver into eight segments as described by Coinaud: **(A)** as observed in the anatomical position in the patient; **(B)** as observed ex vivo. *(From Vincent S. Yip V, Fenwick S. Hepatic, biliary and pancreatic anatomy. In:* Hepatobiliary and Pancreatic Surgery: A Companion to Specialist Surgical Practice, *2, 17–40.)*

with maintaining a pump program, and the improved effectiveness of modern chemotherapy, adjuvant HAI therapy has not gained universal acceptance.

Other hepatic-artery based therapeutic strategies, including yttrium-90 transarterial radioembolization (^{90}Y TARE) and transarterial chemoembolization (TACE) have also been studied, particularly in the management of unresectable CRLM. An important study is the SIRFLOX trial that randomized 549 patients with unresectable CRLM to first-line chemotherapy with or without ^{90}Y TARE. Although there was no difference in OS, the TARE group experienced increased adverse events. Although TARE should not be used as a first-line treatment, it is still occasionally considered in patients with isolated unresectable CRLM following induction systemic chemotherapy. TACE and drug-eluting bead (DEB)-TACE are not commonly used in the current management of unresectable CRLM.

SPECIFIC CLINICAL SCENARIOS

Initially Unresectable Disease

A substantial proportion of patients with metastatic CRC will present with unresectable bilateral or locally advanced CRLM. Given the effectiveness of systemic chemotherapy, neoadjuvant chemotherapy has the potential to downsize unresectable CRLM and convert initially inoperable lesions to resectable disease in up to 40% of patients. FOLFOX or FOLFIRI with or without a biologic agent are

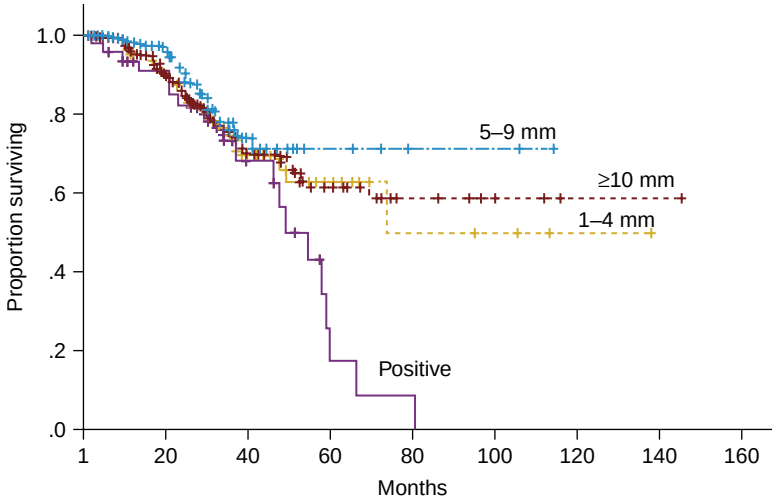


FIG. 5 Survival after hepatic resection of colorectal liver metastases, stratified by margin status. Median survival was 49.6 months in patients with positive margins and was not yet reached in patients with negative margins (P = .005). No significant difference in survival was seen in patients with a negative surgical margin, regardless of the width of the margin (all P > .5). *(From Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases.* Ann Surg. *2005;241(5):715–722.)*

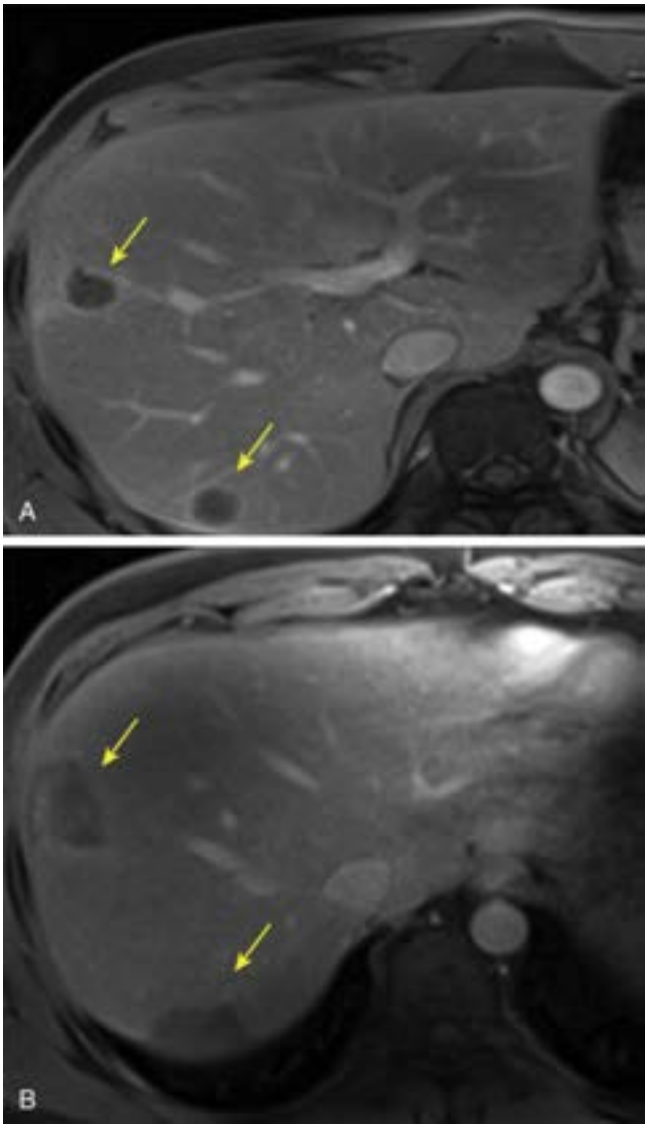


FIG. 6 Long-term appearance of microwave-ablated lesions in the liver. **(A)** Classical portal venous phase appearance of metastatic colorectal cancer lesions *(arrows);* dark lesions with hyperemic rim. **(B)** Unperfused ablated areas 3 years later.

suggested for induction therapy, though higher response rates and thus resectability rates may be observed with triplet regimens such as FOLFOXIRI. As discussed, HAI therapy can also be used for patients with initially unresectable CRLM. When used in a first-line setting in combination with systemic chemotherapy, conversion to resectability may occur in as high as 70% of patients. Response to conversion therapy should be assessed every 2 months with cross-sectional imaging, and liver resection should be considered when metastases become resectable.

Bilateral Metastatic Disease

Although bilateral metastases present increased complexity, several strategies exist to extend the benefits of surgery to patients with advanced CRLM (Fig. 7). The preferred surgical approach depends on the burden and location of the bilateral disease. For example, a single-stage approach with multiple PSHs can be utilized for small and peripherally located tumors. PSH can be combined with ablation for more central tumors to avoid the need for major hepatectomy. When a right or extended right hepatectomy is required, careful assessment of the anticipated left FLR after resection of the left-sided metastases is necessary. Those patients with inadequate FLR may be considered for two-stage hepatectomy (TSH). In the first stage, the FLR is cleared of metastatic disease. Portal vein embolization (PVE) is then performed followed by a second-stage hepatectomy of the remaining metastases once there has been adequate hypertrophy of the contralateral liver. An alternative to TSH is associated liver partition and portal vein ligation for staged hepatectomy (ALPPS). During the first operation, a right portal vein ligation is first combined with parenchymal transection and clearance of the FLR of metastases. A second operation to remove the affected liver is then performed 1 to 2 weeks later during the same hospital admission once adequate hypertrophy is confirmed. Management of advanced bilateral CRLM requires multidisciplinary expertise to achieve optimal perioperative and oncologic outcomes.

Synchronous Colorectal Metastases

For patients with synchronous CRLM, the timing of hepatic resection remains controversial. The classic approach involves first resecting the primary tumor, administering chemotherapy, and then managing the liver disease. In the liver-first approach, the liver disease is resected following neoadjuvant chemotherapy; once recovered, additional chemotherapy or radiation therapy is given as needed and then eventually resection of the asymptomatic primary is performed. This approach is particularly advantageous for advanced CRLM and when preoperative radiation is required for rectal cancers. Increasingly,

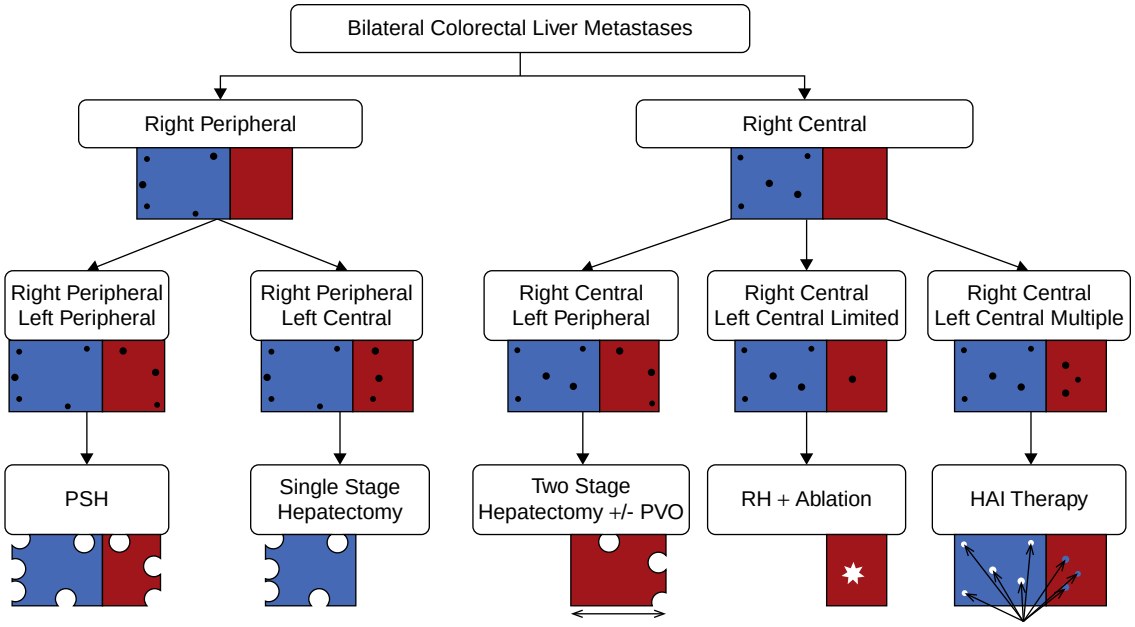


FIG. 7 A systematic algorithm for assessing the distribution and extent of bilateral colorectal liver metastases that informs operative treatment strategy. Each scenario is modeled with the right liver in *blue* (representing ≈65% of total liver volume and the left liver in *red* representing ≈35% of total liver volume). Tumors are represented as *closed circles*, parenchymal sparing resections as *open circles*, and ablations as *open stars*. *PVO*, Portal vein occlusion; *RH*, right hepatectomy. *(From Cloyd JM, Aloia TA. Hammer versus Swiss Army knife: Developing a strategy for the management of bilobar colorectal liver metastases.* Surgery. *2017;162(1):12–17.)*

primary CRCs and liver metastases are resected in a combined or simultaneous approach. Although the combination of major liver resections and complex colorectal resections should be avoided, in general, the combined approach, when feasible, tends to be associated with a shorter total length of hospital stay and less morbidity but with comparable oncologic outcomes.

CONCLUSION

The management of CRLM continues to evolve but largely depends on experienced multidisciplinary teams working collaboratively at high-volume centers. The cornerstone of potentially curative therapy remains surgical resection, and advances in perioperative and surgical technique have expanded the number of patients eligible for surgery. In addition, improvements in systemic therapies as well as locoregional treatments have not only improved outcomes for patients with advanced disease but also led to improved conversion rates that result in resection for those with initially inoperable disease. Given the importance of locoregional control in the overall management of patients with metastatic CRC, expanding the role of surgery for CRLM should lead to improved outcomes for patients with advanced CRC.

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Ablation of Colorectal Carcinoma Liver Metastases

Naomi M. Sell, MD, MHS, Zhi Ven Fong, MD, PhD, and Kenneth K. Tanabe, MD

INTRODUCTION

The liver is the most common site of metastases for patients with colorectal cancer. Approximately one-third of patients have liver metastases at the time of diagnosis, with others developing metastases over the course of their treatment. The ease of spread to the liver is facilitated by drainage of the portal venous system with a direct path from the colon to the liver. Surgical resection is the treatment of choice when feasible. The addition of neoadjuvant chemotherapy that may shrink hepatic metastases now enables more patients to undergo surgical resection. However, there are still many patients with colorectal cancer liver metastases (CLM) who are deemed unresectable. Reasons for unresectability include tumor location, inadequate remnant liver volume, and comorbid conditions that may preclude an operation.

Ablative treatment modalities were developed to provide treatment options for patients with unresectable CLM. Since the 1980s, multiple ablation techniques have been developed, beginning with cryotherapy and now including radiofrequency ablation (RFA), microwave ablation (MWA), irreversible electroporation (IRE), and laser thermal ablation (LTA).

ABLATION MODALITIES

Cryotherapy

Cryotherapy was one of the first methods of ablative therapy for treatment of liver tumors. It was first introduced in the 1950s to treat hepatocellular carcinoma (HCC). By the 1980s, it was also used for CLM. Early cryotherapy systems instilled liquid nitrogen for direct contact with the tumor at temperatures as low as −190°C. Freezing followed by thawing results in cell death. Eventually, liquid nitrogen systems were replaced with argon and helium gas systems to achieve hypothermia. Insulated probes are placed into the liver tumor and argon gas is passed under high pressure to freeze, followed by helium gas to thaw. Repeated freeze-thaw cycles cause protein denaturation, cellular dehydration, and ultimately tumor cell death. Bleeding is a known complication of cryotherapy. The interface between the ice ball and unfrozen liver can "crack" and result in bleeding from the liver parenchyma. An additional complication is "cryoshock," which is a cytokine-mediated complication. The mechanism of this complication is poorly understood and can occur when the lesion completely thaws before refreezing (double-freeze cycle). Cryoshock affects 1% of cryotherapy patients and results in a severe coagulopathy with the potential for disseminated intravascular coagulation and multiorgan failure.

Radiofrequency Ablation

RFA has become the most widely used liver ablative treatment modality. It can be performed via laparotomy, laparoscopically, or percutaneously via image guidance in which ultrasound (US) or computed tomography (CT) is used to place electrodes directly into the CLM lesion (Fig. 1). A radiofrequency generator conducts high-frequency alternating currents of 5000 to 9000 MHz between the intratumoral electrode and the grounding pad on the patient.



FIG. 1 Radiofrequency electrode designs. An expandable multilined probe with its array deployed.

This creates friction from agitation of ions within the tissue, resulting in the generation of heat that leads to coagulative necrosis of the tissue surrounding the electrode. Thermistors within the electrodes on the RFA needle allow close temperature regulation. Cell death occurs at 60°C. Care must be taken to not allow tissue temperatures to rise excessively. At very high temperatures, the effectiveness of ablation is decreased due to increased electrical impedance from the formation of char in the tissue and on the electrode. This increases the risk of incomplete tumor ablation. In total, approximately 30 minutes are required to perform a 3 to 5 cm ablation.

The efficacy of RFA decreases as tumor size increases. Some of the energy transmission is reliant on conduction. Consequently, tumor cells located further from the probe heat less efficiently. Retrospective studies have shown higher local recurrence rates when RFA is performed on tumors larger than 3.5 cm in size. RFA is also less effective for metastases that are located in close proximity to vascular structures. The continuous blood flow within the vessels maintains physiologic temperatures (37°C) for tumor cells along the blood vessel walls. Large blood vessels act as "heat sinks" that dissipate heat away from the tumor, which prevents necessary tumor heating and tumor destruction.

To date, no prospective randomized clinical trials comparing RFA with any other treatment modality have been performed in patients with CLM. There have been numerous nonrandomized trials that compare RFA with resection, chemotherapy, or other ablative modalities, yet the heterogeneity and bias inherent in retrospective study design limits meaningful comparison and interpretation. Overall, RFA has been shown to be inferior to resection when analyzing both local recurrence and overall survival (OS). However, these studies were not randomized trials. Some patients treated with RFA in these comparative reports were not surgical candidates, indicating worse disease progression or underlying tumor biology. Five-year OS after RFA has been estimated to be 18% to 22%. The best outcomes are observed after ablation of solitary liver lesions that are smaller than 3 cm.

Serious complications are uncommon following RFA. A study of 3554 RFA-treated lesions in 2320 patients by Livraghi and colleagues found the incidence of major complications to occur in 2.2% of patients. Major complications included intrahepatic abscess, hemorrhage, neoplastic seeding, and intestinal perforation. The most common adverse event is postablation syndrome that occurs in approximately one-third of patients. The symptoms are flulike and often include malaise, myalgias, low-grade fever, nausea, and vomiting. It is self-limiting and typically lasts for only a few days.

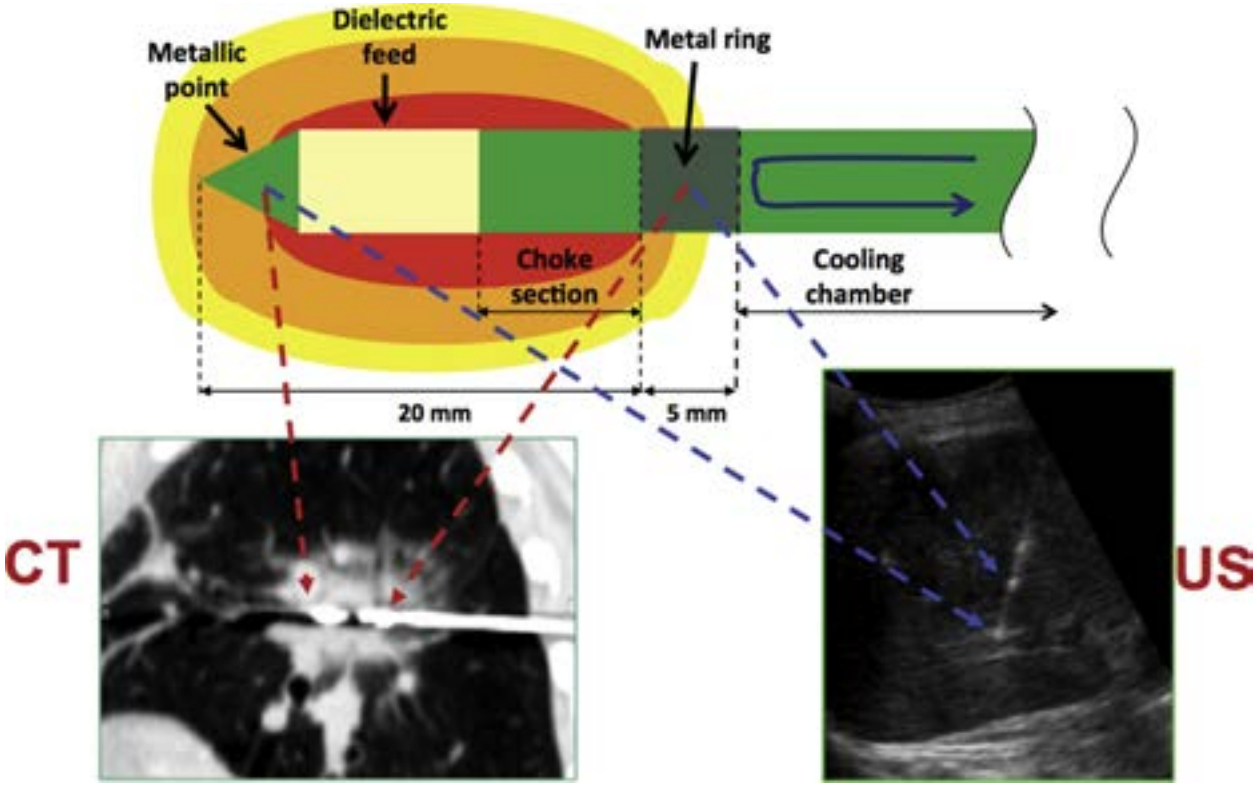


FIG. 2 Microwave ablation electrode, with intraprocedural imaging of a CT-guided ablation of a lung tumor *(left)* and US-guided ablation of a liver tumor ***(right)***. *(Images courtesy H.S. Hospital Services S.p.A, Rome, Italy.)*

Microwave Ablation

MWA is the other commonly utilized ablative therapy. Like RFA, it relies on heating of the tumor and coagulative necrosis. It uses high-frequency (900–2500 MHz) oscillating electromagnetic field "microwaves" delivered through antenna probes (Fig. 2). The microwaves cause agitation of water molecules within the tissue that generates friction and ultimately heat. Lesions with higher concentrations of water are more susceptible to heating by MWA.

MWA has been demonstrated to have some advantages over RFA. (1) MWA can reach higher temperatures faster than RFA. (2) With MWA, multiple ablations can be performed simultaneously. This allows for treatment of multiple tumors simultaneously and larger ablation zones. (3) Because heating of the tumor is less reliant on conduction, MWA is less affected by the "heat sink" phenomenon than RFA, making it more suitable for metastases located near vessels. (4) MWA results in less tissue charring than RFA, resulting in decreased impedance and more effective ablation of larger lesions. (5) MWA takes less time than RFA. MWA ablation times average between 2 to 5 minutes, while RFA takes approximately 30 minutes.

Like RFA, MWA can be performed by open, laparoscopic, or percutaneous access. Open and laparoscopic ablations are typically used in patients who have tumors in locations that are not accessible percutaneously, or when combined with resection. Percutaneous ablations are ideal in patients who are not surgical candidates. Similar to RFA, MWA can be performed under either US or CT guidance. General anesthesia is typically used for patient comfort and to decrease motion during the procedure. Recently, dual application probes have been created (Amica) that have the capability of delivering both RFA and MWA ablative techniques through the same hardware (Fig. 3).

Complication rates are comparable to RFA. Mortality rate is approximately 0.5% while ablation related complication rates range from 2% to 5%. The most common complications reported are skin burn, liver abscess, bile leak, hemorrhage, portal vein thrombosis, and pleural effusion. In evaluating multiple retrospective studies of MWA, the local recurrence rates range between 5% to 20% at 3 years and 3-year OS from 50% to 85%. No randomized controlled trials have been performed comparing the two approaches in CLM, but on meta-analysis, the disease-free survival (DFS) and OS rates are comparable between MWA and RFA (Table 1).

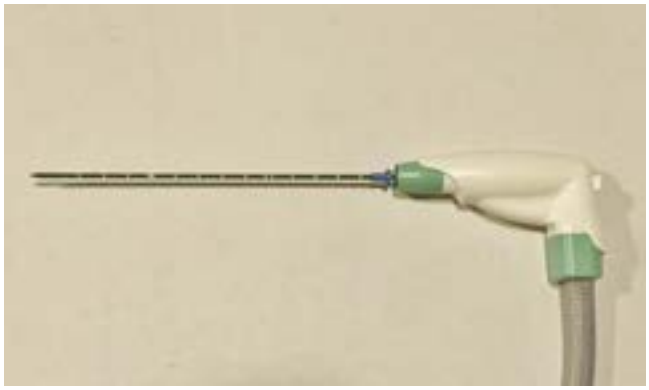


FIG. 3 Dual ablation system by Amica. This apparatus can deliver both RFA and MWA utilizing the same probe. The device contains a built-in thermocouple that allows for temperature monitoring and has an internal water-cooling property that serves to avoid probe overheating.

Irreversible Electroporation

IRE is a nonthermal ablation technique that uses high-voltage electrical shocks rather than heat to induce cell death. IRE is delivered by the placement of multiple electrodes near the tumor that each

TABLE 1 Outcomes of Local Ablative Techniques on Colorectal Liver Metastases

Study	n	Follow-up (mo)	1y DFS (%)	5y DFS (%)	1y OS (%)	5y OS (%)	LTP (%)	AE (%)	SAE (%)	Mortality (%)
CRYOTHERAPY										
Littrup 2016	77	20	—	—	80	20	21	—	—	—
Wallace 1999	20	14	—	—	84	—	—	—	4	0
RADIOFREQUENCY ABLATION										
Aliyev 2013	44	31	69	10	90	47	18	5	—	0
Boostrom 2011	12	—	74	36	83	46	37	—	—	—
Chiou 2005	63	22	—	—	—	—	14	11	5	0
Gu 2008	37	—	—	—	—	—	—	—	3	0
He 2016	21	—	76	5	86	14	—	0	0	0
Knudson 2009	24	—	—	32	—	49	—	—	0	0
Ko 2014	36	27	—	—	90	34	—	5	5	0
Otto 2010	17	—	52	18	100	38	—	—	—	0
Snoeren 2015	28	27	40	—	95	—	32	—	—	0
Vietti-Violi 2018	52	—	—	—	—	—	21	25	—	0
Wang 2018	60	20	—	—	—	—	10	—	—	—
Yang 2017	46	44	46	18	96	43	—	—	—	—
MICROWAVE ABLATION										
Franzese 2018	61	24	—	—	—	—	24	—	0	0
Seki 1999	15	—	—	—	—	—	—	7	0	0
Shady 2014	26	8	—	—	—	—	8	7	13	0
Shibata 2000	14	—	—	—	71	—	—	14	0	0
Song 2017	28	55	95	38	88	52	—	7	0	0
Yang 2017	71	39	80	39	80	58	1	11	—	0

AE, adverse events; *DFS*, disease-free survival; *LTP*, local tumor progression; *n*, number of subjects; *OS*, overall survival; *SAE*, severe adverse events.
Data from Di Martino M, Rompianesi G, Mora-Guzmán I, et al. Systematic review and meta-analysis of local ablative therapies for resectable colorectal liver metastases. *Eur J Surg Oncol.* 2020;46(5):772–781.

delivers 2 to 3 kV pulses that each last only 70 to 100 microseconds. These voltages create pores in cell membranes in the surrounding tissue. This damage is irreversible and results in tumor cell apoptosis. Compared with thermal ablation techniques, IRE efficacy is not adversely impacted by the heat sink effect, and there is minimal destruction of the extracellular matrix in surrounding tissue. Bile ducts and blood vessels maintain their integrity because of the extracellular matrix. This makes IRE a suitable option for metastases situated in close proximity to large blood vessels or bile ducts.

IRE is a relatively newer technique, approved by the US Food and Drug Administration (FDA) in 2006, and it has not yet been widely adopted. The equipment is more expensive than RFA and MWA systems, and there is a learning curve with positioning the ablation probes effectively. The probes cannot be repositioned in the middle of an ablative treatment. IRE also requires general anesthesia with paralysis because the high voltages can cause arrhythmias and muscle spasms. To reduce the risk of arrhythmias, the IRE electrical generator is connected to an ECG sensor and IRE pulsations are administered in the cardiac refractory period.

A majority of studies to date are small in size and often include patients with multiple different liver malignancies (CLM, HCC, cholangiocarcinoma). The first report of IRE results in patients with CLM was published in 2014. A total of 11 patients with 22 lesions less than 5 cm were treated. From this group, 55% of lesions were completely ablated and there was local tumor recurrence in 6 of the 11 patients by 9 months. Often the patients included in these studies were poor candidates for other ablative techniques due to tumor location. In a larger, mixed patient series of 58 patients with 75 lesions, there was a 6- and 12-month local DFS of 87% and 70%, respectively.

Across the limited number of studies, IRE has been reported to have a complication rate of 10% to 16%. The most common complications were portal vein thrombosis, cholangitis, and pleural effusion. The rate of arrhythmia is approximately 5%.

Laser Thermal Ablation

LTA is a percutaneous technique that uses light energy delivered via flexible quartz optical fibers that are inserted directly into tumors to deliver high-energy laser radiation. The most commonly used lasers are diode (wavelength 800–980 nm) and neodymium:yttrium aluminum garnet (1064 nm), both within the infrared spectrum, which

achieves optimal light penetration. This method relies on coagulative necrosis, and the light energy can generate temperatures of up to 150°C, creating a thermal injury zone of approximately 12 to 15 mm in diameter. Up to four optical fibers can be utilized at one time to increase the ablation zone. LTA is most effective in lesions less than 4 cm in size.

In one of the largest series of this technique, Vogl et al. described 594 patients with CLM ≤5 cm who were treated with LTA. The 3- and 5-year survival rates were 28% to 74.2% and 10% to 37%, respectively, which is comparable to RFA and MWA. LTA use is limited and is primarily utilized in Europe. The equipment is expensive, and placement of the fibers is difficult in the inexperienced hand. LTA is not as extensively studied as the other ablation modalities, and there has been no evidence of its superiority to RFA or MWA.

PATIENT SELECTION

Patients with CLM should undergo evaluation for all sites of metastases. Necessary imaging includes a CT scan of the chest, abdomen, and pelvis, and in some situations positron emission tomography (PET) CT. Contrast-enhanced MRI is the most sensitive tool to evaluate CLM.

Surgical resection of CLM remains the standard of care when feasible. However, ablative therapies offer a treatment option to patients who are either not surgical candidates or have unresectable disease. Given the number of treatment options available, all patients should be evaluated by a multidisciplinary care team with specialists including but not limited to surgeons, medical oncologists, radiation oncologists, pathologists, and interventional radiologists. Before choosing ablation as a treatment regimen, each patient should be reviewed for the possibility of surgical resection before or after chemotherapy, or combined resection and ablation.

Tumor Characteristics

Larger tumors (>5 cm) are associated with an unacceptably high risk of recurrence when treated with ablation due to incomplete tumor destruction. In select patients with larger tumors, surgical resection of larger tumors may be combined with ablation of smaller tumors to offer the best chance at long-term DFS. For example, a patient with a large metastasis in the left lobe and two smaller metastases located deep in the right lobe may benefit from left hepatectomy combined with ablation of the two right lobe lesions. Although RFA is the most commonly used ablation modality, MWA should be considered when the tumor is larger than 3 cm or in close proximity to a large blood vessel. For lesions adjacent to major vessels or central bile ducts, IRE may be appropriate to minimize adjacent vessel or ductal injuries that may lead to strictures.

Use of Systemic Therapies

Despite advances in systemic chemotherapies that have led to response rates as high as 70%, durable complete clinical responses are still rare with systemic chemotherapy alone. It has been postulated that aggressive cytoreduction with ablation combined with chemotherapy may be more effective than chemotherapy alone. This concept was examined in the Chemotherapy + Local Ablation Versus Chemotherapy (CLOCC) trial, a study in which patients with CLM were randomized to treatment with chemotherapy alone, versus chemotherapy plus RFA. Eligible patients had up to 9 CLM lesions ≤4 cm and were considered unresectable. No difference in 30-month OS rate was observed between the two groups (61.7% for combined treatment vs. 57.6% for chemotherapy alone, $p = 0.22$). However, the 3-year DFS rate for the combined treatment group was higher than that of the chemotherapy-only group (27.6% vs. 10.6%, $p = 0.025$). These results dispel the notion that chemotherapy combined with ablation is a superior approach to chemotherapy alone. However, use of ablation instead of chemotherapy to allow for a "chemotherapy holiday" has merit in selected patients.

PATIENT EVALUATION

Baseline Hepatic Function

Before consideration for ablation, all patients need to undergo a baseline evaluation of hepatic function. Serum liver function tests (LFTs) and carcinoembryonic antigen (CEA) levels should be checked for a pretreatment baseline. LFTs can assess for cholestasis or liver inflammation. Evaluation of pretreatment scans should include assessment for portal hypertension, which places patients at increased risk for complications following ablation. The majority of CLM patients have liver function to support liver tumor ablation.

Extrahepatic Metastases

In accordance with National Comprehensive Cancer Network (NCCN) guidelines, patients with metastatic colon cancer should undergo a CT and PET scan to evaluate for extrahepatic metastatic disease. Patients whose metastases are limited to the liver remain the best candidates for ablation. Patients with extrahepatic metastases should be considered on a case-by-case basis. Those with concurrent pulmonary metastases require evaluation by a thoracic surgeon for possible lung-directed treatment particularly those with minimal lung metastasis, such as a small solitary lesion. Patients with peritoneal or bulky nodal metastases are not suitable candidates for ablation of liver metastases because it will not lead to benefit.

CHOOSING A TREATMENT MODALITY

Tumor-Specific Considerations

In choosing which ablative treatment modality to utilize, the size, number, and location of the CLM should be considered. An ideal lesion for ablation is a small tumor, deep in the parenchyma, not abutting any major blood vessels that is not amenable to resection. Preferred lesions for ablation include those less than 4 cm in size. As tumor size increases, so does the chance of local recurrence after ablation. Location of the metastases is important to assess. Close proximity to large blood vessels renders MWA a better choice than RFA. Close proximity to a major bile duct is a relative contraindication for both RFA and MWA. When deciding on an operative technique, whether open, laparoscopic, or percutaneous, proximity of the lesion to surrounding organs must be taken into consideration as well as the potential for combination with surgical resection.

Treatment Approach

There are two principal approaches to CLM ablation: percutaneous or operative (open or laparoscopic) (Fig. 4). Percutaneous ablation is the least invasive approach and is associated with lower morbidity rates and cost than operative ablation. It can be performed under US, CT, or MRI guidance. Patients generally require conscious sedation for this procedure. This is an ideal approach when aiming to avoid the morbidity of an operation and for patients who may require repeat applications.

For lesions not accessible percutaneously, feasibility of accessing the tumor location by either laparoscopic or open approach should be considered. Open and laparoscopic techniques allow



FIG. 4 **(A)** Patient set up for a CT-guided percutaneous MWA of a hepatocellular carcinoma in an Interventional Radiology suite. **(B)** Laparoscopic MWA of a hepatic tumor under the guidance of intraoperative ultrasound. *(Photo courtesy Dr. R. Santambrogio, HPB and Digestive Surgery, San Paolo Hospital, University of Milan, Italy.)*

for the opportunity for visual inspection of the abdomen, which improves staging. Up to 10% to 20% of patients are found to have radiographically occult extrahepatic metastases, which are a relative contraindication to ablation. And use of intraoperative US can identify additional liver metastases not appreciated on CT or MRI. Additionally, a surgical approach (open or laparoscopic) is ideal for patients who may also require laparotomy or laparoscopy for combined resections with ablations. The most frequent types of combination operations are hepatectomy combined with liver tumor ablation, and colectomy for removal of the primary colorectal malignancy combined with liver tumor ablation. Once all the lesions are identified and mapped out, the placement of the ablation probes must be planned carefully to avoid major vessels and bile ducts. Surrounding organs should be retracted out of harm's way when necessary. Cholecystectomy should be performed if the gallbladder is at risk of thermal injury. The probes should always be placed under US guidance into the lesion. If multiple overlapping ablation zones are required, the probe should be placed at the sonographically "deepest" portion of the lesion first. Temporary hepatic blood flow occlusion maneuvers, such as the Pringle maneuver or hepatic artery occlusion, can minimize the "heat sink" effect during ablation and increase the size of the ablation zones. Use of an operative approach has been reported to have an ablation site recurrence rate of approximately 3% compared with 8% for the percutaneous approach. Operative ablation techniques are associated with a higher morbidity than percutaneous ablation.

Technical Considerations

Ablation via the laparoscopic approach can often be achieved with two ports: an umbilical port (for the laparoscope) and a second port for the laparoscopic US probe. The ablation probe can be placed percutaneously and does not require an additional port. The first step in performing operative ablation of CLM is a thorough evaluation of the abdominal cavity to exclude extrahepatic metastases (peritoneal surfaces, diaphragm, etc.). Intraoperative liver US should then be performed to evaluate the location of the tumor(s), identify any additional tumors not seen on preoperative imaging, and assess the relationship of tumors to major vascular and biliary structures. Under intraoperative US guidance, the ablation electrode is then placed into the target lesion, and the array deployed within. A tourniquet may be placed around the porta hepatis for inflow occlusion.

Thermal ablation is then initiated, and specifically for RFA, monitoring is performed to maintain a maximum parenchymal temperature of about 100°C to 110°C to minimize charring. Monitoring is performed via different approaches depending on the manufacturer; Rita Medical uses temperature control via sensor electrodes embedded in the tips of the tines, whereas Boston Scientific uses impedance control where the ablation power is slowly ramped up until the tissue impedance reaches a preset threshold. Once the temperature or impedance level is reached, the energy source is turned off to allow tissue vaporization to settle, after which energy is reapplied at a lower level or terminated completely.

Clinical Follow-up of Ablated Tumors

Following CLM ablation, LFTs should be monitored as they may acutely rise after ablation but should progressively return to baseline. CEA should also be followed every 3 months as a rise in CEA is concerning for disease recurrence. Postablation imaging by CT or MRI is performed to evaluate the efficacy of the procedure. In contrast to HCC, CLM are hypovascular, which makes it challenging to differentiate residual tumor from areas of necrosis. An optimal strategy is to compare pre- and postprocedural images with particular attention to the size, shape, and location of the necrosis zone. Ideally, a 5- to 10-mm margin of ablation should be achieved circumferentially. The International Working Group on Image-Guided Tumor Ablation recommends a baseline study (CT or MRI) to be performed within 1 week and no greater than 4 weeks postablation. This helps to expediently identify any residual disease as a result of incomplete ablation. Subsequent surveillance imaging may then be performed every 3 to 4 months (Fig. 5). PET scans have been demonstrated to be sensitive for detection of recurrence in patients who are at least 3-months postablation after inflammation has subsided. NCCN guidelines recommend follow-up imaging every 3 to 6 months for the first 2 years after ablation, which may then be performed annually thereafter.

SUMMARY

For patients with unresectable CLM or who are not candidates for surgical resection, liver ablation modalities provide an option to improve both DFS and OS. Ablation also offers the potential for a cure in some patients with limited, small CLM lesions. Additionally, it can be used as an adjunct along with resection in the treatment of select patients with bilobar disease. Additional research is needed within this field, particularly comparative clinical trials, to truly improve patient selection for these techniques and to better delineate outcomes between different modality types. Ablation technology continues to improve and hopefully will be able to offer more patients a chance for improved outcomes.

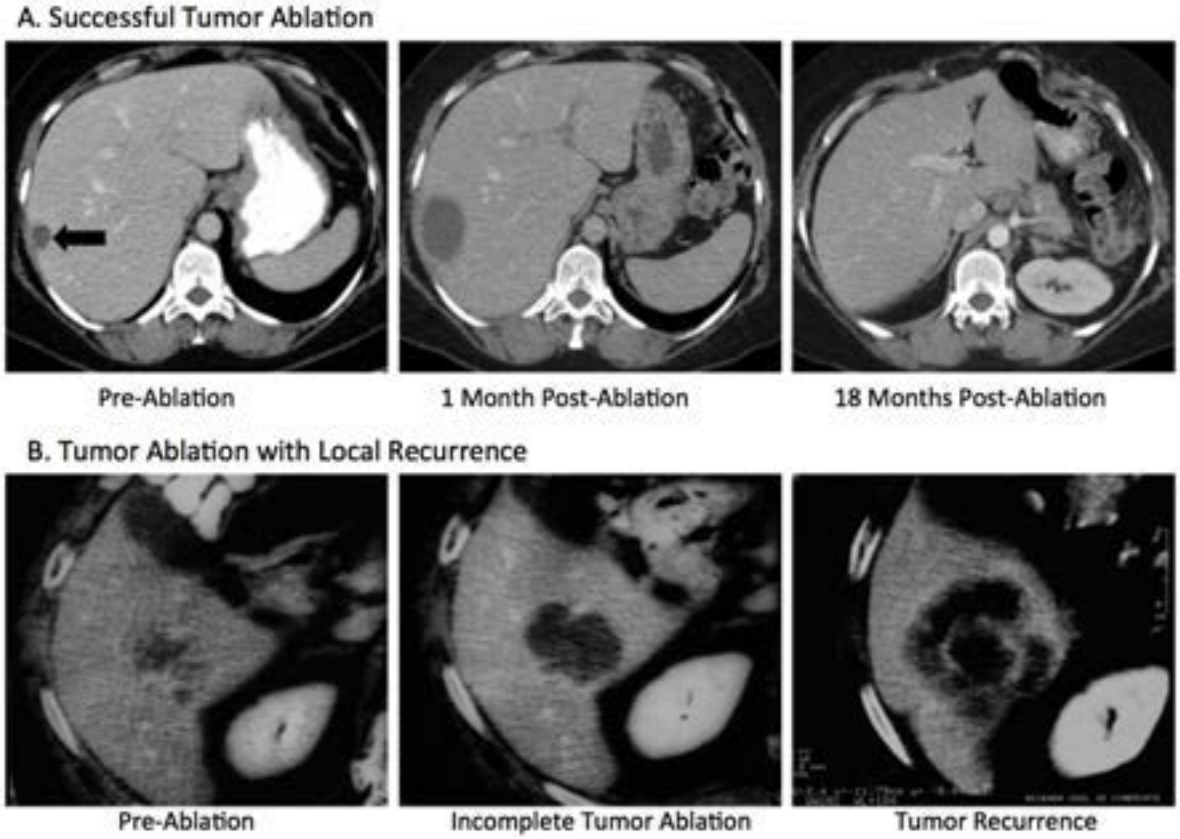


FIG. 5 **(A)** Successful RFA of a colorectal carcinoma liver metastasis, with CT imaging demonstrating the lesion in segment VI preablation, necrosis zone from ablation at 1 month, followed by radiographic resolution at 18 months postablation. **(B)** Incomplete ablation of colorectal carcinoma liver metastases, with CT imaging showing the lesion preablation, postablation imaging demonstrating the irregularity in the contour of ablation affected by adjacent vessels, and postoperative CT revealing local ablation-site recurrence resulting from incomplete ablation.

Suggested Readings

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Management of Hepatic Abscess

Daniel L. Eisenson, MD, and Jonathan B. Greer, MD

Hepatic abscess, with an incidence of 3 cases per 100,000 people in the United States, is a rare but life-threatening disease. In the first half of the twentieth century, liver abscesses were most often seen in the setting of untreated appendicitis, when ruptured viscera led to ascending septic thrombophlebitis of the portal venous system, and these abscesses were associated with an up to 80% mortality rate. Although the etiologies and management strategies have changed considerably over the past 100 years, liver abscesses continue to be lethal. Indeed, despite improved outcomes with better diagnostic tools, antibiotics, and the advent of percutaneous drainage, mortality rates remain between 4% and 10%.

Liver abscesses may be divided into three major categories according to their causative organisms: pyogenic (bacterial) liver abscess, amebic liver abscess, or fungal liver abscess. Of these categories, pyogenic liver abscesses (PLAs) are most commonly seen in the United States, while amebic liver abscesses (ALAs), caused by the parasite *Entamoeba histolytica* and relatively common in tropical low- and middle-income countries, are typically only seen in the United

States after travel to an endemic area. Fungal abscesses are associated with immunosuppression and carry the highest risk of mortality.

Treatment varies by category, but the general principles of therapy include antibiotics, percutaneous drainage (except in cases of ALA), and rarely open drainage or liver resection in cases that fail to respond to minimally invasive treatment.

PYOGENIC LIVER ABSCESS

The epidemiology of PLAs has evolved over the past several decades. Although ascending portal venous infection originating from appendicitis or diverticulitis remains an important cause of PLAs, enteric sources of infection are more promptly diagnosed and more effectively treated than they were in the first half of the twentieth century and are less likely to progress to pylephlebitis. Instead, changes in diet and exercise have led to an epidemic of obesity and associated biliary disease: biliary obstruction with subsequent infection has become the most frequent cause of PLAs.

Pathophysiology

As discussed earlier, PLAs may have several different sources, including (1) biliary obstruction from cholelithiasis, malignancy, or intrahepatic cholangiopathy in the setting of liver transplant with subsequent infection, (2) portal vein pyemia from ascending enteric infection, (3) blunt or penetrating trauma, (4) hematogenous seeding from systemic circulation via the hepatic artery, and (5) unknown, or "cryptogenic."

The microbes implicated reflect the various sources of infection. PLAs of biliary origin are frequently associated with *Escherichia coli, Klebsiella* spp., and *Enterococcus,* whereas PLAs of enteric origin are associated with *Bacteroides fragilis* and other anaerobes. Most infections are polymicrobial. Of note, while gram-negative organisms appear to be the most common causative pathogens in Europe and Asia, two large population-based studies of PLAs in the United States identified *Streptococcus* spp. as the most common isolated pathogens.

PLAs occurring in the absence of biliary disease, enteric infection, or trauma, termed *cryptogenic* PLAs, are frequently associated with *Klebsiella pneumoniae* infection. In contrast with the polymicrobial composition of PLAs originating from biliary and enteric sources, cryptogenic PLAs are more often monomicrobial. Recent studies have suggested that there may be an association between cryptogenic PLAs and colon cancer. Based on these studies, some advocate colonoscopy following diagnosis of cryptogenic PLA to rule out occult malignancy.

Risk factors for the development of PLAs include age, diabetes, biliary malignancy or instrumentation, immunosuppression, and history of liver transplant. In addition, a case control study of over 1300 patients from Taiwan found proton pump inhibitor use as an independent and potentially modifiable risk factor for PLAs. Although the mechanism is unknown, loss of gastric acid may allow overgrowth of bacteria in the stomach and duodenum, which may subsequently colonize the biliary tree.

Diagnosis

Most patients present with fever (90%) and abdominal pain (60%), but vague and nonspecific symptoms including malaise and weight loss are also common. Physical examination may reveal jaundice or right upper quadrant pain, although neither of these findings is specific for liver abscess. Laboratory evaluation may demonstrate leukocytosis (90%), elevation in alkaline phosphatase (80%), as well as hyperbilirubinemia (50%) and transaminitis (50%).

Imaging is critical for diagnosis of PLA. Computed tomography (CT) with intravenous contrast is most sensitive and can provide additional information about underlying etiology (Fig. 1). PLAs will appear hypoattenuated and may have loculations and peripheral rim enhancement (uncommon though specific for liver abscess). Ultrasound is less sensitive but is the preferred initial diagnostic test in pediatrics (Fig. 2).

Treatment

Antibiotics

Given the broad range of possible microbes, blood cultures (positive in over one-half of PLAs) and abscess cultures are essential to guide antibiotic therapy. Until culture results are available, empiric antibiotic therapy should cover streptococci, gram-negative bacilli, and anaerobes, and it should consider the possible source. Piperacillin/tazobactam monotherapy or ceftriaxone plus metronidazole are reasonable empiric regimens, but in patients with history of biliary instrumentation or

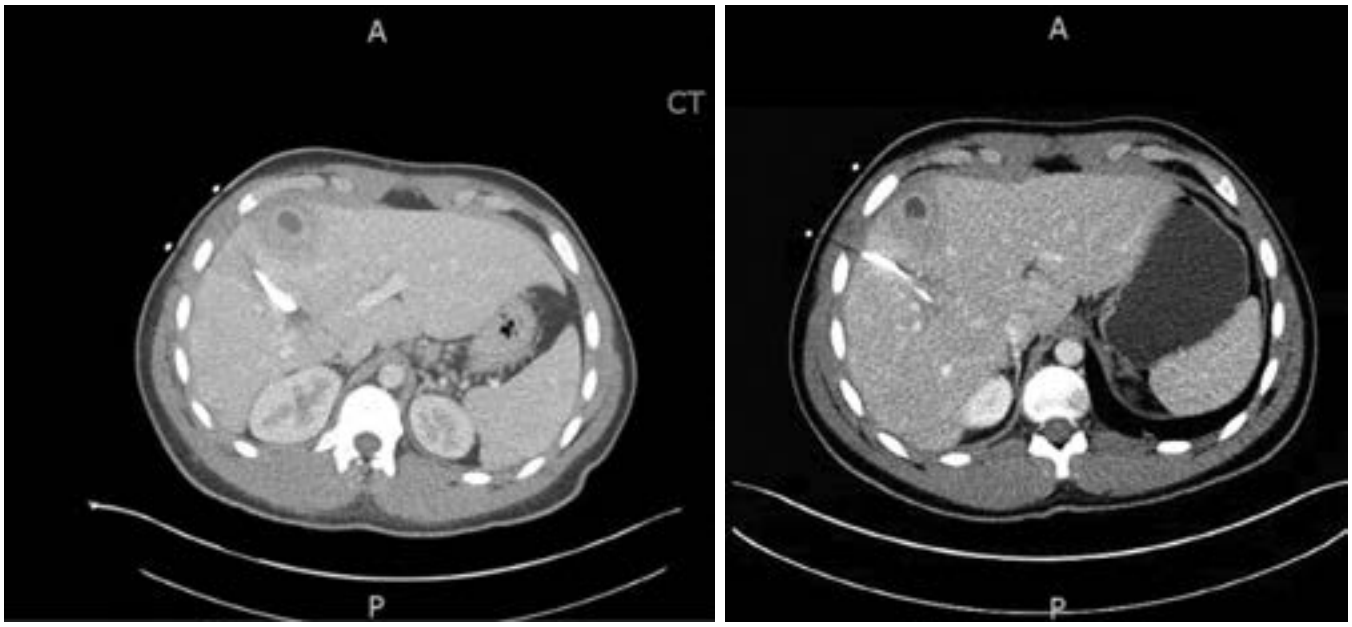


FIG. 1 CT images show liver abscess with rim enhancement.

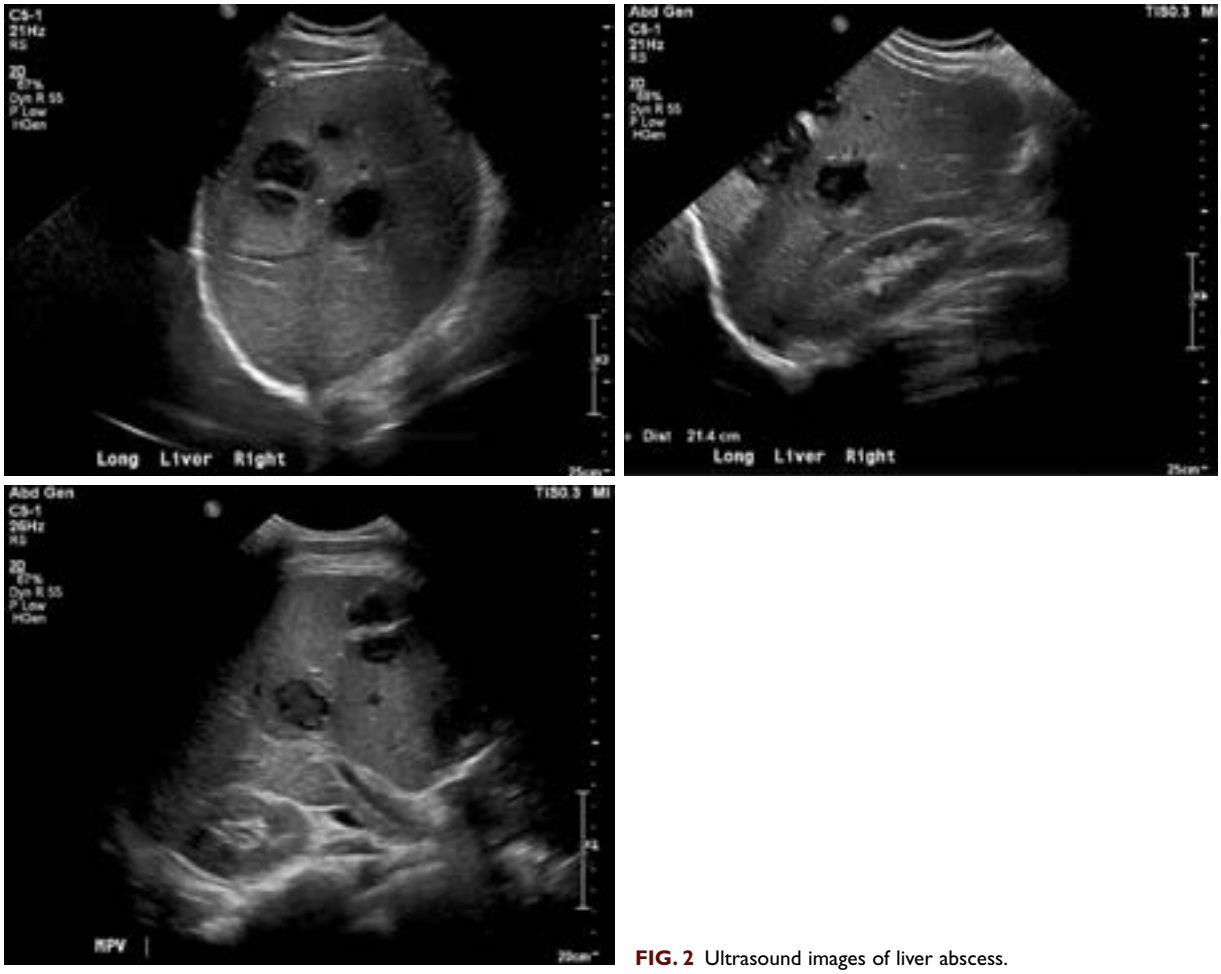


FIG. 2 Ultrasound images of liver abscess.

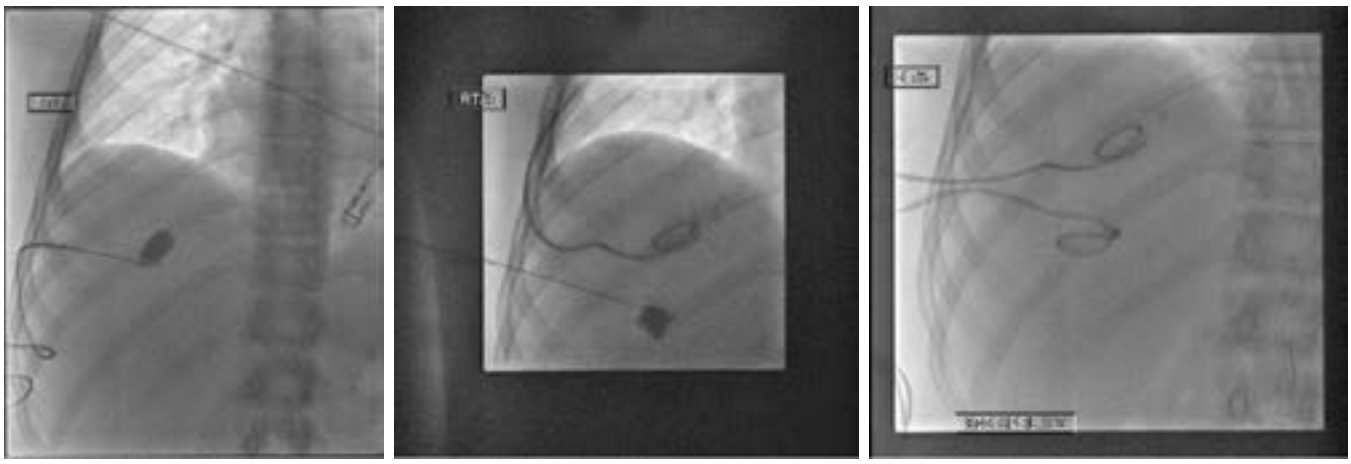


FIG. 3 Radiographic images show drain in place.

liver transplantation, providers may consider carbapenems for empiric extended-spectrum beta-lactamase (ESBL) coverage. The duration of antibiotic treatment should be determined by clinical response and resolution of abscess on follow-up imaging at 4 to 6 weeks.

Percutaneous Drainage

Drainage is the standard of care for PLAs, and most are managed with minimally invasive percutaneous catheter drainage. Catheter placement is recommended for any abscess >5 cm, as studies have demonstrated superior outcomes when compared with needle aspiration alone. Percutaneous catheter drainage can also be safely employed to manage very large abscesses >10 cm (though sometimes multiple catheters are needed) and is therefore recommended as first-line management of all PLAs (without evidence of abscess rupture or concurrent intraabdominal abscess) given lower morbidity as compared with surgical drainage (Fig. 3). In cases in which the abscess is <3 cm

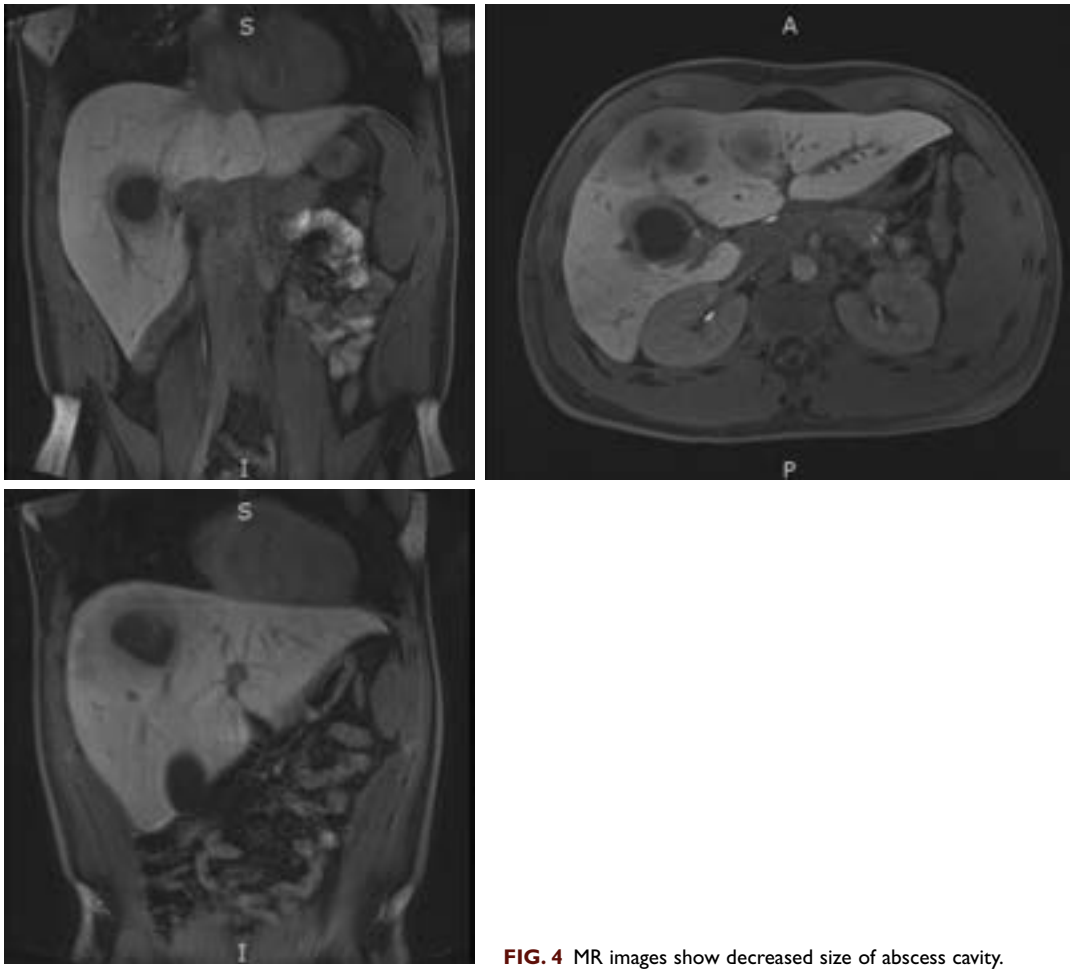


FIG. 4 MR images show decreased size of abscess cavity.

and too small for catheter placement, aspiration should be attempted (if technically feasible) to help guide antibiotic treatment (Fig. 4).

Drainage catheters should remain in place until output is low and clear for several days. As drainage clears, providers should watch for bile in the drains, which may indicate abscess communication with the biliary tree. Suspicion for biliary tree communication should be investigated with hepatobiliary iminodiacetic acid (HIDA) or magnetic resonance cholangiopancreatography (MRCP)/endoscopic retrograde cholangiopancreatography (ERCP). Abscess communication with a large bile duct may mandate additional drainage procedures such as sphincterotomy or percutaneous biliary drain placement.

Surgical Drainage or Resection

Antibiotics plus percutaneous drainage is an effective treatment strategy for 80% to 90% of patients; however, in the rare cases that fail a percutaneous treatment strategy—more often large, multiloculated abscesses or abscesses that communicate with the biliary tree—surgery may be required. In general, minimally invasive surgery is preferred, although the recommended approach depends on abscess location and etiology, as some situations, such as PLA with simultaneous diverticulitis and intraabdominal abscesses, may be best served by laparotomy.

Although some studies advocate partial hepatectomy of a diseased segment as the optimal definitive treatment strategy for large and multiloculated abscesses that fail percutaneous drainage, there is no evidence that this method is superior to standard surgical drainage with irrigation and drain placement. Moreover, manipulation of diseased liver during resection may result in acute septic shock.

Outcomes

Outcomes have improved dramatically with expedited diagnosis, antibiotics, and percutaneous catheter drainage. However, mortality remains high, between 4% and 10%. Retrospective studies have found that diabetes mellitus, underlying malignancy, and cirrhosis are associated with increased length of stay and increased mortality. Studies have also shown that abscess size is an independent risk factor for prolonged hospitalization and mortality. This may be a function of higher bacterial load, more severe inflammatory syndrome, and increased extrahepatic manifestations. In one series, more than one-half of patients with abscesses >10 cm had an ipsilateral pleural effusion and an increased risk of liver abscess rupture with subsequent purulent peritonitis.

AMEBIC LIVER ABSCESS

ALAs, caused by the protozoan *E. histolytica*, are a common source of hepatic abscess worldwide and should be considered in the differential diagnosis among patients with suspected PLA. However, most cases of ALA in the United States are seen in male patients (8:1 male-to-female predominance) with a history of travel to an endemic area.

Pathophysiology

ALA arises from colonic amebiasis, where ingestion of mature protozoan cysts or trophozoites through fecally contaminated food or water leads to colitis with trophozoite invasion of intestinal mucosa. In patients with ALA, trophozoites seed the liver through the portal

system. This process typically occurs 2 to 4 months after symptoms of colonic amebiasis. Abscesses contain necrotic hepatocytes and trophozoites in a thick, proteinaceous, brown fluid, classically described as "anchovy paste."

Diagnosis

As with PLA, patients with ALA present with fever (80%) and right upper quadrant pain (60%). They often have leukocytosis and elevations in alkaline phosphatase, bilirubin, and transaminases. Although *E. histolytica* is a protozoan parasite, eosinophilia is not commonly seen. ALA cannot be reliably differentiated from PLA on imaging.

Given the similarity of presentation between PLA and ALA, providers must be sure to ask about travel history and to ask about history of remote antecedent diarrheal illness. All patients with recent travel to an endemic area should undergo further diagnostic testing with serology.

Amebic serologic testing (antibody or antigen) is highly sensitive and is useful to rule out ALA. Antigen testing is more specific than antibody serology, as one-third of patients with prior *E. histolytica* infection will have antibodies even if they do not have active infection.

Treatment

Antibiotics

Treatment of ALA requires treatment of both the liver abscess and its source: colonic amebiasis. Oral metronidazole (500–750 mg three times daily for 7–10 days) is highly effective treatment for ALA, with clinical improvement in over 90% of patients. However, an additional antiparasite regimen is required to eliminate intestinal cysts and prevent recurrence, typically oral paromomycin (10 mg/kg three times daily for 7 days) or oral diiodohydroxyquin (650 mg three times daily for 20 days).

Whereas treatment duration for PLAs is guided by resolution of abscess on imaging, ALA treatment duration is standardized as appropriate antibiotic regimens will lead to quick clinical recovery in most patients. Repeat imaging is still recommended, but abscess resolution may take several months and is not necessary for antibiotic cessation.

Drainage

Another critical difference in management of ALAs as compared with PLAs is that aspiration/drainage is only recommended when there is no clinical response to antibiotic therapy alone. This is not because there is increased risk with manipulation of ALA (routine percutaneous aspiration of hydatid cysts caused by *Echinococcus granulosus* is discouraged given the risk of anaphylaxis), but simply because prospective studies have failed to demonstrate any benefit to early drainage.

In cases that fail to respond to standard ALA therapy, clinicians should broaden antibiotics to include coverage for PLA, as bacterial secondary infections are not uncommon, and they should pursue percutaneous catheter drainage.

FUNGAL HEPATIC ABSCESS

Invasive fungal infections involving the liver are almost exclusively seen in immunocompromised patients. Those at highest risk include patients who have undergone orthotopic liver transplantation (OLT) or hematopoietic stem cell transplantation (HSCT), patients with human immunodeficiency virus (HIV), and patients with hepatobiliary malignancy. As with PLAs, there are multiple possible sources of infection. Patients undergoing OLT may develop hepatic artery thrombosis, which can lead to intrahepatic cholangiopathy that predisposes them to the development of fungal abscess; patients undergoing HSCT may experience breakdown of the intestinal mucosal barrier with translocation of candida from the gut into the portal system; and patients with hepatic tumors who have undergone ablation may be left with a fertile necrotic lesion that becomes superinfected with fungi.

These abscesses are associated with the highest risk of death, with retrospective studies demonstrating that almost one-half of patients with fungal hepatic abscesses succumb to disseminated infection. Even with appropriate antifungal treatment, mortality remains around 20%.

Treatment

Prompt recognition of mycotic infection is critical, and clinicians must maintain a high index of suspicion for fungal infection in at-risk patients. In transplantation, the risk of developing invasive fungal infections is mitigated by routine antifungal prophylaxis, and mortality in transplant patients with fungal hepatic abscess has improved with early empiric antifungal coverage.

Fungal liver abscesses are managed according to the same treatment paradigm as PLAs: antimicrobials and percutaneous drainage. As with PLAs, antifungal treatment should be guided by culture data, and duration of treatment should be determined by resolution of lesions on repeat imaging. Most fungal liver abscesses are caused by *Candida* spp., and either amphotericin B or an echinocandin such as caspofungin or micafungin would be appropriate empiric therapy.

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Transarterial Therapies for Primary and Metastatic Liver Tumors

Nariman Nezami, MD, and Clifford R. Weiss, MD

INTRODUCTION

Image-guided locoregional therapies play an important role in the treatment of patients with primary or metastatic hepatic tumors. Today, various intraarterial therapeutic modalities (Fig. 1) are available, ranging from bland embolization (BE), transarterial chemoembolization (TACE), drug-eluting beads chemoembolization (DEB-TACE), to selective internal radioembolization therapy (SIRT), or even hepatic artery infusion (HAI). The rationale behind intraarterial therapies is to reduce systemic toxicity while offering more effective local tumor control. Extensive evidence has supported the benefit of image-guided locoregional therapies, which eventually resulted in the addition of some of procedures to the National Comprehensive Cancer Network treatment guidelines. This chapter reviews how intraarterial therapies (IATs) could be incorporated into a multidisciplinary approach, with the goal of treating cholangiocarcinoma and metastatic liver tumors to downstage for resection, as a bridge to transplantation, or to provide palliation.

TRANSARTERIAL THERAPIES

The normal liver parenchyma has a dual blood supply; mainly, it is supplied by the portal vein (70%–75%), which delivers deoxygenated blood from the small intestine and contains nutrients, while 25%

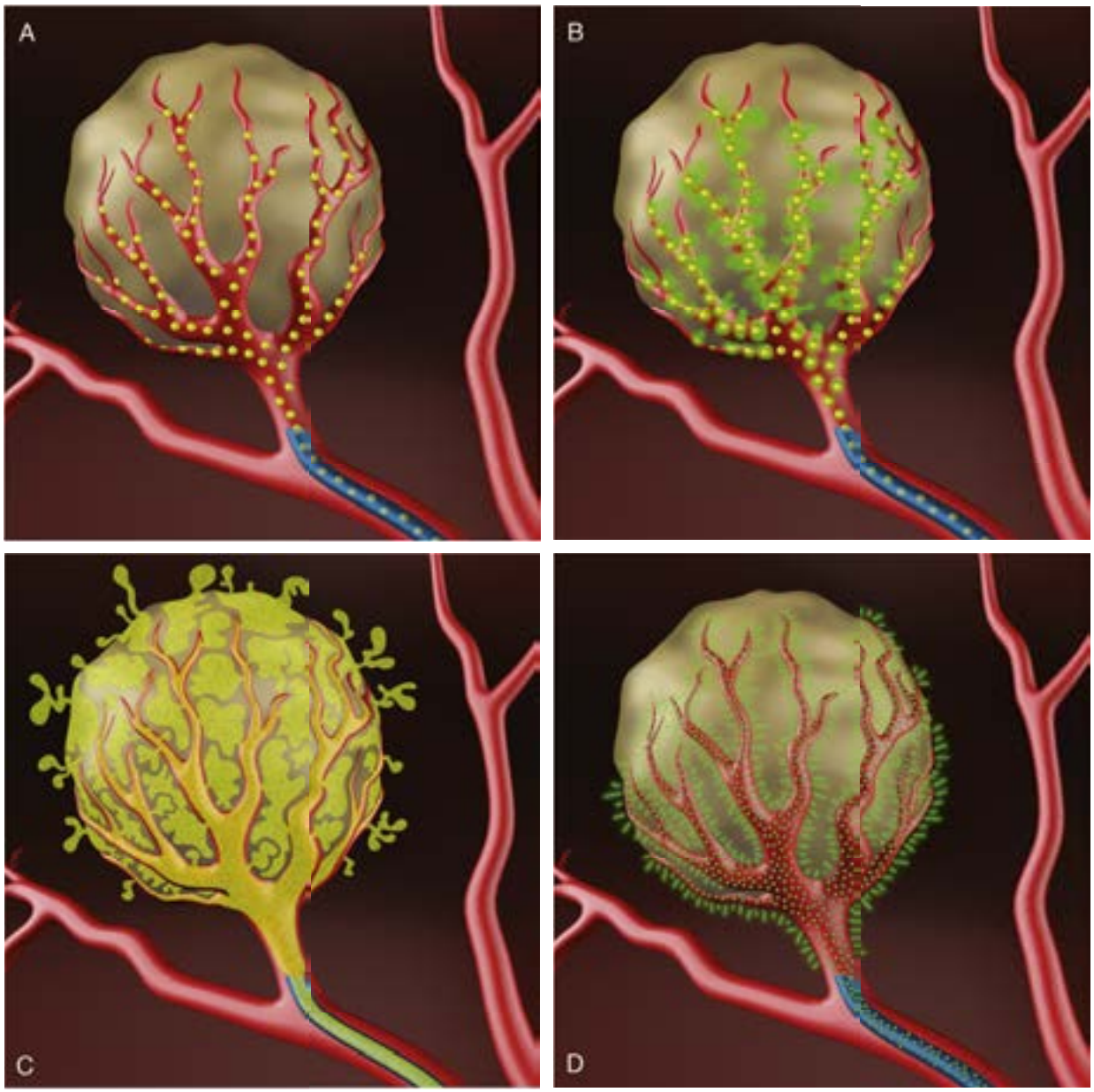


FIG. 1 Transarterial embolization approaches. **(A)** BE. **(B)** cTACE. **(C)** DEB-TACE. **(D)** SIRT.

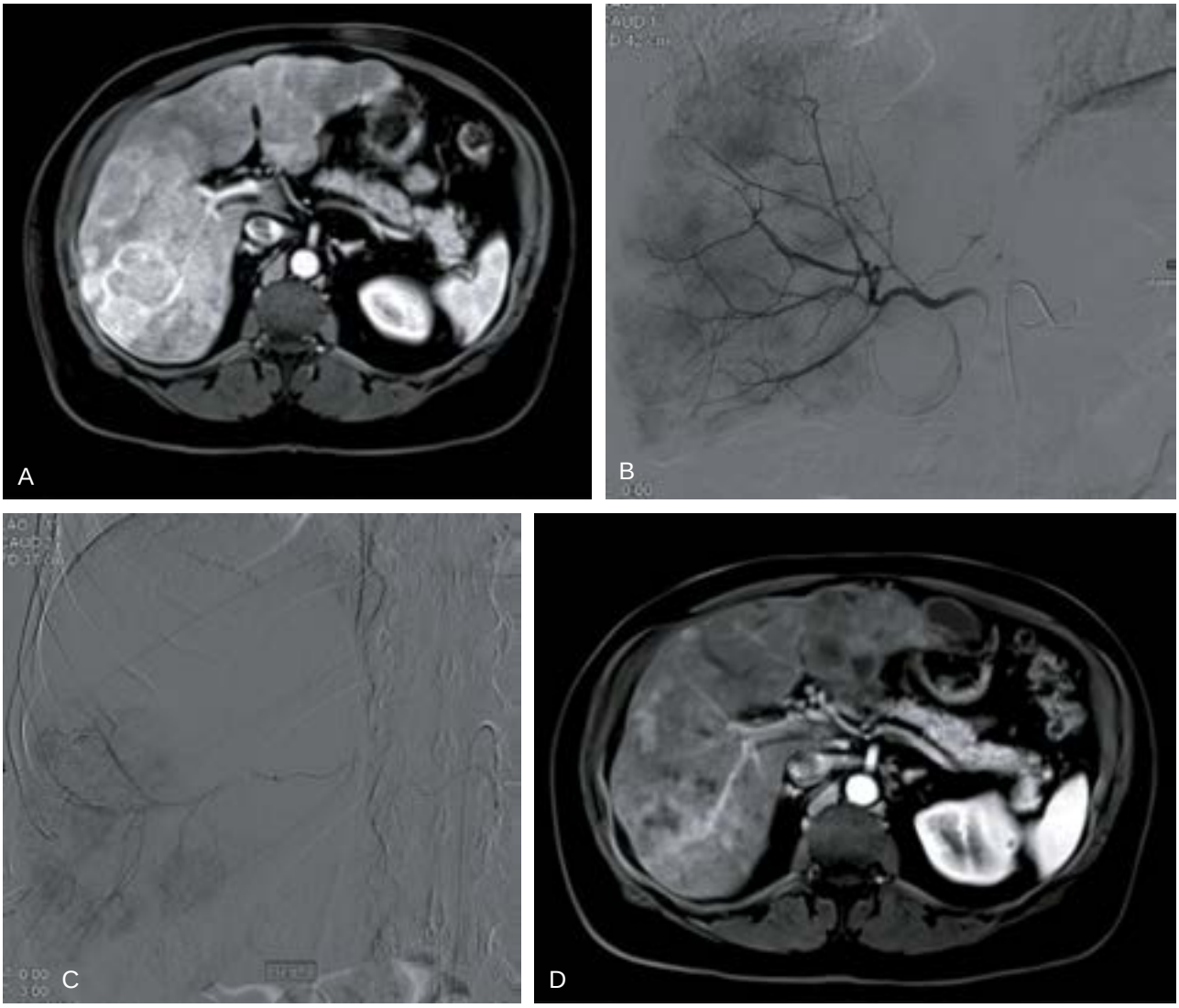


FIG. 2 Bland embolization in a patient with numerous NET liver metastases. **(A)** Axial arterial enhanced MRI shows multifocal metastatic lesions in both hepatic lobes, with the major burden in the right hepatic lobe. **(B)** Digital subtraction angiogram also reveals multifocal tumor blush in the right hepatic lobe. **(C)** Digital subtraction angiogram shows selective angiogram and bland embolization of segment VI. **(D)** Axial arterial-enhanced MRI after 4 weeks demonstrates multifocal tumor necrosis and partial response. *(Courtesy Dr. Aran Chary, Emory University School of Medicine.)*

to 30% is supplied by the hepatic artery, which delivers oxygenated blood from the general circulation. The efficacy of TACE relies on the fact that primary and secondary liver neoplasms are exclusively fed by hepatic artery branches because of tumor-induced neoangiogenesis. Therefore, the intraarterial delivery of a tumoricidal drug will primarily target tumor cells, while sparing the liver parenchyma. Currently, there are four different intraarterial therapeutic options for treating patients using a catheter-based approach. Multiple studies have failed to show whether the efficacy of any of these approaches is superior to the others. Thus, the choice of a transarterial approach is operator/institution-dependent and sometimes depends on the patient's arterial anatomy (multiple blood supply to a tumor or an existing significant shunt).

Bland Embolization

The rationale for the use of BE for *hypervascular* tumors is that the majority of tumors are perfused by the hepatic artery. BE results in antitumor effects solely by blocking blood supply and inducing ischemia and infarction of tumor tissue. During BE, embolic particles are used to achieve complete stasis in the hepatic artery branches that supply the target tumor (Fig. 2). TAE could be nearly as effective as TACE. Therefore, the patient could still benefit from embolization if chemotherapy is contraindicated (e.g., maximum amount of lifetime doxorubicin is reached or the patient is allergic).

Conventional Transarterial Chemoembolization

Conventional transarterial chemoembolization (cTACE) is referred to as Lipiodol-based TACE. This is the originally described conventional TACE method. It involves the transcatheter delivery of a mixture of chemotherapy and lipiodol into the target tumor, followed by particle embolization (Fig. 3). The chemotherapy mixture consists of any combination of cisplatin (100 mg), doxorubicin (50 mg), and mitomycin C (10 mg). This is mixed with lipiodol (Ethiodol) in a 1:1 or a 2:1 (chemotherapy:lipiodol) volume ratio depending on flow characteristics. The aqueous-to-lipid phase ratio affects the emulsion stability and the drug release rate. A 1:1 ratio is more viscous and is used for high-flow states, whereas the 2:1 ratio is less viscous and is used in low-flow states.

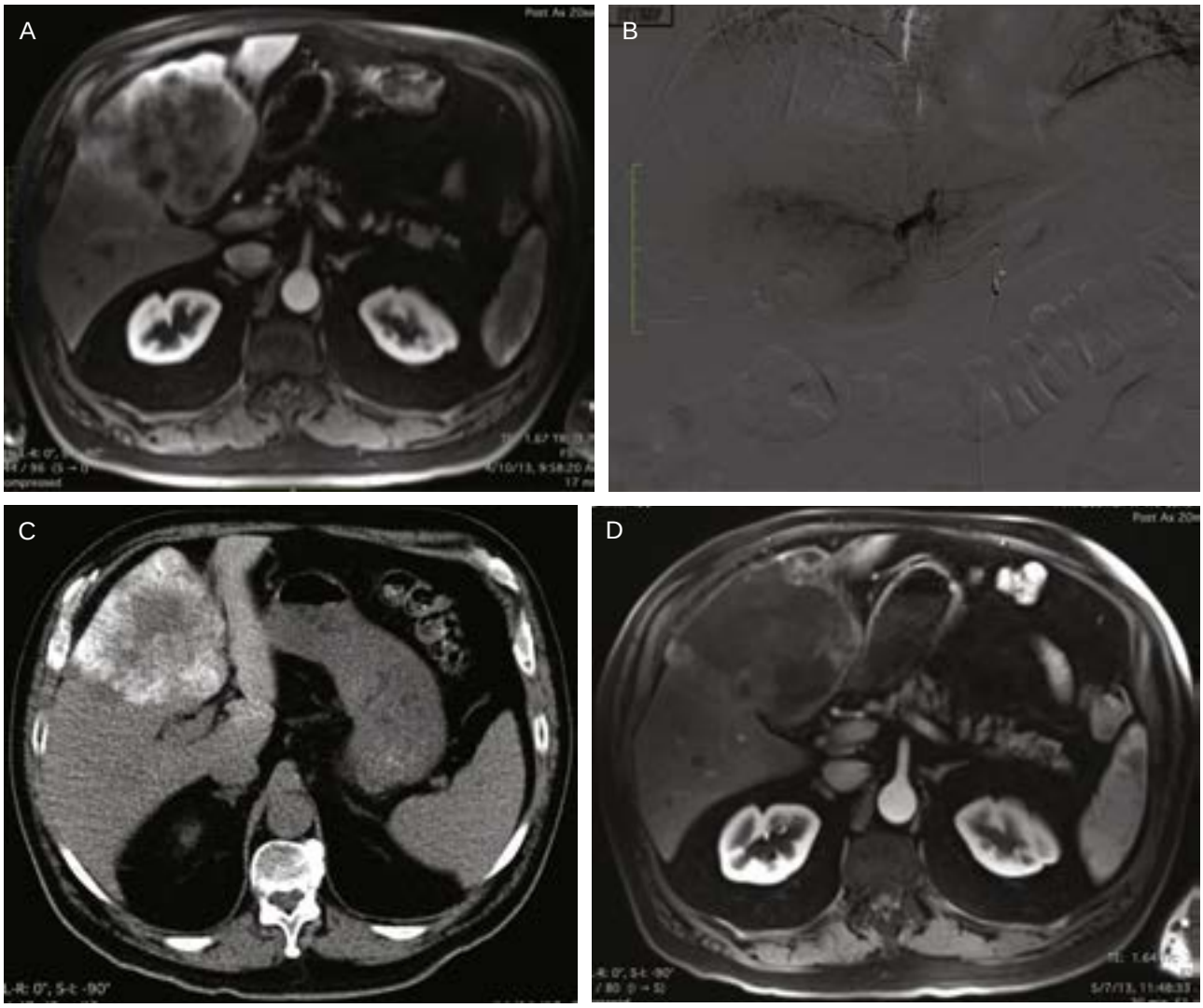


FIG. 3 cTACE in a 70-year-old woman with intrahepatic cholangiocarcinoma. **(A)** Axial arterial enhancement MRI shows a large intrahepatic cholangiocarcinoma in the right hepatic lobe. **(B)** Digital subtraction angiogram reveals tumor blush in the right hepatic lobe and blood supply from the right hepatic artery. **(C)** Immediate postembolization axial noncontrast CT shows dense lipiodol deposition within the tumor. **(D)** Axial arterial enhancement MRI after 4 weeks shows extensive tumor necrosis.

Drug-Eluting Beads Transarterial Chemoembolization

One of the latest developments is the introduction of spongelike particles that can be preloaded with chemotherapeutics. These particles are used to embolize the target tumor similar to conventional TACE without the addition of lipiodol. Over a period of time, these particles elute chemotherapy drugs, maintaining a high intratumoral dose and a low plasma concentration. DEBs allow only one chemotherapy drug to be loaded, which is most commonly doxorubicin or, recently, irinotecan.

Selective Internal Radiation Therapy

SIRT is the intravascular administration of microspheres that contain a radioisotope, which allows delivery of a higher dose of radiation directly to the tumor than traditional radiation with an external beam, while exposing healthy liver tissue to only a small dose. SIRT has been proven to be safe and effective, and is recommended for patients with unresectable tumors who are refractory to systemic therapy and have liver-only or liver-dominant disease. The injected microspheres embolize the microvasculature surrounding the tumor and emit high-energy beta-radiation. The normal liver parenchyma is largely spared since healthy liver tissue is mainly supplied by the portal vein.

Microspheres (~30 μm) are loaded with radioactive isotopes, such as yttrium-90 (^{90}Y) or holmium-166 (^{166}Ho), and delivered through a microcatheter in the hepatic artery. ^{90}Y-resin microspheres (SIR-Spheres, Sirtex) are Food and Drug Administration (FDA)-approved and CE-marked for treatment of metastatic colorectal cancer. ^{90}Y -glass microspheres (TheraSphere, BTG/Boston Scientific) and ^{166}Ho microspheres (QuiremSpheres, Quirem) are CE-approved for this indication but are not FDA-approved. ^{166}Ho microspheres are the most recently developed agents that emit high-energy β particles while also producing γ radiation, which allows for quantitative, single-photon emission computed tomography (SPECT) imaging. Interestingly, ^{166}Ho microspheres are paramagnetic, enabling monitoring with magnetic resonance imaging (MRI).

Two approaches have been described for SIRT: lobar or sublobar (Fig. 4) versus segmentectomy (Fig. 5). A lobar or sublobar approach

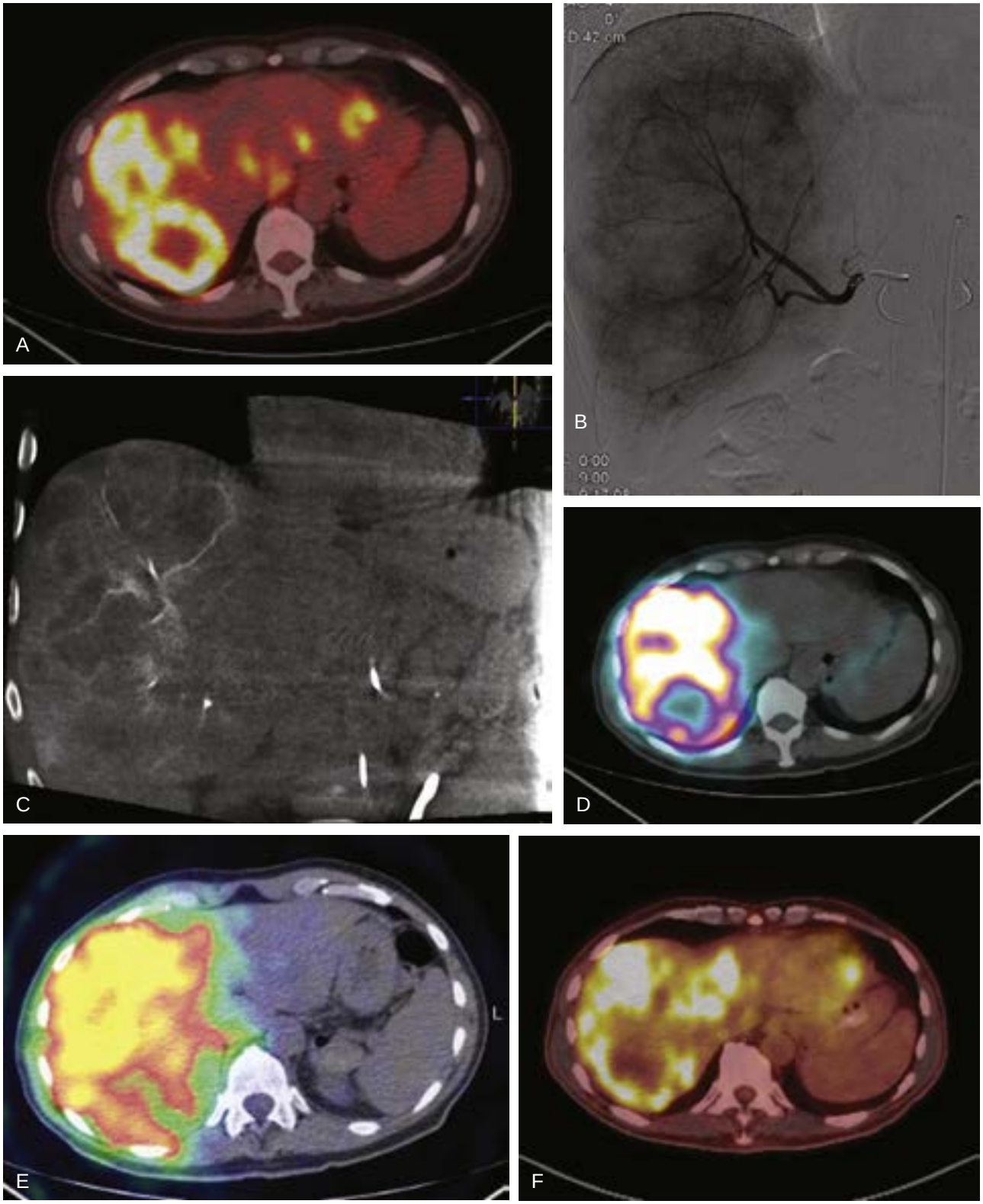


FIG. 4 Lobar SIRT in 65-year-old man with colorectal liver metastases. **(A)** Axial PET CT scan shows extensive FDG avidity in the right hepatic lobe. **(B)** Digital subtraction angiogram reveals tumor blush in the right hepatic lobe and blood supply from the right hepatic artery. **(C)** Intraprocedural cone-beam CT scan confirms corresponding perfusion. **(D)** Nuclear medicine SPECT CT immediately post-MAA mapping/shunt study shows MAA deposition within the tumor region. **(E)**. Nuclear medicine SPECT CT demonstrates dense resin-based ^{90}Y retention within the right hepatic lobe. **(F)** Axial PET CT scan shows partial response in the right hepatic lobe tumor. *(Courtesy Dr. Aran Chary, Emory University School of Medicine.)*

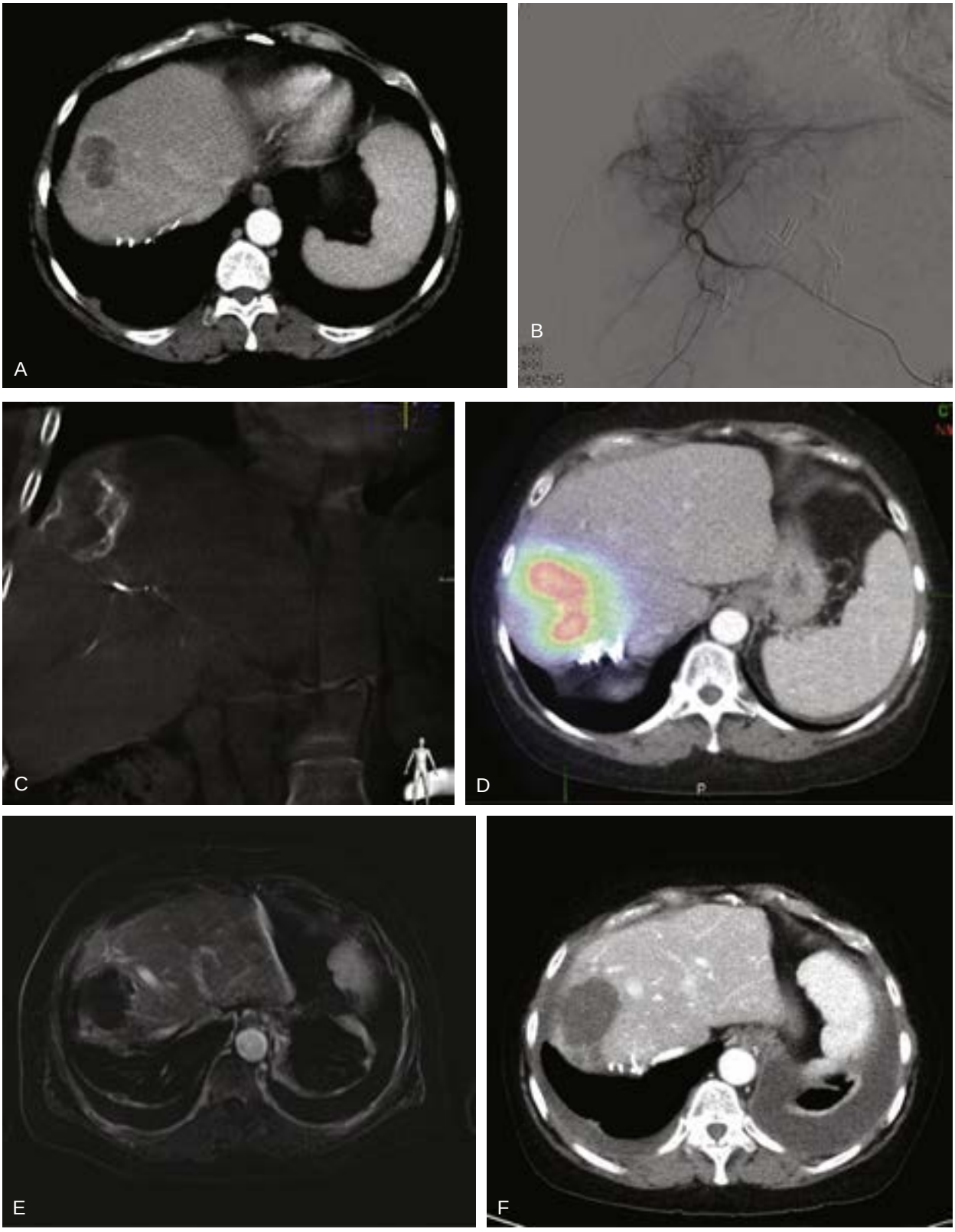


FIG. 5 SIRT, segmentectomy in a 58-year-old woman with a surgical history of colectomy, cholecystectomy, right hepatectomy, on multiple lines of chemotherapy and SIRT with a single colorectal liver metastasis. **(A)** Axial arterial enhanced CT scan shows a single metastasis in the right hepatic lobe. **(B)** Digital subtraction angiogram reveals tumor blush with corresponding blood supply from segment VII of the hepatic artery. **(C)** Intraprocedural cone-beam CT confirms the corresponding perfusion from segment VII of the right hepatic artery branch. **(D)** Nuclear medicine SPECT CT demonstrates dense glass-based ^{90}Y retention within the tumor. Immediate post-SIRT SPECT CT shows dense ^{90}Y glass deposition within the tumor. **(E)** Follow-up axial arterial enhanced MRI after 6 weeks shows extensive necrosis and complete response of the metastatic lesion in segment VII. **(F)** Follow-up axial arterial enhanced CT scan shows no change in the complete response of the metastatic lesion in segment VII. *(Courtesy Dr. Aran Chary, Emory University School of Medicine.)*

is chosen when there is multifocal disease, while segmentectomy is offered to those patients with a solitary tumor ≤5 cm and liver-only disease when the tumor can be isolated angiographically.

Hepatic Artery Infusion

HAI chemotherapy is administered in the proper hepatic artery by a surgically implanted pump, a hepatic arterial port, or through a percutaneously placed catheter connected to an external pump (Fig. 6). Certain drugs with a high first-pass extraction can be delivered into the arterial circulation with the goal of increased local concentration of the agent, which increases the therapeutic response with decreased systemic exposure and toxicity.

Indications and Patient Selection

1. Colon cancer
   a. If surgery or ablation is not an option and there are no systemic options
   b. To maintain tumor size if planned surgery is significantly delayed
2. Intrahepatic cholangiocarcinoma (ICC)
   a. If systemic chemotherapy fails or in conjunction with systemic chemotherapy
   b. To target a portion of the tumor along a precarious resection margin, thus aiding surgery
3. Neuroendocrine cancer
   a. If symptomatic
   b. There are clinically significant laboratory abnormalities, such as hypoglycemia from metastatic insulinoma, or hyperglycemia from metastatic glucagonoma
   c. Rapid growth
   d. High Ki-67 index
4. Other (pancreatic, breast, melanoma)
   a. TACE for such neoplasms is less well studied and should be tailored to each individual patient
5. Developing indications
   Three novel indications are:
   a. The use of preimmunotherapy TACE to bolster immune response
   b. Preoperative TACE to address micrometastasis or microvascular components
   c. Combined with ablation/systematic therapies for improved outcome

Contraindications to Transarterial Chemoembolization

Major Contraindications

1. ECOG 3
2. Decompensated or borderline liver function
3. Severely reduced portal vein blood flow (acute and chronic portal vein tumor thrombosis)
4. Extensive tumor involving the entirety of both liver lobes
5. Untreatable arteriovenous fistula
6. Renal insufficiency, including creatinine ≥2 mg/dL or creatinine clearance <30 mL/min
7. Total bilirubin >4 or rapidly rising total bilirubin
8. Active bacterial infection

Relative Contraindications

1. Severe comorbidities (acute cardiovascular or lung disease)
   a. Bilioenteric anastomosis or biliary stents, bile duct occlusion
2. Life expectancy <6 months

Contraindications to SIRT Application (FDA Recommendation):

1. Prior liver irradiation
2. Coexistence of ascites and/or liver failure
3. The presence of liver dysfunction
4. The presence of metastases to organs other than the liver
5. A Capecitabine treatment in the last two months before the surgery
6. Portal vein thrombosis
7. Pregnancy
8. Abnormal test results: WBC <2.5 thousand, Neu <1.5 thousand, PLT <60 thousand, AST/ALT >5 × normal, bilirubin >2 mg/dL, albumin < 3 g/dL, creatinine >2.5 mg/dL
9. Irregularities in the anatomical structure of the venous system in the liver

Patient Preparation

1. Preprocedural fasting for 6 to 8 hours in preparation for conscious sedation or general anesthesia
2. Premedication:
   a. Dexamethasone (20 mg intravenously), which reduces the extent of postembolization syndrome
   b. Proton pump inhibitors, which reduce the risk of gastritis/duodenitis and mitigate the significance of nontarget embolization
   c. Hydration, which reduces fatigue, nausea
   d. Antibiotics. Prophylaxis administration is necessary if the integrity of the biliary system has been compromised by prior biliary intubation or post-Whipple. The recommended regimen is moxifloxacin 400 mg by mouth daily beginning 3 days before and continuing for 7 days postembolization.
   e. Somatostatin analogs. For neuroendocrine tumors (NETs) with a carcinoid origin. These patients are at risk of developing a carcinoid crisis during or immediately after intervention. The ideal scheme and dosing of octreotide to prevent the development of a carcinoid crisis have not been clearly established and are mostly operator-dependent.

Techniques: Angiogram and Embolization Technique

1. Vascular access. Transarterial embolization can be performed either via common femoral arterial (CFA) or radial arterial (TRA) access. In both approaches, a 5-6 Fr vascular sheath is used. If the radial approach is chosen, a Barbeau's test is first performed to minimize the risk of hand ischemia. Upon TRA access, a cocktail of heparin and one or more vasodilators (nitroglycerin, verapamil, or nicardipine) is administered. Administration of this cocktail is not necessary for CFA access.
2. Diagnostic arteriograms. An angiogram is performed to:
   a. Delineate the vascular anatomy related to the tumor and assess the best treatment delivery route.
   b. Map any nontarget and collateral vessels at risk for inadvertent chemoembolization and plan an approach to minimize the risk. A superior mesenteric arteriogram is performed first. This excludes replaced/collateral vascular anatomy to the liver and shows whether the portal vein is patent or not. Then, a celiac arteriogram is performed. This shows the target (hepatic artery branches) and nontarget arteries (i.e., left and right gastric artery, supraduodenal artery, cystic artery, and umbilical artery).
3. Treatment.
   a. TACE. Once the target arteries are chosen, a microcatheter is used to obtain super-selective access. The ideal location for the tip of the catheter is one in which an infusion from that point would cover the entire tumor and, at the same time, spare as much of the normal liver parenchyma as possible. Once the catheter is in the optimum position, the treatment mixture is delivered. Whether cTACE or DEB-TACE, this is done under continuous fluoroscopic observation. As the cocktail is administered, target arterioles embolize and flow dynamics may change. cTACE is continued until stasis is achieved and the peribiliary venous plexus is seen, while DEB-TACE is stopped once substasis (slow blood flow) is noticed on the angiogram. Overaggressive embolization may result in antegrade reflux around the catheter and inadvertently reach

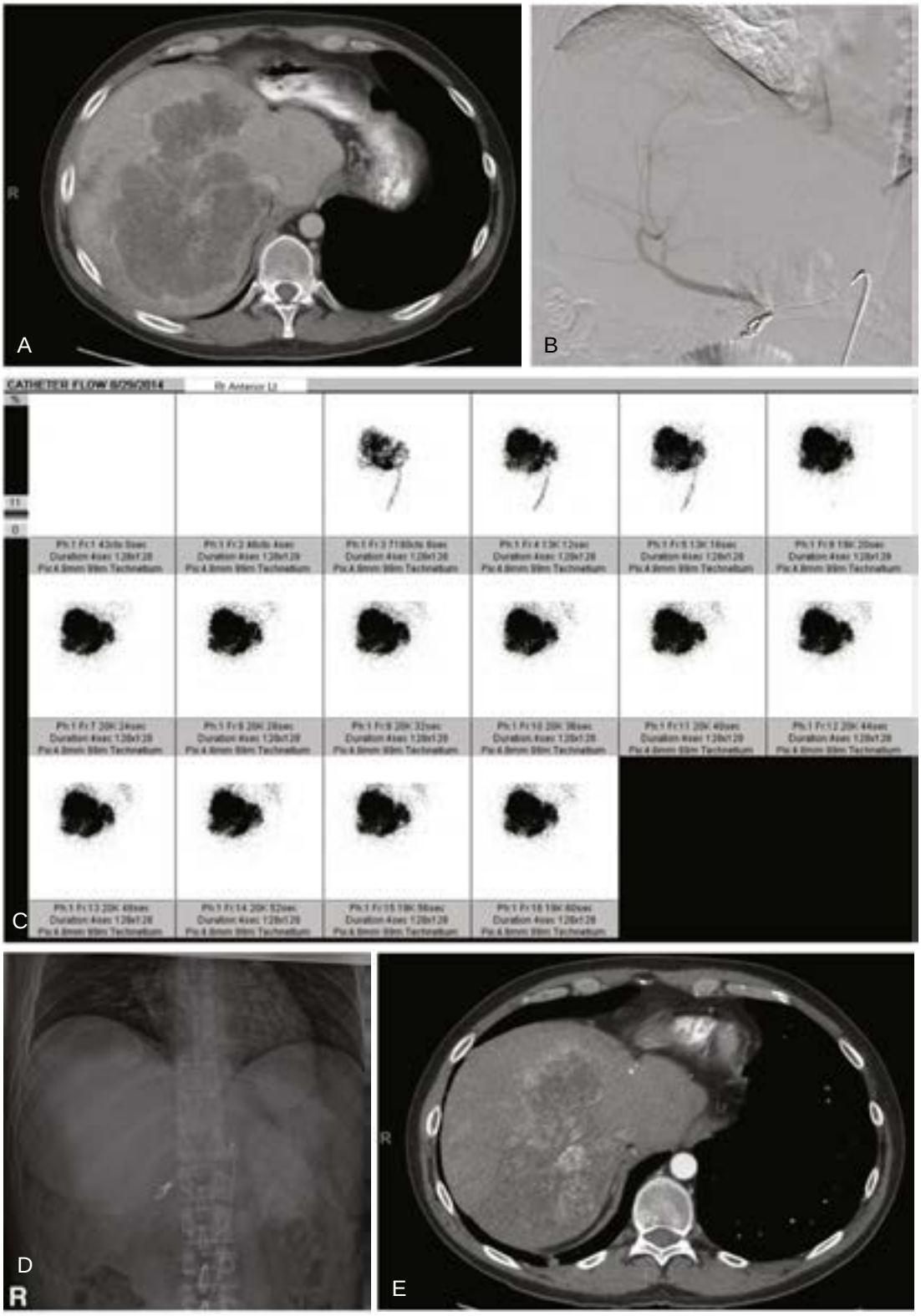


FIG. 6 Irinotecan hepatic artery infusion for 2 days in a 34-year-old man with CRC liver metastasis. **(A)** Axial arterial enhancement CT shows a large metastasis in the right hepatic lobe. **(B)** Angiogram demonstrates the right hepatic lobe blood supply from the right hepatic artery. The gastroduodenal artery is coiled to protect against nontarget embolization. **(C)** The NM study was performed using Tc99m MAA to exclude extrahepatic nontarget chemotherapy infusion. **(D)** A KUB image shows the stability of the infusion catheters during the infusion period. **(E)** Follow-up axial arterial enhancement CT shows the lesion has significantly decreased in size. *(Courtesy Drs. Rony Avritscher, Kamran Ahrar, and Ravi Murthy from MD Anderson Cancer Center.)*

nontarget organs. The organs most commonly at risk are the duodenum, stomach, and pancreas as a result of the proximity of their arterial supply to the hepatic artery. The technical objective is to deliver the entire treatment mixture into the target tumor and reach blood flow stasis within the artery that supplies it. Additional particle use may be necessary to achieve stasis. If multiple tumors are targeted, it is best to target each individual tumor as selectively as possible, as opposed to treating an entire lobe. Although more time-consuming and technically challenging, selective embolization carries a lesser risk of liver injury and results in a better response.

If lipiodol is used in the TACE mixture, intraprocedural cone-beam CT or noncontrast computed tomography can be obtained after the procedure to assess the extent of lipiodol deposition (Fig. 3C), which reflects the treated area.

Note that, in general, only one lobe (right or left) can be treated at any one time because TACE results in transient liver enzymes elevation, with the treated liver recovering by approximately 2 weeks. During the recovery period, adequate remaining liver function must be ensured. In cases in which multiple subselective TACEs can be performed without affecting a significant portion of the normal liver parenchyma, bilateral disease can be treated in one session.

b. SIRT. Patients undergo a diagnostic angiogram, as described earlier, followed by technetium-99m macroaggregated albumin (Tc-99m MAA) shunt study approximately 2 weeks before SIRT (Fig. 4C). Approximately 4 mCi of Tc-99 m MAA is administered, either into the common hepatic artery or into right and left hepatic arteries in a split-dose fashion depending on the distribution of the tumor. The selection of the proper supply artery to the targeted tumors from a specific microcatheter position is ascertained with cone-beam CT if segmentectomy is pursued. After the injection of Tc-99m MAA and termination of the angiogram, the patient is transferred to the nuclear medicine department for SPECT/CT to assess any possible shunt (specifically lung shunt) and to ensure the proper deposition of Tc-99m MAA in the targeted area. The dose of ^{90}Y to be administered is calculated using different models depending on the disease, microparticle of choice, and the operator's preference, such as the Partition model, the MIRD model, or the body BSA model. On the day of treatment, ^{90}Y is administered from the same position where Tc-99m MAA was injected for the shunt study. If patient requires bilobar treatment, the hepatic lobe with the larger disease burden is treated first, then the remaining lobe is treated 4 to 6 weeks following the initial treatment. ^{90}Y SPECT/CT is obtained immediately following SIRT for each patient (Fig. 4D and Fig. 5D). Liver volume, tumor volume, and the corresponding radioactive counts are then calculated manually and using the software-generated dose-volume histograms.

c. HAI. The Seldinger technique is used percutaneously to reach the hepatic artery and place infusion catheters. The left subclavian and femoral artery represent the most frequent peripheral accesses, although the hypogastric, subclavian, and brachial arteries have all been used as well. The common femoral arterial access is technically easier as the vessel is superficial and less tortuous. There are several techniques used for the placement of the tip of the catheter, such as the "fixed-catheter-tip" technique, where the distal tip of the catheter has been fixed to the gastroduodenal artery, whereas the injected drug flows into the proper hepatic artery through a side hole, or the "long tapered catheter placement" technique, in which the catheter is positioned, but not fixed, as distally as possible into the common hepatic artery with the side hole placed at the origin of the proper hepatic artery.

4. End of procedure. Once the technical objective is reached, the catheters and sheath are removed, and depending on the access site, TRA, or CFA, hemostasis is secured. The latter can be achieved by either a 15-minute manual compression or by the use of a vascular closure device. The use of any closure devices for CFA access obviates the need for manual pressure and allows the patient to ambulate after 2 hours rather than 4 hours. However, the patient could ambulate right away after the procedure if TRA access was used.
5. Patient recovery. Patient recovery is centered around symptom prevention and control, and requires approximately 24 hours. Postprocedural hydration, as-needed antiemetics and stool softener, and pain control are the mainstay of recovery. In patients with severe abdominal pain, a patient-controlled analgesia pump is very beneficial. Postchemoembolization syndrome is the most common set of symptoms, reported in at least in 60% of patients, and includes fatigue, fever, and abdominal pain. These symptoms gradually subside over approximately 2 weeks. Other symptoms that could be encountered include nausea, anorexia, and more rarely, alopecia (4%) and night sweats. The volume of embolization and the degree of tumor necrosis have been correlated with the severity of symptoms.

POSTPROCEDURE FOLLOW-UP

Regardless of the transarterial approach method (BE, cTACE, DEB-TACE, or SIRT), the follow-up protocol is usually the same. It includes a repeat multiphasic MRI with intravenous gadolinium-based contrast or a multiphasic CT of the abdomen with intravenous iodine-based contrast, laboratory tests (comprehensive metabolic panel, complete blood count, international normalized ratio, relevant tumor markers), and a clinic visit to reassess the patient's performance status. Follow-up is generally at 1 month and then 3-month intervals, but this must be tailored to each patient and according to treatment goals. The first follow-up cross-sectional images are commonly obtained 1.5 to 2 months after SIRT to differentiate post-SIRT inflammatory changes from residual disease.

There is no limit to the number of TACE treatments a patient can receive. Further treatment should be aborted, however, if any contraindications develop (please refer to the earlier list), if the initial indication is no longer valid, or if, after three cTACE treatments, the targeted lesion fails to respond as expected. Studies have shown that failure of the initial two cTACE treatments does not predict failure of the third treatment; however, if three TACE treatments fail to result in tumor response, additional treatment is unlikely to have any benefit. Also, the number of SIRT sessions is limited by the lung dose of no more than 30 Gy in a single SIRT session or no more than 50 Gy in multiple SIRT sessions.

TOXICITIES AND COMPLICATIONS

Complications related to embolization are summarized in Table 1. A majority of patients (>60%) will have the described postembolization syndrome. It is always self-limiting and only symptomatic care is indicated. The most serious complication is acute liver decompensation resulting from embolization-related acute liver injury. The related risk is small (<1%) and only considered when there is underlying liver disease (cirrhosis, severe steatohepatitis, significant history of systemic chemotherapy). However, unilateral TACE all but eliminates this risk in cases of metastatic disease. Another concern is developing encephalopathy, which is also unlikely since TACE for secondary liver disease is usually performed in patients with intact liver function. A previous history of encephalopathy is the major risk factor for worsening encephalopathy. Both acute liver failure and the risk of encephalopathy can be further mitigated by subselective treatments. Another concern is biliary complications, including stricture and abscess formation. The biliary tree is known to be supplied by the hepatic artery. Therefore, overzealous embolization (especially

TABLE 1 Transarterial-Related Complications

Toxicities	Risk (%)	Mitigating Factors	Comment
Acute liver failure	Rare	Subselective embolization	Higher risk with bilobar treatment or underlying liver parenchymal disease
Liver decompensation	<1	Selective embolization	Increased risk with underlying liver parenchymal disease
Encephalopathy	<1	Selective embolization	Increased risk with concurrent cirrhosis or a prior episode of encephalopathy
Liver abscess	2–4		If intact sphincter of Oddi
	10–20 >60	If pretreated with antibiotics If not pretreated	If compromised sphincter of Oddi, colonized biliary system
Cholangitis	10–15	Symptomatic treatment	Higher risk with smaller drug-eluting beads
Renal failure	<2	Hydration and possibly dialysis in severe cases	Most likely in chronic renal insufficiency
Nontarget embolization	<1	Perform diagnostic arteriogram, cone beam CT, and selective embolization	Variant anatomy increases risk

with DEB) could result in ischemic strictures and hyperbilirubinemia, particularly in patients without underlying liver parenchymal disease or when using smaller beads with BE or DEB-TACE, specifically in NETs. If the sphincter of Oddi has been violated (hepatojejunostomy or biliary stent), there is a very high risk of intrahepatic abscess formation. Bacterial colonization becomes an abscess as a result of embolization-related biliary ischemia in more than 60% of such patients. Pre- (1 week) and post-TACE (2 weeks) treatment with broad-spectrum antibiotics (i.e., moxifloxacin 400 mg, by mouth every day) reduces the risk to less than 10%. Another potentially serious complication is inadvertent embolization of nontarget vessels. This specifically plays an important role in SIRT since nontarget embolization could result in serious adverse reactions, such as pneumonitis, gastritis, or skin necrosis. Performing a detailed diagnostic arteriogram before embolization and a selective embolization nearly eliminates this risk. Aberrant vascular anatomy further increases this risk, with the vessels most at risk being left or right gastric arteries, the supraduodenal artery, and the umbilical artery.

OUTCOMES

Lesion-Based Response

With the introduction of precision medicine, an assessment of early response to transarterial therapies is essential for "go" versus "no go" decisions for these treatments. The standard response criteria requires a critical interrogation, cross-verification, and update. Many new criteria have been developed to address these evolving paradigms. There are 1D, 2D, and 3D methods to measure postintervention response, each subdivided into two more subcategories, based on the ratio of total size to the size of the enhancing component. The Response Evaluation Criteria in Solid Tumors (RECIST) measurements are based on the sum of the longest one-dimensional (1D) diameter, whereas the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria suggest measuring changes in tumor enhancement as a biomarker of tumor viability. The World Health Organization (WHO) introduced an evaluation system for solid liver tumors based on the sum of the product of the two-dimensional (2D) diameters of tumor lesions, whereas the European Association for the Study of the Liver (EASL) has recommended measuring tumor response based on changes in the uptake of contrast medium by the tumor tissue. Yet, all 1D and 2D evaluation methods are flawed, with a limited reproducibility and an essential inaccuracy when assessing the entity of necrotic and heterogenic tumor lesions. These clinically relevant limitations have led to the development of three-dimensional (3D) quantitative image analysis techniques that are able to achieve a reproducible, biologically accurate, and clinically practicable tumor evaluation. Although volumetric analysis (vRECIST) considers the height component of the tumor, assessing the changes in enhancing tumor volume using quantitative EASL (qEASL) goes beyond these boundaries. The PET Response Criteria in Solid Tumors (PERCIST) is another response assessment criteria developed for PET scans.

Imaging Response Criteria

Based on the chosen response criteria (see earlier), the response of the lesion(s) to the transarterial therapy could be categorized based on the operator or study preference, according to Table 2.

Overall Survival, Progression-Free Survival, and Hepatic Progression-Free Survival

Overall survival (OS) has long been considered by the FDA and the European Medicines Agency as the gold standard for the evaluation of new oncologic therapies. Progression-free survival (PFS) is the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease, but the disease does not worsen. In a clinical trial, measuring the PFS is one way to determine

TABLE 2 Definition of Different Terminologies for Image-Based Changes in Tumor After Intervention

Detailed Standard Response	Simplified Response	Control-Based
Complete response Partial response	Response	Controlled disease
Stable disease	Stable disease	
Progressive disease	Progressive disease	Uncontrolled disease

how well a new treatment works. Hepatic progression-free survival (HPFS) is calculated at the time from the first regional treatment until the first date of documented progression in the liver.

CANCER-SPECIFIC OUTCOMES

Intrahepatic Cholangiocarcinoma

ICC is the second most common primary liver malignancy, accounting for up to 20% of primary liver cancers. Up to 70% of these patients are diagnosed at an advanced stage, precluding curative surgical intervention. A recent systematic review and met-analysis by Mosconi et al. showed a median survival of 14.2 months after TACE and 13.5 months after SIRT in patients with unresectable ICC, confirming a beneficial effect when compared with traditional systemic chemotherapy regimens. Another comparative effectiveness analysis by Boehm et al. also revealed survival of 12.4 months for cTACE, 12.3 months for DEB-TACE, and 13.9 months for SIRT without a significant difference between these modalities. A recent Phase II clinical trial on 38 patients with unresectable ICC treated with HAI of floxuridine in combination with systemic gemcitabine and oxaliplatin reached a 58% objective radiographic response and 84% disease control.

Metastatic Colorectal Cancer

Synchronous colorectal cancer (CRC) liver metastases are present at the time of diagnosis in 15% to 20% of patients, and 50% of patients will develop metachronous metastases. In up to 40% of patients, the liver is the sole site of metastasis, but the lesions are resectable in only <20% of patients. A recently published meta-analysis by Zhao et al. showed that transarterial therapies have been underappreciated in the context of liver-dominant metastatic CRC. A study by Vogl et al. in 2009 reported 14.7% of patients with a partial response and 48.2% with stable disease in a cohort of 463 patients with unresectable CRC liver metastases that were refractory to systemic chemotherapy and who were treated with TACE. The 1- and 2-year survival rates after TACE was 62% and 28%, respectively. Meta-analyses by Levy et al. demonstrated the relative advantage of TACE among transarterial therapies, with nonrandomized and randomized studies (median OS DEB-TACE, 17.6 months), and Zacharias et al. demonstrated that TACE appears to be more effective in the second-line setting (median OS, 21.0 months). Both DEB-TACE and HAI, when combined with systemic regimens, appear to provide approximately one in three patients the chance for resection. Compared with HAI, DEB-TACE offers the additional benefit of enhancing cytotoxic effects through ischemia, without the need for port implantation. DEB-TACE loaded with irinotecan in 28 patients with metastatic CRC resulted in 15% with a complete response, 30% with a partial response, and 20% with stable disease, thus achieving a median OS of 13 months. A major network meta-analysis showed that SIRT, using ^{90}Y resin microspheres, is effective compared with the best supportive care in patients with mCRC. A multicenter review of a large cohort of patients with CRC liver metastases who were treated with SIRT ^{90}Y glass microspheres indicates that survival outcomes are not only consistent with, but nearly identical to, previous reports of patients treated with resin microspheres, with a median OS of 10.5 months. This was in accordance with a structured meta-analysis by Vente et al., which showed, in a salvage setting, a response rate of 79% for SIRT combined with 5-fluorouracil/leucovorin (5-FU/LV) and a rate of 79% SIRT combined with 5-FU/LV/oxaliplatin or 5-FU/LV/irinotecan, and, in a first-line setting, both showed a rate of 91%.

Metastatic Neuroendocrine Tumors

NETs are the second most common gastrointestinal malignancy after colon cancer. Up to 90% of patients with NETs develop liver metastases, which are a major determinant of symptoms and survival. Carcinoid and pancreatic islet cells have a predilection to metastasize to the liver, and those patients with liver metastases have a poorer prognosis and quality of life. Surgical resection is curative but is possible only in less than 10% of patients. Progression to hepatic metastases is accompanied by hormonal synthesis and released into the circulation that can lead to a constellation of systems known as *carcinoid syndrome* (rash, flushing, diarrhea, and electrolyte disorders). With this development, treatment of the liver would be for palliation of the carcinoid syndrome symptoms. TACE can be used in patients with unresectable, hormonally active NETs and strongly contributes to the elimination of hormonal symptoms. A report by de Mestier et al. reported a 76% chance of symptom control, a 56% chance of biomarker response, and a 50% chance of objective tumor response. TACE was very well-tolerated, and disease progression was delayed by 12 to 18 months. A prominent meta-analysis of 23 studies reporting response outcomes after SIRT in NETs reported an objective response rate of 51% and a mean disease control rate of 88%. The median OS after SIRT was 32 months. The RETNET trial is an open-label, prospective, multicenter randomized controlled trial designed to determine the optimal embolotherapy technique for NET liver metastases, initially comparing three embolotherapy techniques, BE versus cTACE versus. DEB-TACE. However, the DEB-TACE arm of the trial was closed because it was associated with a high rate of serious hepatobiliary complications.

Metastatic Renal Cell Carcinoma

About 20% of renal cell carcinoma (RCC) patients have metastatic spread at the time of diagnosis, and of patients who have already undergone curative nephrectomy, 20% to 40% develop RCC metastases. The liver is one of the common sites for metastasis, which could result in a dramatic drop in the 5-year survival rate to 20%. A retrospective analysis of 14 patients with metastatic liver RCC who had undergone cTACE (n = 9) and SIRT (n = 5) revealed a median OS of 11.6 months. Another retrospective review by Kis et al. of 18 patients with liver-dominant metastatic RCC showed a complete response in 16 patients and a partial response in one patient, as evaluated according to the mRECIST criteria after SIRT.

Metastatic Breast Cancer

Liver metastases eventually develop in approximately 20% of patients with breast cancer, which carry a poor prognosis. Most of these patients with metastasis are not surgical candidates and have chemoresistant and multiorgan disease. A recent meta-analysis of transarterial therapies by Rivera et al. in patients with liver metastasis from breast cancer reported 7.2% complete responders and 38.1% partial responders in patients who underwent TACE. Median OS from six studies showed a median of 19.6 months, with 1-year survival ranging from 32% to 88.8%. N0 status, stage I or II disease, and Child-Pugh A at the diagnosis of liver metastasis were predictors of improved outcomes. The same meta-analysis reported the cumulative results of nine SIRT studies. In total, there were 2.3% complete responders, 37.6% partial responders, and 36.5% with stable disease after SIRT. The SUVmax response, a lower volume of hepatic parenchyma involvement, chemotherapy after SIRT, the presence of the PI3K mutation, and the radiologic response to treatment were positive predictive factors for improving OS. This meta-analysis also reported 1.2% complete response in the pooled cohort of 158 patients, followed by 30.4% partial response, and 31% stable disease. ECOG status, hormone receptor status, maximum size of liver metastasis, and response to systemic chemotherapy were reported as factors that contributed to OS.

Metastatic Melanoma

For patients with metastatic melanoma, the median OS falls to approximately 6 to 10 months, with only 8% of patients surviving up to 2 years. A recent meta-analysis and systematic review by

Rodriguez-Vidal et al. successfully collected and reported the results for transarterial therapies for melanoma. The average survival of the TACE studies is about 10 months, but this option has never been used as a first-line treatment, which could result in bias when interpreting the results. SIRT could offer a median OS of about 18 months when used as the first-line therapy. When combined with immunotherapies, the OS increased to 26 months in the study by Levey et al. The reported median OS of the HAI studies was approximately 15 months. The multicenter trial of Leyvraz et al., which studied HAI with fotemustine, reached an OS of 14 months. However, the study by Boone et al. barely achieved 3 months of OS with melphalan HAI.

Metastatic Sarcomas

Sarcomas are a heterogeneous group of solid tumors and account for 1% of all cancers in adults. Resection with or without radiation therapy is the mainstay treatment for localized primary or oligometastatic liver disease. However, many intermediate- and high-grade sarcomas are not amenable to surgery. A retrospective analysis showed that liver-directed transcatheter therapies are safe and may have a role in the elective management of unresectable primary and metastatic liver sarcomas.

NEW DEVELOPMENTS AND FUTURE DIRECTIONS

Radiopaque Beads

In recent years, the development and use of imageable beads, rendered radiopaque by the incorporation of a radio-absorber, such as iodine, zinc, tantalum, bismuth, or barium, have provided direct real-time feedback during the embolization procedure or on follow-up imaging.

Various Drug-Loaded Beads

Multiple studies have reported the successful loading of other chemotherapy or cytotoxic agents to drug-eluting beads, such as arsenic, idarubicin, irinotecan, or sorafenib.

Immunoembolization

Immunoembolization is the embolization of the hepatic artery with granulocyte-macrophage colony-stimulating factor (GM-CSF). In theory, immunoembolization could attract and stimulate antigen-presenting cells in liver tumors and improve the uptake of tumor antigens released from necrotic tumor cells. Inflammatory responses that develop in or near the tumor may eliminate residual tumor cells. In addition, local stimulation of the immune system may produce a systemic immune response against tumor cells, which thereby suppresses the growth of extrahepatic metastases.

Nanoparticles

The introduction of novel theranostic nanoparticles into the interventional radiology field can help diagnose disease, report the location, identify the stage of the disease, and provide information about the treatment response. Such nanoparticles can carry therapeutic agents to the tumor, which can provide the necessary concentrations of the carried agents via molecular and/or external stimuli.

Combination with Systemic Therapies

The targeted therapies that have been studied have been mostly MAPK inhibitors, including sunitinib, sorafenib, imatinib, cabozantinib, and selumetinib, in combination with transarterial therapies. Some other studies have looked into combining transarterial therapies with other therapies, such as immunotherapy (ipilimumab, nivolumab, pembrolizumab, or IL-2). All studies have shown positive results with improved outcomes.

Combination with Percutaneous Therapies

Combining embolization techniques with liver ablation may enhance the therapeutic benefit of each and result in improved patient survival. The majority of studies have demonstrated the safety and efficacy of a combined, two-step, single-session transarterial and percutaneous ablation treatment for unresectable hepatic metastases, specifically for lesions >3 cm in diameter.

Preoperative TACE

Preoperative TACE was correlated with an improved prognosis after surgical resection for patients with hepatocellular carcinoma (HCC) beyond the Milan criteria, whereas there was no significant difference in perioperative complications. Among the patients with ICC with microvascular invasion who were undergoing curative-intent partial hepatectomy, postoperative adjuvant TACE improved OS and time to recurrence in those who had an elevated CA19-9, or who did not undergo lymphadenectomy.

SUMMARY

Although there is level I evidence about the efficacy of transarterial therapies for the treatment of unresectable primary liver cancer, including HCC or ICC, a growing body of lower-level evidence confirms the benefit of transarterial therapies in selected patients with metastatic liver disease. A multidisciplinary approach for the selection of appropriate patients and tumors has an important role in optimizing outcomes and the success of transarterial therapies. These approaches could not only help downstage lesions for resection in some diseases, such as CRC, but also could halt liver disease and provide stability when other curative treatment options cannot be offered to patients. Transarterial therapies also play a crucial role in both symptom and hormonal control, along with objective tumor response in metastatic NETs. Finally, the search for new transarterial therapy approaches and planning for level I evidence is mandated, given the complexity and variability of metastatic liver diseases and the continuously emerging novel therapies.

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Portal Hypertension: Role of Shunting Procedures

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INTRODUCTION

Defined as a portal venous pressure gradient greater than 5 to 7 mm Hg, portal hypertension develops when resistance to portal blood flow increases. Although the etiology of portal hypertension is broad, it is classified as *prehepatic, intrahepatic,* or *posthepatic* (Table 1). In instances of prehepatic and posthepatic portal hypertension, mechanical obstruction of the portal or hepatic veins is the causative event. In contrast, underlying liver disease with resultant cirrhosis is the primary cause of intrahepatic portal hypertension. In North America, cirrhosis remains the leading cause of portal hypertension, with noncirrhotic etiologies accounting for approximately 10% of all cases. Worldwide, Budd-Chiari, schistosomiasis, and portal vein thrombosis are more frequent etiologies.

As resistance to portal flow increases, a number of physiologic changes occur. Important among these is splanchnic vasodilation and increased flow through portosystemic venous collaterals. The pathophysiology of portal hypertension results in increased cardiac output and total blood volume with decreased systemic vascular resistance. Subsequent volume expansion occurs with sodium and water retention. As a result of these changes, complications arise and include ascites, hepatorenal syndrome, and the development of portosystemic collaterals or varices. Fifty percent of patients with cirrhosis have gastroesophageal varices, and approximately one-third of these patients will go on to develop variceal hemorrhage. The progression from varices to hemorrhage is directly correlated with hepatic function and mortality. Hemorrhage from portal hypertensive gastropathy and esophageal varices may be life threatening. Mortality from variceal bleeding ranges from 5% to 68% among Child-Turcotte-Pugh class A and C cirrhotic patients, respectively. Surveillance and management of portal hypertension and varices can avoid considerable morbidity and mortality.

The management of patients with portal hypertension involves treating the underlying etiology when it is reversible; reducing pressure within the portal system via medical, interventional radiographic, or surgical means; or removing and replacing the diseased liver. When portal hypertension is caused by cirrhosis, liver transplantation remains the gold standard for both curing the underlying liver dysfunction and the complications of portal hypertension. Although liver transplantation remains a curative therapy, it is not appropriate for all individuals, specifically those with noncirrhotic etiologies of portal hypertension and those who are not suitable transplant candidates. In such instances, or while awaiting transplantation, medical and procedural interventions are available to minimize symptoms related to portal hypertension. In current practice, these therapies consist of β-blockers, diuretics, endoscopic control of esophageal and gastric varices, transjugular intrahepatic portosystemic shunt (TIPS) placement, and surgical shunt placement. Although the TIPS procedure has largely replaced surgical shunt placement, surgical shunts provide a safe and effective tool in select patient populations.

COMPLICATIONS OF PORTAL HYPERTENSION

Portal hypertension is associated with several complications including hepatic encephalopathy, ascites, and the formation of esophageal and gastric varices. Of these complications, the most immediately life-threatening is variceal bleeding.

Varices generally develop as the hepatic venous pressure gradient increases above 12 mm Hg (Table 2). Nearly one-half of cirrhotic patients have esophageal varices, and one-third of patients with varices experience a variceal bleed within the first year following diagnosis. Although variceal hemorrhage may resolve spontaneously in some patients, bleeding events are associated with significant risks including rebleeding, infection, progressive liver decompensation, and death, which may occur in more than 50% of patients with severe liver disease.

To prevent morbidity and mortality associated with variceal bleeding, patients with newly diagnosed cirrhosis or portal hypertension undergo endoscopic screening surveillance at the time of diagnosis and every 6 to 12 months thereafter. Primary prevention of bleeding is a priority. As mentioned, nonspecific β-blockade (propranolol, nadolol) achieving target reduction in heart rate is important and reduces the risk of bleeding, the development of ascites and spontaneous bacterial peritonitis, and the risk of death. Endoscopic variceal banding is useful for patients with medium to large varices. Sclerotherapy is less effective in prevention and associated with complications.

In instances of active variceal bleeding, management in conjunction with resuscitation includes vasoconstrictive agents such as octreotide, somatostatin, or vasopressin plus vasodilator (e.g., nitroglycerin) infusions. Endoscopic band ligation is highly effective, with sclerotherapy useful when visualization is difficult. When endoscopic therapy is either not available or is ineffective, hemorrhage may be temporarily halted by balloon tamponade using the Sengstaken-Blakemore or Minnesota tubes. Complications such as aspiration as well as esophageal and gastric necrosis may occur with incorrect use of these tubes, and placement should be limited to 24 hours.

In the 10% to 20% of cases in which hemorrhage episodes are refractory to medical and pharmacologic intervention, TIPS

placement is highly effective. These are successful in over 90% of cases. Historically, surgical shunts were shown to be very effective. In select cases when TIPS placement is not feasible, such as in patients with noncirrhotic portal hypertension or well-compensated cirrhosis where patients have a limited ability to assume appropriate follow-up care, surgical shunts may still provide the means of reducing portal pressures and the associated risk of future variceal bleeding.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Widely adopted in the late 1980s and 1990s in the treatment of complications related to portal hypertension, the TIPS procedure is accomplished by initially accessing the hepatic veins via the internal jugular vein under fluoroscopic guidance. The portal vein is subsequently accessed, creating a tract through the liver parenchyma across which a stent is placed. This stent effectively creates a side-to-side portocaval shunt. This shunt lowers portal venous pressure and as a result decreases ascites formation, decompresses varices, and reduces the risk of bleeding. TIPS is not without risk. Because of the increased portosystemic shunting that occurs as a result of this procedure, there is an approximate 20% to 30% risk of hepatic encephalopathy. Selection of well-compensated cirrhotic patients and subsequent medical management of encephalopathy with agents including lactulose and rifaximin can minimize the incidence and consequences of this adverse event.

Although historically TIPS procedures were complicated by occlusion requiring repeated intervention, the incidence of shunt dysfunction along with the risk of variceal rebleeding have improved with the introduction of polytetrafluoroethylene (PTFE) stents. In addition to safely managing symptoms in patients awaiting transplantation, TIPS has the added advantage of being removed entirely with the explanted liver at the time of transplantation. This is in contrast with surgically placed shunts, which require ligation or revision during liver transplantation.

Although the timing and application of TIPS remains an area of active investigation in patients with liver failure, its primary indications remain refractory ascites, acute variceal hemorrhage, and prevention of recurrent variceal hemorrhage. Contraindications include unfavorable anatomy resulting from thrombosed hepatic or portal veins, severe liver dysfunction (i.e., a Model for End-Stage Liver Disease [MELD] score >18), severe pulmonary hypertension, congestive heart failure, and preexisting hepatic encephalopathy.

The advantages of TIPS placement are well-documented and include improved secondary prevention of variceal bleeding compared with endoscopic or medical therapies, reduced ascites production, and better optimization of liver function than medical therapy alone, making it a useful tool in symptom control and in bridge to transplant. Although rebleeding is reported to occur in 5% to 15% of patients post-TIPS placement, the majority of such episodes occur in the setting of stent occlusion caused by stenosis or thrombosis. With reported 1- and 3-year patency rates of 93% and 75%, respectively, TIPS placement requires frequent Doppler ultrasound examinations to evaluate patency and determine the need for subsequent intervention. As many as 80% of patients may require at least one postprocedure intervention to ensure adequate shunt patency and function. Because of this requirement for postprocedure care, TIPS placement may not be the best choice in patients with difficulty accessing medical care. Surgically created shunts can provide more favorable outcomes given the need for fewer postoperative interventions, with similar outcomes in terms of ascites management and in the prevention of variceal rebleeding.

TABLE 1 Causes of Portal Hypertension by Location

Location	Etiologies
Prehepatic	Portal vein thrombosis Splenic vein thrombosis Congenital thrombosis of the portal vein Arteriovenous fistula, resulting in excessive inflow
Intrahepatic	***Presinusoidal*** Primary biliary cholangitis (primary biliary cirrhosis) ***Sinusoidal*** Cirrhosis Infiltrative liver diseases Idiopathic portal hypertension Congenital hepatic fibrosis Nodular regenerative hyperplasia Polycystic liver disease ***Postsinusoidal*** Veno-occlusive disease
Posthepatic	Budd-Chiari syndrome Inferior vena cava webs or thrombosis Congestive heart failure Constrictive pericarditis Tricuspid valve disease

SURGICAL SHUNTS

Although the TIPS procedure has provided a useful and far less invasive means of decompressing the portal system in patients suffering from complications of portal hypertension, surgical shunts remain an important treatment option in patients who are not eligible for TIPS placement, particularly those with prehepatic causes of portal hypertension. Surgical shunts are well-suited for patients who (1) have well-compensated cirrhosis without access to TIPS or who are unable to access the required follow-up care; (2) have

TABLE 2 Common Sites of Varices

Portal Inflow	Systemic Outflow	Collaterals
Left gastric vein, short gastric veins	Intercostal, diaphragmatic, and esophageal veins	Gastroesophageal varices
Superior hemorrhoidal vein	Middle and inferior hemorrhoidal veins	Hemorrhoids
Left portal vein via falciform ligament	Umbilicus and abdominal wall veins	Caput medusa
Liver via lienorenal ligament	Left renal vein	Retroperitoneal collaterals

portal hypertension without cirrhosis and thus would not benefit from liver transplant; or (3) require decompression as a bridge to transplantation after failing medical, endoscopic, and interventional therapies.

As the primary goal of surgical shunts is to decompress the portal venous system by diverting a proportion of portal inflow to the systemic circulation, surgically placed shunts are classified by the extent and selectivity of portal venous diversion. Shunts are therefore classified as either *total* or *partial* and *selective* or *nonselective*.

Total nonselective shunts completely divert all blood flow from the portal vein to the systemic circulation. Although these shunts are very effective at decompressing the portal venous system, they can result in significant encephalopathy and liver dysfunction after placement. In contrast, partial nonselective shunts and selective shunts decompress the portal venous system while still maintaining flow to the liver, reducing the risk of hepatic encephalopathy and decompensation as a result.

Total Nonselective Shunts

Created to entirely divert all portal venous blood flow into the lower resistance systemic circulation, totally diverting nonselective shunts are 10 to 12 mm or greater in diameter and are created between the portal venous system and the inferior vena cava. Examples of these shunts include the end-to-side and large side-to-side portacaval shunts, as well as interposition mesocaval and central splenorenal shunts. The end-to-side shunt procedure can be performed with moderate speed and little blood loss and may be better tolerated when there is retrograde flow from the liver within the portal vein.

Although the resolution of portal hypertension resulting from these shunts is an effective means of treating bleeding esophageal varices in as many as 90% of cases (as well as in treating refractory ascites in the case of side-to-side shunts), they may result in significant complications. Because of such significant portosystemic shunting, significant encephalopathy may occur in as many as 40% of patients, while diversion of hepatotropic substrates present in the mesenteric blood and diminished antegrade hepatic flow may accelerate hepatic decompensation, resulting in progressive liver failure and sometimes death. These shunts are seldom performed as definitive therapy in the current era.

Partial Nonselective Shunts

Because of the consequences of total nonselective shunts, narrower diameter conduits were developed to refine portosystemic shunting and control consequences including encephalopathy. With conduits of 8 mm in diameter, partial shunts may be created in a variety of configurations. Traditionally, these configurations have consisted of side-to-side mesocaval and portacaval (Sarfeh or interposition "H" graft) shunts. Either an autologous graft (e.g., internal jugular vein) or prosthetic graft (e.g., PTFE) is used to create a conduit between either the portal vein or superior mesenteric vein and the inferior vena cava (Fig. 1). The interposition mesocaval shunt is the easiest, quickest, and safest of all mesenteric systemic decompression operative procedures, and has been frequently chosen as the means of managing portal hypertension in the emergent or semi-emergent situation. Construction of a functional side-to-side total shunt, such as the mesocaval interposition shunt, is an effective treatment for ascites, whereas a selective shunt is not.

The interposition "H" portacaval shunt requires ligation of portosystemic collaterals. The umbilical vein within the falciform ligament, the coronary (left gastric) vein, the gastroepiploic vein along the greater curve of the stomach, and the inferior mesenteric vein are usually divided. Unlike total nonselective shunts, smaller-diameter conduits allow for persistent portal perfusion of the liver in approximately 80% of patients, resulting in a lower incidence of postoperative encephalopathy and liver failure without compromising results

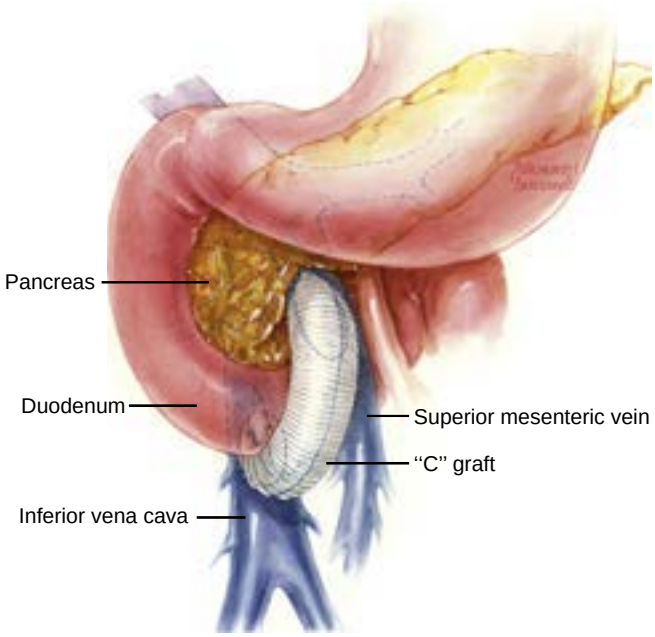


FIG. 1 Mesocaval shunt using ringed PTFE to create a "C" graft.
(From Cameron J, Sandone C. Shunts. Atlas of Gastrointestinal Surgery. *2nd ed. Vol 1. Hamilton, ON: BC Decker Inc; 2007:193–222.)*

in terms of control of variceal bleeding and ascites. Because of the smaller nature of these shunts, however, thrombosis may occur and require percutaneous intervention.

Randomized trials have not demonstrated any difference in outcome between interposition mesocaval and side-to-side portocaval shunts. Although patients undergoing mesocaval shunts are reported to have a higher thrombosis risk compared with portocaval shunts (particularly as smaller-diameter shunts are used), mesocaval shunts remain a good option for those awaiting liver transplantation as dissection within the porta hepatis is avoided.

Finally, an important but uncommon population are patients who present with Budd-Chiari syndrome (BCS) caused by hepatic vein thrombosis. BCS is caused by mechanical obstruction of the hepatic venous outflow and can gradually result in cirrhosis and portal hypertension. Presentation can be fulminant however, and treatment in this scenario is liver transplantation, although anticoagulation may help prevent disease progression. TIPS placement has proven to be a valuable tool to bridge such patients to transplantation. If access to completely occluded hepatic veins is not possible, direct intrahepatic portosystemic shunt (DIPS) placement can be performed. Surgical shunting using a mesocaval interposition or side-to-side portocaval shunt may also be performed but has been replaced by TIPS placement. The compensatory hypertrophied caudate lobe present may make performance of a surgical side-to-side portocaval shunt difficult or impossible. Finally, of historic interest in BCS, a mesoatrial shunt has been used effectively when the inferior vena cava is obstructed and consequently not a suitable target recipient of portal flow. This was particularly helpful in the situation in which bridging fibrosis was absent and liver function remained adequate.

Selective Shunts

Designed to avoid total portal venous diversion and its associated complications, selective shunts create two separate drainage systems

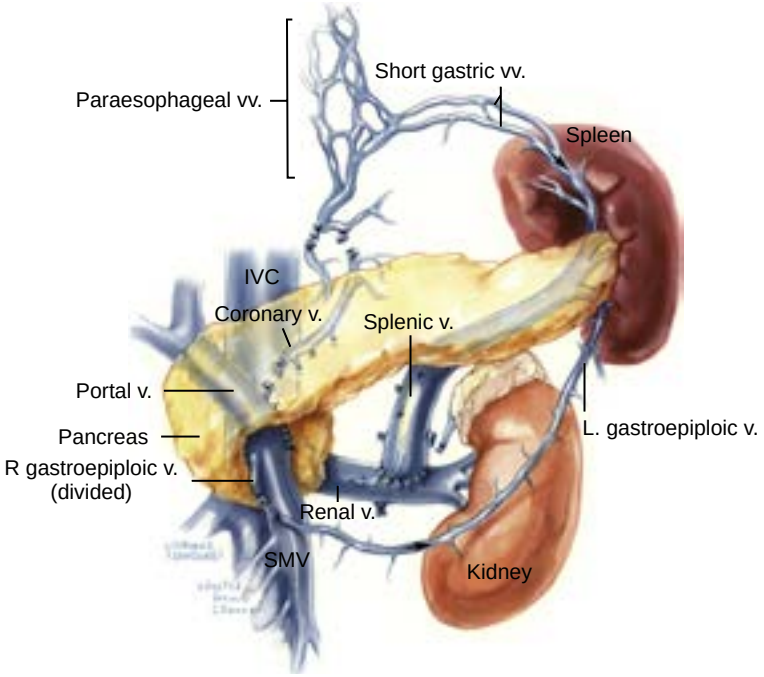


FIG. 2 Completed distal splenorenal shunt with ligated collaterals. *(From Cameron J, Sandone C. Shunts.* Atlas of Gastrointestinal Surgery. *2nd ed. Vol 1. Hamilton, ON: BC Decker Inc; 2007:193–222.)*

within the portal venous network. This results in a decreased esophagogastric pressure while still maintaining adequate mesenteric portal flow and liver perfusion. The most traditional and favored of these shunts is the distal splenorenal shunt of Warren (Fig. 2). This shunt functions by retrograde decompression into the spleen of the gastroesophageal varices via the vasa brevia and left gastroepiploic vessels. Subsequent flow is into the systemic circulation after the creation of an end-to-side anastomosis between the distal splenic vein and the left renal vein. Collaterals are ligated as described earlier as in the smaller caliber, nonselective shunts. Overall, the distal splenorenal shunt is effective at controlling variceal bleeding in over 90% of patients, with low rates of postoperative encephalopathy and liver failure. Importantly, because portal flow and sinusoidal pressure is not decreased, ascites is not relieved and may in fact progress postprocedure, making this shunt contraindicated in patients with massive ascites. The Warren shunt does not require dissection within the porta hepatis, making it an attractive option for patients awaiting liver transplantation.

Operatively, the technically challenging distal splenorenal shunt may be approached via either an upper midline or bilateral subcostal incisions. The lesser sac is opened and extended toward the spleen. Care is taken not to injure the spleen as preservation of the spleen is essential for success of this procedure. The right gastroepiploic vessels and coronary vein are ligated, taking care to preserve the vasa brevia (short gastrics) throughout this dissection. The inferior border of the distal pancreas is mobilized and reflected cephalad after mobilization from its retroperitoneal attachments. When entering the splenic vein, the inferior mesenteric vein is divided, and the splenic vein is carefully mobilized from the pancreas. Attention is then turned to the left renal vein, which is dissected free and mobilized by dividing the adrenal branch. Both vessels are controlled, and the splenic vein is divided and anastomosed to the renal vein in an end-to-side fashion. Some surgeons advocate for a more extensive separation of the splenic vein from the pancreas with ligation of all tributaries as they argue this prevents future dilatation and flow via these collaterals.

Both nonselective side-to-side shunts and distal splenorenal selective shunts have been demonstrated to be equally effective (>90%) in controlling hemorrhage with similar, low rates of rebleeding and no difference in survival. However, the incidence of hepatic encephalopathy is significantly lower following creation of a distal splenorenal shunt compared with nonselective shunts.

Other Surgical Shunts and Devascularization Procedures

Although infrequently performed in current practice, several shunt and devascularization procedures are mentioned as they remain useful in select patient populations or of historic interest in the case of devascularization procedures.

The meso-left portal venous bypass (Rex shunt) involves the use of an autologous jugular vein graft or a transposed, dilated coronary vein to serve as a conduit for blood from the superior mesenteric vein to the intrahepatic portion of the left portal vein. The Rex shunt has been mostly employed in the treatment of children with portal hypertension caused by extrahepatic portal vein thrombosis. This shunt is an effective means of restoring portal flow to the liver and improving complications related to portal hypertension, with a reported success rate of 91% to 93%.

In contrast with shunt procedures, devascularization procedures are aimed at controlling bleeding caused by esophagogastric varices by ligating the veins that drain the stomach and esophagus. These procedures vary in complexity, ranging from esophageal transection with end-to-end anastomosis to the Sugiura procedure. The Sugiura procedure consists of ligation of all gastroesophageal collateral veins, devascularization of the proximal stomach and esophagus, transection and re-anastomosis of the esophagus, and splenectomy. Although rebleeding episodes following these procedures have been reported to occur in as few as 5% of patients, such outcomes are not consistent throughout the literature. Additionally, the morbidity and mortality following devascularization procedures may be high, with mortality rates as high as 35% in some series. Overall, as medical, procedural, and surgical care for patients with portal hypertension and cirrhosis has improved over the past several decades, the utility of devascularization procedures has become increasingly limited.

CONCLUSION

Portal hypertension from intrahepatic causes is definitively managed by transplant. Failing medical therapy and endoscopic banding, when bleeding varices and ascites occur as a consequence of portal hypertension, they are usually well managed by TIPS placement. Shunt surgery is rarely utilized in the setting of acute bleeding but remains an excellent, life-saving therapy, particularly when portosystemic shunting is caused by extrahepatic portal venous obstruction with a patent mesenteric vein and intact liver function, or when transplant and TIPS placement are either unavailable or not feasible.

SUGGESTED READINGS

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Liver Transplantation

Benjamin Philosophe, MD, PhD, and Kiara A. Tulla, MD

HISTORY

The evolution of liver transplantation has been relatively rapid. The first human liver transplant was performed by Thomas Starzl in 1963. Between March 1 and October 4, 1963, Starzl performed five human liver transplants, with the longest survival at 23 days. The patients died with functioning grafts that had little evidence of rejection at autopsy. There was also a single failed attempt in Boston in 1963 and in Paris in 1964 before the operation came to a halt, perceived then to be too difficult. It was not until 1967 that the first liver transplant recipient survived 1 year. Immunosuppression consisted of azathioprine, prednisone, and antilymphocyte globulin. After cyclosporine was introduced in 1980, 1-year survival began to be consistently achieved (Fig. 1).

As a result of these successes, the surgeon general initiated a consensus conference in 1983. It was then concluded that liver transplantation has become a "clinical service" and was no longer considered an experimental procedure. This led to a rapid expansion in the number of centers performing liver transplantation. As the waiting list for liver transplantation grew exponentially, surgical fellows flocked to train under Starzl who had moved to the University of Pittsburgh. The resulting growth of qualified surgeons eventually caught up with the national and international need for liver transplants. The introduction of tacrolimus in 1989 pushed the 1-year survival rates even higher, exceeding 80%, leading to approval by the US Food and Drug Administration (FDA) in 1994. As surgical techniques have progressed, there has been gradual improvement in outcomes; current 1-year patient survival for deceased or living donor transplantation is 92%.

IMMUNOSUPPRESSION

Indications for Liver Transplantation

Acute Liver Failure

Acute liver failure (ALF) is a rare but potentially fatal syndrome characterized by sudden loss of hepatic function in a person without preexisting liver disease. Acute liver failure can also occur in patients with known diseases, such as Wilson's disease, autoimmune hepatitis, or hepatitis B. ALF affects approximately 2000 to 3000 Americans each year. It is commonly classified as *fulminant* or *subfulminant*. Fulminant liver failure is defined as the development of encephalopathy within 8 weeks of the development of symptoms such as jaundice. Subfulminant hepatic failure is reserved for patients with liver disease for up to 26 weeks before the development of hepatic encephalopathy.

Whether fulminant or subfulminant, encephalopathy is an essential component in the definition. The most common cause of ALF in the United States and western Europe is drug-induced liver injury, which accounts for 50% of the cases. Acetaminophen is the leading cause of ALF. Patients who are at increased risk for acetaminophen-induced ALF include those with concomitant alcohol use, malnutrition, or use of medications known to induce CYP450 enzymes (e.g., phenytoin, carbamazepine, or rifampin). In 308 consecutive patients from 17 tertiary care centers participating in the US Acute Liver Failure Study Group, acetaminophen was identified as the etiology of ALF in 40% of patients. The other etiologies identified (in ascending order of prevalence) were malignancy (1%), Budd-Chiari syndrome (2%), pregnancy (2%), Wilson's disease (3%), hepatitis A virus infection (4%), autoimmune hepatitis (4%), ischemic hepatitis (6%), hepatitis B virus infection (6%), and idiosyncratic drug-induced liver injury (13%); 17% of cases were found to be indeterminate.

Patients suspected of having ALF should be immediately transferred to a liver transplant center because this can progress very rapidly to fulminant liver failure and then death. The development of complications, including cerebral edema, hemodynamic abnormalities, coagulopathy, renal failure, infection and sepsis, acid-base disturbances, and pulmonary dysfunction, requires immediate attention.

The common cause of death in patients with fulminant hepatic failure is cerebral edema. Hyperammonemia is considered a critical factor in the development of cerebral edema and herniation. The grades of encephalopathy correlate with the degree of herniation. Cerebral edema develops in about 80% of patients who develop grade 4 hepatic encephalopathy. The resultant increased ICP results in decreased cerebral perfusion pressure, in turn leading to ischemic brain damage and herniation. This accounts for more than one-half of ALF-associated mortality.

ALF-induced encephalopathy, however, is different from that of cirrhosis despite the fact that ammonia levels are elevated in both. Cerebral edema does not develop in the setting of chronic liver disease. As such, lactulose, a nonabsorbable disaccharide used to decrease ammonia levels in cirrhotics, has never been shown to improve survival in the setting of ALF. Rather, therapeutic measures are focused on decreasing intracranial pressure (ICP), including elevation of the head of the bed and minimizing patient stimulation through sedation or paralysis.

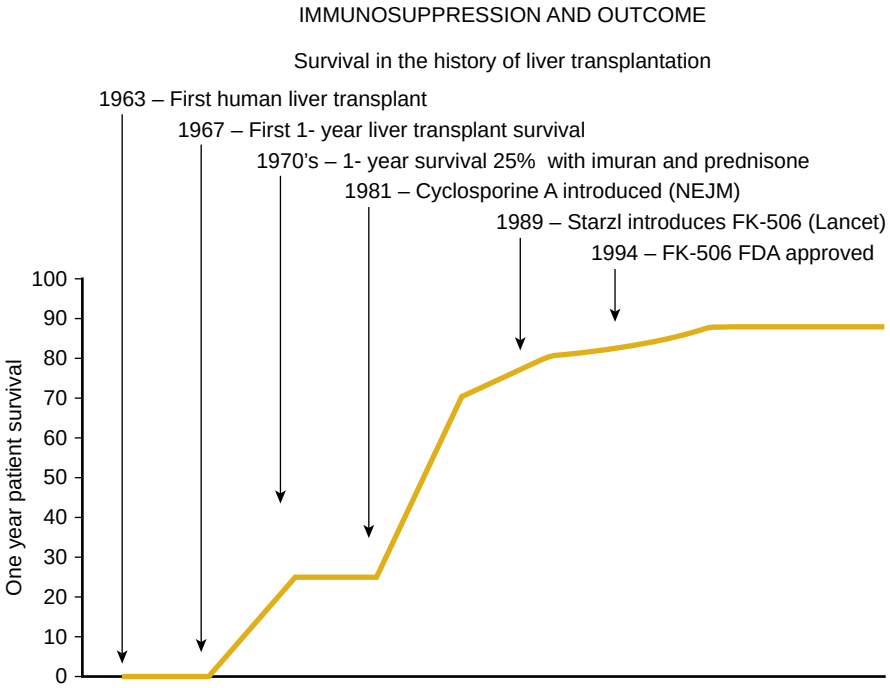


FIG. 1 Historical survival data for liver transplantation.

The development of increased ICP is an ominous sign. Clinical changes on examination occur only after significant cerebral edema has developed and as such are not helpful. Head CT is equally insensitive in the early stages of edema but is helpful with more advanced encephalopathy to rule out other pathology such as intracranial hemorrhage. If cerebral edema is evident on CT, the likelihood of irreversible brain injury or uncal herniation is high, and transplantation is contraindicated at this point. ICP monitoring can help diagnose intracranial hypertension and optimize management. There are various types of ICP monitors, but all carry a significant risk of intracranial hemorrhage following their placement. Whether the benefits of ICP monitoring are worth the risks remains controversial. Some transplant centers routinely utilize ICP monitors, while others do not and rely on clinical signs.

Without a doubt, predicting which patients with fulminant hepatic failure will require a time-sensitive life-saving transplant and which will recover with medical management alone can be very difficult. Many studies have attempted to identify prognostic indicators to guide this clinical decision. The most widely applied is from King's College Hospital in London. The King's College criteria are depicted in Box 1. The positive predictive value of the King's College criteria is 80% to 100% according to most studies, which is higher than many other criteria proposed.

In patients that meet the King's College criteria, liver transplantation is the only definitive treatment option for patients with fulminant liver failure. Farmer et al. performed a single-center retrospective analysis of 204 patients undergoing liver transplantation in an 18-year span. They showed a 73% 1-year patient survival and a 67% 5-year patient survival. Graft survival was 63% and 57%, respectively. More recent registry data showed significant improvement; 1-year and 5-year graft survival was 80% and 73%, respectively.

Chronic Liver Disease

The indications for transplantation have changed over time. Figure 2 shows the diagnosis at the time of listing over the past 15 years.

Alcoholic hepatitis has always been a major cause of chronic liver disease and remains so today. Although alcohol is listed as a primary diagnosis around 20% of the time, it is often a secondary diagnosis, with an overall incidence of 40% to 50%. Interestingly, during the COVID-19 pandemic, the percent of patients listed with a primary diagnosis of alcoholic cirrhosis increased drastically in 2020 (34%) and 2021 (37%). As such, alcoholic cirrhosis is currently the number one diagnosis at the time of listing.

Since hepatitis C was discovered in the early 1980s, it has been a primary cause of chronic liver disease and a leading indication for liver transplantation. For some transplant centers, hepatitis C was the cause in up to 60% of the patients transplanted. However, with the advent of direct-acting antiviral agents with near 100% cure rates, hepatitis C has essentially been eradicated, and in 2021 was a cause in only 7% of the patients listed.

Nonalcoholic steatohepatitis (NASH) is rapidly becoming a major cause of cirrhosis. NASH, often a "silent" liver disease, histologically resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. Steatosis with inflammation and cellular damage including ballooning of hepatocytes is the hallmark of NASH. People with NASH feel well and are not symptomatic until the cirrhosis is more advanced. NASH affects 2% to 5% of Americans. An additional 10% to 20% of Americans have fatty liver, but no inflammation

BOX 1 King's College Criteria for Medical Management of Fulminant Liver Failure

Acetaminophen

pH <7.3 ***or***
INR >6.5 and serum Cr >3.4 mg/dL

Nonacetaminophen

INR >6.5 ***or*** any three of the following variables:
INR >3.5
Bilirubin >17.6 mg/dL
Age <10 or >40 years
Cause: drug toxicity
Time from onset of jaundice to encephalopathy greater than 7 days

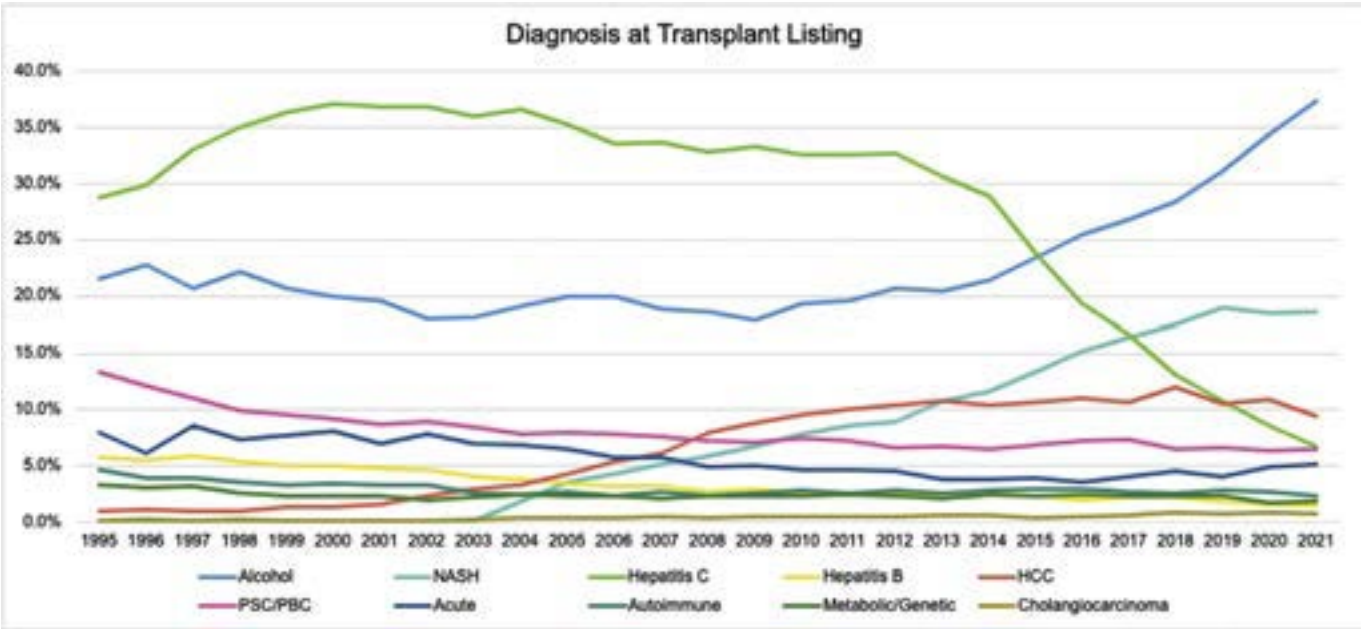


FIG. 2 Diagnosis of liver disease at the time of listing.

or liver damage, a condition called *nonalcoholic fatty liver disease* (NAFLD). It is unclear why 25% of patients with NAFLD go on to develop NASH. Both NASH and NAFLD are becoming more common, possibly because of the greater number of Americans with obesity. In the past 15 years, the rate of obesity has doubled in adults and tripled in children. NASH is now the second leading indication for liver transplantation in the United States in 2021 (19%).

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and the one of the leading causes of death in patients with cirrhosis. The incidence has more than doubled in the past two decades and will continue to increase over the next 20 years. HCC is the third most common indication for liver transplantation in 2021. HCC is associated with cirrhosis in nearly 90% of the cases in the United States, and when caught early, liver transplantation is the best chance for cure. A landmark paper in 1996 showed that for small HCCs, the outcomes following transplantation are excellent if they fall within certain criteria. Since the publication came from a group in Milan, it has become known as the *Milan criteria.* Milan criteria includes HCC candidates with stage T1 (one lesion <2 cm) or stage T2 (one lesion ≥2 cm but <5 cm, or as many as three lesions less than 3 cm each without any vascular invasion). These favorable results established early HCC as a viable indication for transplantation, resulting in changes in organ allocation that have favored transplanting patients with HCC. Even in patients who may appear to be resectable, 5-year disease-free survival is vastly better following transplantation (82%) compared with resection (40%, P <0.001).

In 2002, the United Network of Organ Sharing (UNOS) changed the allocation of livers from a Child-Pugh categorized system to a Model for End-Stage Liver Disease (MELD)-based system that focuses on severity of disease and de-emphasizes waiting time. With the new policy, HCC candidates with stage T1 or stage T2 HCC have priority beyond the degree of hepatic decompensation. The MELD "upgrade" given to HCC patients increases their MELD score at listing reflecting a mortality associated with their cancer rather than liver disease. Currently, there is a 6-month mandatory waiting period for eligible patients meeting criteria. Although HCC upgrades have undergone several revisions, in 2021 a MELD upgrade is defined as the median MELD score at transplant (MMaT) within a 250–nautical mile radius of the transplant center minus 3. In other words, if the median MELD at transplant is 31 for a specific area, the patient with HCC would receive 28 MELD points after a 6-month waiting period no matter what his or her calculated laboratory MELD score is.

Cholangiocarcinoma, long considered a contraindication to transplantation, is reemerging as an indication, especially in patients with primary sclerosing cholangitis (PSC). Early publications in the 1990s showed a 20% to 25% 5-year survival, with no improvement of neoadjuvant or adjuvant therapy. A sentinel paper from the Mayo clinic appeared in 2005 that showed an 82% 5-year survival for patients who underwent a neoadjuvant chemo/radiation protocol followed by transplantation. The protocol was very selective and included only patients with small hilar tumors and excluded patients with previously attempted resections or those with extrahepatic disease on a protocol exploratory laparotomy. The study was criticized because of the loose diagnostic criteria that may have included PSC patients without cancer. In this study, 16 of the 38 patients (42%) transplanted showed no evidence of cancer on the explant. Skepticism was abated, however, when a multicenter trial with 12 participating centers showed similar results. This trial included a larger number of non-PSC patients (71) and PSC patients (143) who underwent liver transplantation for perihilar cholangiocarcinoma. The 10-year recurrence-free survival was 51% and 62%, respectively (P =0.06). Although not as impressive as the initial Mayo Clinic report, the outcomes are significantly more favorable than most of the surgical resection reports. The 5-year survival for the cohort is even better (72%) if UNOS criteria are met (initial hilar mass <3 cm, no evidence extrahepatic or lymph node disease on protocol exploration). Based on these two studies, UNOS now assigns a MELD upgrade for patients with hilar cholangiocarcinoma who meet criteria, similar to HCC patients.

MELD

The MELD was first developed to predict survival in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts. The MELD score uses objective variables and has been shown to be an accurate predictor of survival among different populations of patients with advanced liver disease. The formula to calculate MELD is based on 3

variables found to significantly impact survival and their regression coefficients, the creatinine, bilirubin, and INR:

$$0.957\times\mathrm{Log}_e(\mathrm{Cr})+0.378\times\mathrm{Log}_e(\mathrm{bili})+1.120$$

$$\times\mathrm{Log}_e(\mathrm{INR})+0.643\,]\times10$$

Since the MELD accurately predicts survival in patients with cirrhosis who have infections, variceal bleeding, cholestatic diseases, acute liver failure, and alcoholic hepatitis, it has been modified by UNOS and used to prioritize patients for liver transplantation. The modification for transplant maximizes the score at 40 and assigns a creatinine of 4 mg/dL for patients on renal replacement therapy. The 3-month predicted mortality associated with the MELD score is depicted in Table 1.

Several studies have since shown that the addition of serum sodium into the MELD score (MELD-Na) predicts waiting list mortality better than the MELD alone. The inclusion of serum sodium into the MELD score allowed for a predictive increase in 7% fewer deaths with transplantation eligibility for the end-stage liver population. Therefore, in January 2016, the UNOS listing policy was updated to include serum sodium as a factor in the calculation of the MELD score:

$$\text{MELD Na}=\text{MELD}-\text{Na}-\left[0.025\times\text{MELD}\times(140-\text{Na})\right]+140$$

A recent study used the largest UNOS database of listed patients with decompensated cirrhosis in the United States to demonstrate the MELD-Na. MELD-Na carries a strong predicted value for 6-month mortality with a c-statistic of 0.83, similar to its predicted value for 90-day mortality. This finding is important as it includes patients with severe complications of portal hypertension that are often excluded from prior calculations and who carry increased mortality (Fig. 3).

TABLE 1 MELD Mortality Equivalents

MELD	3-Month Mortality
7	1%
20	8%
24	10%
26	15%
29	20%
31	30%
33	40%
35	50%
37	60%
38	70%
40	90%

MELD, Model for End-Stage Liver Disease.

Waiting List Additions, Removals, and Transplantation

In the past 15 years, the number of patients added yearly to the transplant waiting list has increased from 8055 in 1996 to 13,803 in 2021. The number of deceased donor transplants performed increased initially as acceptable donor criteria expanded, but remained flat between 2005 and 2013. As a result, mortality on the waiting list increased during this time. However, when allocation of livers changed in 2013 to include broader regional sharing of donors for patients with MELD 35 or higher, mortality decreased and the number of deceased donor transplants increased (Fig. 4). In 2021, there were 8667 deceased donor transplants and 569 living donor transplants performed in the United States.

LIVER TRANSPLANTATION

Techniques

The techniques of hepatectomy and implantation have changed over time. The first attempts at liver transplantation utilized venous-venous bypass (VVP), which in itself has evolved to include a centrifugal pump and heparin-coated cannulas, thereby eliminating some of the fatal pulmonary embolisms initially encountered. In 1998, Chari et al. reported that 95% of the centers were using VVP at least during the anhepatic phase. However, VVP is fading away as more and more centers successfully adopt caval preservation and partial clamping techniques.

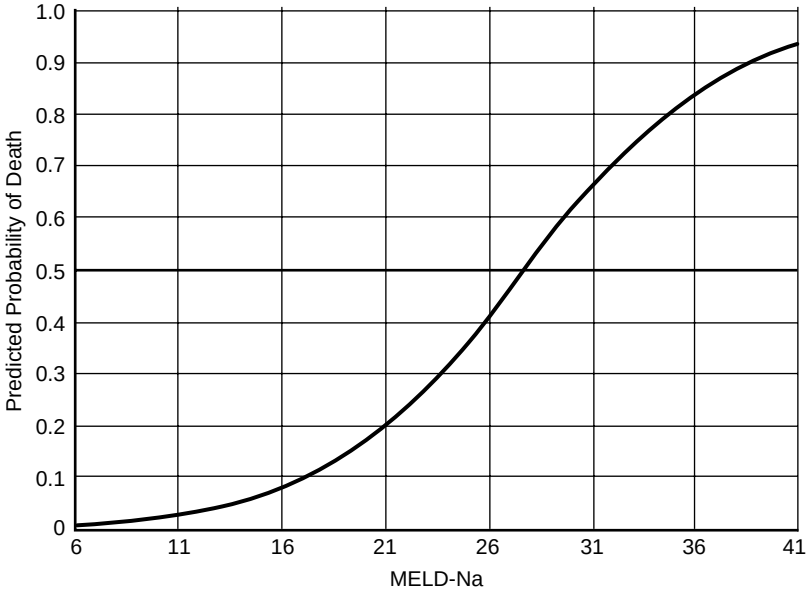


FIG. 3 Predicted probabilities of death at 6 months against the new Model for End-Stage Liver Disease (MELD-Na) scores.

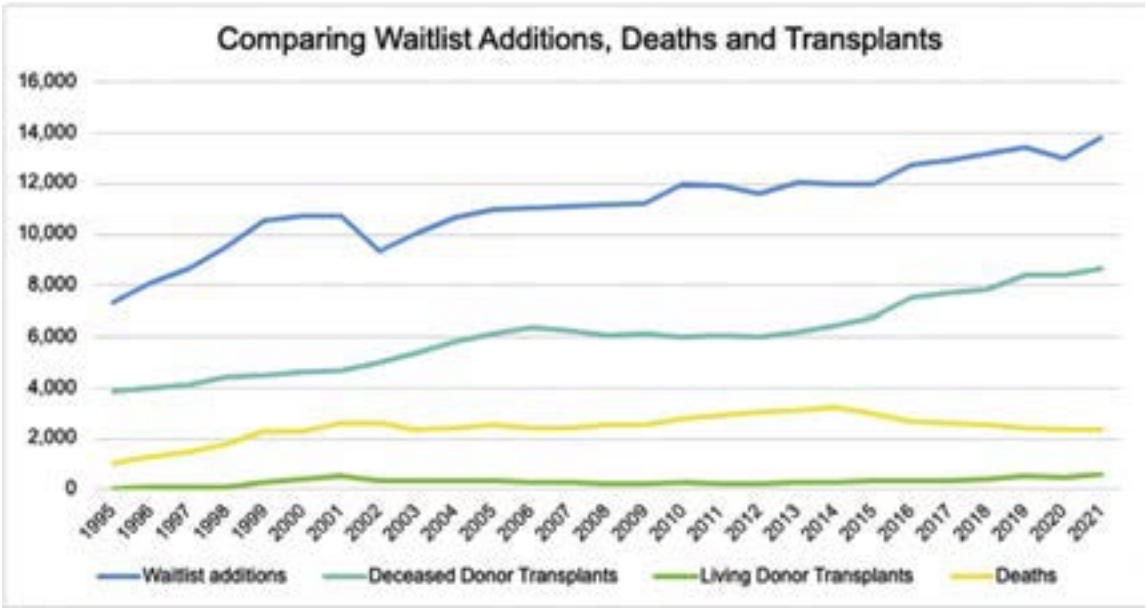


FIG. 4 Waitlist additions, deaths, and liver transplants over time. *(Data from the United States Organ Procurement and Transplantation Network [OPTN]).*

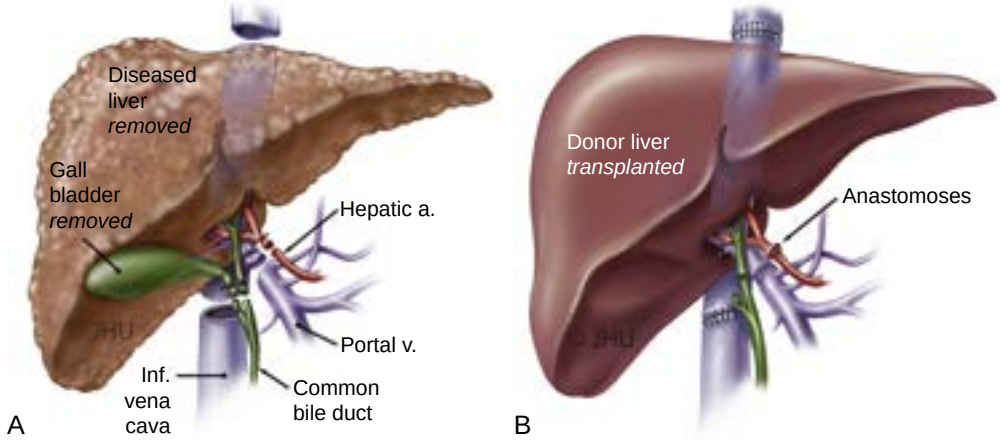


FIG. 5 Classic bicaval anastomosis. The native liver is resected together with the retrohepatic inferior vena cava (IVC) and orthotopically replaced by a donor liver that includes the IVC. *(Illustration Copyright 1998–2003 by The Johns Hopkins Health System Corporation and The Johns Hopkins University; from the Johns Hopkins Division of Gastroenterology and Hepatology [www.hopkinsmedicine.org/gi]. Illustration created by Mike Linkinhoker.)*

Bicaval anastomosis

With this conventional technique, the native liver is resected together with the retrohepatic inferior vena cava (IVC) and orthotopically replaced by a donor liver that includes the IVC (Fig. 5). The native hepatectomy begins with dissection of the hepatic hilum. The dissection isolates the left and right hepatic arteries, which are divided separately. The proper hepatic artery (HA) is dissected beyond the gastroduodenal artery to the common HA because a patch of the gastroduodenal artery and the common HA is often used for subsequent arterial anastomosis. The cystic duct is divided followed by the division of the common duct closer to the hilum to obtain maximal length on the duct. What is left at this point is the portal vein (PV) with surrounding lymphatic tissue. The vein is skeletonized from its bifurcation toward the pancreas, often to the first pancreatic branch. Several centimeters of vein are necessary to allow placement of a clamp or for cannulation with VVP. PV division is not performed until the liver is completely mobilized. This includes dividing the left and right triangular ligaments, mobilizing the right lobe off the diaphragm, and dissecting the retrohepatic IVC to completely mobilize it posteriorly. The adrenal vein is often divided to obtain adequate mobility of the IVC for clamping.

Complete venous clamping with or without VVP is necessary. Complete IVC and PV clamping can result in important hemodynamic consequences with decreased venous return, congestion in the caval and splanchnic bed, as well as decreased renal function. This should be performed when the hepatectomy is nearly complete because the congestion leads to increased bleeding during hepatectomy. For this reason, VVP was introduced in the mid-1980s. However, as anesthetic conditioning improved, VVP can be avoided, especially when the vascular anastomoses are done expediently. Two IVC anastomoses are required: one suprahepatic and one infrahepatic end to end.

Piggyback Technique

In 1989, Tzakis et al. popularized the technique of orthotopic liver transplantation (OLT) with preservation of the IVC, called the *piggyback technique*. This technique involves complete mobilization of the liver off the IVC, including the hepatic veins that are individually oversewn. In the Tzakis report, the transplant was still performed with the use of a VVB. Venous outflow reconstruction was performed between the suprahepatic donor IVC and a common orifice created by opening of the native right, middle, and left hepatic veins, or just the middle and left. Several studies, including a randomized trial, favored the piggyback technique over the traditional bicaval technique, with a shorter anhepatic phase, reduced blood loss, and reduced cost of the procedure in favor of the piggyback technique.

Modified Piggyback Technique

Several reports describing a venous outflow complication rate of up to 5% appeared. These complications included graft congestion and stenosis of the caval anastomosis. For this reason, modifications of the piggyback technique became more popular. In 1992, a side-to-side anastomosis between donor and recipient IVC without the routine use of VVB was described. In this modification, both the suprahepatic and infrahepatic end of the donor IVC is closed, and the anastomosis is created between two new incisions—one made on the recipient IVC and another on the donor IVC (Fig. 6). Cherqui introduced another venous outflow reconstruction. He enlarged the common orifice of three hepatic veins by a caudal incision on the anterior wall of the recipient IVC and anastomosed it with the suprahepatic end of the donor IVC (end-to-side anastomosis). This technique was further modified by closing all hepatic veins and creating an anastomosis between a new incision on the anterior wall of recipient IVC and a V-shape incision on the donor IVC to avoid stricturing of the outflow anastomosis. In certain situations when the suprahepatic IVC cuff is very short, such as in domino LT or in case of outflow complications after piggyback implantation, some authors advocate the use of the infrahepatic cavocaval anastomosis.

Although there are studies comparing the different piggyback techniques, the essential message is to extend the cavostomy on the recipient to create a wide caval anastomosis and avoid some of

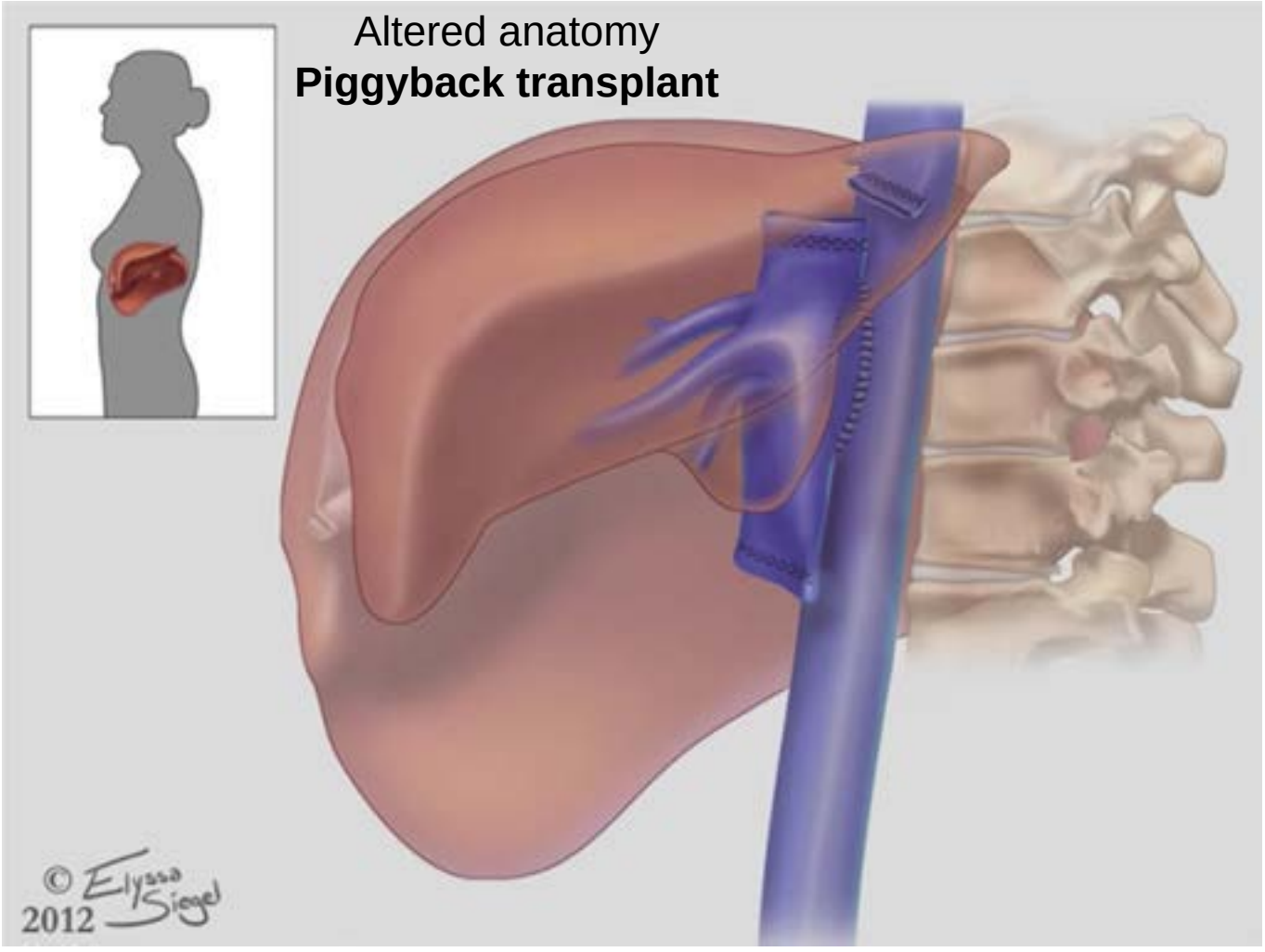


FIG. 6 Modified piggyback technique. In this modification, both the suprahepatic and infrahepatic ends of the donor inferior vena cava (IVC) are closed, and the anastomosis is created between two new incisions—one made on the recipient IVC and another on the donor IVC. In this modification, all hepatic veins are sewn over, and a new incision on the anterior wall of recipient IVC is made. *(From Elyssa Siegel, Art as Applied to Medicine, Johns Hopkins University.)*

the venous stricturing complications that ultimately lead to Budd-Chiari syndrome. One thing is clear however; avoiding VVB with caval-preserving techniques is becoming the norm in many liver transplant centers.

Vascular Reconstruction

The PV reconstruction is usually performed end to end with fine polypropylene suture. There are several important technical considerations to uphold to avoid either stenosis or kinking that can ultimately lead to portal vein thrombosis (PVT). A technique that Starzl initially described is allowing for a "growth factor" when tying after circumferentially running the suture. This allows expansion of the anastomosis to accommodate the distention that occurs when flow is reestablished. Failure to incorporate the growth factor will result in an "hourglass" anastomosis that may be prone to stenosis and thrombosis. The second concept is related to the length. Typically during a liver transplant the operative field is expanded with the use of surgical retractors. This must be taken into account in assessing the length of the donor PV. It is not uncommon to find the PV kinking once the retractors are removed because it was sewn with too much donor length. To avoid this problem, many surgeons will minimize the retraction inferiorly and place laparotomy pads above the liver to bring the liver down before performing the PV anastomosis. If this problem does occur, then it is important to redo the anastomosis after cutting an adequate amount of donor PV. This can be done with minimal hepatic sequelae if performed expediently in the presence of arterial perfusion.

PV Reconstruction in the Presence of Native PV Thrombosis

PVT is being increasingly recognized in patients with advanced cirrhosis and in those undergoing liver transplantation. Reduced portal flow and hypercoagulability that occurs with advanced liver disease is probably responsible for clotting in the spleno-porto-mesenteric venous system. The prevalence of PVT in patients without hepatocellular carcinoma has been reported to be as high as 25% in ultrasound-based studies, with the overall incidence increasing to nearly 40% with time. PVT was long considered a contraindication to liver transplantation, but as reports with favorable outcomes appeared, this is no longer the case. Techniques of native PV thrombectomy have been well described with success rates exceeding 95%. The thrombus often extends to the confluence of the splenic and mesenteric veins often sparing at least the SMV. For this reason, thrombectomy is more successful when the dissection during the hepatectomy is carried out beyond the confluence to reach the tail of the thrombus. Although some authors advocate the use of Fogarty balloons, the clot is often organized and adherent to the vein wall. The extent of the clot can be manually and visually examined. If the thrombus completely occludes portal flow, the PV can be divided at the right and left confluence with the edges held apart using tonsil clamps. This allows the surgeon to separate the clot and the attached intimal layer from the media of the vein circumferentially using a dura elevator. This maneuver is extended as far as necessary, frequently entering the splenic and superior mesenteric veins (SMVs). The free edge of the clot is then clamped with a tonsil or ring clamp and gently rotated and pulled out. Because hypercoagulability is considered a risk factor for PVT, the recipients are often placed on full-dose daily aspirin before discharge. With this technique, a bypass graft from the SMV utilizing a donor iliac vein to reestablish PV inflow is rarely necessary.

In cases of massive portal system thrombosis that involves the SMV and splenic vein, salvage revascularization techniques have been described. Cavoportal hemitransposition has been described by Tzakis when no portal inflow can be achieved. This technique involves ligating (either completely or partially) the infrahepatic recipient IVC. The PV anastomosis is either done end to end inferior to the point of ligation or end to side with partial ligation. Overall survival was poor, so this should be reserved only as a salvage procedure intraoperatively.

Arterial Reconstruction

The arterial reconstruction is usually a direct anastomosis between the donor and recipient HA in an end-to-end fashion. The anastomosis should involve Carrel patches on the donor and recipient ends to decrease the incidence of hepatic artery thrombosis (HAT). The donor artery typically involves the entire celiac trunk with a patch of aorta. This is sewn to a Carrel patch created by the recipient gastroduodenal artery and the proper HA coming off the common HA. In cases in which donor arteriopathy exists, it is important to shorten the artery to a segment free from disease. A donor patch can also be made using the splenic artery takeoff if the remainder of the artery is disease free.

In other cases, the recipient HA is unsuitable for use because of poor inflow from more proximal stenosis, atherosclerosis, or intimal dissection. Options include dissecting more proximally on the recipient artery beyond the takeoff of the splenic artery. If the inflow is adequate at that point, an end-to-side anastomosis to both the celiac and splenic artery confluence can be achieved while preserving flow to the spleen. Alternatively, an end-to-end anastomosis to the celiac can be performed while sacrificing the splenic artery. Although this is an appropriate alternative especially in re-transplants, splenic infarcts and abscesses can result. The most common method to deal with poor arterial inflow is the use of arterial conduit directly from the aorta using a donor iliac artery graft. For this reason, a donor iliac graft is always procured with the liver. The anastomosis can be done to either the supraceliac or infrarenal aorta. The infrarenal aorta is more commonly used because it is safer and easier to access. The graft is commonly tunneled antepancreatic and retrogastric/retrocolic. The infrarenal aorta, however, is more prone to calcification and atherosclerotic disease, especially in older adult patients. The supraceliac aorta is easy to access after the hepatectomy, so it may be used in cases in which arterial reconstruction is planned (e.g., retransplantation with HAT). However, the supraceliac aorta does not hold sutures as well as the infrarenal aorta, and any complications with this segment can result in disastrous consequences. The use of arterial conduits is associated with excellent long-term outcomes and low HAT rates.

Aberrant donor arterial anatomy is present up to 25% of the time and must be recognized during the procurement. An accessory or replaced right HA arising from the SMA is often preserved by procuring the SMA trunk with the celiac. The artery can then be reconstructed on the backtable before implantation. A left accessory or replaced HA arising from the left gastric should also be preserved, although no reconstruction is necessary because it arises from the celiac trunk. Backtable preparation of the accessory left HA requires careful dissection of the left gastric with ligation of all of its branches.

Biliary Anastomosis

The two main techniques of biliary tract reconstruction are direct duct-to-duct and Roux-en-Y hepatico or choledochojejunostomy. If the recipient duct is normal, a duct-to-duct anastomosis is preferable. This preserves the native physiology and anatomy and allows future biliary access via endoscopic retrograde cholangiopancreatography (ERCP). The end-to-end anastomosis is commonly performed with either running or interrupted dissolvable sutures. When a significant size discrepancy exists, a side-to-side anastomosis can be used. Both techniques are acceptable and yield equivalent results.

Roux-en-Y reconstruction is often needed in retransplantation or for patients with PSC. The routine use of Roux-en-Y anastomosis for PSC, however, has become a topic of controversy as many are now

TABLE 2 Patient and Graft Survival Following Liver Transplantation

	1 Year	3 Year	5 Year
PATIENT SURVIVAL (%)			
Deceased donor	91.2	82.8	75.1
Living donor	92.3	88.4	83.9
GRAFT SURVIVAL (%)			
Deceased donor	89.1	80.0	71.8
Living donor	88.0	82.0	77.3

advocating direct duct-to-duct anastomosis in PSC patients with normal-appearing ducts.

The routine use of T-tubes during biliary anastomosis has been challenged for over a decade and has lost favor in the majority of transplant centers. Several pivotal trials have shown that the incidence of biliary complications is actually lower when T-tubes are not used. Duct-to-duct biliary anastomosis, whether end to end or side to side, should be done without any biliary tubes.

OUTCOMES

Despite a progressive increase in the severity of liver disease in transplant recipients, graft survival continues to improve. The national 1-year, 3-year, and 5-year graft and patient survival for patients transplanted between 2008 and 2015 is depicted in Table 2.

The incidence of acute rejection following liver transplantation is lower than in other groups, decreasing below 10% in most reports. The decline is likely related to increased efficacy of immunosuppression and better monitoring.

VASCULAR COMPLICATIONS

Arterial

The interruption or reduction of arterial flow during liver transplantation is frequently associated with biliary ischemia and complications including bile duct necrosis, liver abscesses, and graft dysfunction. This occurs because of the absence of collaterals in liver transplant recipients. In the native liver, HA thrombosis or ligation is usually well-tolerated because of the abundant arterial collateral sources that avoid ischemia of the liver parenchyma. In contrast, disruption of these collaterals inevitably occurs when performing total hepatectomy for transplant. In cases of hepatic artery thrombosis (HAT), the allograft often survives as a result of portal flow and portal oxygen. The biliary tree, however, is dependent primarily on arterial flow and is therefore especially sensitive to interruption of arterial blood. Recognition and prompt management of HAT is of great importance for graft and patient survival. The incidence of HAT is 2% to 5%, with about one-half occurring early within the perioperative period, and one-half occurring late. Early HAT inevitably leads to graft loss and a high mortality rate. For this reason, when diagnosed, patients often have to be retransplanted. Rarely HAT can be caught shortly after it occurs, and graft failure can be thwarted with thrombectomy and revision or reconstruction of the artery.

Measurement of hepatic arterial flow can be easily accomplished using flowprobes (e.g., Transonic). The flowprobes are placed on the reconstructed artery to gently surround the vessel excluding extraneous tissue. By immersing it in saline, a good acoustic contact occurs, and the readings stabilize rapidly with little fluctuation. Hepatic arterial flow is dependent on both cardiac output and portal venous flow. However, it has been shown that arterial flow <200 cc/min is associated with a six fold increase in HAT, and a flow <100 cc/min is associated with a significant increase in the incidence of primary nonfunction. Information on volumetric flow at the time of operation can either be reassuring or may indicate an unexpected problem, which can be fixed at this time.

Hepatic artery stenosis (HAS) occurs 2% to 10% of the time. Chen et al. reported an overall HAS incidence of 2.8%, with an early (<30 days) HAS incidence of 40% versus a late HAS incidence of 60%. The mean time elapsed between transplantation to diagnosis was 91 days. HAS can lead to an insidious form of graft disorder, both in the early and later postoperative stages. Many patients with HAS are asymptomatic and most commonly present only with mildly elevated liver function tests. Because of the insidious nature of HAS, some centers perform routine screening ultrasound examinations at regular time intervals.

The therapeutic management of HAS includes either surgical revision or percutaneous endovascular interventions, such as percutaneous transluminal angioplasty (PTA) with or without stent placement. In one study treating 42 cases of HAS, 81% were successfully treated by PTA, with an incidence of immediate complication of 7% including dissection and arterial rupture. These results compare favorably to surgical approaches, so PTA has become first line therapy for HAS.

Venous

Venous complications are less frequent than arterial complications but can also result in graft failure, especially if they occur in the early postoperative period. Endovascular management has become the treatment of choice for the majority of venous complications.

Portal Vein

The incidence of PV complications is low, estimated around 1%. It is more common in pediatric and living donor transplants. The most common complications are portal vein thrombosis (PVT) and portal vein stenosis (PVS).

PVT

The risk factors for PVT include technical issues (kinking of the PV caused by excess length), preoperative PVT in the recipient requiring intraoperative thrombectomy, hypercoagulability, small PV diameter, and reconstruction with a vein conduit. Early PVT can be devastating and leads to early graft dysfunction and loss, and it is generally less well tolerated than early HAT. Excess length of the PV following anastomosis can easily occur as a result of the presence of retraction during the anastomosis. Once the retractors are released, the operative field collapses, and kinking of the PV can occur. To account for this, laparotomy pads are typically placed behind the dome of the liver, essentially bringing the liver down and facilitating an anastomosis that will not have redundancy. In addition, a "growth factor" is included when tying the final knot to prevent wasting of the anastomosis when flow is reintroduced and the PV expands.

If flow is compromised as a result of any of the aforementioned reasons, then the risk of PVT is increased. It is therefore important to ensure once the retractors are removed that the PV is not kinked or redundant. In addition, measurement of portal venous flow can be easily accomplished using flowprobes. Portal venous flow is dependent on cardiac output and graft size. The range is wide, but in general PV flow should exceed 1 L/min to minimize the risks of PVT. PV hyperperfusion can affect arterial flow, but it is usually only problematic with small grafts and living donor liver transplantation (LDLT).

PVS

PVS is a rare complication of liver transplantation primarily because the majority of patients with PVS are asymptomatic. PVS is a bigger problem in pediatric and living donor transplants because size mismatch is more likely to lead to technical issues that result in PVS.

When PVS does occur, the management is dependent on the timing. Early PVS within the perioperative period should be approached surgically. Late PVS is more amenable to percutaneous approaches, either transhepatic or transjugular. Percutaneous balloon dilation has been reported with good success and has become the treatment of choice. Asymptomatic PVS noted on ultrasound without any graft dysfunction should be observed without any intervention necessary.

Biliary Complications

The most common type of biliary reconstruction is a choledocho-choledochostomy (duct-to-duct anastomosis). Choledochojejunostomy is sometimes necessary in cases in which the native bile duct is diseased or unusable, such as with patients with PSC or redo liver transplants. Duct-to-duct anastomosis has several advantages. The sphincter of Oddi function is preserved, which plays a role in decreasing the risk of ascending cholangitis, and it also allows easy endoscopic access to the biliary tree for diagnostic and therapeutic purposes.

Bile Leak

Bile leaks occurs early up to 20% of the time following liver transplantation. The majority are self-limiting and seal within a few days without any further intervention as long as the leaks are well drained. If the leaks are not well drained, patients could present with abdominal pain, fever, or any sign of peritonitis. Ultrasound or CT scan can often identify a biloma or fluid collection near the porta hepatis, which should raise the suspicion highly. Once bile leak is suspected, ERCP with sphincterotomy and stent placement becomes the diagnostic and therapeutic procedure of choice, assuming there are no intraoperatively placed biliary tubes at the time of anastomosis. The success rate often exceeds 85%, and no further treatment is necessary. In the event that a bile leak is more extensive or involves necrosis of the distal donor duct, surgical reconstruction is necessary to avoid biliary strictures that will become problematic in the future.

Bile Duct Strictures

Biliary stricture is also a common biliary complication, occurring up to 15% of the time with deceased donor transplants. Strictures are classified as anastomotic strictures and non-anastomotic strictures. The approach to each is markedly different, so it is important to distinguish the two. Anastomotic strictures early in the postoperative period are often related to technical issues, including surgical techniques, small-caliber ducts, or burn injury from electrocautery. Later-onset anastomotic strictures are most likely related to ischemia at the end of the donor duct, leading to fibrotic healing. Non-anastomotic strictures are likely caused by ischemia secondary to preservation injury, donation after cardiac death, prolonged use of vasopressors, rejection, HA insufficiency, or recurrent disease.

Although magnetic resonance cholangiopancreatography (MRCP) has high sensitivity and specificity, the diagnostic procedure of choice is ERCP because therapeutic options are often required. For anastomotic strictures, balloon dilation with stent placement is more successful than without stent placement. The stents are generally replaced by larger stents every 3 months to prevent clogging, cholangitis, or stone formation. Serial dilation with dual or multiple stents will prove successful in the vast majority of patients. Surgical intervention is rarely necessary.

Management of patients with nonanastomotic strictures is more difficult as these are prone to developing sludge, casts, and stones, rendering plastic stents less effective. The recent use of metallic wall stents may improve the success of endoscopic management of these strictures. If the disease is limited to the extrahepatic ducts, surgical revision is necessary and requires conversion to a Roux-en-Y hepaticojejunostomy. If the intrahepatic ducts are also involved, retransplantation may be necessary.

LIVING DONOR LIVER TRANSPLANTATION

LDLT for pediatric recipients was introduced in 1989 to overcome the severe shortage of deceased donor organs across the world. In 1993, Tanaka et al. reported the first adult-to-adult right liver LDLT using a right lobe, making liver transplantation feasible for adults in areas of the world where deceased donors are very limited. Since then, living donor grafts for adults have expanded to include right lobes with the middle hepatic vein and left lobes. The centers embarking on LDLT often face ethical issues regarding donor safety when a healthy adult must undergo a complicated major surgery without receiving any health benefit. The complication rate after LDLT ranges widely in the literature between 10% and 50% depending on the severity. Unfortunately, there have been a number of deaths after living donation. The risk of death is estimated to be 0.2% to 0.5% with left lobe donation and 0.3% to 1% with right lobe donation. Because of this as well as a highly publicized death of a living donor in New York City, enthusiasm in the United States waned in 2001 and remained flat for the next 13 years. As the world experience for adult-to-adult LDLTs increased exponentially, the added knowledge and improved techniques resurrected living donation in the United States, resulting

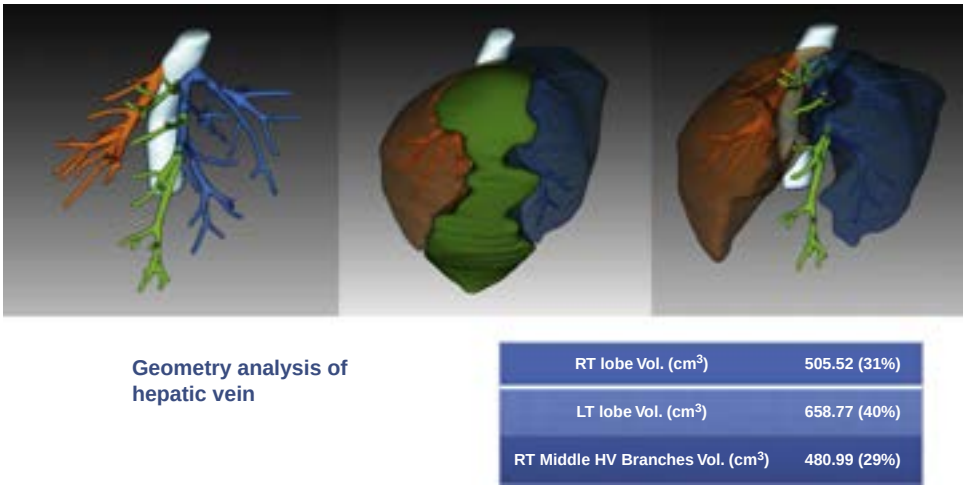


FIG. 7 Three-dimensional reconstruction to assess a living donor liver graft.

in a two fold increase in the number performed annually (see Fig. 4). The 5-year survival is the same for LDLTs and deceased donor transplants (see Table 2).

Graft function following LDLT is highly dependent on graft volume. Although left lobe donation is associated with a lower mortality rate, left lobe volumes are typically smaller, and small-for-size syndrome is more prevalent, especially in the face of significant portal hypertension. As a result, right lobe grafts have been used more commonly in adults. Previous literature has suggested that a graft weight/recipient weight ratio ≥0.8% and a graft weight/standard liver volume ratio of 40% are the safe limits for donor graft size to avoid small-for-size syndrome. Small-for-size syndrome is defined as prolonged cholestasis with ascites void of technical issues. Imaging techniques to predict vascular anatomy and graft weight include MRI with IV contrast and or fine-cut CT with IV contrast. There are multiple software companies that reconstruct the CT or MRI images three-dimensionally to allow the surgeon to more precisely assess graft volume including which segmental drainage of the liver (Fig. 7). These three-dimensional analyses enable the surgical team to better plan resection lines and need for venous reconstruction. Parenchymal transection for right lobe grafts is typically performed immediately to the right of the middle hepatic vein (Fig. 8). Large branches from segment V or VIII draining to the middle hepatic vein may need to be reconstructed to avoid hepatic congestion (Fig. 9).

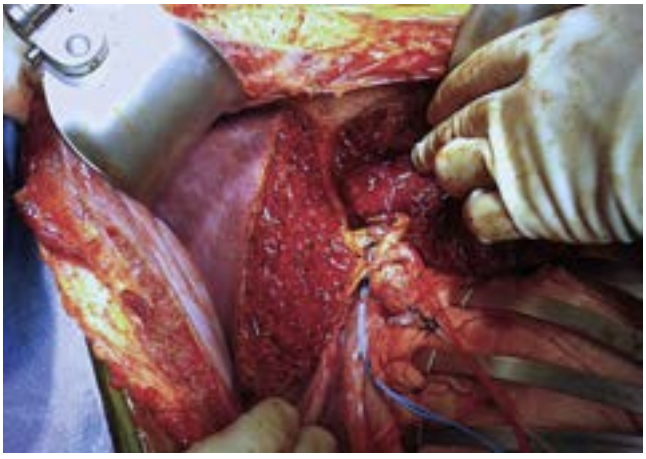


FIG. 8 Parenchymal transection to the right of the middle hepatic vein.



FIG. 9 Right lobe graft after reperfusion with reconstruction of segment V vein.

Biliary complications have been the Achilles heel of LDLTs. Biliary anatomy is highly variable, and the need to anastomose two bile ducts is not uncommon. As a result, the leak and stricture rate can be as high as 30%, higher than for deceased donor transplants.

Despite the technical challenges and higher graft complications, LDLT remains a life-saving procedure for patients with end-stage liver disease.

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Endoscopic Therapy for Esophageal Variceal Hemorrhage

Julie A. Conyers, MD

PORTAL HYPERTENSION AND VARICES

Hemorrhage resulting from rupture of gastroesophageal varices is one of the most lethal complications of portal hypertension. Portal hypertension is a common clinical syndrome defined by the indirect measurement of the hepatic venous pressure gradient (HVPG) > 10 mm Hg. The HVPG is determined by the difference between the free hepatic venous pressure (FHVP) and the wedged hepatic venous pressure (WHVP) or HVPG = WHVP – FHVP (Fig. 1). HVPG serves as a surrogate measurement of portal pressure in sinusoidal causes of portal hypertension.

Endoscopic ultrasound (EUS)-guided measurements of the portal pressure gradient (PPG) as the difference between hepatic venous pressure (HVP) and direct portal venous pressure (PVP), or PPG = PVP – HVP, has been recently been described and theoretically may be accurate for presinusoidal, sinusoidal, and postsinusoidal etiologies of portal hypertension (Fig. 2).

The development of clinically significant esophageal and gastric varices is the result of porto-systemic collaterals secondary to portal hypertension. As the radius of the variceal vessel increases, wall tension exceeds tissue strength resulting in vessel rupture in accordance with Laplace's law and Pascal's principle (Fig. 3). As portal pressure increases, the likelihood of gastroesophageal variceal rupture and hemorrhage also increases.

Although liver cirrhosis is the most common etiology of portal hypertension in Western cultures, schistosomiasis is the most

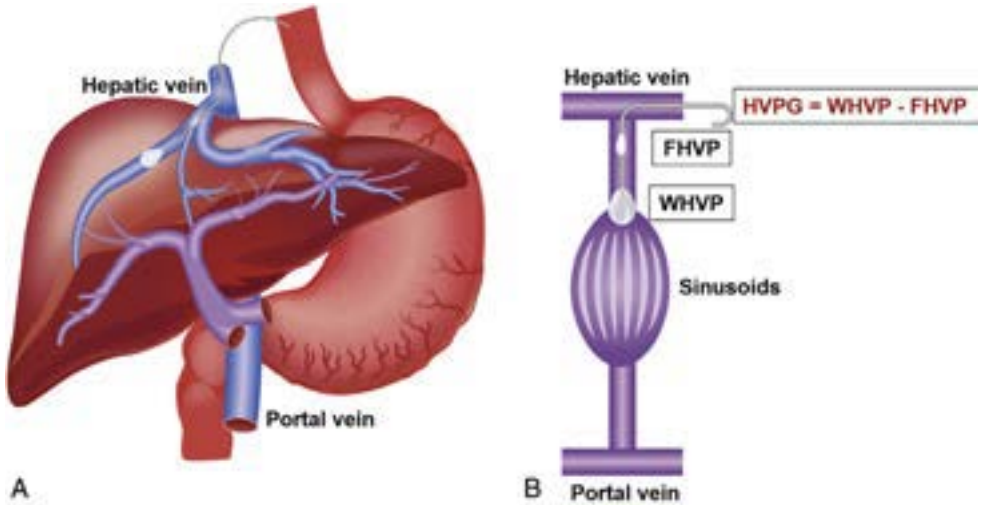


FIG. 1 Hepatic venous pressure gradient *(HVPG)*. **(A)** Transjugular wedge balloon for measuring HVPG. **(B)** HVPG is calculated as the difference between free hepatic vein pressure *(FHVP)* and wedged hepatic vein pressure *(WHVP)*, which is a surrogate for portal vein pressure in sinusoidal causes of portal hypertension. *(From Jirapinyo P, Thompson CC, Ryou M. Effects of endoscopic gastric plication on portal pressure gradient in a patient with nonalcoholic steatohepatitis cirrhosis. VideoGIE. 2021;6:491–494.)*

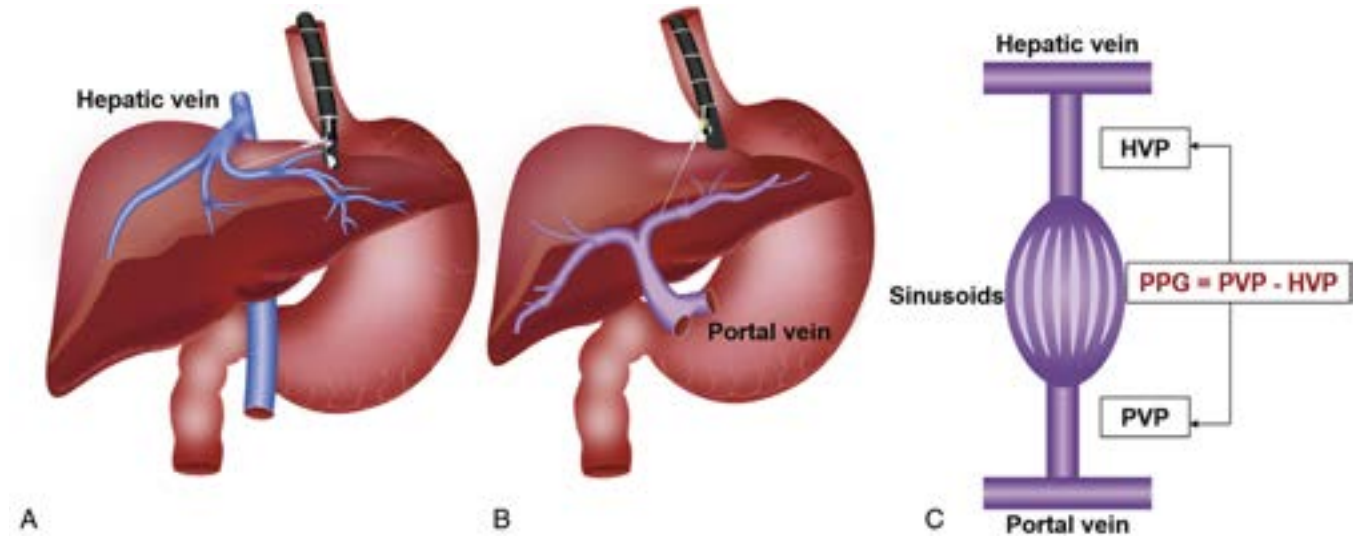


FIG. 2 Endoscopic ultrasound-guided portal pressure gradient *(PPG)* measurement. **(A)** Hepatic venous pressure *(HVP)* measurement. **(B)** Portal venous pressure *(PVP)* measurement. **(C)** PPG represents the difference between the PVP and HVP. *(From Jirapinyo P, Thompson CC, Ryou M. Effects of endoscopic gastric plication on portal pressure gradient in a patient with nonalcoholic steatohepatitis cirrhosis. VideoGIE. 2021;6:491–494.)*

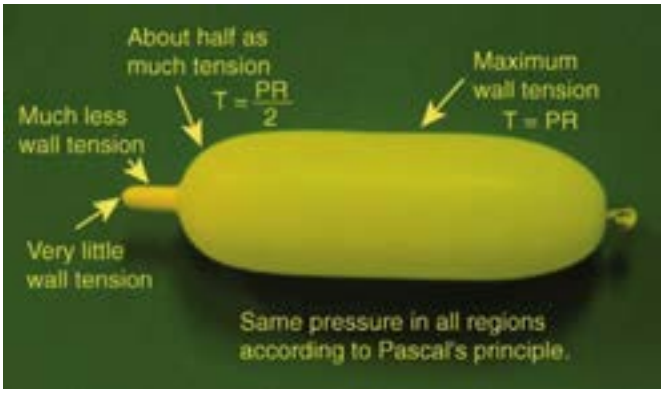


FIG. 3 Laplace's law and Pascal's principle. *(From HyperPhysics by Rod Nave, Georgia State University.)*

common cause of varices in countries in sub-Saharan Africa, with chronic infection in an estimated 440 million people, resulting in 200,000 deaths annually. Although liver function is often well maintained in these patients, hemorrhage from varices is the main cause of death. In absolute numbers, varices from schistosomiasis may be more common than liver cirrhosis.

ENDOSCOPIC SCREENING FOR ESOPHAGEAL VARICES

Prospective studies of the natural history of liver cirrhosis have demonstrated that 50% to 90% develop esophageal varices, and 30% will bleed. Bleeding from esophageal varices is associated with a mortality rate of at least 20% at 6 weeks despite spontaneous resolution of bleeding in 40% to 50%. Mortality from bleeding episodes depends on the severity of underlying liver disease ranging from less than 10% in patients with Child-Pugh grade A compared with over 70% in patients with advanced Child-Pugh grade C. Patients with very high portal pressure (HVPG >20 mm Hg) are at higher risk of rebleeding within 1 week of hemorrhage, have up to 84% risk of failure to control initial bleeding, and demonstrate a 1-year mortality rate of 64%.

TABLE 1 EGD Surveillance for Cirrhosis

Patient	EGD Findings	Repeat EGD
Compensated Cirrhosis	No Varices	Every 2–3 years
Compensated Cirrhosis	Small Varices	Every 1–2 years
Decompensated Cirrhosis		Yearly

In patients diagnosed with liver cirrhosis, the gold standard for screening for gastroesophageal varices is by esophagogastroduodenoscopy (EGD). Varices <5 mm are considered small. Findings at risk for bleeding include varices >5 mm and red whale markings. Figure 4 demonstrates the spectrum of esophageal varices. Table 1 summarizes EGD surveillance consensus recommendations in patients with cirrhosis.

PRIMARY PREVENTION

The strategy for preventing variceal hemorrhage is either by decreasing portal hypertension with nonselective β-blockers (NSBBs), carvedilol, or by endoscopic variceal ligation (EVL). NSBBs may help reduce the progression from small to large varices and the risk of mortality from hemorrhage, but they often are not well tolerated. Also, one must use caution with NSBBs in patients with refractory ascites. Carvedilol is a NSBB with mild anti-α_1 effect, thereby decreasing hepatic vascular resistance. However, carvedilol tends to drop mean arterial pressure (MAP), but may be more effective than EVL in preventing a first bleed if tolerated. The use of isosorbide mononitrate (ISMN) in randomized controlled trials demonstrated higher mortality rates in patients who received ISMN. Consensus among experts is that NSBB and EVL have similar efficacy in preventing a first esophageal bleed, and there is no benefit to combining the two treatments. Table 2 summarizes primary prevention therapies for esophageal hemorrhage.

If β-blockers are not tolerated, elective EVL is an option to prevent esophageal variceal hemorrhage. Banding is recommended only in the distal 5 cm of the esophagus, where the varices are more superficial. Banding more proximal may result in delayed hemorrhage from

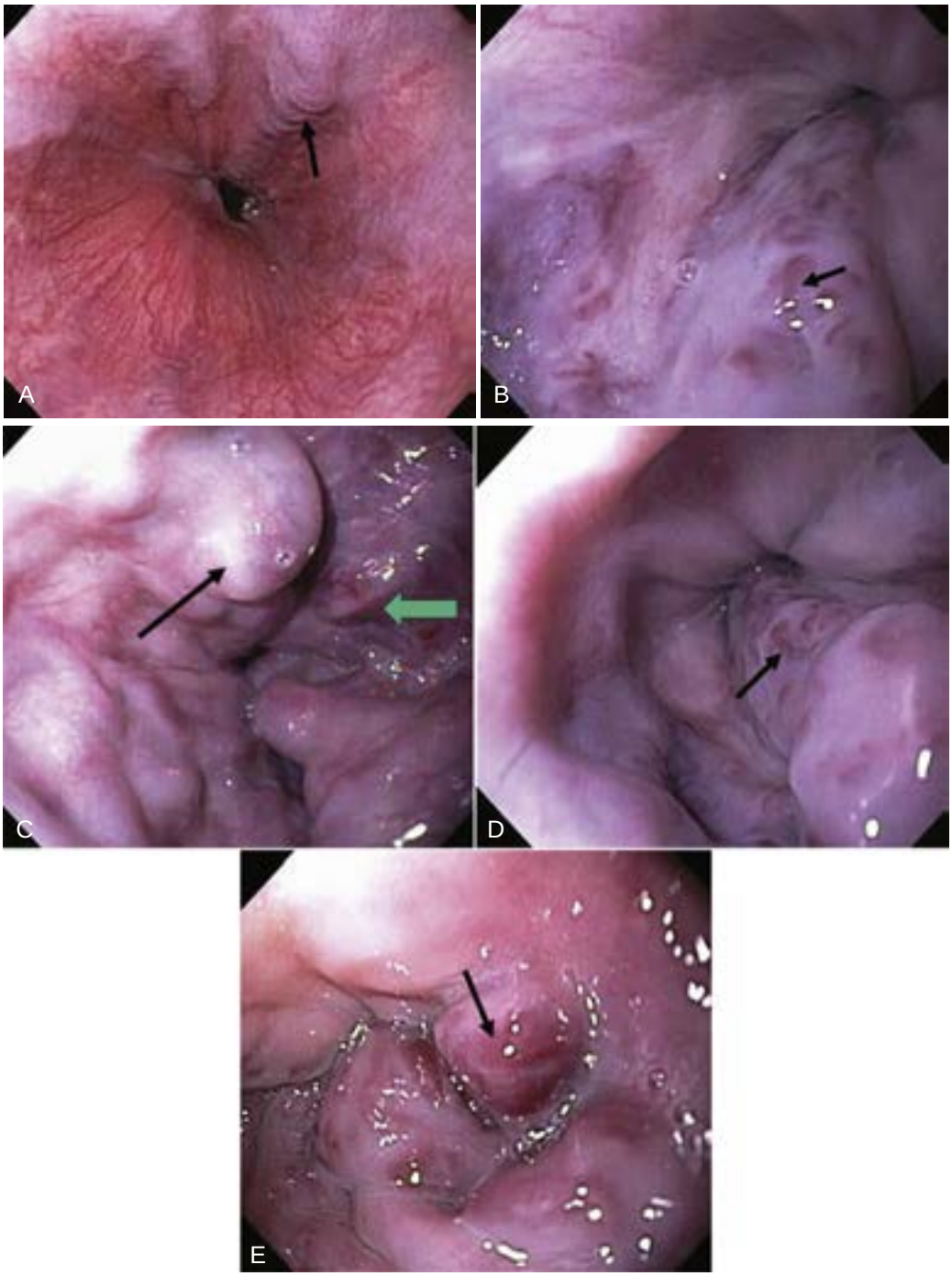


FIG. 4 **(A** and **B)** Endoscopic appearances of esophageal varices. **(A)** EGD demonstrating dilated and straight veins (small esophageal varices) in the distal esophagus *(arrow)*. **(B)** EGD demonstrating large esophageal varices, greater than 5 mm in diameter, with a fibrin plug *(arrow)* indicating the site of a recent bleed. **(C–E)** Large esophageal varices. Endoscopic view of the lower third of the esophagus demonstrating varices greater than 5 mm in diameter. **(C)** Large varix *(arrow)* with a red wale sign. **(D)** Red wale sign—longitudinal whip mark on varix *(arrow)*. **(E)** Large varix with hematocystic spot *(arrow)*. *(A and B from Friedman LS, Brandt LJ, Feldman M.* Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. *11th ed. Elsevier; 2021; C–E from Sanyal AJ, et al:* Zakim and Boyer's Hepatology: A Textbook of Liver Disease. *6th ed. Elsevier; 2012.)*

the varix as the band sloughs, leaving the posterior vessel wall still intact. Also, because bleeding is a potential complication of EVL, this procedure may better serve patients if performed in a high-resource environment. An EVL session every 1 to 8 weeks until eradication is effective. Proton pump inhibitors are used as adjunctive treatment for the 0.3% to 3% of ligation-related esophageal ulcers. Surveillance EGD should be performed in 1 to 3 months after eradication, then every 6 to 12 months to assess for recurrence.

TABLE 2 Primary Prevention of Variceal Hemorrhage in Patients With Small Varices With Red Spots or Varices >5 mm

Therapy	Therapy Dose	Therapy Goals	Maintenance
Propranolol	20–40 mg BID	HR 55–60 per minute	Check HR
	Max: 320 mg/day	SBP >90 mm Hg	Indefinitely
	160 mg/day with ascites		No F/U EGD
Nadolol	20–40 mg daily	HR 55–60 per minute	Check HR
	Max: 160 mg/day	SBP >90 mm Hg	Indefinitely
	80 mg/day with ascites		No F/U EGD
Carvedilol	6.25 mg daily	SBP >90 mm Hg	Indefinitely
	After 3 days 6.25 mg BID		No F/U EGD
	Max: 12.5 mg/day		
EVL	Every 2–8 weeks until eradication	Variceal eradication	EGD 3–6 months after eradication then every 3–6 months

BID, Twice a day; *EGD,* esophagogastroduodenoscopy; *EVL,* endoscopic variceal ligation; *FU,* follow-up; *HR,* heart rate; *SBP,* systolic blood pressure.

MANAGEMENT OF ACUTE GASTROESOPHAGEAL VARICEAL HEMORRHAGE

Resuscitation

Patients who present with upper gastrointestinal bleeding (UGIB) (hematemesis, melena, currant jelly stools) with findings suggestive of portal hypertension or cirrhosis (ascites, thrombocytopenia, elevated prothrombin time, history of cirrhosis) should be suspected of gastroesophageal variceal hemorrhage. Patients often present in hemorrhagic shock with altered mental status. Initial resuscitation should focus on the orderly evaluation of airway, breathing, and circulation. Hematemesis can result in aspiration, especially in patients with developing encephalopathy caused by hyperammonemia, so one should consider early intubation. Intravenous access with at least two large-bore IVs is essential. Restrictive balanced blood volume resuscitation should be initiated based on the physiologic response rather than hemoglobin levels while avoiding fluid overload from crystalloid, which may increase portal pressures. Quantification of blood loss is more challenging in gastrointestinal bleeds, but initiation of a massive transfusion protocol may help facilitate blood products and resources in patients at risk of exsanguination. Many cirrhotic patients have an existing coagulopathy that may require earlier initiation of platelet and fresh-frozen plasma transfusions.

Resuscitation of a hemodynamically unstable patient precludes waiting for laboratory values. However, restrictive resuscitation studies are mostly based on laboratory values and may be considered in hemodynamically stable patients. Restrictive resuscitation in previous prospective studies, defined by a hemoglobin transfusion threshold of <7 g/dL, was associated with higher survival, decreased rebleeding, and no significant increases in HVPG or portal pressures compared with a liberal hemoglobin transfusion threshold of <9 g/dL. Interestingly, in one prospective study, patients received significant volumes of crystalloid recorded averaging 5.5 L within the first 72 hours in both restrictive and liberal arms. More studies may be indicated to determine whether survival is influenced by also practicing restrictive crystalloid resuscitation in the setting of gastroesophageal variceal hemorrhage. A recent randomized clinical trial (HALT-IT) of over 12,000 patients with gastrointestinal bleeding demonstrated no benefit of tranexamic acid.

Intravenous Antibiotics

The risk of infection is about 60% in cirrhotic patients with gastrointestinal hemorrhage, with the exception of patients with Child-Pugh grade A cirrhosis, whose infection risk is only 5%. Antibiotics will significantly reduce the rate of infections, mortality, rebleeding, and transfusion requirements as demonstrated in clinical trials. Ceftriaxone 1 g/day for 7 days seems to be favored in patients with encephalopathy, ascites, malnutrition, and known quinolone resistance.

Vasoactive Agents

Vasoactive agents, such as octreotide, somatostatin, terlipressin, and vasopressin, have been shown to reduce all-cause mortality and decrease transfusion requirements. Octreotide and vasopressin are available in the United States. An octreotide IV bolus of 50 μg followed by an infusion of 50 μg/hour should be given over 2 to 5 days and should be initiated before endoscopy.

Prokinetics

The use of metoclopramide or erythromycin may help with visualization at endoscopy and is associated with a lower incidence of need for repeat EGD in UGIBs, but it has not affected survival. NGTs and lavage are not effective in evacuating clotted blood from the stomach or diagnosing UGIBs.

Balloon Tamponade

In patients for whom definitive treatment is not available, balloon tamponade with an esophagogastric tube is very effective until the patient can reach definitive treatment. Figure 5 illustrates three different variations of balloon tamponade tubes. Patients should be intubated before placing these tubes because of the risk of aspiration and poor tolerance. The Minnesota tube has four separate ports including a suction port and a balloon port for the esophagus. The tube must be placed well into the stomach (at least 50 cm) before inflating the gastric balloon to avoid esophageal perforation. Traction is placed on the tube until mild resistance is met. The placement must be verified by x-ray demonstrating the air-filled balloon in the

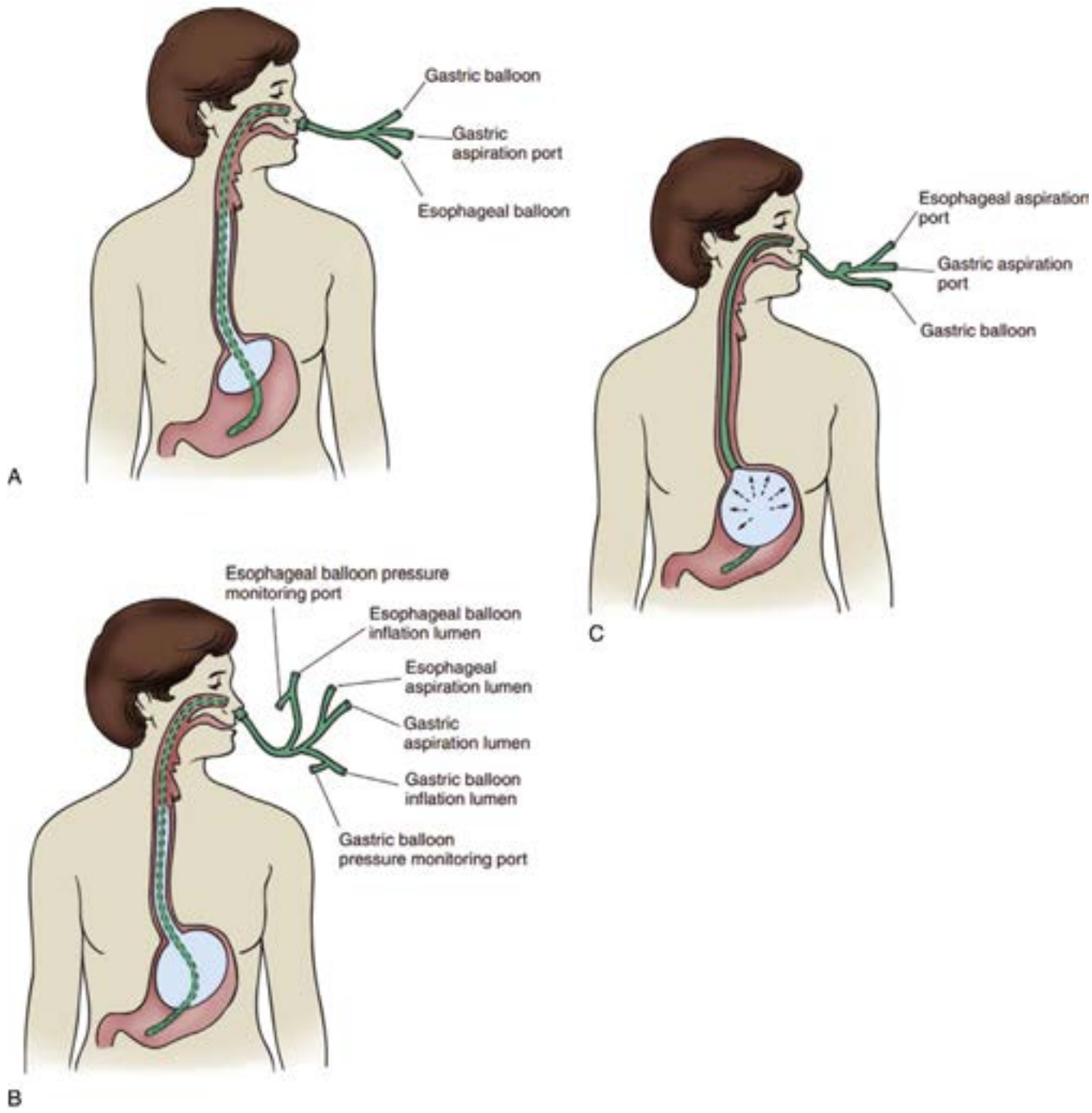


FIG. 5 Esophageal tamponade tubes. **(A)** Sengstaken-Blakemore tube. **(B)** Linton-Nachlas tube. **(C)** Minnesota tube.
(From Urden LD, et al. Priorities in Critical Care Nursing. *5th ed. Mosby, 2008.)*

stomach. Because most gastroesophageal varices are at the gastroesophageal junction, tamponade can usually be accomplished by only filling the gastric balloon. Mild traction is placed on the balloon of 0.5 kg to 1.0 kg using saline IV bags. If bleeding is seen from the esophageal suction port, the esophageal balloon can be carefully inflated. For clinicians practicing in low-resource areas, familiarity with the operation and location of a balloon tamponade tube can be life saving. The tube should not remain for more than 24 hours. Although these tubes can control bleeding in 80% of patients, they are associated with complications secondary to aspiration, migration, esophageal perforation, or esophageal necrosis.

Endoscopic Variceal Ligation

Once the patient is hemodynamically stable, an urgent EGD should be performed within 12 hours of admission with the patient intubated to avoid the risk of aspiration. EVL is the favored treatment over endoscopic sclerotherapy (EST) for controlling esophageal variceal hemorrhage as well as for secondary prevention. Several prospective, randomized trials comparing EVL to EST demonstrated that EVL was superior to EST for rapidly eradicating varices, less recurrent bleeding, increased survival, and fewer complications. These findings were validated in a meta-analysis. One study demonstrated

decreased rebleeding with EVL combined with a β-blocker. Several commercial multiband preloaded devices are available with transparent caps. Once the varix is identified, the cap or tip is placed up to the varix with application of continuous suction to bring the varix within the cap for deployment of the band. Visualization of the bleeding varix may be a challenge in a bloody field requiring active flushing and suction. Consensus guidelines recommend EVL every 1 to 2 weeks until eradication to avoid rebleeding in the absence of prospective trials typically requiring 2 to 4 sessions. During secondary prophylaxis sessions, bands are placed at the gastroesophageal junction working proximally in a helical fashion within the palisade and perforating zones (Fig. 6). Because esophageal varices can recur, surveillance EGD should be performed every 3 to 6 months after EVL. The presentation of EVL band-induced bleeding ulcer may occur in up to 14% of patients. PPIs may provide adjunctive therapy in preventing bleeding after EVL, but prospective trials are lacking.

Endoscopic Sclerotherapy

EST has been used to treat variceal hemorrhage for over 50 years and was adopted more widely in the 1970s. The advent of flexible endoscopy in the 1980s resulted in rapid progress of endoscopic treatment of variceal hemorrhage. Commonly used agents include ethanolamine oleate, polidocanol, sodium morrhuate, sodium tetradecyl sulfate, and ethanol at varying concentrations, volumes, and intervals. Trials have not defined a single most effective agent. EST is 90% effective in controlling esophageal variceal bleeding and may be performed in patients in whom EVL may be technically difficult. EST is also a less expensive option in lower-resource locations. Techniques include paravariceal injection adjacent to the varix or direct intravariceal injection of the sclerosant. Gastric varices in continuity with esophageal varices (GOV1) below the gastroesophageal junction may be treated with EST. Reported local and systemic complications of EST vary greatly in trials and may be related to operator experience and follow-up of patients. Complications may include retrosternal chest pain, dysphagia, esophageal ulcers with subsequent bleeding, esophageal strictures, esophageal perforation secondary to extensive necrosis, mediastinitis, bronchoesophageal fistula, bacteremia, acute respiratory distress syndrome, and death in 2%.

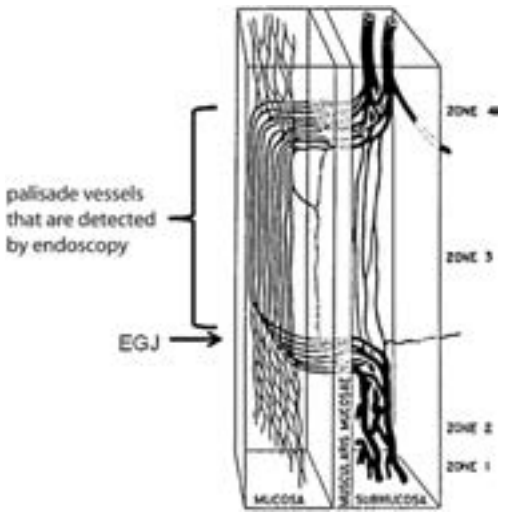


FIG. 6 Schema of the lower esophagus anatomy drawn by deCarvalho in 1966. Zone 3 is the junction of the area drained by the portal vein system and the systemic circulation. This segment begins caudally from the transition between the esophageal and gastric mucosa and ends cranially at the level of diaphragmatic penetration, spanning the entire abdominal portion of the esophagus. These longitudinal vessels, called *palisade vessels,* present in the mucosal layer of the lower esophagus, are detected by endoscopy. *EGJ,* Esophagogastric junction. *(From Ishimura N, Amano Y, Kinoshita Y. Endoscopic definition of esophagogastric junction for diagnosis of Barrett's esophagus: importance of systematic education and training.* Dig Endosc. *2009;21:213–218; adapted from De Carvalho C. Sur l'angio-architecture veineuse de la zone de transition oesophagogastrique et son interpretation fonctionelle. Cells Tissues Organs. 1966;64:125–162.)*

Other Endoscopic Techniques

Argon plasma coagulation has been combined with EVL to eradicate esophageal varices with a low recurrence rate and no recorded complications. However, this technique is expensive, and this equipment is not available in many endoscopic centers.

The technique of endoscopic clipping has also been described in treating acute variceal bleeding and for prevention, with favorable outcomes in small controlled trials, but it is not widely implemented or studied.

The use of detachable nylon mini-loops with similar efficacy as EVL has been largely abandoned after the development of preloaded multiband devices for EVL.

Injection of adhesives (e.g., cyanoacrylate-based tissue adhesives) compared with EVL for the treatment of esophageal varices demonstrated more minor complications and higher variceal recurrence rates. Complications include embolic events and equipment damage.

MANAGEMENT OF ENDOSCOPIC TREATMENT FAILURES

Transjugular Intrahepatic Portosystemic Shunt Placement

Placement of a transjugular intrahepatic portosystemic shunt (TIPS) by interventional radiology in the setting of acute variceal hemorrhage may be a salvage procedure for refractory or recurrent bleeding. This shunt is created by placing a covered metal stent between the hepatic vein and portal vein with the goal of decreasing portal pressure and decompressing esophageal varices as well as GOV1 and GOV2 gastric varices.

Esophageal Stent for Refractory Bleeding

In small studies, the use of self-expandable esophageal covered metal stents as a bridge therapy for refractory bleeding shows promise. These stents can stay in for days, allowing for optimization of the patients. One small randomized controlled study comparing esophageal stenting versus balloon tamponade in 28 patients demonstrated better control of bleeding, decreased transfusion requirements, and lower serious adverse events in the stenting group. Figure 7 shows an example of a self-expandable covered metal stent.

Gastric Varices

Gastric varices bleed less frequently than esophageal varices and account for 10% to 30% of all variceal hemorrhages; however, gastric variceal hemorrhages tend to be more severe, with higher mortality and rebleeding rates. The endoscopic and interventional radiology procedures are often predicated on the classification and pathophysiology of the gastric varices. As with esophageal varices, the risk of rupture increases with the size of the varix. If possible, patients with gastric varices may be better served at experienced, high-resource multidisciplinary centers because of their complexity and acuity.

Classification

Sarin's classification of gastric varices is the most commonly used, and gastric varices are classified into four types based on location (Fig. 8). Sarin's classification of gastric varices, prevalence, and incidence of bleeding are listed in Table 3.



FIG. 7 Self-expandable covered metal stent.

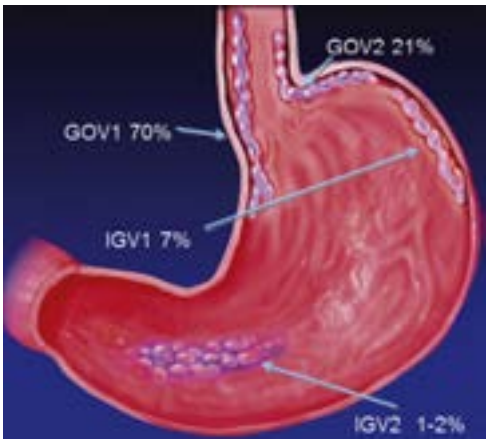


FIG. 8 Sarin's classification is the most commonly used for risk stratification and management of gastric varices. GOV type 1 (GOV1): EV extend below the cardia into the lesser curvature. GOV2: EV extend into the fundus. Isolated GV1 (IGV1) are located in the fundus. IGV2 are located elsewhere in the stomach. *EV,* Esophageal varices; *GV,* gastric varices; *GOV,* gastroesophageal varices; *IGV,* isolated gastric varice. *(From Elmunzer BJ, Chandrasekhara V, Khashab MA, Muthsamy VR.* Clinical Gastrointestinal Endoscopy. *3rd ed. Elsevier; 2019.)*

TABLE 3 Sarin's Classification of Gastric Varices, Prevalence, and Bleeding Risk

Classification	Location	Prevalence	Bleeding Risk
Gastroesophageal varix type 1 (GOV1)	Lesser curvature	70%–74%	25%
Gastroesophageal varix type 2 (GOV2)	Greater curvature	21%–24%	60%
Isolated gastric varix type 1 (IGV1)	Greater curvature	2%–7%	90%
Isolated gastric varix type 2 (IGV2)	Stomach/ duodenum	1%–2%	15%

Endoscopic Treatment of Gastric Varices

Endoscopic treatment of bleeding gastric varices includes the following:

- Band ligation with or without detachable snares
- Sclerotherapy
- Obturation with tissue adhesives or glue
- Thrombin injection
- Combined therapy
- Endoscopic ultrasound-guided therapy

Only limited data are available regarding the treatment of bleeding gastric varices. Results from limited prospective studies are often variable and uncontrolled; therefore, it is difficult to draw conclusions about the efficacy of one treatment over another.

In contrast with esophageal varices, band ligation does not appear to be the preferred treatment of gastric varices because of high rebleeding rates likely resulting from the failure to obliterate the entire feeding vessel. Also, sclerotherapy has been less effective in gastric varices as opposed to esophageal varices. Gastric varices often require larger volumes of sclerosant, especially with GOV2 and IGV1, resulting in more complications including large ulcerations, perforations, and mediastinitis. In acute gastric variceal bleeding, sclerotherapy may control bleeding in 60% to 100% of cases, with unacceptable rebleeding rates up to 90%. Sclerotherapy may be effective in treating GOV1 hemorrhage, but it should be avoided in GOV2 and IGV1 bleeding varices because of low success of primary hemostasis and the high rate of rebleeding.

Gastric variceal obturation (GVO) with tissue adhesives (e.g., *N*-butyl-2-cyanoacralate or fibrin glue) when compared with ligation or sclerotherapy appears to be the most effective endoscopic intervention for the treatment of acute gastric variceal hemorrhage. The endoscopic technique consists of injecting small aliquots (1–1.5 mL) of cyanoacrylate into the varix followed by a normal saline flush of volume equal to the needle catheter dead space as the needle is withdrawn from the varix. The tissue adhesives with fast polymerization using small aliquots appear to be associated with lower incidents of embolic complications that occur in 1% to 5%. Bacteremia is another complication of GVO, so antibiotics should be administered. Equipment damage from tissue adhesives is another complication. Several studies have reported initial hemostasis in 90%, with recurrent rebleeding rates of 15% to 30%. One to three sessions may be required for eradication, with success in GOV1, GOV2, and IGV1. Injection therapy of cyanoacrylate-based compounds for the treatment of gastric varices is not approved by the US Food and Drug Administration.

Direct injection of thrombin into a bleeding gastric varix published in several small series appears to show promise with high efficacy and low complications and may have a treatment role. Combination endoscopic therapy using ligation and sclerotherapy, GVO and ligation, and GVO with sclerotherapy have been described in small series with mixed results. EUS-guided injection of tissue adhesives and/or EUS-guided coil embolization into perforating veins has recently emerged as a possible tool for treatment of gastric varices in several small series.

Radiologic Intervention for Gastric Varices

When endoscopic treatment fails, TIPS may provide salvage therapy with initial hemostasis of 87% to 100% and a rebleeding rate of 10% to 30%. Frequent complications of TIPS include encephalopathy and shunt stenosis or occlusion.

Of note, gastric varices classified as IGV1 can be seen in patients with cirrhosis and portal hypertension and in patients with splenic vein or portal vein thrombosis. These patients may present with massive hemorrhage. Because 80% to 85% of IGV1 drain via a gastrorenal shunt into the left renal vein, this provides a pathway to varix outflow for interventional radiologists to perform balloon-occluded retrograde transvenous obliteration (BRTO). During this procedure, the varix is occluded with a balloon followed by the delivery of coils

and sclerosants with the goal to obliterate the varix. Although BRTO has been shown to be as effective as TIPS in the treatment of gastric variceal bleeding, it does not produce encephalopathy, but BRTO does increase portal pressure, which may worsen esophageal varices. Major complications include shock and atrial fibrillation.

SUMMARY

Although mortality from gastroesophageal variceal hemorrhage has decreased over the decades with the advent of advanced endoscopic and image-guided treatments, variceal bleeds still result in significant morbidity and mortality. Hence, primary prevention of gastroesophageal bleeding plays an essential role in reducing morbidity and mortality. The optimal management of acute gastroesophageal variceal hemorrhage with early intubation, balanced, restrictive resuscitation of blood products, IV antibiotics, vasoactive agents, and endoscopic intervention remain the cornerstone of managing these patients. For bleeding esophageal varices, band ligation remains the gold standard treatment. Tamponade by gastroesophageal balloon tubes or self-expandable fully covered esophageal stents provide bridging treatments. Gastric variceal hemorrhage treatment is often based on the classification, location, and drainage pattern of the varix with gastric variceal obturation by tissue adhesives as the most effective therapy. Image-guided interventions include TIPS, EUS-guided embolization, and BRTO. High-resource centers are able to provide these patients with the multidisciplinary treatment options.

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Transjugular Intrahepatic Portosystemic Shunt

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INTRODUCTION

The creation of a transjugular, intrahepatic, portosystemic shunt (TIPS) was put forth as a possible treatment for the symptoms of portal hypertension in the early 1970s, with the first TIPS placement performed in 1989. TIPS is an artificial connection between the portal and hepatic vein, bypassing the liver, and a durable solution for portal hypertension with a long-term efficacy of 90%. Meticulous technique and stringent patient selection are critical to keep the morbidity and mortality in patients with portal hypertension at a minimum. Refinement of the technique and additional techniques deployed by interventional radiologists, including direct intrahepatic portosystemic shunt (DIPS) and adjunct techniques for treatment of variceal bleeding (such as balloon- or plug-assisted transvenous obliteration), have expanded treatment options for patients with complications of portal hypertension.

INDICATIONS

Causes of portal hypertension are summarized in Table 1. Whatever the causative pathophysiology, TIPS can directly reduce or normalize the elevated portal pressure and reduce or ameliorate symptoms. Current indications for TIPS, which are expanding, along with contraindications are summarized in Table 2. TIPS can be performed on an emergent basis or as an elective procedure. Multidisciplinary communication between hepatologists, interventional radiologists, and transplant surgeons is necessary to identify and select appropriate patients for TIPS.

Acute Variceal Bleeding and Secondary Prophylaxis

Portal hypertension can cause varices along the entire gastrointestinal tract from the esophagus to the rectum to divert the elevated portal flow to the heart. Gastroesophageal varices, formed between the

TABLE 1 Causes of Portal Hypertension

Presinusoidal	Perisinusoidal	Postsinusoidal
Portal, splenic, or superior mesenteric vein thrombosis	Cirrhosis	Budd-Chiari syndrome
Idiopathic portal hypertension	Congenital hepatic fibrosis	Veno-occlusive disease (Sinusoidal obstruction syndrome)
Mass effect (i.e., tumor)	Sarcoidosis	Chronic passive congestion (Nutmeg liver)
Schistosomiasis		Mass effect (i.e., tumor)
Primary biliary cirrhosis		
Alcoholic central sclerosis		
Endothelitis (liver rejection, radiation injury)		
Arterio-portovenous fistula (traumatic or Osler-Weber-Rendu)		
Hyperdynamic splenomegaly (infectious or myelodysplastic)		
Nodular regenerative hyperplasia		

TABLE 2 Indications and Contraindications for TIPS

Indications		Contraindications	
Indication	**Condition**	**Absolute**	**Relative**
Portal variceal hemorrhage	Refractory to medical/ endoscopic management	Uncorrectable bleeding diathesis	Hepatic vein thrombosis
Recurrent ascites	Refractory to medical management		Portal vein thrombosis
Recurrent, hepatic hydrothorax	Refractory to medical management		Poor liver function reserve
Hepatorenal syndrome	May help in Type 2		Severely elevated right heart pressure
Hepatopulmonary syndrome	Scant evidence		Severe encephalopathy
Budd-Chiari syndrome	Bridge to transplant		Active infection
Portal gastropathy	Refractory to β-blockers		

coronary vein (also known as the *left gastric vein*) and the lower esophageal veins, are the most likely to rupture and bleed because of the high transluminal pressure gradient caused by the negative esophageal luminal pressure during inspiration. Primary treatment of bleeding gastroesophageal varices is medical management (i.e., somatostatin or octreotide) followed by endoscopic management (i.e., sclerotherapy/ epinephrine injection, band ligation, clip placement). Even though endoscopic management is often temporarily successful, recurrent bleeding is expected in more than half of the patients. Unlike medical or endoscopic management, TIPS addresses the underlying portal hypertension and, outside of liver transplant, is the only definitive treatment. In patients at high risk of treatment failure (i.e., Child-Pugh class B with active bleeding at index endoscopy or Child-Pugh class C score lower than 14 points), TIPS placement is indicated at an early time point, which is within 72 hours (ideally <24 hours).

Ascites

Ascites is the most common complication of cirrhosis. In addition to severe limitations in lifestyle, ascites poses risks for bacterial peritonitis, renal failure, and increased mortality. Initial management of ascites is medical and includes diuretics, aldosterone antagonists, and sodium restriction. Intermittent paracentesis generally follows, which is often done on an outpatient basis. In advanced stages, ascites becomes refractory to medical management and repeat paracentesis becomes burdensome. TIPS is very effective in eliminating ascites, but as the root causes of ascites are hemodynamic/hormone related, the response is not immediate. It may take 2 to 4 weeks after TIPS for ascites to resolve, during which time paracentesis may be necessary. Often, drainage of ascites before TIPS placement is performed to decrease movement of the liver.

Hepatic Hydrothorax

Hepatic hydrothorax is defined as the accumulation of at least 500 mL of pleural fluid in a patient with cirrhosis, without cardiopulmonary disease. Even though this definition is not highly specific to hepatic hydrothorax, additional signs such as isolated right-sided hydrothorax and concurrent ascites help confirm the diagnosis. It occurs in less than 10% of patients with cirrhosis as peritoneal fluid

permeates via diaphragmatic communications. Initial management is sodium restriction and diuretics; in nonresponsive patients, TIPS will eliminate hydrothorax in most and decrease the frequency of thoracentesis in the rest.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) portends a poor prognosis for the cirrhotic patient, as it occurs during the late stages of the hemodynamic changes related to cirrhosis. Alterations in vasoactive hormones responding to these hemodynamic changes result in splanchnic vasodilation, renal artery vasoconstriction, and the opening of small intrarenal arteriovenous communications. The result is renal hypoperfusion and ensuing renal failure.

Two distinct forms of HRS have been identified: *type 1 HRS*, which progresses rapidly, and *type 2 HRS*, which evolves slowly. Type 1 HRS is precipitated by either an event that incites acute-on-chronic liver failure, an exaggerated systemic inflammatory response, or kidney dysfunction as part of a broader multiorgan failure. Targeting the precipitating event is the hallmark of treatment for type 1 HRS. Type 2 HRS results from the reduction of effective arterial blood volume created by a shift of fluid from the intravascular compartment to the extravascular compartment (i.e., ascites). Noncontrolled studies suggest using TIPS to reduce the production of ascites in type 2 HRS.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is the presence of intrapulmonary vasodilation and multiple small right-to-left shunts that result in impaired gas exchange. Because of the lack of data, TIPS cannot be recommended as standard treatment for hepatopulmonary syndrome. However, in selected cases, especially in severely compromised patients on the liver transplant list, TIPS may prove a lifesaving bridge to transplant.

Budd-Chiari Syndrome

Budd-Chiari syndrome is an uncommon condition caused by obstruction of the hepatic venous outflow tract, resulting in cirrhosis and portal hypertension. The etiology of Budd-Chiari syndrome encompasses several conditions; it is deemed primary when the hepatic venous outflow obstruction is primarily a venous problem (patients with hypercoagulable states resulting in thrombus, venous webs) and secondary when it relates to extrinsic compression (compression from tumors, cysts, or abscesses). Clinical presentation may be asymptomatic, fulminant, acute, subacute, or chronic.

The treatment for patients presenting with fulminant Budd-Chiari syndrome, which develops within a few days with severe liver failure, abrupt onset of ascites, and hepatomegaly, is liver transplantation. If caused by a hepatic venous web, angioplasty and placement of a TIPS or DIPS has proven to be a valuable tool in bridging these patients with fulminant Budd-Chiari syndrome to transplant.

In the nonfulminant forms of Budd-Chiari syndrome, anticoagulation is the first-line therapy. When anticoagulation fails, TIPS is a reasonable and accepted next step, as is DIPS if the hepatic veins are occluded. The use of TIPS in this patient population was examined in a large retrospective study that showed 1-year and 10-year transplant-free survival were much greater than expected. The American Association for the Study of Liver Diseases (AASLD) now recommends creation of a TIPS in patients with Budd-Chiari syndrome who fail to improve with anticoagulation.

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy (which is distinguished from vascular ectasia) is the diffuse dilation of gastric veins that, along with the inflamed and fragile mucosa of the stomach, predispose the patient to bleeding. Gastric varices occur less frequently than esophageal varices but are associated with massive bleeding events and higher mortality rates. Various treatment modalities, including pharmacotherapy and endoscopic treatment, can be used as prophylactic agents and acute treatment of bleeding portal gastropathy. However, without portal decompression, rebleeding is imminent. TIPS can help decrease portal pressures, which can help decompress and control variceal bleeding, and is indicated in portal hypertensive gastropathy. However, patients with poor hepatic reserve, as defined by the Model for End-Stage Liver Disease (MELD) score >17–19, are shown to have a significantly higher 3-month mortality rate than those with lower MELD scores. In patients with isolated portal hypertensive gastropathy, balloon-occluded retrograde transvenous obliteration (BRTO) and TIPS have been well described in the literature as effective procedures in managing gastric varices with low rebleeding rates.

TECHNIQUE

Patient Preparation

Many complications of TIPS can be avoided or reduced by proper patient workup. Review of pertinent cross-sectional imaging confirms a patent (nonthrombosed) portal vein. This minimizes the number of attempts to engage the portal vein and minimizes associated risk for bleeding. Good hydration minimizes risk of acute renal failure. Initiation of metronidazole or lactulose mitigates the risk of encephalopathy. Patients should be blood-typed and cross-matched in the event of a bleeding complication. Finally, relevant risks, especially the 30-day mortality, which ranges from 1% to 3% for elective procedures in well-compensated patients to 30% for emergent TIPS in patients with advanced liver disease, should be understood by the treating physicians, the patient, and their family. Detailed steps with rationale for the TIPS placement procedure are shown in Figure 1.

Diagnostic Assessment

Optimizing the TIPS outcomes requires not only anatomic assessment, but also functional assessment of the patient's hemodynamic status. One strong contraindication to TIPS is elevated right heart pressure; ensuring that the right atrial pressure is not severely elevated is mandatory. If this is not done, shunting of portal venous blood to an overburdened right heart can result in pulmonary congestion, frequently necessitating intubation. Right atrial pressures below 15 mm Hg are generally safe, whereas pressures above 20 mm Hg predispose patients to acute right heart failure. There are no specific guidelines; thus, sound clinical judgment is important; for example, an unstable patient with ongoing variceal bleeding and a right atrial pressure of 16 mm Hg should not be automatically precluded from a potentially lifesaving TIPS.

After selecting the right hepatic vein, free and wedged hepatic venous pressures are measured and usually confirm portal hypertension. Normal corrected pressures are not accurate in general and should not necessarily terminate the procedure. In fact, they are wholly inaccurate in cases of presinusoidal (e.g., Budd-Chiari syndrome) portal hypertension.

If the direct portal pressure is within normal limits, TIPS creation is abandoned irrespective of the clinical picture. If a TIPS is not possible or contraindicated, the gastroesophageal varices can be embolized via a catheter to stop the hemorrhage without placing a TIPS. Balloon-assisted transvenous obliteration (BRTO) and its derivative procedures are very effective but temporary; the ongoing portal hypertension will likely cause new varices to form (Fig. 2).

If the direct portal pressure is elevated, the stent is advanced through the larger sheath, keeping it constrained and in position. The sheath is pulled back into the right atrium, uncovering the stent. The distal 2 cm of the stent are uncovered and flare out on withdrawal of the sheath. The rest of the stent is then fully expanded under fluoroscopy.

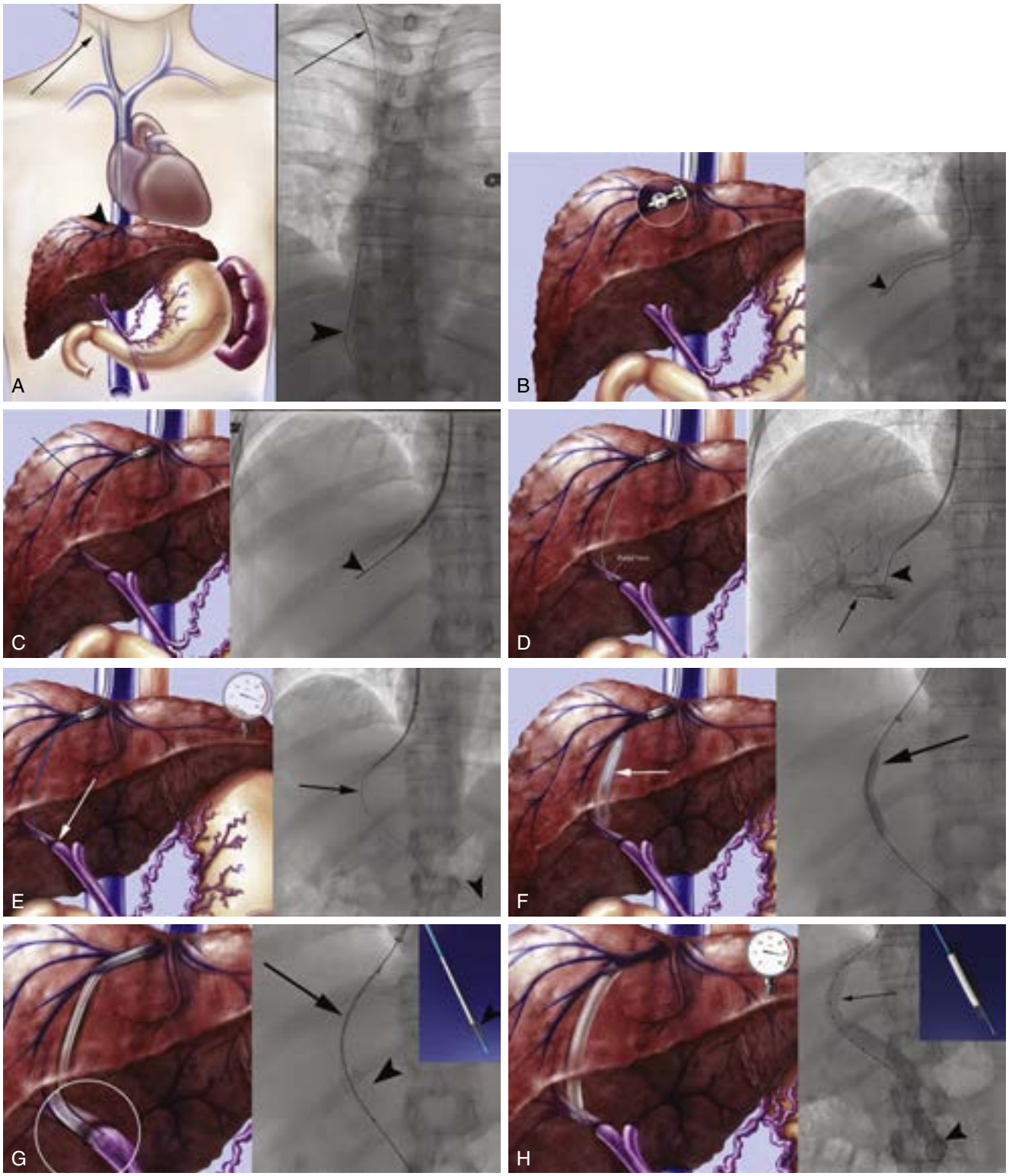


FIG. 1 Steps of performing a transjugular intrahepatic portosystemic shunt (TIPS) placement. **(A)** Access into the right hepatic vein *(black arrowhead)* is achieved through the right internal jugular vein *(black arrow)* to the inferior vena cava (IVC). Once the right hepatic vein is selected **(B),** a balloon catheter *(black arrow)* may be used to measure indirect portal pressures. Right portal vein is accessed through the liver parenchyma **(C)** from the right hepatic vein with a long needle *(black arrow)*. Confirmation of proper portal vein access is obtained with contrast injection **(D)** via a catheter *(black arrow)*. A wire *(arrows)* is then advanced deep with its tip *(arrowhead)* into the portal vein **(E).** At this point direct portal pressures are obtained. If no portal hypertension is found, the operator must exclude presinusoidal causes (i.e., splenic vein thrombosis, narrowing). If no presinusoidal cause is found, TIPS is aborted. Balloon dilation of the liver tract is performed **(F)**. The traversed liver parenchyma is fibrotic and difficult to cross unless predilated. A small caliber (4- to 6-mm diameter) balloon *(white arrow)* is used to predilate the liver parenchyma between the right portal and hepatic veins. The TIPS stent *(arrow)* is partially deployed in the portal vein **(G)**. Its distal 2 cm *(black arrowheads)* are self-expandable and used to anchor the stent while the operator pulls the stent back for positioning. Once position is satisfactory **(H)**, the rest of the stent is fully extended *(arrow)*. Final pressures are measured and a portal venogram is performed via a catheter *(arrowhead)* to confirm proper positioning and function. *(Color images courtesy Jeni Fairman and Dr. Cory Sandone, Department of Art as Applied to Medicine, Johns Hopkins University.)*

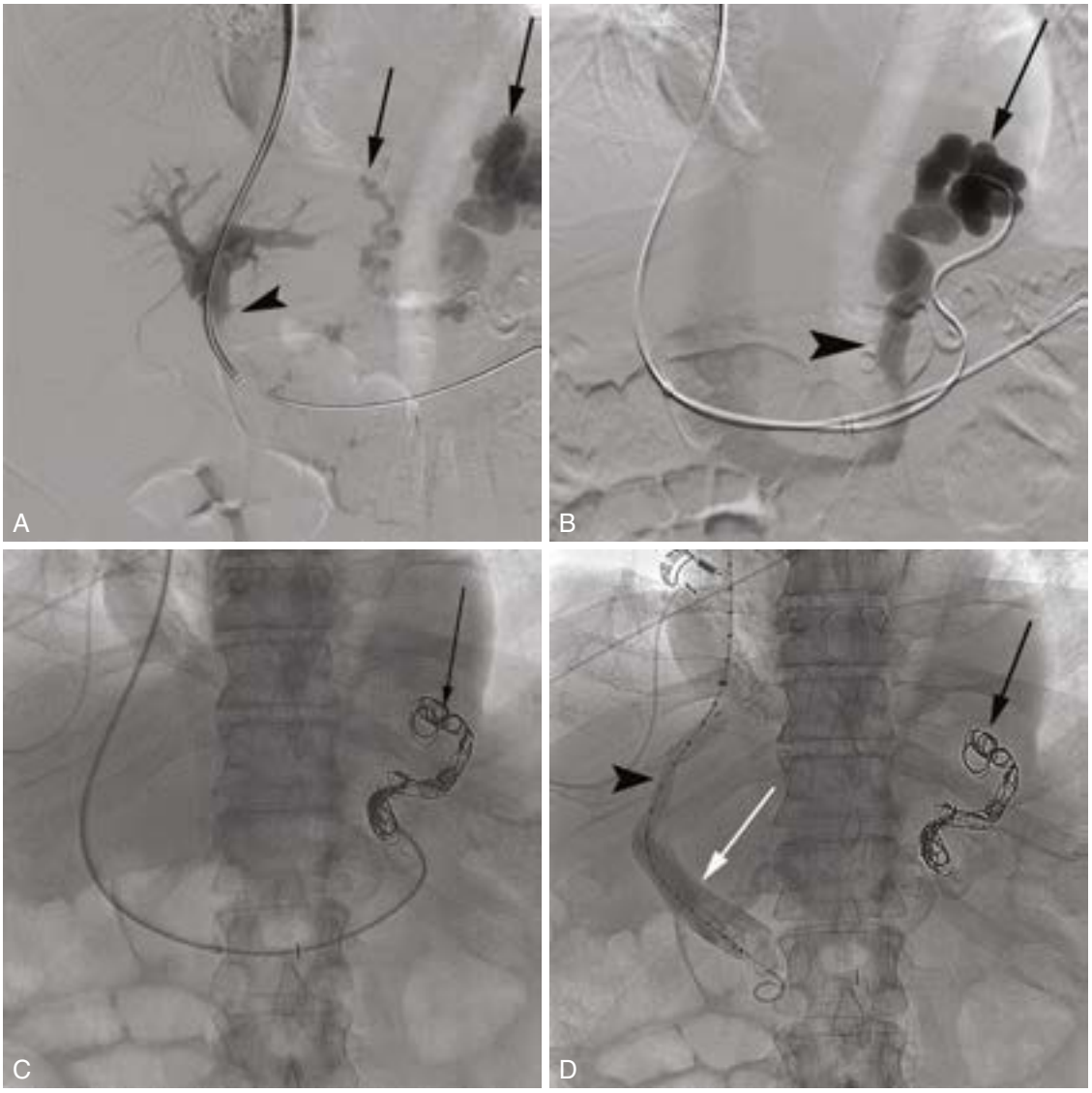


FIG. 2 Transjugular intrahepatic portosystemic shunt (TIPS) with partially occlusive portal vein thrombus and balloon retrograde transvenous obliteration (BRTO). **(A)** Portal venogram obtained through tract from the inferior vena cava (IVC), through the right hepatic vein and into the portal vein demonstrates a filling defect in the portal vein *(black arrowhead)* consistent with thrombus. Large varices visualized in the left upper quadrant of the abdomen *(black arrows)*. Selective catheterization of large varix **(B)** with para-esophageal varix *(black arrow)*. A large draining vessel is visualized *(black arrowhead)*. Deployment of embolization coils **(C)** in the previously visualized varix *(black arrow)*. TIPS shunt **(D)** subsequently deployed into the portal vein. Coils from embolized varix visualized *(black arrow)*. Portal venogram demonstrates a patent proximal portal vein *(white arrow)*.

Shunt Evaluation

Usually a 10-mm diameter stent is used, and initially it is dilated up to 8 mm in diameter. The direct portal pressure is measured again; if it is not satisfactory, a 10-mm balloon is used to open the stent to capacity. The smaller the stent diameter, the lower risk of encephalopathy postprocedure. A final portal venogram is performed to document flow and lack of variceal filling.

SPECIAL CASES

Direct Intrahepatic Portosystemic Shunt

DIPS is a recently developed modification to the TIPS procedure. Using intravascular ultrasound guidance, DIPS has been shown to decrease radiation dose and procedural time compared with TIPS. DIPS uses the caudate lobe as a parenchymal tract to create a side-to-side portocaval shunt, which removes the possibility of hepatic vein stenosis. Portal venous access is then accomplished, and a shunt can be created using a polytetrafluoroethylene-covered stent graft. Creation of specific stent-graft devices have improved patency rates.

In patients with an occluded TIPS, challenging anatomy, calcification of the portal vein, or portal vein thrombosis due to hepatocellular carcinoma, DIPS is of value. Additionally, the creation of a TIPS in a patient with Budd-Chiari syndrome is especially challenging because the hepatic veins are thrombosed (Fig. 3). This appears as the classic spider vein appearance on a hepatic venogram. Although portal decompression is best accomplished by placing the TIPS from the hepatic to the portal vein, DIPS is often the best option when the hepatic veins are occluded.

Parallel Transjugular Intrahepatic Portosystemic Shunt

Rarely, despite a previous TIPS, the patient's symptoms may not be alleviated completely. If revision has already been attempted, a second TIPS may be placed using the other hepatic and portal veins (Fig. 4).

Transumbilical, Transplenic, or Direct Portal Access

When access into the portal vein is challenging due to anatomy or thrombosis of the portal vein, the operator has several other options. First, access into the umbilical vein, which is usually dilated, provides a conduit to the left portal vein. A catheter there allows opacification of the portal venous system, which provides a better target for TIPS.

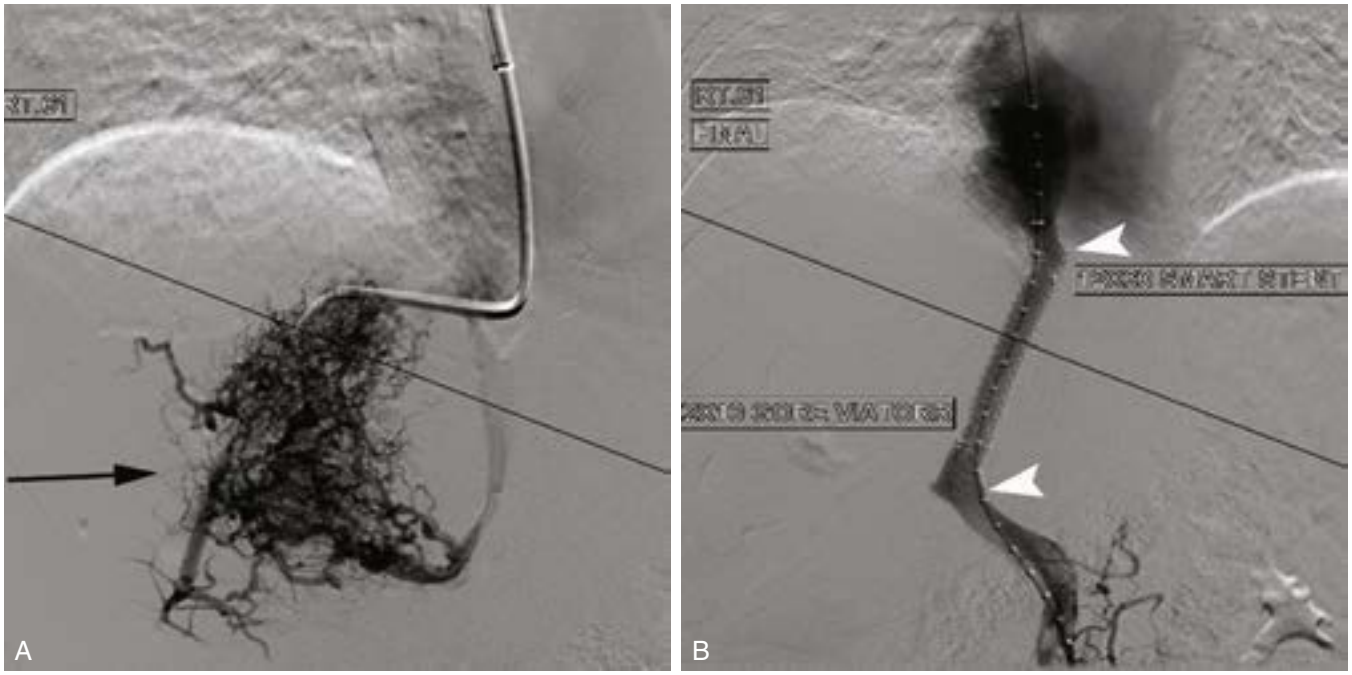


FIG. 3 Direct intrahepatic portosystemic shunt (DIPS) in a patient with Budd-Chiari. Frontal subtracted hepatic **(A)** and post-TIPS portal **(B)** venograms in a patient with Budd-Chiari. Hepatic venogram (A) shows the "spider-like" appearance *(arrow)* of multiple small collateral draining veins. The TIPS stent *(arrowheads)* allows the venous drainage to bypass the thrombosed hepatic veins (B). Because the hepatic vein is thrombosed, the stent extends directly from the inferior vena cava (IVC) directly to the right portal vein.

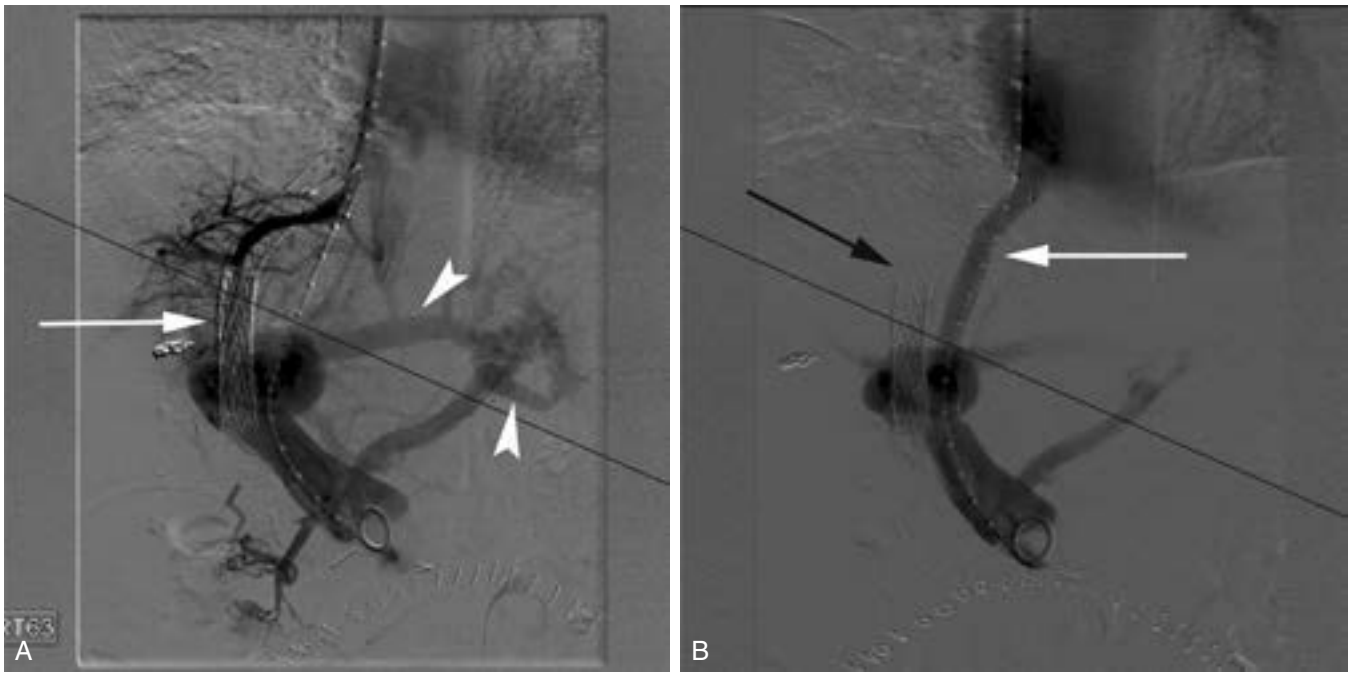


FIG. 4 Parallel TIPS. Frontal subtracted portal venogram **(A)** via a catheter placed through the middle hepatic vein shows the previously placed right hepatic to right portal vein TIPS *(white arrow)* to be occluded. Because of this, the patient had recurrent bleeding from gastric varices *(white arrowheads)*. Repeat portal venogram **(B)** after placement of a parallel TIPS *(white arrow)* shows antegrade flow into the right atrium and lack of filling of the gastric varices. Previously placed TIPS stent *(black arrow)* is unchanged and does not contribute to flow.

Second, access through a naturally occurring portosystemic shunt, such a splenorenal shunt, sometimes can be used to gain access to the portal circulation. Finally, direct access through the spleen into the splenic vein is an option (Fig. 5). When these options are not feasible, direct percutaneous access into the right or left portal vein can allow for contrast opacification and targeting.

Reversal or Revision of Transjugular Intrahepatic Portosystemic Shunt

Occasionally, a TIPS reversal or revision is necessary. This is most commonly in the setting of recurrent bleeding or ascites, in which case a duplex ultrasound of the stent can determine flow and detect stenosis. This can be addressed by placing a second stent and/or balloon angioplasty. Limited liver reserve or overzealous shunting may result in liver failure or intractable encephalopathy. In such cases, the interventional radiologist has the option to decrease the shunting or shut down the TIPS altogether. Several maneuvers exist to reduce shunting, including placing a stent within the TIPS, two stents side-by-side, or even a waisted (hourglass-like) stent (Fig. 6). If these interventions are not possible or inadequate, the entire TIPS can be shut down. TIPS shutdown is a rarely performed and advanced procedure.



FIG. 5 Transsplenic TIPS in patient with complete portal vein occlusion and worsening ascites. The thrombosed portal vein makes splenic vein access necessary. **(A)** Splenic venogram via direct percutaneous splenic puncture *(black arrowhead)*. Angiography demonstrates prominent varices and collateral vessels *(black arrows)*. Angioplasty of the splenic vein **(B)** near the confluence *(black arrowhead)* through the transsplenic catheter *(white arrow)*. A catheter has been placed in the right internal jugular vein and hepatic vein. A long needle used for creation of the parenchymal tract *(black arrowhead)* extends partially into the hepatic parenchyma. The balloon was used as the target for the TIPS needle. Incidental note is made of a plastic internal common bile duct drain *(white arrowhead)*. After wire access *(black arrow)* to the portal vein *(white arrow)* via the right hepatic vein **(C)** through the portal vein the transgressed hepatic parenchyma is dilated *(black arrowheads)*. After TIPS shunt deployment **(D)**, final portal venogram through the transsplenic catheter *(black arrowhead)* demonstrates patent flow through the stent placed in the proximal splenic and portal veins *(white arrow)* and TIPS stent connecting the right portal vein and right hepatic vein *(black arrowhead)*.



FIG. 6 TIPS stent revision in the setting of persistent encephalopathy. To reduce flow through the TIPS stent, a second longer stent can be partially opened *(white arrow)* through the original stent *(black arrow)*. Pressures are sequentially measured as the second stent is gradually deployed to desired effect.

TIPS in Transplanted Livers

TIPS is often used to bridge to liver transplantation in patients with end-stage liver disease. Before transplantation, TIPS is used to manage complications of portal hypertension and ensure patients can remain as transplant candidates. The same etiologies that resulted in native liver failure in the first place can occur in the transplanted liver, leading to the recurrent portal hypertension. For this reason, indications for TIPS in transplanted livers are the same as those for patients pretransplantation. Studies have shown that TIPS can be effective in addressing early complications such as portal vein thrombosis and delayed graft functions. Understanding of the venous anastomosis of the inferior vena cava is critical to performing a TIPS in a transplanted liver; the piggyback technique to TIPS can be used to address this challenge. In this technique, TIPS placement is performed in the left internal jugular vein rather than in the right.

Fewer shunt stenoses and procedural complications have been recorded in posttransplant patients compared with pretransplant patients. Approximately 10% to 20% of stents in patients with transplants require revision compared with 70% in patients without transplants. However, patients with transplants who undergo TIPS have higher risks of infection, renal failure, and neurologic complications than patients without transplants. Clinical success rate of TIPS in patients without transplants is much higher than in patients with transplants (93% vs. 77%).

TIPS in the Setting of Portal Vein Thrombus

Originally, portal vein thrombosis was considered a contraindication to TIPS. However, a large recent meta-analysis has shown that portal venous recanalization performed with TIPS is a safe and highly successful option (recanalization rates >85%) in patients with portal vein thrombus. Because portal vein thrombosis is a relative contraindication to transplant, the treatment of portal vein thrombus with TIPS is now routinely practiced at several large transplant centers in the United States and even in patients with complete portal vein thrombus (see Fig. 5). Either transsplenic or transhepatic access is required to assist with recanalization. Recanalization techniques can be complex, particularly in the setting of tortuous collateral formation. The primary complication of portal vein recanalization is perisplenic bleeding; thus, dropping hemoglobin after the procedure should warrant a search for a perisplenic hematoma and potentially embolization. Additionally, portal vein rupture, which is a very rare complication, should be prepared for in the setting of angioplasty and appropriately sized stent grafts should be on hand to treat rupture if necessary.

CLINICAL OUTCOMES

Clinical Response to TIPS

Regardless of whether TIPS is performed as an elective or emergent procedure, admission overnight to the critical care unit is routine. If the postoperative course is uneventful, a patient who underwent an elective TIPS can be discharged the next day. Follow-up of liver function tests (LFTs) and evaluation for encephalopathy are performed during the inpatient stay directly following TIPS placement; a small increase in LFTs is expected postprocedurally.

TIPS is the most effective option for treating gastroesophageal variceal bleeding. The rebleeding rate after TIPS placement is 4% per year, the lowest amongst all treatment options, including endoscopic management. TIPS is reserved for use after failure of endoscopic management, only because of the greater risks associated with it, particularly encephalopathy. Cessation of bleeding is evident almost immediately after TIPS creation.

TIPS also has been shown to be effective in treating ascites, as well as reducing the risk of ascites by 50% to 80% over the patient's life. In addition, TIPS has been shown to improve survival and transplant-free survival compared with other treatment options. Resolution of ascites may take up to 4 weeks after TIPS placement.

In patients with HRS, TIPS can improve renal function in 62% of patients. However, it can occasionally be difficult to distinguish noncirrhotic-related chronic renal insufficiency from HRS.

Complications and Management

The complications related to TIPS are shown in Table 3. The most feared complication is liver failure, which usually results from excessive portohepatic venous shunting in a liver with limited baseline reserve. If patients with limited liver reserve are excluded appropriately, the risk of liver failure is 2% to 4%.

Encephalopathy can be seen in up to 12% of patients with compensated liver disease and up to 50% of patients with decompensated liver disease. Flagyl and lactulose provide significant relief for such patients, but a small percentage (~4%) will not respond and may require TIPS reversal.

Death from sepsis is rare (<1%). Bacteremia results in TIPS stent seeding; the stent graft infection can be very challenging or impossible to treat. Broad-spectrum antibiotics may clear the bacteremia, but in some cases, it recurs after cessation of treatment, as the seeded stent elutes more bacteria. Active infection is an absolute contraindication to TIPS, and any infection must be cleared before intervention.

The overall post-TIPS 30-day mortality ranges from less than 2% to 30% and is mostly dependent on whether the procedure is performed emergently or electively. Higher mortality rates are seen

TABLE 3 Complications of TIPS

Complication	Predisposing Factor(s)	Mitigating Factors
Liver failure	Limited reserve High bilirubin Overshunting	Reduce or close the TIPS
Encephalopathy	History of encephalopathy High ammonia levels Limited reserve	Reduce or close the TIPS Flagyl or lactulose
Bleeding	Difficult anatomy Abnormal coagulation profile	Correct coagulation profile
Sepsis	Active infection	Treat infection before TIPS
Renal failure	Elevated creatinine Dehydration High contrast load	Hydrate Bicarbonate Utilize CO_2

in patients with poorly compensated liver disease who are having TIPS placed on an emergent basis, usually for life-threatening variceal bleeding. For patients with compensated liver disease who are having an elective TIPS created, mortality is less than 5%. It is therefore important to carefully select patients and refer for TIPS before an emergency. Administration of vasoactive drug therapy, such as somatostatin and octreotide, in patients presenting with acute variceal hemorrhage has been shown to reduce the risk of mortality at 7 days, in addition to improving hemostasis and shortening length of stay.

The MELD score, routinely used to predict survival with end-stage liver disease and allocate transplants, was initially developed to predict poor survival in patients after creation of a TIPS. The cut-off score for high-risk short-term mortality (expected survival of less than 3 months after TIPS creation) was 18. Subsequent research using the Na-MELD score that also incorporates serum sodium (Na) has been shown to be a more accurate predictor of risk post-TIPS (≥15). Most versions of the MELD score are more accurate predictors of risk after TIPS than the Child-Pugh score.

Follow-Up

Long-term TIPS follow-up is based mostly on clinical signs and symptoms. Ultrasound surveillance is useful if signs or symptoms of recurrent portal hypertension occur; importantly, TIPS ultrasound should generally be avoided for the first 2 weeks after TIPS creation. This is because the newly placed TIPS has air trapped within it, which limits ultrasound penetration and can simulate the sonographic appearance of an occluded TIPS. Recurrent variceal bleeding or ascites is a very specific indicator of TIPS restenosis or occlusion and should prompt a diagnostic venogram or intervention.

SUMMARY

The most important determinant of clinical outcomes after TIPS placement is proper patient selection and preparation. Cirrhotic patients with portal hypertension should be under surveillance and referred for TIPS after conservative management fails but before complications of portal hypertension manifest into an emergency. This, along with optimal patient preparation, can help reduce the once high morbidity and mortality related to TIPS. The benefits of TIPS include reduced drop-off rate from the liver transplant list, improved lifestyle quality (i.e., resolution of ascites), and reduction of many portal-hypertension-related complications. Most importantly, TIPS is often a lifesaving procedure for those with variceal hemorrhage.

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Management of Refractory Ascites

Justin Brilliant, MD, and James P. Hamilton, MD

INTRODUCTION

Ascites, the abnormal accumulation of fluid in the peritoneal cavity, is one of the major complications of portal hypertension in cirrhosis and portends a poor prognosis. Ascites is the most common complication of cirrhosis with approximately 50% of patients developing ascites within 10 years. The initial workup for a cirrhotic patient with ascites should include evaluation of the ascitic fluid and kidney function because of common complications such as spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome. All patients should restrict their daily sodium intake to 2 grams to minimize fluid retention, consume at least 1 g/kg of their body weight of protein each day to avoid malnourishment, and start diuretics for a goal of 0.5 kg of fluid loss each day. In the meantime, prompt referral for liver transplant should be undertaken as one-half of all cirrhotic patients with ascites die within 5 years.

However, as cirrhosis progresses with worsening ascitic fluid retention, patients have greater difficulty maintaining their effective arterial blood volume leading to impaired renal solute-free water excretion and renal vasoconstriction. This complication is known

as refractory ascites and is defined as fluid that cannot be mobilized despite a 2-gram sodium-restricted diet and high-dose diuretic treatment (160 mg of furosemide and 400 mg of spironolactone) or that reaccumulates rapidly after therapeutic paracentesis. Signs of diuretic failure include lack of weight loss, inadequate sodium excretion in the urine (<78 mEq/day), and development of complications such as progressive azotemia, hepatic encephalopathy, or progressive electrolyte imbalances. Refractory ascites only occurs in 10% of patients with both cirrhosis and ascites. Importantly, detailed assessment of dietary and medicine compliance, abstinence from alcohol and medications that reduce effective arterial blood volume (e.g., nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, etc.), and exclusion of infection should be done before the diagnosis and subsequent management of refractory ascites.

Urinary Electrolyte Measurement in Refractory Ascites

Patients who gain weight on maximum diuretics but excrete less than 78 mEq of sodium per day from the urine are refractory to diuretics. To measure urinary sodium excretion, a 24-hour urinary collection is necessary as an inadequate collection can underestimate the true value; however, it can be difficult to obtain an accurate 24-hour urinary collection in a real-life setting. A random urinary sodium/potassium ratio can quickly estimate urinary sodium excretion. Approximately 90% of patients with a urine sodium/potassium ratio greater than 1 excreted more than 78 mEq/day of sodium in a 24-hour collection. In patients with excretion of more than 78 mEq of sodium per day from the urine, they are identified as being diuretic-sensitive, thus ruling out refractory ascites; these patients should theoretically lose weight if adherent to a sodium-restricted diet and diuretics.

SPONTANEOUS BACTERIAL PERITONITIS

Diagnosis

Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid in the absence of an intraabdominal, surgically treatable source. SBP represents the most frequent bacterial infection in patients with cirrhosis with the clinical presentation ranging from no symptoms to mild abdominal pain to sepsis. One-half of the episodes of SBP are present at the time of hospital admission, and therefore, prompt recognition of SBP, ideally within 6 hours, via a diagnostic paracentesis is essential in patients hospitalized with both cirrhosis and ascites. The diagnosis is made in the presence of an elevated polymorphonuclear leukocyte (PMN) count of 250 cells/mm^3 or higher in the ascitic fluid, with or without a positive culture in the ascitic fluid, in the absence of other causes of peritonitis.

Empiric Treatment

When the ascitic fluid PMN count is 250 cells/mm^3 or higher, empiric antibiotic therapy is indicated even before cultures grow bacteria to mitigate risks of sepsis, end-organ damage, and mortality. Patients who meet the PMN criterion but have negative ascitic fluid cultures have been labeled with *culture-negative neutrocytic ascites*. These patients have the same symptoms and mortality as those with SBP and thus require the same treatment as SBP. Patients with fewer than 250 cells/mm^3 of PMN in their ascitic fluid, but who have positive bacterial fluid culture, have been labeled with *nonneutrocytic bacterascites*. The positive bacterial fluid culture in this setting may represent a short-lived, reversible colonization that may not warrant antibiotics; it has been reported that 62% to 86% of cases resolve spontaneously. However, if a follow-up paracentesis is performed (~48 hours later) and the bacterial fluid culture remains positive, empiric treatment is recommended, especially if patients develop any convincing signs of infection including sepsis, fever, abdominal pain, and encephalopathy. Finally, the recognition of secondary bacterial peritonitis is critical in patients who have localized abdominal symptoms, polymicrobial growth in ascitic fluid culture, elevated ascitic protein concentration, or worsening symptoms on broad-spectrum antibiotics because dedicated imaging with surgical management may be necessary.

Choice of Antibiotics

Broad-spectrum antibiotic therapy is warranted for the treatment of SBP. The treatment of choice is a third-generation cephalosporin including cefotaxime or ceftriaxone because it provides coverage against 95% of the three most common bacterial species that cause SBP. Piperacillin-tazobactam or meropenem may be options in patients with suspected healthcare-associated or nosocomial SBP because of higher incidence of bacteria resistant to third-generation cephalosporins. Furthermore, empiric coverage with carbapenems such as meropenem may have decreased in-house mortality compared with third-generation cephalosporins among critically ill patients. However, carbapenem-resistant bacteria have emerged over the past decade necessitating alternative treatment regimens, such as combining β-lactams or carbapenems with β-lactamase inhibitors, that are still currently being investigated. Five days of treatment has been shown to be efficacious, and treatment may be narrowed based on sensitivities of cultured organisms. Oral-based regimens including ofloxacin were as effective as third-generation cephalosporins in asymptomatic SBP but is not routinely recommended until additional trials are performed. Patients who had received fluoroquinolones as prophylaxis against SBP should be treated with nonfluoroquinolone-based regimens secondary to risk of microbial resistance to the former regimen.

Intravenous Albumin Infusion

The administration of albumin can theoretically improve the decreased effective arterial blood volume to reduce the risk of renal failure that afflicts 30% to 40% of patients with SBP. In addition to the previously discussed antibiotics, IV albumin 25% (1.5 g/kg within 6 hours on the first day followed by 1 g/kg on day 3) has been shown to decrease mortality in SBP. The beneficial effect of albumin was shown particularly in patients with hepatic decompensation or renal dysfunction (serum bilirubin ≥4 mg/dL, BUN ≥30 mg/dL, and serum creatinine ≥1 mg/dL).

β-Blockers

Recent studies have called in to question the previous notion that there was higher mortality in SBP associated with continuation of nonselective β-blockers for prevention of variceal hemorrhage in portal hypertension. Previously, β-blockers in SBP increased the risk for hepatorenal syndrome and acute kidney injury, the time of hospitalization, and reduced transplant-free survival. However, mortality seems to be more related to the degree of impaired systemic perfusion. Therefore, nonselective β-blockers may be considered or reintroduced as long as patients have no evidence of circulatory dysfunction (e.g., mean arterial pressure <65 mm Hg). Future studies are needed to clarify the optimal duration of nonselective β-blockers and scenarios when the risk of complications outweighs their benefits.

Follow-Up Paracentesis

A repeat paracentesis to document resolution of SBP is generally not necessary. Most cirrhotic patients with SBP and typical ascitic fluid analysis will show clinical response on antibiotic treatment. However, if symptoms persist or worsen, atypical organisms grow in culture, or suspicion of secondary peritonitis arises, then a repeat paracentesis can be performed to evaluate for unresolved infection.

MEDICAL TREATMENT CONSIDERATIONS IN REFRACTORY ASCITES

β-Blockers

As stated previously, there may be a role for nonselective β-blockers in refractory ascites, but they should be used with extreme caution because patients are predisposed to circulatory collapse. Several recent studies have shown that increased left ventricular systolic function via activation of β-1-receptors serves as a compensatory mechanism due to peripheral vasodilation and decreased effective arterial blood volume. This physiologic state may underlie the association from prior studies between nonselective β-blockers that suppress this cardiac response and poor survival in patients with refractory ascites. However, only when arterial perfusion pressure falls below a certain threshold (blood pressure <90/60 mm Hg) does risk of renal failure, circulatory dysfunction, and mortality increase. Therefore, a therapeutic window exists for nonselective β-blockers, and they should be used with caution in patients with hypotension, hyponatremia, or acute kidney injury. These medications offer a survival benefit in variceal bleeding prophylaxis and should be carefully reintroduced if appropriate; doses greater than 160 mg/day of propranolol or 80 mg/day of nadolol should be avoided.

Vasoconstrictors and Albumin

Vasoconstrictors have been used in the management of hepatorenal syndrome and the prevention of hemodynamic instability after large volume paracentesis (LVP), along with albumin. The use of vasoconstrictors with intravenous albumin in patients with cirrhosis can improve sodium excretion, circulatory function, and ascites control as long as kidney function is preserved. When taken for at least 30 days, midodrine, an α-1 receptor agonist, has been shown to be as effective as albumin in reducing morbidity and mortality among patients undergoing an LVP at a significantly lower cost. Midodrine can treat severe hypotension with systolic blood pressures in the 70s or 80s characteristic of patients with refractory ascites and improve sensitivity to diuretics while preserving hemodynamic stability (along with cessation of a β-blocker, if applicable). The addition of midodrine to standard medical therapy for refractory ascites can improve renal perfusion, increase renal sodium excretion, and reduce ascites. Octreotide, a somatostatin analogue, can cause splanchnic vasoconstriction and improve renal perfusion. Parenteral octreotide has been effective with oral midodrine and albumin in reversing type-1 hepatorenal syndrome. In one study analyzing patients with hepatorenal syndrome, therapy with midodrine, octreotide, and albumin compared with albumin alone was associated with resolution of kidney injury and decreased mortality. Terlipressin, a vasopressin derivative, also induces splanchnic vasoconstriction and can be used to control ascites. Although terlipressin is not available in the United States, it has been widely used in Europe and other parts of the world for hepatorenal syndrome. Recently, a large randomized, double-blind, placebo-controlled trial (CONFIRM trial) comparing the safety and efficacy of terlipressin and albumin in patients with hepatorenal syndrome to those treated with placebo and albumin was performed. This trial showed that terlipressin and albumin is associated with a higher likelihood of reversal of hepatorenal syndrome for at least 30 days and 10-day survival without renal replacement therapy when compared with placebo. However, patients who received terlipressin were more likely to have respiratory failure within 90 days after the first dose. Terlipressin is not yet approved in the United States for the management of type-1 hepatorenal syndrome until safety concerns are resolved.

INTERVENTIONAL METHODS IN THE TREATMENT OF REFRACTORY ASCITES

Liver Transplantation

Liver transplantation is the definitive therapy for patients with cirrhosis and refractory ascites. The development of refractory ascites confers a poor prognosis, with approximately half of patients dying within 1 year without transplantation. Therefore, suitable candidates should be referred to a liver transplant center.

Large Volume Paracentesis with Albumin Replacement

LVP with albumin replacement is one of the first-line treatments for refractory ascites while patients are awaiting liver transplantation. This procedure ameliorates the characteristic symptoms of large volume ascites such as early satiety, bloating, abdominal pain, and shortness of breath. Based on the available studies, an infusion of albumin is recommended after a paracentesis that removes 5 liters or more of ascitic fluid; the recommended dose of albumin is 6 to 8 g/L of ascites removed. The use of albumin in patients requiring the removal of at least 5 liters of ascitic fluid reduced electrolyte abnormalities, renal dysfunction, and postparacentesis circulatory dysfunction (PPCD). Although there has traditionally been no set limit on the amount of volume removed, limiting each LVP session to less than 8 liters with additional albumin (9.0 ± 2.5 g/L of ascites removed) in one study may reduce mortality and preserve renal function over a mean period of 2 years despite the onset of PPCD in 40% in this cohort of patients. Furthermore, albumin infusion can be considered in patients who have <5 L of ascites removed and either systolic blood pressure <90 mm Hg, hyponatremia (Na <130 g/dL), or an acute kidney injury. Patients can be scheduled for serial LVPs every 2 weeks as an outpatient, but this treatment is not an ideal long-term solution because repeated LVPs cause protein depletion, leading to worsening malnutrition.

The preferred site for needle entry is 3 cm medial and 3 cm superior to the anterosuperior iliac spine on the left lower quadrant of the abdomen. The right lower quadrant is less desirable because the cecum can become distended in patients who take lactulose. A distended cecum has a higher risk of perforation. The needle should avoid areas with cutaneous infection, abdominal wall hematoma, scars, or visibly engorged subcutaneous areas. Bedside ultrasound is useful in locating a safe site for needle entry away from vascular structures.

The paracentesis needle can be inserted with either the angular technique or the Z-track technique. In the angular technique, the needle is inserted obliquely from the cutaneous site into the peritoneum. In the Z-track technique, cutaneous tissues are pulled down and the needle is inserted straight into the peritoneum. These techniques ensure that cutaneous and peritoneal needle entry sites do not directly overlap, thereby minimizing postprocedure ascitic fluid leakage (Fig. 1).

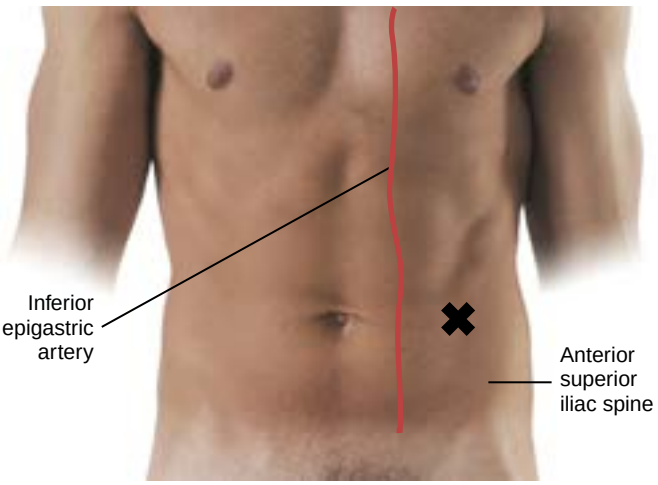


FIG. 1 Preferred needle entry site for paracentesis.
(From Drake R, Vogel AW. Gray's Atlas of Anatomy. Philadelphia: Elsevier; 2007.)

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is an artificial communication between the portal vein and hepatic vein usually placed by an interventional radiologist (Fig. 2). The direct result of TIPS placement is a significant reduction in portal pressure through the creation of an alternative pathway for portal venous flow. Before and after TIPS placement, the proceduralist can quantify the degree of portal hypertension by measuring the portosystemic gradient. The benefit of TIPS is in reversing portal hypertension, the cause of many complications of cirrhosis. After successful TIPS procedure, ascites may completely resolve along with portosystemic shunts (e.g., esophageal varices) over the span of months.

Under fluoroscopic guidance, the interventional radiologist accesses the liver through the internal jugular vein in the neck. Once venous access is confirmed, the radiologist inserts a guidewire and introducer sheath that enables access to the hepatic veins by passing the superior vena cava and inferior vena cava. Once the catheter enters the hepatic vein, the radiologist injects contrast to locate the portal vein and advances a needle through the liver parenchyma to connect the two veins. An inflated angioplasty balloon creates a channel for the shunt along the needle tract. Last, the shunt forms by placing a polytetrafluoroethylene-covered stent to maintain the tract. The covered stent has been a standard for many years. It has a higher patency interval compared with the older uncovered stent.

Absolute contraindications for TIPS include heart failure, severe tricuspid regurgitation, and severe pulmonary hypertension. TIPS in the setting of these conditions can lead to severe cardiac volume overload because blood flow is diverted past the liver and into the right heart. Sepsis, biliary obstruction, and severe hepatic encephalopathy are other absolute contraindications to TIPS placement. Patient selection and the timing of a TIPS procedure are very important predictors of patient outcome. The Model for End-Stage Liver Disease (MELD) score, now used to prioritize organ allocation in liver transplantation, was initially developed to predict the 3-month mortality after TIPS. Patients with a MELD score of ≥18 have poorer outcomes after TIPS. The use of smaller diameter (8–10 mm) stents has been associated with a lower incidence of hepatic encephalopathy following TIPS with no reduction in ascites clearance. One study showed that earlier TIPS placement after patients developed ascites improved 1-year transplant survival compared with patients receiving serial LVPs, albumin infusions, and diuretics (93% vs.

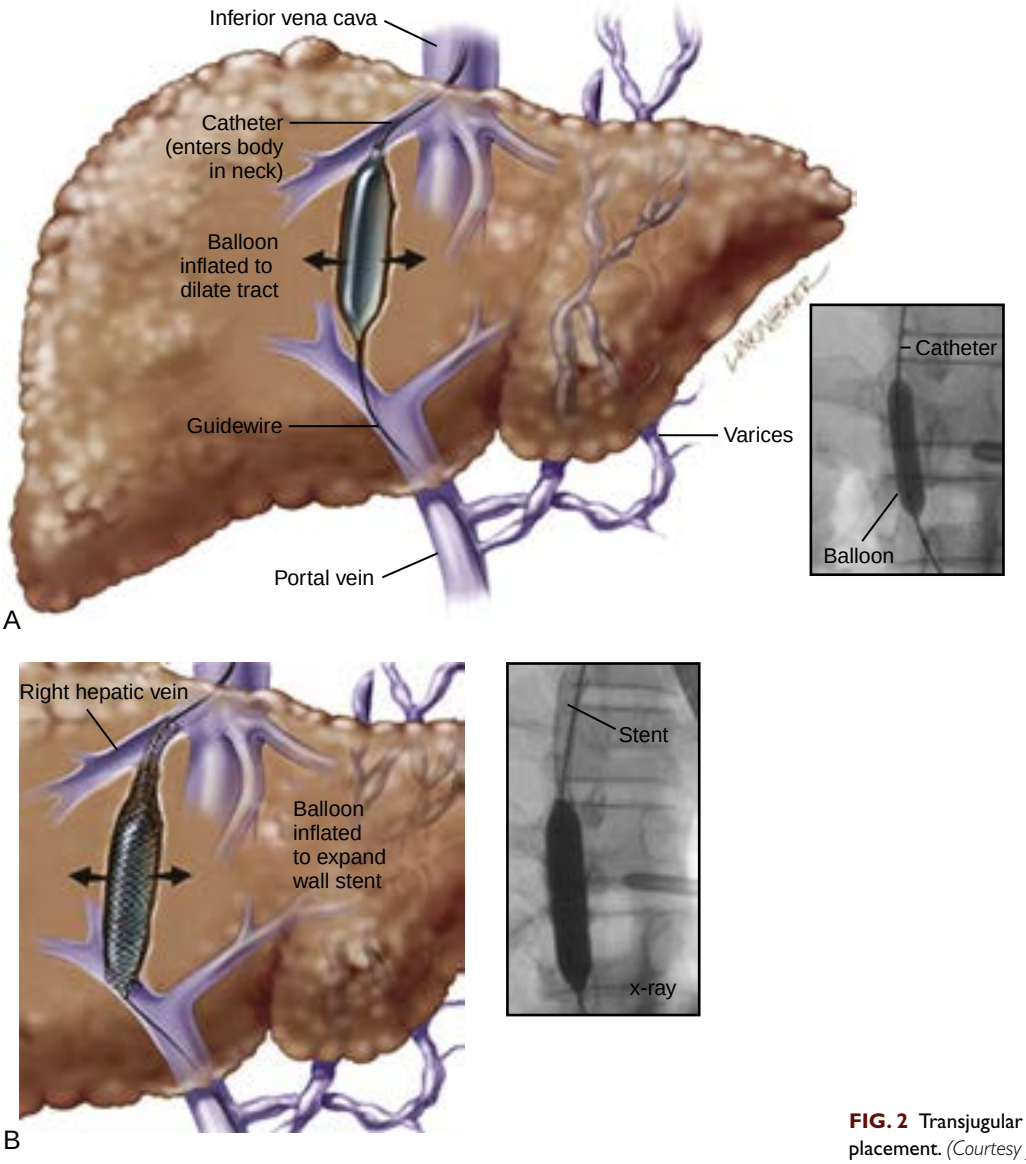


FIG. 2 Transjugular intrahepatic portosystemic shunt placement. *(Courtesy Johns Hopkins Medical Institutions.)*

53%, respectively). With additional studies, the optimal timing of TIPS with appropriate selection criteria can be investigated for safe and expedited stent placement to improve mortality before liver transplant.

Peritoneovenous Shunts

Peritoneovenous shunts drain ascitic fluid from the peritoneal cavity into systemic veins, such as the superior vena cava. The Denver shunt, popular in the 1970s, is the only peritoneovenous shunt still manufactured today. Although historically requiring an invasive approach, today it is placed percutaneously in a minimally invasive procedure through an internal jugular or subclavian route. The shunt is made of soft tubing connected to a pump chamber that lies subcutaneously over the lower ribs. Ascitic fluid flows spontaneously from the peritoneum to the superior vena cava, but manual pumping helps avoid buildup of proteinaceous material in the shunt. Nonetheless, because of poor long-term patency and complications such as obstructions, coagulopathy, superior vena cava thrombosis, and sepsis, peritoneovenous shunts are infrequently used today.

Peritoneal Catheters

A peritoneal catheter (PleurX) inserted into the peritoneum can be an option for ascites removal in patients with the goal of palliation. Given the risk of introducing infection into the peritoneum, this option is typically reserved for patients who are near the end of life. The catheter can be placed with minimal discomfort using a small incision. It is then sutured in place to the skin and connected to a catheter bag. Patients may open the catheter to the bag at their convenience, allowing patients who may be less mobile to avoid traveling to medical facilities for repeated paracenteses.

EXPERIMENTAL OPTIONS

Clonidine and Midodrine

Clonidine is an α-2-adrenergic receptor agonist that suppresses the renin-aldosterone system, which is activated in patients with refractory ascites. Clonidine has shown promise when used in combination with furosemide and spironolactone in refractory ascites with one study showing a 60% diuretic-response rate after 3 months. The combination of clonidine with midodrine, an oral α-1-receptor agonist, and standard medical therapy (sodium restriction, use of diuretics, and serial LVPs as needed) was investigated in one trial. The effect of combination therapy on systemic hemodynamics, renal function, and control of ascites was not greater than clonidine or midodrine by themselves when used with standard medical therapy.

Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are medications that are now used in type 2 diabetes mellitus for treating hyperglycemia. These medications block a major transport protein, SGLT2, in the proximal tubules of the kidney to block nearly 90% of the kidney's glucose reabsorption. SGLT2 inhibitors have been shown to exhibit protective effects on the liver, heart, and kidney through natriuresis, deactivation of the renin-angiotensin-aldosterone system, and antiinflammatory effects. In three patients who had cirrhosis due to nonalcoholic steatohepatitis and diabetes along with fluid retention, SGLT2 inhibitors were associated with reduction in ascites and peripheral edema. Serum sodium levels improved as well. Clinical trials are needed to investigate the safety and efficacy of SGLT2 inhibitors in refractory ascites.

Low-Flow Ascites Pump (ALFApump)

European surgeons and radiologists have collaborated to develop a pump (ALFApump) that moves ascitic fluid from the peritoneal cavity into the urinary bladder. Previous studies showed a decrease in the need for large-volume paracentesis in those with refractory ascites, with most patients not requiring paracentesis after implantation of the pump system. In a multicenter randomized controlled trial including 60 patients with refractory ascites, the median time to first LVP was not reached after 6 months in patients with an ALFApump compared with 15 days for the standard-of-care group. Improved quality of life was also seen in the ALFApump group. However, the frequency of severe adverse events, including acute kidney injury and reintervention for pump-related issues, was significant in the ALFApump group but did not impact survival. Commonly observed complications in low-flow ascites pumps include blockage of the peritoneal catheter, infections, and bleeding. Careful discussion on the risks and benefits of these devices need to be undertaken with close longitudinal follow-up. Currently, the ALFApump is not available in North America but is currently under clinical investigation in the United States and Canada.

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Management of Hepatic Encephalopathy

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Hepatic encephalopathy (HE) is characterized by a spectrum of neurocognitive changes, ranging from subclinical symptoms to life-threatening coma, and results from chronic liver disease, acute liver failure (ALF), or portosystemic shunting (PSS).

PATHOPHYSIOLOGY

The pathogenesis of HE is multifactorial and not completely understood, though prevailing hypotheses frequently implicate the effects of ammonia on brain function (Fig. 1). Ammonia is produced in the gut by colonic bacteria and mucosal enzymes that break down protein. It then enters portosystemic circulation and, under normal conditions, is excreted from the body mainly via urea production in the liver. When hepatocyte function is impaired, or if the liver is bypassed as in portosystemic shunting, hyperammonemia results. Ammonia can also be processed via glutamine synthetase in skeletal muscle. However, with sarcopenia, or low muscle mass, being common in patients with cirrhosis, this pathway of excretion is often limited.

The gastrointestinal tract and microbiome play an important role in the regulation of ammonia. In hepatic dysfunction, there is decreased bile acid secretion to the gut, leading to changes in gut microbiota. Patients with liver dysfunction and HE are more likely to have an increased proportion of potentially pathogenic microbiota, which are linked to systemic inflammation, endotoxemia and cognitive impairment, though these underlying pathways remain a topic of research.

At the cellular level, ammonia crosses the blood-brain barrier, and excess ammonia in the brain results in neuronal dysfunction. Astrocytes convert ammonia and glutamate to glutamine, and in hyperammonemia, accumulation of glutamine leads to cerebral edema. Additionally, ammonia acts on benzodiazepine receptors, leading to decreased excitatory neurotransmission. There is additional evidence for increased inflammation in the brain as well as changes in cerebral blood flow. Other toxins that have been implicated in HE include manganese, mercaptans, lactate, and dopamine metabolites.

DIAGNOSIS AND GRADING

HE is diagnosed clinically, after other etiologies of altered mental status and neurocognitive dysfunction are excluded. There are three major types of HE based on etiology: type A HE results from ALF, type B HE results from portosystemic bypass/shunting, and type C HE results from cirrhosis. The severity of HE can range from subclinical symptoms to coma and is graded based on the West Haven Criteria (Table 1). Overt HE (grade >2) is considered a clinical manifestation of decompensated liver disease and should be treated promptly.

HE can lead to various cognitive, behavioral, and motor changes, though these do not necessarily occur in parallel, and presentations can vary. Cognitive and behavioral changes can be more formally evaluated using neuropsychometric and neurophysiologic testing, though there are no tests specifically studied for HE. Early stages of HE are often characterized by reduced awareness of surroundings, decreased attention, and impaired balance. In later stages of HE, patients often exhibit impairment of consciousness with fluctuating attention and slow responses, and progression to stupor. On physical examination, asterixis is a characteristic sign of overt HE that

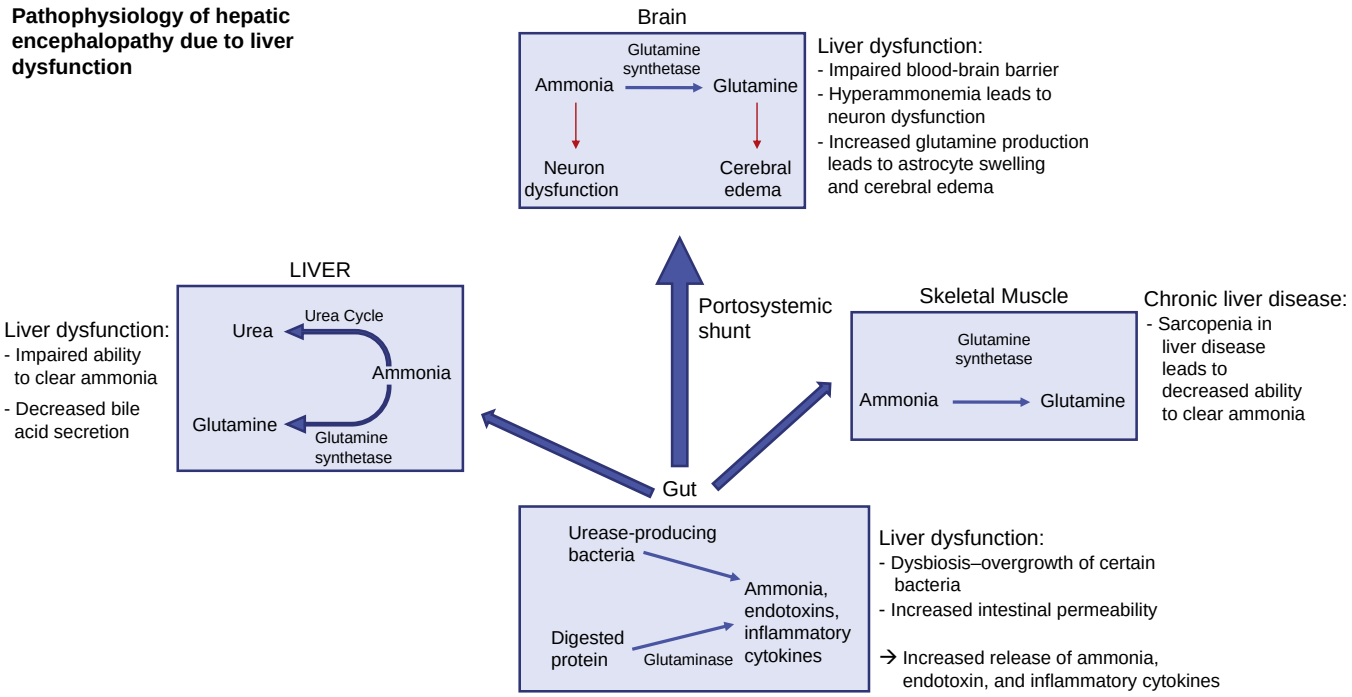


FIG. 1 Pathophysiology of hepatic encephalopathy due to liver dysfunction.

TABLE 1 Grading of Hepatic Encephalopathy

Grade/Severity		Description
Minimal	Covert	Alterations of psychometric or neurophysiologic tests without clinical evidence of mental change
Grade 1	Covert	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Altered sleep rhythm
Grade 2	Overt	• Lethargy or apathy • Disorientation to time • Inappropriate behavior • Asterixis
Grade 3	Overt	• Somnolence • Confusion • Gross disorientation
Grade 4	Overt	• Coma

represents loss of postural tone and can be elicited by hyperextension of the wrists. This can occur in other disease states as well, however, so it should not be considered pathognomonic for HE. Other motor disturbances seen in HE include hypertonia, hyperreflexia, and a positive Babinski sign.

HE is associated with changes in electroencephalographic (EEG) pattern, including dyssynchronization of fast activity, dysrhythmicity, and slower delta activity and disorganization. Triphasic-wave patterns appear in grade 2 or 3 HE and disappear in the comatose state. Brainstem-evoked potentials may be helpful for detection of subclinical HE. It should be noted that EEG findings are not necessary for diagnosis of HE, and in assessment of patients with potential HE, EEG may be most useful in ruling out nonconvulsive status epilepticus.

Measurement of serum ammonia levels has limited utility in the diagnosis and management of HE in chronic liver disease. There is wide variability and lability of serum ammonia levels related to sample collection, fasting state, and protein load which may confound interpretation. Studies have shown that ammonia testing does not improve outcomes in HE. The American Association for Study of Liver Disease/European Association for the Study of Liver guidelines recommends against using ammonia levels alone for managing HE (grade IIA recommendation).

Differential Diagnosis

HE remains a diagnosis of exclusion, so it is critical to evaluate for other causes of altered mental status before initiating treatment. Some common etiologies that may produce a similar clinical picture are listed in Table 2. Alcohol intoxication or withdrawal can result in delirium and slurred speech. Wernicke-Korsakoff's syndrome, in particular, can produce an altered state including inattention and amnesia, though it is additionally associated with ophthalmoplegia, gaze-evoked nystagmus, and ataxia. Metabolic derangements including hyponatremia, hypoglycemia, and metabolic alkalosis should be screened for and can be corrected as clinically appropriate. Nonconvulsive status epilepticus must also be considered and requires careful interpretation of EEG findings. Chronic or acute subdural hematoma may mimic some signs of HE, and liver dysfunction increases risk of intracerebral hemorrhage; thus, CT scans are often part of the initial assessment in patients with suspected HE.

TABLE 2 Differential Diagnosis for Hepatic Encephalopathy

Disorders	Comments
Alcohol	Alcohol intoxication or withdrawal Consider Wernicke-Korsakoff's syndrome
Drugs/toxins	Benzodiazepines, opiates, neuroleptics
Electrolyte disorder	Common electrolyte abnormalities include hyponatremia, hypoglycemia, metabolic alkalosis
Nonconvulsive epilepsy	Consider EEG to evaluate seizure activity
Psychiatric disorder	Consider psychiatric evaluation
Intracranial bleeding or stroke	CT scan is often part of initial workup

TABLE 3 Precipitating Factors of Hepatic Encephalopathy

Precipitating Factors	Notes
Infection	Diagnostic paracentesis is indicated in initial workup to rule out spontaneous bacterial peritonitis (SBP), in addition to blood, urine and imaging studies.
GI bleeding	Consider history of varices, portal hypertensive gastropathy
Diuretic overdose	Due to low albumin, patients with cirrhosis may have edema but be intravascularly dry
Electrolyte disorder	Prone to electrolyte derangements due to liver dysfunction as well as commonly prescribed diuretics and laxatives Some patients may have chronic hyponatremia
Constipation	Noncompliance with laxatives, particularly lactulose is common
Sedating agents	Benzodiazepines, opiates, hypnotic agents, alcohol

PRECIPITATING FACTORS

Patients with overt HE often present with precipitating factors (Table 3), and identification and management of these factors are an important initial step in treatment of HE.

Infection is a common precipitant of HE, and patients with chronic liver disease may be prone to infection due to a proinflammatory state. Sources of infection to consider in initial evaluation include spontaneous bacterial peritonitis (SBP), in addition to urinary tract, pulmonary, and skin and soft tissue infections. Empiric antibiotic therapy should be initiated if there is high clinical suspicion for infection. Empiric coverage for SBP may have slightly different dosing compared with other infections.

Gastrointestinal bleeding is another common precipitant of HE. In addition to overt evidence of bleeding, high blood urea nitrogen-to-creatinine ratio or history of known varices or portal hypertensive gastropathy may be clues. Gastrointestinal bleeding decreases perfusion to key organs in ammonia clearance including the liver and kidneys. In addition, blood also acts as a large protein substrate in the gut, leading to increased production of ammonia.

Patients with cirrhosis are at risk for volume depletion and electrolyte imbalance, each of which can precipitate HE. Overdiuresis or misuse of laxatives can both cause and exacerbate volume depletion.

TREATMENT FOR HE IN CHRONIC LIVER DISEASE

Nonabsorbable Disaccharides

Lactulose is recommended by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines as first-line treatment for overt HE (grade II B) (Table 4). It is a nonabsorbable disaccharide that is thought to acidify the gut environment, making it less favorable to ammonia-producing bacteria. It also increases bowel movement, increasing excretion of nitrogen-containing compounds.

Lactulose is titrated to effect and required dose varies among patients. Initially it should be started at 20 to 30 g every hour until defecation occurs. It can then be spaced to 20 to 30 g every 4 to 6 hours depending on clinical improvement. In patients unable to take oral lactulose, enteral access may be obtained via nasogastric tube for lactulose administration. In some patients, placement of a nasogastric tube may be contraindicated (i.e., esophageal varices or recent banding), and lactulose can also be administered rectally by enema.

After an initial episode of HE, lactulose is recommended to prevent recurrent episodes of HE and is generally titrated to 2 or 3 bowel movements per day. Recent studies, however, suggest that fewer bowel movements may be as effective. Common side effects include nausea, bloating, and diarrhea. Lactinol is another nonabsorbable disaccharide with comparable effectiveness; however, it is not available in the United States.

Oral Nonabsorbable Antibiotics

Rifaximin is the primary nonabsorbable antibiotic used for the treatment of HE. It suppresses intestinal flora and thus decreases their production of ammonia and associated toxins in the gut and has been studied for treatment in HE in several clinical trials. Rifaximin has mainly been studied as an addition to lactulose therapy. There is some evidence that rifaximin monotherapy may be appropriate in those who have HE refractory to lactulose or with lactulose intolerability, though further research is needed. Unfortunately, rifaximin is often not covered by insurance and is expensive as an outpatient therapy. Currently, rifaximin is recommended for use in combination with lactulose for prevention of recurrent HE (grade IA recommendation).

TABLE 4 Medical Treatments for Hepatic Encephalopathy

Drug	Dosing	Comments
GUIDELINE RECOMMENDED FIRST-LINE THERAPIES		
Lactulose	Oral: *Initial:* 20 to 30 g every hour until defecation. Reduce to 20 g every 4–6 hours until clinical improvement. *Maintenance:* 20 g every 8–12 hours, titrated to goal 2–3 stools/day Rectal: Enema. 200 g lactulose in tap water Repeat every 4–6 hours	First-line guideline recommended therapy SE: bloating, nausea, diarrhea Recent studies suggesting increased number of BMs may not be needed for lactulose to be effective
Rifaximin	Oral: 550 mg twice a day	Guideline recommended Add on to lactulose or as alternative if lactulose not tolerated Can be expensive and may not be covered by insurance
ALTERNATIVE THERAPIES		
Polyethylene glycol (PEG)	Oral: PEG-based electrolyte solution: 4 L administered over 4 hours or 2 L every 12 hours PEG powder: 17 g twice daily to three times daily, titrated to 2-3 bowel movements daily	Second-line therapy May be more effective than lactulose, further studies needed
BCAA	No standard dosing	Add-on or alternative therapy IV BCAA not effective
LOLA	IV: 30 g daily	Add-on or alternative to first-line therapy Oral LOLA not effective *Not available in the United States*
Probiotics	Varies	Many different types available commercially, most effective for HE appear to be *Lactobacilli* and *Bifidobacteria* species
Zinc	Varies depending on zinc level	Patients should be screened for zinc deficiency; empiric supplementation has less evidence

BCAA, Branched-chain amino acids; *BM*, bowel movement; *LOLA*, L-ornithine and L-aspartate; *SE*, side effects.

Alternative Therapies for HE

Polyethylene glycol (PEG) has been used both as a PEG-based electrolyte solution (Golytely, Nulytely) and in powder form (MiraLAX). It has been shown to improve measures of HE as well as outcomes such as hospitalization and survival in patients with HE. Recent studies show that it may be more effective than standard therapy with lactulose. It is not yet recommended in guidelines as a first-line treatment; however, it is a good alternative, especially in patients unable to tolerate lactulose. Other laxatives have been studied, but more research is required to examine their efficacy and safety in HE.

Branched-chain amino acids (BCAA) including valine, leucine, and isoleucine enhance ammonia detoxification to glutamine, particularly in skeletal muscle. BCAA supplementation may also reduce malnutrition and decrease loss of muscle mass common in severe liver disease. Studies in patients with HE showed improvement in outcomes in patients with or without symptoms of muscle wasting. However, BCAAs also carry side effects such as disruption of certain metabolic pathways and altered neurotransmission, and thus further research is needed to evaluate their use in patients with HE.

L-Ornithine and L-aspartate (LOLA) are involved in the urea cycle and help glutaminase convert ammonia and accelerate its elimination from the body. Although LOLA is not widely used, it is a good option, particularly for patients with HE due to portosystemic shunting. LOLA is recommended as an adjuvant treatment, not as a monotherapy, but it is not currently available in the United States.

OTHER THERAPIES REQUIRING FURTHER RESEARCH

Probiotics are cultures of live microorganisms that help balance the normal flora of the gut. Most commercially available probiotic products are derived from food sources, especially milk products. There are many microorganisms that have been studied, with the most efficacious species for HE being *Lactobacilli* or *Bifidobacteria*. Some studies have suggested benefit in prevention of recurrent HE. However, more data are needed for a strong recommendation for the treatment or prevention of HE.

Zinc is a cofactor in the urea cycle and may facilitate ammonia clearance. Zinc deficiency should be screened for and repleted in all patients with HE. Clinical trial data regarding empiric zinc supplementation is lacking; however, it has few side effects.

Metabolic ammonia scavengers act as urea surrogates and have been used in treatment for inborn errors of the urea cycle. Ornithine phenylacetate and glyceryl phenylbutyrate have been studied for HE; however, further clinical trials are needed for clinical recommendation.

Flumazenil is an antagonist of benzodiazepine receptors. It has been shown in small randomized controlled trials to transiently improve mental status, however, is not commonly used for this indication and is not recommended for routine treatment of HE.

Phenylbutyrate reduces glutamine availability, suppressing ammonia production. It also promotes ammonia detoxification via glutamine synthetase reaction. Studies have shown that use of glycerol phenylbutyrate and sodium phenylbutyrate in patients with recurrent HE resulted in fewer episodes of HE. However, phenylbutyrate also causes a decrease in BCAA in the blood.

Other antibiotics: Neomycin was previously used in treatment of HE. It is a nonabsorbable antibiotic, a known glutaminase inhibitor and functions similarly to rifaximin. However, it has been shown to have some systemic absorption with ototoxic and nephritic side effects and thus is not recommended for long-term first-line use. Metronidazole has similarly been studied as a short-term therapy, but is also associated with ototoxicity, nephrotoxicity, and neurotoxicity.

Other laxatives: Other laxatives, without the prebiotic properties of disaccharides, may also be beneficial by increasing bowel movement. However, further research is needed before these can be recommended in routine use.

OTHER CONSIDERATIONS

Nutrition

Nutrition plays a crucial role in patients with cirrhosis and especially HE, as they are prone to malnutrition and sarcopenia. Muscle tissue in particular plays a compensatory role in HE through metabolism of ammonia via glutamine synthetase. Protein restriction, previously recommended in this patient population, is no longer routinely advised. Recent studies recommend daily intake of energy of 35 to 40 kcal/kg and 1.2 to 1.5 g protein/kg (grade IA recommendation). Regular caloric ingestion with frequent meals or snacks is also recommended (grade IA recommendation), as conversion of amino acids for glucose production in gluconeogenesis depletes tissue protein stores and produces ammonia. Consultation with a nutritionist is often helpful in tailoring an optimal diet.

Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portostytemic shunt (TIPS) is often performed in patients with chronic liver disease for management of bleeding esophageal varcies or refractory ascites. HE is a major complication after TIPS, and patients must be carefully selected before undergoing TIPS. Lactulose and rifaximin are not recommended prophylactically after TIPS; however, they can be used if HE develops. Post-TIPS HE may be refractory to conventional management, and in these cases shunt diameter reduction, or higher goal portal pressure, can be helpful.

Portosystemic Shunts

Recurrent HE with relatively preserved hepatic function should lead to investigation for spontaneous portosystemic shunts. Depending on the type of shunt, it may be possible to embolize the shunt, with resolution of HE in many patients.

Liver Transplantation

HE alone is not considered an indication for liver transplantation (LT). However, in some patients with relatively good liver status, HE may be severe and significantly worsen quality of life, and LT may be considered. Although HE should improve after LT, those with large PSSs may have persistent symptoms. Additionally, patients may develop confusion during the postoperative period due to the toxic effect of immunosuppressant drugs.

Acute Liver Failure

ALF is defined as severe liver injury in the absence of prior liver disease with development of coagulopathy (INR >1.5) and HE. In the developing world, acetaminophen toxicity is the most common etiology, while viral hepatitis is the most common in the developing world. Given the potential for rapid deterioration, early transfer to the Intensive Care Unit for monitoring and management is recommended. Patients with grade 3 HE or higher will likely require intubation for airway protection and should have regular neurologic checks to evaluate for signs of elevated intracranial pressure (ICP). Patients with ALF should be transferred to a liver transplant center early in their course for evaluation for LT.

In contrast to chronic liver disease, arterial ammonia levels have been shown to correlate with severity of HE in ALF. Ammonia levels >200 have been associated with increased risk of cerebral edema and intracranial hypertension. Conventional treatments for HE, lactulose and rifaximin, have not been shown to be beneficial in ALF. Continuous renal replacement therapy (CRRT) is an effective method of rapid and clinically meaningful ammonia clearance.

CT scans should be carefully considered in these patients, as moving patients with severe HE can lead to surges of ICP. Furthermore, CT scans may be insensitive to small changes in ICP, though they are helpful in

the diagnosis of intracranial hemorrhage and cerebral herniation. Other neuroprotective interventions include elevation of the head to 30 degrees, avoiding fever, and maintaining euglycemia. It is also recommended to maintain serum sodium between 140 and 145 mmol/L with use of hypertonic saline when needed. Development of clinical signs of increased ICP should be treated with hypertonic saline (200 mL, 2.7% or 20 mL, 30%) or intravenous mannitol (150 mL, 20%) given over 20 minutes. Hyperventilation to reduce arterial $PaCO_2$ to 25 to 30 mm Hg may also be beneficial in the acute setting to promote cerebral vasoconstriction.

The use of invasive ICP monitoring devices is controversial, especially given high risk of bleeding in patients with ALF. In patients with monitored ICP, the goal pressure is below 20 to 25 mm Hg, and the cerebral perfusion pressure should be above 50 mm Hg. Noninvasive techniques such as transcranial Doppler ultrasound and jugular venous oximetry may be helpful as another tool for risk stratification.

Extracorporeal Liver Support Devices

Extracorporeal liver support (ELS) is an invasive option in patients with ALF, with limited data showing benefit in HE but no clear mortality benefit. The Molecular Adsorbent Recirculating System (MARS) dialyzes blood across an albumin-impermeable membrane, with protein-bound and water-soluble toxins removed through a secondary circuit. Randomized trials have not shown overall benefit effect of MARS on morality in patients with ALF or acute on chronic liver failure, though some nonrandomized trials have suggested benefit in HE symptoms or in need of transplantation. The fractionated plasma separation, adsorption, and dialysis technology of the Prometheus system separates patients' albumin and plasma from blood and then uses two columns of absorbents and a high-flux dialyzer to clear toxins. One study showed safety and efficacy in patients with ALF, though it did not improve survival of patients with acute on chronic liver failure. Single pass albumin dialysis (SPAD) uses a specialized high-flux albumin impermeable membrane and addition of HSA to a standard dialysis setup. In the few studies thus far, it has not shown to have an impact on survival or referral to transplantation. High volume therapeutic plasma exchange (HVP) is based on removal of toxins and harmful inflammatory mediators, as well as replacement of beneficial plasma proteins (such as coagulation factors) and in small studies has been shown to have a survival benefit, though further research is needed.

ELS is used at some centers in patients with ALF as a bridging option to either transplant or recovery of liver function, though studies for these indications are still needed. In addition, ELS has been used in cases of secondary liver failure, for example, in hypoxic hepatitis or in conjunction with extracorporeal life support (i.e., extracorporeal membrane oxygenation [ECMO]). Studies have shown improvement in HE and a trend toward decrease in mortality; however, there is still no clear data showing a benefit in mortality and morbidity in specific patient populations, for example, as a bridge to transplant or in concurrence with ECMO.

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Management of Budd-Chiari Syndrome

Joseph DiNorcia, MD, and Ronald W. Busuttil, MD, PhD

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare disorder that results from the obstruction of hepatic venous outflow, leading to progressive liver damage and portal hypertension. In 1845, George Budd, a British internist, first described the clinical syndrome as a triad of abdominal pain, hepatomegaly, and ascites. In 1899, Hans Chiari, an Austrian pathologist, described the pathologic features of BCS as occlusion of the hepatic veins. This venous occlusion can be due to various causes. *Primary* BCS results from intrinsic thrombosis of the hepatic veins secondary to prothrombotic, hypercoagulable states or a congenital venous web. *Secondary* BCS results from thrombosis due to extrinsic compression or invasion of the hepatic veins, for example, due to a tumor, granuloma, cyst, or abscess (Box 1).

PATHOGENESIS

Hepatic venous outflow obstruction causes increased pressure in the hepatic sinusoids, leading to venous congestion and decreased intrahepatic portal venous perfusion within the liver. The congestion induces hepatic fibrosis that progresses over time to cirrhosis with resultant portal hypertension, collateral venous flow, and ascites. The decreased intrahepatic portal venous perfusion further contributes to ischemia, hepatocyte necrosis, and fibrosis that causes hepatic dysfunction. Gross pathologic examination of livers with BCS commonly demonstrates large regenerative nodules. Acute histologic features include marked sinusoidal dilatation with centrilobular congestion, edema, and hemorrhage, which progresses in the chronic setting to hepatocyte necrosis, fibrosis, and cirrhosis. Central venous thrombi may be seen as well.

PRESENTATION

The clinical presentation of BCS depends on the onset, severity, and duration of the disease and can be categorized as *acute liver failure* (life-threatening symptoms of acute liver injury), *acute* (rapid symptom onset without acute liver failure), *subacute* (insidious symptom onset before cirrhosis), and *chronic* (late symptom onset after the development of cirrhosis). Acute liver failure secondary to BCS is rare and results from massive liver necrosis causing coma, severe coagulopathy, and hypoglycemia. The chronic form of BCS is more common, presenting with stigmata of end-stage liver disease such as fatigue, hepatic encephalopathy, jaundice, gastrointestinal bleeding, abdominal distension due to ascites, renal dysfunction, sarcopenia, and lower extremity edema. Right upper quadrant abdominal pain, hepatosplenomegaly, and an enlarged caudate lobe, which can be felt as a mass in the epigastrium, are additional signs and symptoms. About 10% of patients may be asymptomatic.

BOX 1 Etiologies of Budd-Chiari Syndrome

- Myeloproliferative disorders
  - Essential thrombocythemia
  - Polycythemia vera
  - *JAK2* mutation
  - Idiopathic myelofibrosis
- Hypercoagulable disorders
  - Hyperhomocysteinemia
  - Factor V Leiden mutation
  - Prothrombin gene mutation G20210A
  - MTHFR C677T mutation
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin deficiency
  - Antiphospholipid syndrome
  - Paroxysmal nocturnal hemoglobinuria
  - Thalassemia
- Malignancy
  - Cholangiocarcinoma
  - Hepatocellular carcinoma
- Benign hepatic lesions
  - Adenoma
  - Cyst
  - Cystadenoma
  - Polycystic liver disease
- Infection
  - Hepatic abscess
  - Invasive aspergillosis
  - Mucormycosis
  - Mycotic aortic aneurysm
  - Syphilitic gumma
- Oral contraceptives
- Pregnancy
- Alpha-1 antitrypsin deficiency
- Behçet syndrome
- Systemic lupus erythematosus
- Hypereosinophilic syndrome
- Idiopathic granulomatous venulitis
- Inflammatory bowel disease
- Protein-losing enteropathy
- Minimal change nephrotic syndrome
- Mixed connective tissue disease
- Neurofibromatosis
- Sarcoidosis
- Sjögren's syndrome
- Trauma
- Torsion of the liver
- Membranous web
- Venoocclusive disease
- Idiopathic



FIG. 1 CT scan of a patient with chronic Budd-Chiari syndrome shows a heterogeneous appearance of the liver with regenerative nodules *(arrowhead)* and caudate lobe hypertrophy *(white arrows)*. Black arrow points to an occluded transjugular intrahepatic portosystemic shunt (TIPS).



FIG. 2 Direct hepatic venography demonstrates the classic "spiderweb" morphology of intrahepatic venous collaterals. Percutaneous access via the right internal jugular vein allowed the catheter to traverse the occluded hepatic veins *(arrow)*.

DIAGNOSIS

The diagnosis of BCS should be considered in any patient with acute or chronic liver disease. Routine laboratory tests reflect hepatocyte injury and dysfunction. Elevated transaminases, alkaline phosphatase, bilirubin, and prothrombin time are common, and the albumin level may be low depending on the degree of liver dysfunction and protein loss in ascites. When present, the ascites is characterized by a high serum–ascites albumin gradient (>1.1 g/dL).

The initial diagnostic imaging to assess the hepatic venous outflow is Doppler ultrasound. Secondary studies include contrast-enhanced cross-sectional imaging, either CT or MRI, to image the inferior vena cava (IVC), hepatic veins, and consequent venous collaterals from the obstruction. Historically, invasive hepatic venography played a major role in the diagnosis of BCS, but advances in noninvasive imaging have made it less important in the diagnosis. Now, direct hepatic venography is performed at the time of endovascular intervention. Classic imaging findings include an enlarged caudate lobe and "spiderweb" appearance of intrahepatic venous collaterals (Figs. 1 and 2). Additional diagnostic studies for patients with BCS include upper endoscopy to assess varices and workup for hypercoagulable disorders.

MEDICAL MANAGEMENT

The management of patients with BCS involves prevention of thrombus propagation, restoration of hepatic venous outflow to

decompress the liver, and prevention and treatment of complications of portal hypertension. Initial management involves prompt identification and treatment of the underlying cause of the venous outflow obstruction. Early initiation of anticoagulation is essential to treat any hypercoagulable state and prevent propagation of thrombus. When patients have signs and symptoms of portal hypertension, prophylaxis against variceal bleeding with beta-blockade, endoscopy for surveillance and banding of varices, and control of ascites with sodium restriction, diuretics, or paracentesis become very important management tools.

Anticoagulation can mitigate the disease, but once the hepatic venous outflow is significantly compromised, interventions will be needed to try to restore venous drainage of the liver. Percutaneous transluminal angioplasty (PTA) with or without thrombolysis or stent can be effective, particularly in patients with short-length occlusion of the hepatic vein. The interventional radiologists can use transjugular, transfemoral, or, rarely, transhepatic routes for percutaneous access to the hepatic venous system. They can use transsplenic, transparaumbilical vein, or transhepatic routes to access the portal venous system for direct portography.

A graded approach is used, beginning with direct hepatic venography and pressure measurements as a diagnostic step. Venography can help define the anatomy and degree of occlusion while pressure measurements can assess for portal hypertension, defined as an hepatic venous pressure gradient (HVPG) of >10 mm Hg. Thrombolysis may be needed initially to enable the traverse of the area of obstruction. Balloon venoplasty then can be used to open the outflow. Additional thrombolysis may be added to remove thrombus, using both tissue plasminogen activator (tPA) infusion and mechanical thrombectomy with suction. Finally, a stent may need to be placed to treat the area of obstruction if it is recalcitrant to thrombolysis and balloon venoplasty alone. Postintervention venography and HVPG measurements can assess the response to treatment.

If recanalization of the hepatic veins is not possible or if portal hypertension persists despite attempts at treatment, transjugular intrahepatic portosystemic shunt (TIPS) may be effective in reducing pressure in the portal venous system and decompressing the congested liver (Fig. 3). TIPS thus can treat the complications of portal hypertension, often relieving variceal hemorrhage and ascites. In cases where the hepatic veins are completely obliterated, interventional radiologists can create a shunt directly between the IVC and the portal vein, a direct intrahepatic portosystemic shunt (DIPS) or direct extrahepatic portosystemic shunt (DEPS), depending on which portion of the portal vein is shunted. These technical modifications of TIPS also have been effective in relieving portal hypertension in patients with BCS.

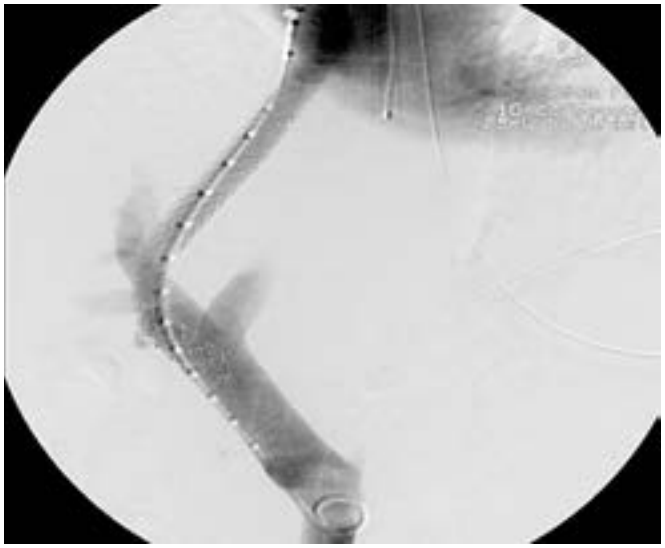


FIG. 3 A transjugular intrahepatic portosystemic shunt (TIPS) extends from the right portal vein into the right atrium, traversing the diseased hepatic venous outflow tract of a patient with Budd-Chiari syndrome.

SURGICAL MANAGEMENT

Surgery may be needed when minimally invasive, endovascular interventions fail to restore hepatic venous outflow. Options include surgical shunts and liver transplantation. With advances in interventional radiology techniques, surgical shunts are rarely performed, reserved for highly select patients with preserved hepatic function and favorable anatomy. Surgical shunts can have excellent long-term outcomes when performed early before the development of irreversible liver damage. However, once the liver damage has progressed to fibrosis and cirrhosis, liver transplantation is the only option to treat BCS definitively. It is important to note that any intervention for BCS should be performed at an experienced center in collaboration with the liver transplantation team because of the real risks of hepatic decompensation and procedural complications.

Surgical Shunts

The goal of a surgical shunt is to drain the portomesenteric venous system into the systemic venous system. Portocaval, mesocaval, and splenorenal shunts can be considered if the IVC is patent and without a significant pressure gradient between the infrahepatic and suprahepatic sections of the IVC. If the IVC is obstructed, mesoatrial or cavoatrial shunts are options to bypass the compromised portion of the IVC, the latter performed in conjunction with a porto- or mesocaval shunt to decompress the port-mesenteric system.

Careful study of cross-sectional imaging is essential for operative planning to decide which is the optimal shunt for the individual patient. The surgeon can evaluate the anatomy and patency of the portomesenteric veins and IVC as well as the extent of caudate lobe hypertrophy. Attention to the caudate lobe is important because its hypertrophy, particularly the paracaval portion, may render a portocaval shunt impossible. Doppler ultrasonography to demonstrate size and patency of saphenous or internal jugular veins is a useful preoperative adjunct when considering an autologous vein graft for creation of the shunt. It also is important for the surgeon to review the available biologic and synthetic graft lengths and diameters in case the autologous vein is insufficient in size or quality. Finally, the surgeon can make a biologic graft by paneling or tubularizing patches of decellularized bovine pericardium or acellular collagen scaffolding, when available.

First and foremost, the creation of any surgical shunt requires proximal and distal control of the involved vasculature. Dissection of the vasculature in the presence of portal hypertension can be challenging because of venous collaterals and requires planning, patience, and purposeful attention to tissue planes. The surgical shunts can be created directly between veins or via grafts in a side-to-side or end-to-side fashion depending on the anatomy and degree of shunting needed. Grafts that can be used include autologous vein grafts (e.g., internal jugular vein or saphenous vein), biologic grafts (e.g., cryopreserved saphenous vein or various acellular matrices), or synthetic grafts (e.g., Gore-Tex or polytetrafluoroethylene [PTFE]).

A *portocaval* shunt connects the portal vein and the IVC, *mesocaval* the superior mesenteric vein and the IVC, and *splenorenal* the splenic vein and the left renal vein. A *mesoatrial* shunt connects the superior mesenteric vein to the right atrium, and a *cavoatrial* shunt connects the IVC with the right atrium, both via a conduit. If no large portosystemic collateral veins have formed during the progression of BCS, a cavoatrial shunt to bypass the obstructed section of the IVC

will be performed in conjunction with a portocaval or mesocaval shunt to ensure adequate drainage of the portomesenteric venous system. A meso-cavo-atrial shunt also is an option, where the superior mesenteric vein is shunted directly into the cavoatrial graft. Systemic heparin administration (50 units per kg) should be discussed with anesthesiology before applying the vascular clamps to the target veins. The anastomoses are created using fine polypropylene sutures with appropriate venting maneuvers to de-air any grafts and to evacuate any thrombus that may build up behind the clamps. Doppler ultrasound (US) can be used to document patency of the shunts postoperatively, and patients should be anticoagulated indefinitely.

Liver Transplantation

For the patients with BCS who fail anticoagulation, PTA, or endovascular or surgical shunt creation, liver transplantation is the only treatment with excellent patient survival in large series. Liver transplantation for BCS can be the most technically challenging of liver operations and should be approached with the utmost caution and care.

Liver transplantation for BCS involves multidisciplinary evaluation to assess the primary cause of the hepatic venous occlusion, the degree of liver dysfunction, and the medical, surgical, and psychosocial fitness of the patient to undergo liver transplantation. If deemed an appropriate candidate, the patient will be waitlisted and ranked by Model for End-Stage Liver Disease (MELD) score (ages ≥12) or Pediatric End-Stage Liver Disease (PELD) score (ages <12), which estimate the 3-month mortality risk without liver transplantation. Decompensated liver disease should be reflected in the score, but if the score does not adequately capture the severity of disease in a particular patient, the transplant center can appeal to the National Liver Review Board for additional exception points for BCS. The appeal should document failure of standard medical management, etiology of hypercoagulable state (when present), specific contraindications to TIPS or reasons for TIPS failure, manifestations of decompensated portal hypertension (e.g., hepatic hydrothorax requiring thoracentesis for more than 1 L per week), and the absence of extrahepatic malignancy.

Preoperative planning is essential, particularly for patients with prior endovascular or surgical portosystemic shunts. For example, the proximal and distal extent of TIPS should be determined by cross-sectional imaging to plan the dissection needed for proximal (i.e., portal vein) and distal (i.e., suprahepatic IVC) clamping. Similarly, the trajectory of DIPS or DEPS should be studied to ensure complete removal of the portions of portal vein and IVC that the stent penetrates. Any portal vein thrombosis should be noted, and thromboendovenectomy or mesenteric venous conduit should be planned.

The hepatectomy in BCS can be very challenging. The congested liver and enlarged caudate lobe can make mobilization of the liver difficult. Large venous collaterals often develop in the perihepatic ligaments, which need to be ligated and divided securely. Thrombosis of the hepatic veins often leads to dense, inflammatory adhesions between the liver, diaphragm, and IVC, therefore extra care must be taken when dissecting and clamping the suprahepatic IVC. Depending on the extent of thrombosis, the suprahepatic IVC may need to be dissected completely from the diaphragm up to the right atrium to ensure complete removal of the entire diseased hepatic venous outflow. Occasionally, dividing the diaphragm from the abdominal incision or median sternotomy may be needed for adequate control of the suprahepatic IVC within the pericardium. The cardiac surgery team should be notified and cardiopulmonary bypass should be available in cases where the most distal control of hepatic venous outflow will involve clamping of the right atrium, such as extensive thrombosis or prior atrial shunts. Equal attention also should be paid to the infrahepatic IVC, which also may have thrombus. Simple thrombus can be thrombectomized, though chronic, extensive thrombosis that extends below the renal veins often can be left alone as venous collaterals provide adequate drainage. In such rare cases, only a suprahepatic IVC anastomosis will be needed for reconstruction of the hepatic venous outflow.

In cases of liver transplant for acute BCS, complete clamping of the IVC can cause hemodynamic instability, and portosystemic venovenous bypass may be needed to preserve venous return and provide drainage of the splanchnic vasculature (Fig. 4). In cases of chronic, advanced BCS, complete clamping of the IVC usually is well tolerated because portosystemic venous collaterals have formed and provide venous return to the heart. With the widespread use of TIPS, fewer patients with BCS have had a prior surgical portosystemic shunt, but when present, shunts must be dissected and ligated to ensure adequate portal inflow to the new liver. It is best to ligate these shunts after reperfusion of the new liver, if possible, to avoid acutely worsening portal hypertension during the hepatectomy (Fig. 5).

Because the obliterated hepatic veins and diseased IVC need to be removed completely with the explanted liver, the IVC will need to be replaced. A deceased donor liver, whether a whole or trisection split allograft, will include the donor IVC, and reconstruction of the venous outflow involves suprahepatic and infrahepatic IVC anastomoses with polypropylene sutures. A living donor liver allograft will not have the IVC but rather hepatic veins for outflow, the exact hepatic vein depending on the type of graft procured (e.g., right lobe with or without middle hepatic vein or left lobe with middle and left hepatic veins). The use of a living donor liver allograft in a patient with BCS will require reconstruction of the IVC with either a biologic or synthetic interposition graft. The hepatic vein or veins of the living donor allograft then can be sewn into the side of the interposition graft with polypropylene sutures, taking care to ensure an adequate orifice for excellent hepatic venous outflow.

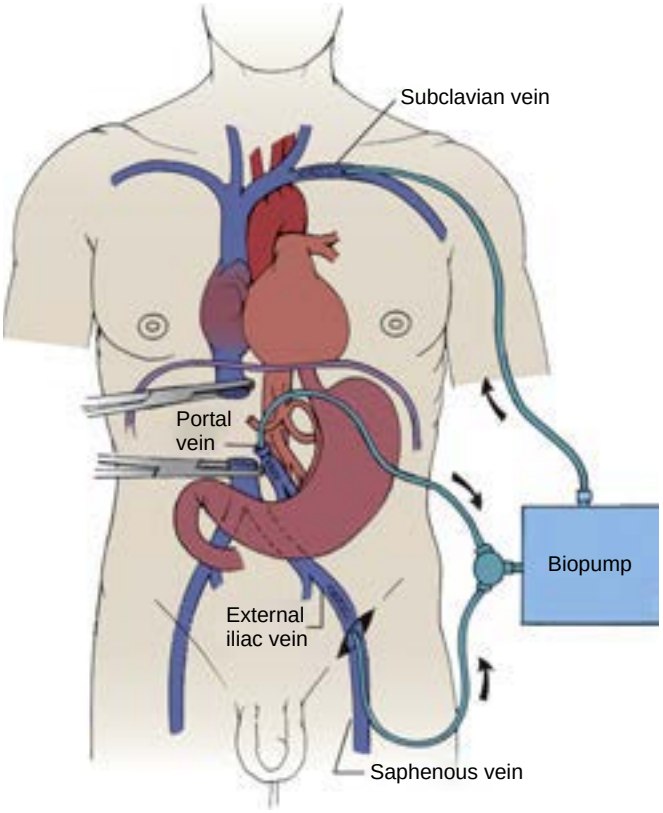


FIG. 4 Venovenous bypass. Immediately before completion of the hepatectomy, the axillary, saphenous, and portal veins are cannulated. A centrifugal pump returns systemic and portal venous blood to the heart via the axillary vein while the patient is anhepatic.

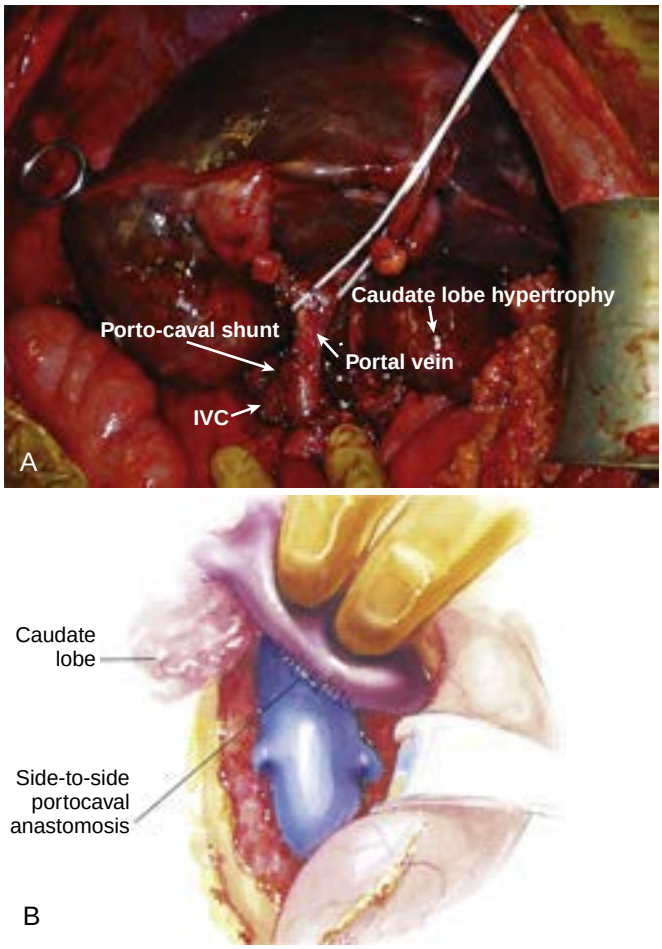


FIG. 5 **(A)** At the time of liver transplant for Budd-Chiari syndrome, a prior surgical portocaval shunt. Note the caudate lobe hypertrophy. **(B)** A side-to-side portocaval shunt. *IVC;* Inferior vena cava. *(Courtesy Corinne Sandone, Johns Hopkins University.)*

Recurrent hepatic venous outflow obstruction is a concern post-transplant for BCS. Anticoagulation needs to be initiated postoperatively as soon as the liver function has recovered and the patient is not bleeding. Anticoagulation will need to be continued indefinitely. Recurrent posttransplant BCS can be treated with interventional techniques as discussed earlier. Retransplantation is reserved for highly select patients with favorable anatomy who fail less invasive management.

CONCLUSION

BCS is a rare disease with varied clinical presentation depending on the acuity of onset and degree of liver dysfunction. Treatment requires multidisciplinary care; input from hematology, hepatology, interventional radiology, and transplant surgery are particularly important. Management first involves anticoagulation to treat the underlying prothrombotic disorder followed by the prevention and treatment of sequelae of portal hypertension. In patients with preserved liver function, percutaneous endovascular interventions aim to restore hepatic venous outflow. Minimally invasive shunts have essentially replaced surgical portosystemic shunts. When these interventions fail or in cases of irreversible liver damage, liver transplantation becomes the only treatment. The operation is very challenging, and the surgeon should be prepared to control the intrapericardial IVC when needed to remove the entire diseased hepatic venous outflow tract. Both whole and partial liver allografts can be used, though the latter will require reconstruction of the IVC with an interposition graft. Thoughtful preoperative planning and meticulous execution are essential to ensure excellent outcomes after liver transplantation for patients with BCS.

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Management of Asymptomatic (Silent) Gallstones

Theodore N. Pappas, MD, and Christopher R. Reed, MD

NATURAL HISTORY OF CHOLELITHIASIS

The first description of incidental gallstones probably dates back to the 14th century, a relatively recent observation in the grand scheme of pathologic observations. This has been attributed to the relative rarity of gallstone formation before modern diets. These postmortem findings preceded the first descriptions of symptomatic gallstones by about 200 years, perhaps a testament to their frequently asymptomatic nature. Without the benefits of modern ultrasonography, open cholecystectomy became the preferred treatment modality for symptomatic gallstone disease throughout the early 1900s, and it was not until the 1980s that incidental, asymptomatic cholelithiasis became a very common clinical problem.

The decreased morbidity of laparoscopic cholecystectomy introduced considerable interest in surgery for the treatment of asymptomatic gallstones. With increasing availability of and expertise with laparoscopic cholecystectomy throughout the 1990s, the surgical approach to asymptomatic gallstones became increasingly heterogeneous. This ultimately resulted in the National Institutes of Health convening of a Consensus Development group that set forth now-familiar guidelines recommending cholecystectomy only for symptomatic or otherwise complicated cholelithiasis in 1992. This guidance is the basis of the prevailing expectant approach to patients with silent gallstones for the past 30 years.

Since that time, both the natural history of gallstones and the outcomes associated with laparoscopic cholecystectomy have been better described (Fig. 1). Asymptomatic cholelithiasis is quite common. In a large, prospective, cross-sectional study of 11,229 asymptomatic gallbladders with ultrasonography, Festi and colleagues demonstrated an incidental cholelithiasis rate of 7.1% among Italian adults. This probably underestimates the incidence in the United States, where smaller cross-sectional studies show an incidence closer to 15%. In certain ethnic groups and geographic locations in the United States, the rate exceeds 20%, implicating a familiar myriad of demographic and environmental factors in formation of gallstones (estrogen, age, obesity, Hispanic, and Native American). Regardless of their exact incidence, asymptomatic gallstones remain a common dilemma for referring physicians and surgeons alike, and the surgical management of asymptomatic cholelithiasis should ultimately be individualized based on the risk of progression to symptomatic disease and the estimated morbidity associated with expectant management. To thoughtfully approach this predicament, a general understanding of the relative risks of expectant management versus cholecystectomy is crucial.

RISK OF PROGRESSION TO SYMPTOMATIC CHOLELITHIASIS

Gallstone disease is generally thought of as a sequence from asymptomatic to symptomatic cholelithiasis (i.e., stone formation initially with subsequent development of pain, infection, pancreatitis, or cancer), although the time between development of stones and symptoms is not currently estimable. Through a combination of cross-sectional and longitudinal studies, it has been demonstrated that only a minority of patients with asymptomatic gallstones will ultimately develop symptoms. In their large, longitudinal investigation of 673 European subjects with asymptomatic cholelithiasis and a median follow-up of nearly 20 years, Shabanzadeh and colleagues found that only 20% of gallstones were ultimately found to cause any disease, which has been reiterated by smaller studies. The majority of disease was uncomplicated (i.e., biliary pain without acute cholecystitis, choledocholithiasis, or pancreatitis).

There are some demographic and ultrasonographic characteristics that are associated with increased risk of symptoms, especially with complicated presentation. Female sex, immobility of stones, numerous stones, and large (>10 mm) or small (<5 mm) stones all are independently associated with increased incidence of symptoms and complicated presentation (Fig. 2).

Over about 20 years' follow-up, Shabanzadeh and colleagues found that about 8% of their subjects with asymptomatic gallstones ultimately presented with acute cholecystitis, choledocholithiasis, or gallstone pancreatitis. None of the patients developed carcinoma of the gallbladder or cholangiocarcinoma during the study period. Festi et al. found a single case of gallbladder carcinoma in follow-up of their 856 patients with asymptomatic gallstones (0.12%).

These longitudinal studies may reflect some inherent bias toward identification of patients who will not develop symptoms, as only patients who were asymptomatic at the time of ultrasound were included, and the duration of cholelithiasis at the time of diagnosis was not known. Regardless, both studies clearly demonstrate that only a minority of patients with asymptomatic gallstones will have complicated gallbladder disease during their lifetime and therefore would have benefited from cholecystectomy at the time of asymptomatic gallstone identification.

MORBIDITY ASSOCIATED WITH LAPAROSCOPIC CHOLECYSTECTOMY VERSUS EXPECTANT MANAGEMENT

A modern discussion of the management of asymptomatic gallstones should include a modern appraisal of the risks associated with laparoscopic cholecystectomy in comparison to potential benefits. It

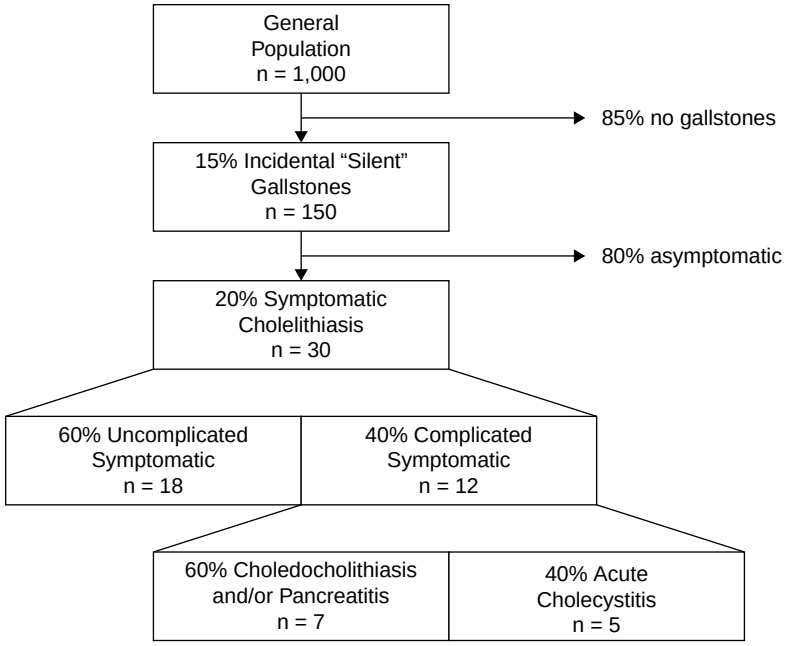


FIG. 1 Flowchart demonstrating the incidence of silent gallstones, symptomatic cholelithiasis, and complicated gallstone disease in an illustrative group of 1000 adults representative of the general population. *(Based on data from Festi D, Reggiani ML, Attili AF, et al.* J Gastro Hep. *2010; 25:719–724; Shabanzadeh DM, Sørensen LT, Jørgensen T, et al.* Gastroenterology. *2016;150: 156-167.e1.)*

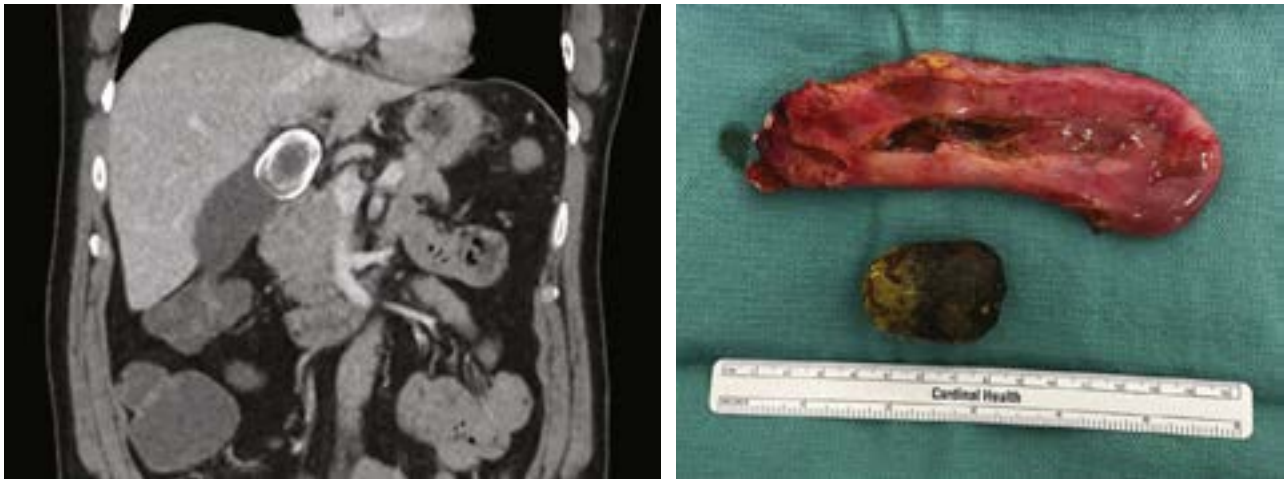


FIG. 2 Large gallstones are associated with increased risk of symptom development.

is worthwhile to note that consensus guidelines that recommend reserving cholecystectomy only for symptomatic or complicated gallstone disease originate from an early era of laparoscopy, which may consider additional morbidity due to the early learning curve in adopting the procedure. The overall mortality and bile duct injury rates for modern laparoscopic cholecystectomy are less than 0.1% and 0.3%, respectively. Overall significant morbidity of laparoscopic cholecystectomy is about 5%, including hernia formation, bowel obstruction, and both deep and superficial surgical site infections. In the absence of acute inflammation, the morbidity associated with elective laparoscopic cholecystectomy performed for asymptomatic gallstones may be even lower, although there are no large, controlled studies addressing the question since cholecystectomy is so rarely performed prophylactically. Conversely, the ready availability of and low morbidity associated with procedures to treat the potential complications of cholelithiasis (endoscopic retrograde cholangiopancreatography [ERCP] for choledocholithiasis, for example) mean that complications of contemporary expectant management may also be less morbid.

Given that the rate of any symptom development after identification of incidental gallstones is about 20%, complicated disease development is about 8%, and major morbidity of laparoscopic cholecystectomy is roughly 5%; decisions regarding the approach to asymptomatic gallstones should be individualized to the patient, with careful consideration of the potential consequences of complicated gallbladder disease versus operative morbidity and fitness at the time of diagnosis.

SPECIFIC PATIENT POPULATIONS

Cancer Risk Reduction

Although gallbladder cancer is very uncommon in the United States (about 1 in 100,000 US adults) and only one patient in the two largest longitudinal studies of asymptomatic cholelithiasis developed this malignancy, there is undeniably a connection between gallstones and cancer. Between 75% and 90% of patients with gallbladder cancer have cholelithiasis, and many of the risk factors for gallbladder

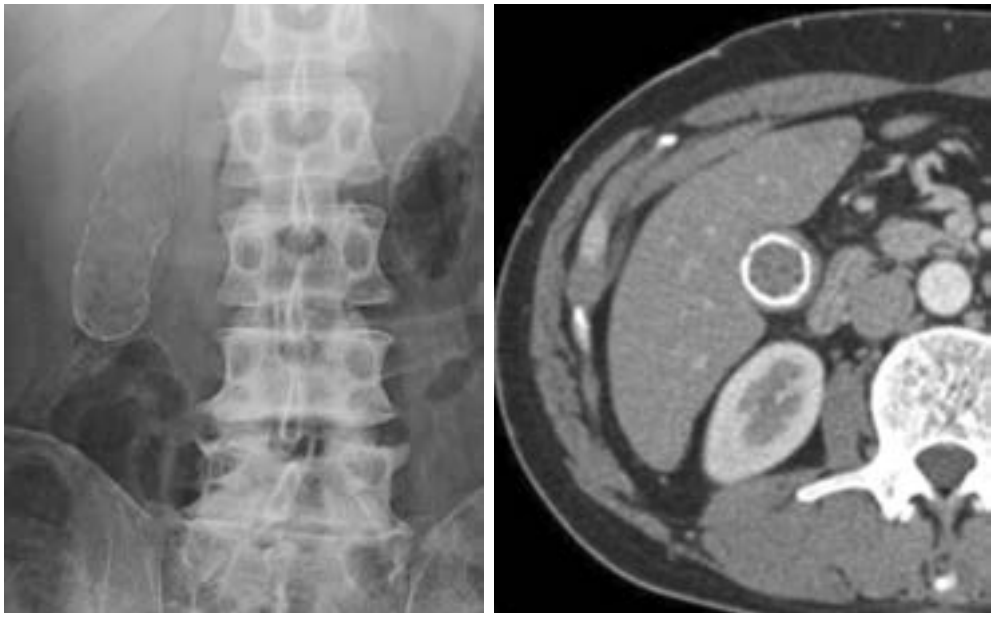


FIG. 3 Mural calcification (porcelain gallbladder) is associated with increased risk of primary gallbladder malignancy, although the lifetime risk has been historically overestimated and is probably about 5%.

carcinoma are identical to those for gallstone formation. Therefore, the relative rarity of this malignancy in the United States probably precludes prophylactic cholecystectomy for risk reduction in the otherwise average-risk patient with gallstones. Special consideration should be given to patients who are at higher risk for this cancer, and an understanding of the risk factors for gallbladder cancer beyond silent gallstones will help inform decision making.

Mural calcification, or porcelain gallbladder, has traditionally been an indication for cholecystectomy to reduce the risk of malignancy (Fig. 3). Early reports demonstrated 30% to 60% lifetime cancer risk associated with this finding. However, reexamination of malignancy risk in this special population has demonstrated much lower (but still elevated) risk of approximately 5%. There is no consensus on the management of this unusual radiographic finding in the absence of symptoms, and the approach should again be individualized to the patient, their overall condition, and risk of malignancy.

Finally, very large (>3 cm) gallstones have demonstrated a small but significant increase in the risk for malignancy. Given that these stones have a higher risk of lifetime symptom development as well, special consideration should be given to cholecystectomy in otherwise appropriate patients with very large gallstones.

Weight Loss Surgery

There is no question that obesity is an independent risk factor for gallstone formation. Moreover, rapid weight loss appears to change the chemical composition of bile and promote stone formation, leading to a further increased risk of gallstone formation beyond obesity alone. This connection has been studied and is quite profound. In a prospective study involving 51 obese adults dieting for weight loss, 25% of dieting subjects had developed new gallbladder sludge or stones after 8 weeks of weight loss, whereas 0% of nondieting controls had new gallbladder abnormalities.

Cholecystectomy has historically been performed during open Roux-en-Y gastric bypass for weight loss for patients with preexisting gallstones. This was justified given (1) the association between weight loss and gallstone formation, (2) historical difficulty in endoscopic management of complications from gallstones (i.e., choledocholithiasis) with Roux-en-Y anatomy, and (3) local adhesion formation causing a "hostile" and scarred environment for future cholecystectomy. With the increasing performance of sleeve gastrectomy and improved availability of push enteroscopy and other advanced endoscopic biliary management techniques, most surgeons have elected to avoid concomitant cholecystectomy for asymptomatic cholelithiasis during laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy. Furthermore, performance of laparoscopic cholecystectomy is safer and simpler in patients who do ultimately develop symptoms after they have undergone weight loss, with decreases in the size of their abdominal wall and liver.

Additional consideration should be given to patients with asymptomatic gallstones who are undergoing biliopancreatic diversion/duodenal switch procedures for weight loss. The additional dissection and division of the duodenum and difficulties presented in endoscopy for choledocholithiasis lead many surgeons to continue the practice of cholecystectomy for asymptomatic gallstones during performance of this procedure.

Gastrectomy

Cholecystectomy in patients with asymptomatic gallstones had been historically performed at the time of open gastrectomy (i.e., for cancer or peptic ulcer disease). However, with the emergence of laparoscopic techniques for gastric resection that effect minimal scarring and increasing availability of ERCP, most surgeons feel that concomitant cholecystectomy adds unnecessary morbidity without adequate benefit. As in the weight loss surgical population, the decision should ultimately be individualized to each patient based on their risk for complications from cholelithiasis.

Diabetes

After early uncontrolled studies demonstrated an increased risk of complications following surgical treatment of acute cholecystitis among diabetic patients, there was some enthusiasm for prophylactic cholecystectomy in diabetics with gallstones. However, data eventually emerged demonstrating acceptable outcomes for these patients from cholecystectomy. Most surgeons currently recommend cholecystectomy only for those patients with symptomatic cholelithiasis and diabetes, similar to those guidelines for the general population. One caveat is that mild symptoms may herald the development of both more severe symptoms as well as complications (i.e., acute cholecystitis or pancreatitis), and diabetics with early symptoms should be medically optimized and offered surgery if otherwise appropriate to prevent complications and the need for urgent cholecystectomy.

Hemolytic Anemias

Rapid bilirubin catabolism can lead to formation of pigmented gallstones, with a characteristic black appearance on gross examination. The most commonly encountered congenital hemolytic anemias are sickle cell disease (and trait) and thalassemia, both of which cause enhanced formation of gallstones. Acquired hemolytic anemias, such as immune-mediated hemolysis, may also predispose patients to gallstone formation. The management of asymptomatic gallstones in patients with hemoglobinopathy is somewhat controversial. The frequency of asymptomatic cholelithiasis in these patients (roughly 25% in a cross-sectional study), abdominal pain of other etiologies, and likelihood of symptom development make the treatment of asymptomatic gallstones among these patients distinct from the general population. In particular, sickle cell disease deserves special mention. Many surgeons perform cholecystectomy for asymptomatic gallstones at the time of splenectomy, such that cholecystitis may be excluded as a potential etiology for abdominal pain during vaso-occlusive crises. The pre- and perioperative management of patients with sickle cell disease (hemoglobin SS) in particular involves careful management of volume status, oxygenation, and analgesia. Ideally, surgery should be performed in a center with experience in the management of these patients with cooperation among surgery, anesthesia, and hematology teams.

Intestinal Insufficiency (Short Gut Syndrome)

Patients with chronic intestinal insufficiency are a highly specialized population but one with which all surgeons must be familiar nonetheless. Long-term parenteral nutrition dependence leads to biliary stasis and clearly predisposes to development of both gallstones and attendant complications. In one small but illustrative series, 5/5 (100%) patients with severe intestinal insufficiency and parenteral nutrition dependence developed symptomatic cholelithiasis or complications. It is also worthwhile to note that decreasing remaining viable bowel as well as parenteral nutritional dependence are both independent risk factors for development of symptomatic cholelithiasis. Given the relative rarity of this chronic problem as well as the likelihood of complicating factors (i.e., prior abdominal surgery, inflammatory bowel disease), the decision regarding prophylactic cholecystectomy should be individualized to the patient based on their individual risk factors for symptomatic cholelithiasis and potential morbidity from the procedure.

Asymptomatic Choledocholithiasis

Asymptomatic choledocholithiasis, typically an incidental finding on ultrasonography or CT ordered for a separate indication, presents an uncommon but important clinical dilemma to surgeons. Due to the high rate of complications associated with common bile duct stones, cholecystectomy is typically recommended in good candidates to prevent recurrence and complications. Cholecystectomy should be performed after endoscopic stone retrieval, sphincterotomy, or surgical common duct clearance procedures in appropriate surgical candidates.

Spinal Cord Injury

Perhaps through autonomic dysfunction and biliary stasis, patients with spinal cord injuries are at very high risk for the development of gallstones. Compared with age- and gender-matched controls, patients with spinal cord injuries are about three times as likely to develop gallstones in their lifetime. One of the most feared complications of apparently asymptomatic gallstones in this unique patient population is the late, complicated presentation of acute on chronic cholecystitis due to sensory neuropathy. In select patients with asymptomatic gallstones, prophylactic cholecystectomy may be reasonable to prevent a late and complicated presentation after development of cholecystitis.

SUMMARY

Asymptomatic cholelithiasis remains a common clinical dilemma, and the lifetime risk of complicated disease from initially silent gallstones is low but not negligible (estimated at 8%). Although the relative morbidity of laparoscopic cholecystectomy continues to decline since its advent in the 1980s, there is still occasional major morbidity associated with the procedure (roughly 5%, with the majority being infectious complications). Therefore, a thorough understanding of the relative risks of the procedure versus conservative management are foundational to individualizing surgical treatment recommendations for each patient.

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Management of Biliary Dyskinesia

J. Bart Rose, MD

EPIDEMIOLOGY

Biliary dyskinesia is a rare diagnosis. However, up to 20% of the cholecystectomies performed annually in the United States are for a diagnosis of functional gallbladder disorder. The incidence in the United States has risen from 43 cases/million to 89 cases/million in the decade between 1991 to 2001. This is in stark contrast to the 25 cases/million noted in countries outside of the United States. This increase has been most prominent in the pediatric patient population with a sevenfold increase between 1997 and 2010. It is unclear if the discrepancy noted in incidence between the United States and other countries represents a difference in patient population or overdiagnosis.

CLINICAL PRESENTATION, EVALUATION, AND DIAGNOSIS

Patients presenting with biliary dyskinesia often have vague abdominal complaints centered around recurrent episodes of abdominal

pain. Biliary dyskinesia is a diagnosis of exclusion and more common causes of episodic abdominal pain should be excluded before intervention, such as irritable bowel syndrome, peptic ulcer disease, gastroesophageal reflux disease, chronic constipation, costochondritis, muscular skeletal disorders, coronary artery disease, or liver capsular pain in patients with cirrhosis. If these other more common entities are excluded, then biliary dyskinesia can be considered if specific pain symptoms are present as outlined in the Rome IV diagnostic criteria (Box 1). These criteria have been designed by expert consensus to establish an accepted definition of biliary pain such that patients must have epigastric or right upper quadrant pain that (1) builds up to a steady level and lasts for 30 minutes or longer, (2) occurs at different intervals (not daily), (3) are severe enough to interrupt the patient's daily activity or lead to an emergency room visit, (4) are not significantly related to bowel movements, and (5) are not related to postural changes or acid suppression. Additional supportive criteria include pain associated with nausea or vomiting, radiation of pain to the back or to the right infrasubscapular area (Boas' sign), or pain that wakes the patient from sleep.

To be diagnosed as having a functional gallbladder disorder patients must meet all the biliary pain criteria previously mentioned and have the absence of gallstones or other structural pathology based on either imaging or laboratory analysis suggesting biliary obstruction. Supportive diagnostic criteria can be a low calculated gallbladder ejection fraction (GbEF). It is important to emphasize that cholescintigraphy is recommended only to support the diagnosis and not to make the diagnosis. When considering the use of cholescintigraphy, it is necessary to understand the history of this test. The highest level of data suggesting GbEF is useful in making treatment decisions for biliary dyskinesia is based on a study of 21 patients with abnormal cholescintigraphy randomized to either surgery or observation. This study suggested that abnormal GbEF was predictive of symptom improvement postcholecystectomy. However, these data must be interpreted cautiously as it was underpowered and did not compare surgery to medical management. A subsequent pilot study attempted to address this by randomizing patients with low GbEF to surgery or medical management with amitriptyline and found that the feasibility of a larger trial is doubtful given high crossover to the surgical arm due to clinician bias and lack of a "gold-standard" medical treatment. Reliance on GbEF to predict clinical response to cholecystectomy is problematic when considering up to 80% of patients with functional biliary pain and normal GbEF still have symptom relief after cholecystectomy.

BOX 1 Diagnostic Criteria for Biliary Pain

Must meet the following:

- Builds to a steady level and lasts ≥30 minutes
- Occurs at differing intervals (not daily)
- Severe enough to disrupt daily living or requires an emergency room visit
- Does not change in character with bowel movements, acid suppression usage, or postural changes (>20% of the time)

Pain may be associated with:

- Nausea and vomiting
- Radiation to back and/or right infrasubscapular regions (Boas' sign)
- Waking from sleep

Data from Rome IV criteria. Cotton PB, Elta GH, Carter CR, Pasricha PJ, Corazziari ES. Gallbladder and sphincter of Oddi disorders. *Gastroenterology*. 2016;150:1420–1429.

The definition of an abnormally low GbEF can also be a moving target as reported cutoffs have ranged from <35% to <50% depending on how the test is done. Most modern series will use <35% as a cutoff, defining hypokinesis as described in a 2019 Cochran review based on standardized techniques. However, GbEFs of <35% have been reported in up to 25% of asymptomatic patients. Multiple confounders may artificially lower GbEF such as exercise, hormone replacements, anticholinergics, and proton pump inhibitors. Much of the variability in this test can be attributed to nonstandardized administration. An attempt to curb irregular test execution was undertaken by the Society of Nuclear Medicine, which defined practice guidelines to "assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of hepatobiliary scintigraphy in adults and children". Their recommendations rely on the use of synthetic cholecystokinin for stimulation of GbEF as the use of fatty meals or other stimulants are nonstandardized. However, a subsequent national shortage of synthetic cholecystokinin led to a reevaluation of this recommendation and found that use of fatty meals may be adequate. These disparate recommendations again add variability to interpretation. A study looking at the reproducibility of an abnormally low GbEF when repeated a month later found that half of patients will normalize when using a standardized method (Fig. 1). These many caveats are cautionary that a low GbEF should only be considered as supporting the diagnosis of biliary dyskinesia and not be utilized to make the diagnosis.

If a patient presents with symptoms of biliary colic by Rome criteria, has no other diagnosis that can explain the symptoms, and supporting data are considered carefully, only then can biliary dyskinesia can be diagnosed by exclusion. Patients meeting this recommendation are more likely to have an improvement in symptoms following cholecystectomy. The operative description of a laparoscopic cholecystectomy utilizing the "critical-view of safety" technique is described in the previous chapter. On pathologic examination there should be no evidence of gallstones or microlithiasis (i.e., sludge) if

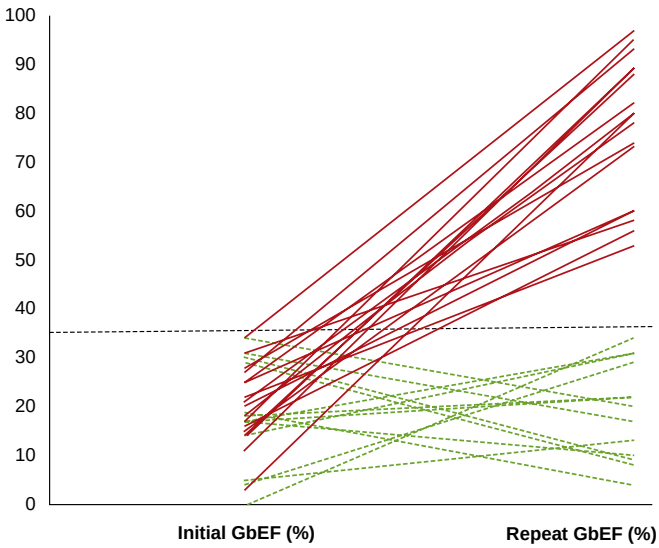


FIG. 1 Initial and repeat gallbladder ejection fraction (GbEF) results of biliary scintigraphy in 30 patients. Green lines indicate results in 14 patients in whom the GbEF test remained positive for abnormally low GbEF on retesting. Red lines show 16 patients in whom the GbEF fell into the normal range (≥35%) on retesting. *(From Rose JB, Fields RC, Strasberg SM. Poor reproducibility of gallbladder ejection fraction by biliary scintigraphy for diagnosis of biliary dyskinesia. J Am Coll Surg. 2018;226:155–159.)*

the correct diagnosis was made. Interestingly, 80% of resected specimens will show signs of chronic inflammation microscopically.

For some patients, the alternative approach of observation can be considered given this is a benign process. The natural history of biliary dyskinesia is not well studied, and it is unclear how many of these patients will improve with watchful waiting. To date, only one study has randomized patients to surgery versus observation and found that cholecystectomy was more likely to improve symptoms. However, many other retrospective series have reported outcomes in patients undergoing nonoperative therapies. An analysis of these studies showed an average of 50% of patients will improve without an operation if given time. It should be noted that the smallest improvement reported in this meta-analysis was in the aforementioned randomized study. While these limited data are hard to interpret, it is likely that we can expect some patients to improve with observation. Further work is needed to correctly identify those patients who would most benefit most from observation or cholecystectomy.

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Management of Acute Cholecystitis

Ryan C. Broderick, MD, and Bryan M. Clary, MD

INTRODUCTION

Cholecystolithiasis is estimated to be present in 10% of the population, with one-third of those developing symptoms. Acute cholecystitis (AC) is most commonly a result of gallstone-mediated obstruction of the cystic duct, although acalculous cholecystitis can occur in low-perfusion states or biliary stasis in critically ill patients. Obstruction of the cystic duct by gallstones leads to mucosal inflammation and edema, distension of the gallbladder wall, and eventual ischemia. Not infrequently, untreated AC results in perforation with abscess formation or, more rarely, diffuse peritonitis.

The diagnosis of AC is based on a combination of clinical signs and symptoms with confirmatory imaging. Signs and symptoms include right upper quadrant (RUQ) pain/tenderness lasting more than 4 to 6 hours, associated nausea/vomiting, and fevers. On physical examination, patients are tender in the RUQ and/or epigastrium. Exacerbation of pain by palpating the right subcostal location in conjunction with deep inspiration may be elicited (Murphy's sign). Abdominal ultrasound (US) of the RUQ is often performed in patients with characteristic presentations to confirm pericholecystic fluid, gallstones, and gallbladder wall thickening. Abdominal CT scans are not infrequently obtained, especially in patients presenting via the emergency room and/or with presentations that are not quite classic. Ultrasound has a higher sensitivity in visualizing gallstones and can be used to assess for pain directly overlying the gallbladder ("sonographic Murphy's sign"). Standard treatment in low medical risk patients is early, same-admission laparoscopic cholecystectomy. Patients with equivocal presentations/imaging, or those with significant medical comorbidities, are approached with medical management and delayed cholecystectomy once the diagnosis is confirmed or the medical situation stabilized. Resolution of AC with intravenous antibiotics alone is quite common. Percutaneous cholecystostomy is performed in nonoperative patients when antibiotics alone fail. When performing laparoscopic cholecystectomy for AC, anatomic difficulties such as high body mass index (BMI) or variant ductal anatomy can be exacerbated by a severe inflammatory response. Therefore, surgeons should be proficient and prepared for conversion to open cholecystectomy or utilizing bailout options described later.

Robotic cholecystectomy is becoming increasingly popular. The robot is a tool, just as laparoscopic instruments are, but it allows for more fine motor control and 3D visualization. Indocyanine green (ICG) cholangiography is also being reported more frequently. It allows for real-time anatomic verification, which may improve efficiency when used in conjunction with the "critical view of safety" technique.

CLINICAL PRESENTATION, EVALUATION, AND DIAGNOSIS

Patients presenting with AC experience symptoms of upper abdominal pain (RUQ and/or epigastric) that lasts more than 4 to 6 hours. Often, careful history taking can elicit prior episodes of similar symptoms of shorter duration and less severe pain. Nausea and vomiting are often concomitant symptoms. Fever may also be present but objectively occurs less frequently. The patient may have a known history of gallstones from prior episodes or incidentally from prior imaging, allowing some focus in diagnostic workup.

The most common physical examination finding is RUQ tenderness to palpation; an inflammatory mass may also be palpated depending on body habitus and this finding often portends very difficult dissection. A classic physical finding is Murphy's sign: inspiratory arrest with palpation over the gallbladder. This is often reported during diagnostic US as a "sonographic Murphy's sign." Despite these classic signs and symptoms, the presentation can be highly variable, especially in patients who are obese, diabetic, advanced in years, or immunosuppressed from various causes. There is also significant symptom overlap with other intraabdominal or thoracic causes.

The most important differentiation a surgeon makes is determining AC from other biliary disease, such as biliary colic or choledocholithiasis. AC needs immediate diagnosis, evaluation, and treatment to prevent progression of disease, while biliary colic can often be managed with symptom control and outpatient cholecystectomy. Choledocholithiasis is covered elsewhere, but treatment often initially involves other treatment modalities before laparoscopic cholecystectomy. Although not typical, some patients present with both AC and common duct complications (cholangitis, pancreatitis). Many patients with chronic biliary colic arising from

cholecystolithiasis may have a thickened gallbladder without other manifestations of AC. In general, such patients should undergo elective cholecystectomy unless medical comorbidities dictate otherwise. As mentioned earlier, a number of other intraabdominal processes have overlapping symptom presentations including pancreatitis, peptic ulcer disease, hepatitis, mesenteric ischemia, colitis, and perforated appendicitis. Extraabdominal diseases with symptom overlap include myocardial ischemia and pneumonia. History taking and physical exam should focus efforts on ruling out other sources of symptoms as well as guide laboratory and imaging studies.

There are no pathognomonic laboratory studies for AC. Mild leukocytosis is common. Leukocytosis over 18,000 per mm^3 may be a predictor of severe inflammation. Liver transaminase (AST and ALT) and alkaline phosphatase levels are often normal or slightly elevated. Serum bilirubin is generally normal. Markedly elevated alkaline phosphatase and bilirubin levels should prompt consideration of common bile duct (CBD) pathology (cholangitis, choledocholithiasis), whereas profound elevations of liver transaminase levels may reflect intrinsic liver issues (hepatitis). Serum amylase and lipase are sent to evaluate for pancreatitis.

The optimal choice of imaging depends on the likelihood of cholecystitis as well as study sensitivity, availability, and cost of the study. US, CT, hepatobiliary iminodiacetic acid (HIDA) scan, and magnetic resonance cholangiopancreatography (MRCP) are all capable of diagnosing AC, each with advantages and weaknesses. For patients with a typical presentation of AC, US is the diagnostic test of choice. It is inexpensive, widely available, and has adequate sensitivity/specificity. Findings on US that suggest AC include pericholecystic fluid, gallbladder wall thickness over 4 mm, gallbladder distension, a gallstone lodged in the cystic duct/neck of the gallbladder, and a sonographic Murphy's sign. Although US is 90% sensitive at diagnosing gallstones, it is only 60% to 70% sensitive for identification of objective signs of AC. It is common for a patient to present with classic history and laboratory findings of AC and an US showing gallstones but with no other objective findings. In this setting, abdominal CT may be useful to rule out other abdominal conditions, although for surgically low risk patients, proceeding straight to laparoscopy with anticipation of cholecystectomy is appropriate. It is not uncommon for surgeons to be consulted after CT imaging has already been obtained. CT is more sensitive than US at evaluating objective signs of AC including pericholecystic fluid, inflammation, and gallbladder thickening. If the CT scan has characteristic findings of AC, then it is not necessary to perform an US even when stones are not radiographically visible.

Another common scenario is the patient with an atypical presentation and US findings without clear evidence of cholecystitis. A full review of the patient and available data are needed, and the surgeon must decide whether there is significant likelihood of an alternate diagnosis not involving the biliary tract; at this point, CT of the abdomen and pelvis can be obtained to rule out other intraabdominal pathology and potentially rule in AC. It should be noted, however, CT scan is less sensitive in milder disease of the gallbladder and should not be used as the initial/gold standard study in uncomplicated AC.

In the unusual case where US and CT imaging are inconclusive, an HIDA scan may be informative. An HIDA showing nonvisualization of the gallbladder is consistent with cholecystitis from an obstructing gallstone, but it should be noted that false positives are possible in fasting patients. HIDA imaging is highly sensitive and specific for cholecystitis but provides no useful information for other sources of symptoms in the event of a negative study. We use HIDA very rarely, most commonly in patients with atypical presentations, significant comorbidities, and inconclusive US and CT scans. MRI is highly sensitive for AC but is more expensive and less expeditious. MRI/MRCP is typically reserved for patients with significant elevations in either bilirubin or alkaline phosphatase levels to rule out choledocholithiasis and malignancy, which may necessitate significantly different treatment approaches.

SURGICAL MANAGEMENT

Laparoscopic cholecystectomy is the standard treatment for AC. Early, index admission cholecystectomy in most patients has been proven to be clinically advantageous. Surgery treats the current episode of complicated gallstone disease, and potential subsequent episodes of AC or biliary tract complications related to gallstones are eliminated or minimized, respectively. All patients diagnosed with AC should be started on appropriate antibiotics at diagnosis. Antibiotics are directed to treatment of common pathogens in bile cultures including *E. coli, Klebsiella, Enterobacter*, and *Bacteroides* species.

The decision regarding the appropriate treatment strategy, surgery or medical management depends on the overall medical condition of the patient plus the severity and duration of symptoms. Patients with minimal medical comorbidity presenting early in the disease process should generally be managed with surgery. Those with significant, optimizable comorbidities but mild cholecystitis may merit a trial of medical therapy or "cool down" period followed by cholecystectomy after 6 to 12 weeks. Those who are critically ill or with severe comorbidities and severe AC are often best managed with early percutaneous cholecystostomy tube placement in conjunction with antibiotics and delayed cholecystectomy once their medical condition is satisfactory.

It is widely accepted that cholecystectomy should be completed as soon as feasible following diagnosis during the index hospitalization. No demonstrable difference is found in mortality rate, major bile duct injury, postoperative pain, or other significant complication in patients treated with early or delayed cholecystectomy. Multiple studies have shown the safety and efficacy of early, same-admission cholecystectomy in the management of cholecystitis. The practice of "cooling off" until there is an opening in the operating room convenient for the surgeon is specifically unwarranted as is a general practice of treating with antibiotics to facilitate discharge and surgery in an elective setting. These approaches serve only to extend hospitalization unnecessarily and place patients at risk for ongoing symptoms or complications from their stone burden. While laparoscopic cholecystectomy is the procedure of choice, surgeons must be familiar with laparoscopic and open approaches as the average conversion rate in AC is 10%.

Robotic cholecystectomy, as an extension of the laparoscopic toolset, is preferred by some surgeons. Robotic port placement and technique is theoretically equivalent to laparoscopic cholecystectomy, as the robot is a laparoscopic device. Three-dimensional visualization and wristed instrument movement are described as advantages by frequent robotic users. Additionally, the latest iterations of the DaVinci robot have fluorescent cholangiography (FC) capability.

ICG cholangiography during minimally invasive cholecystectomy allows for real-time identification of biliary structures during cholecystectomy and in the current era is straightforward to perform. Selective intraoperative intraluminal contrast cholangiogram (IOC) can also be useful in confirming difficult anatomy, and its timing of use is discussed later.

Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy is the approach of choice in AC for most patients. Those with significant prior open upper abdominal surgery can be approached laparoscopically with expectations of a higher rate of conversion. Multiple studies have demonstrated less morbidity, shorter length of hospital stay, lower cost, and faster

recovery to normal function compared with the open approach. Surgical technique is the same as for elective laparoscopic cholecystectomy in patients with biliary colic, although with more difficult target anatomy due to acute inflammation; the addition of more trocars or other techniques for improving visualization may be needed.

The patient is positioned supine with an arm tucked to allow for potential intraoperative cholangiogram, although some prefer both arms out. The abdomen and lower chest should be prepped and draped in a manner that can accommodate a retractor system of choice in the event of conversion to an open procedure. In addition, the patient should be well secured to the bed to allow for steep reverse-Trendelenburg positioning. The gallbladder fundus is grasped and retracted cephalad and the region of the infundibulum retracted laterally to provide exposure for dissection of the cystic structures until a critical view of safety is obtained. Intraoperative cholangiogram should be considered when the anatomy is unclear. Given the potential presence of cystic duct obstruction, intraluminal contrast cholangiograms require injection of the dye directly into the cystic duct and not via the gallbladder. Intraoperative ICG (fluorescence cholangiography) is now available in most centers and allows for real-time identification of anatomy including the CBD and cystic duct, although tissue thickness and inflammation may limit near-infrared (NIR) light penetration. Additionally, it is possible only part of the cystic duct is visible with fluorescent view in the setting of a gallstone obstructing the duct.

Although crucial for safe anatomic dissection, grasping the fundus of an inflamed, distended gallbladder may prove difficult in practice. This can often be improved with decompression. The use of either a laparoscopic needle-aspirator attached to a syringe or insertion of a 14-gauge angiocatheter through an RUQ stab incision can usually facilitate decompression. If neither of these options is successful, a 5-mm trocar can be driven directly into the fundus of the gallbladder and a laparoscopic suction device used to aspirate its contents. Spillage of gallbladder contents must then be prevented from the cholecystostomy with Endoloop or suture placement. Stones escaping the field must be searched for and retrieved so as to prevent the development of late perihepatic abscesses.

A very inflamed gallbladder, even with decompression, may not be amenable to grasping with routine laparoscopic devices. Inability to retract via the fundus results in poor visualization during the dissection of the cystic structures, placing the patient at greater risk of bile duct injury. In this scenario, claw or rat-tooth graspers may prove useful. Alternatively, a dome-down approach with the assistant instrument grasping the inflamed peritoneum and lifting the liver cephalad while the surgeon retracts the gallbladder may be necessary. Significant care and attention must be directed to gallbladder anatomy during this dissection as loss of bearings medially can lead to high injury of the common hepatic duct. If a dome-down approach is being considered as a result of significant inflammation of the infundibulum, one should also consider alternative bailout techniques.

Once the fundus of the gallbladder is grasped and retracted, the dissection begins. It is common to have adjacent organs such as omentum, duodenum, and colon adherent to the gallbladder; these organs should gently be peeled down bluntly. This is best done by identifying the plane where the organs meet the gallbladder and peeling downward and parallel to the gallbladder wall (rather than outward/perpendicular). A plane just deep to the serosa of the gallbladder is the better choice when the gallbladder and adjacent organs are too difficult to separate. Adhesions to the adjacent liver capsule may be difficult to dissect bluntly, and a low threshold to divide these sharply, without cautery, should be used to prevent capsular tears that could make the dissection more difficult in a bloody field. We have found that energy sealing devices are excellent options in dissecting the gallbladder fundus away from the liver bed when approaching in a dome-down manner, especially when a plane just deep to the cystic plate in the liver parenchyma is taken. If this plane is chosen during a dome-down approach, a transition to a plane superficial to the cystic plate (or in the wall of the gallbladder) must be entered once the lower region of the gallbladder fossa is reached, so as to avoid injury to the hilar structures and CBD.

Once the gallbladder is exposed, dissection at the infundibulum begins. The peritoneum and fatty tissue surrounding the infundibulum and cystic duct are divided with cautery and blunt dissection. A high dissection at the infundibulum should be utilized. If the node of Calot is visible, then limiting the line of peritoneal/serosal division to the upside (gallbladder side) of this structure helps to minimize the risk of CBD injury. With rare exceptions, this lymph node lies immediately on top of the cystic artery and thus serves an important role in identifying the cystic artery and cystic duct. Calot's lymph node is often not appreciable in AC and care should be taken to avoid injury to the portal structures. After the peritoneum is divided high along the infundibulum, the dissection is carried at an upward angle toward the cystic plate on the medial gallbladder; if dense inflammation is encountered, lateral dissection may be needed first to improve mobility of the infundibulum and facilitate medial dissection. A combination of electrocautery and blunt dissection may be needed as the tissue edema can limit cautery at times. It is critical to maintain the same standards of visualization as in elective cholecystectomy. A firm critical view of safety should be obtained before ligation and division of any structures. Blind clipping for hemostasis should be avoided to prevent major bile duct injury.

Occasionally, the cystic duct may be foreshortened and/or thickened due to inflammation. If it is too large to close with clips, an Endoloop or laparoscopic surgical stapler may be necessary. In either case, when a duct appears too large to clip, the surgeon should be absolutely sure of the anatomy before using these devices. In this situation, extended dissection or cholangiography is needed to confirm anatomy. When used, the stapler should be positioned so as not to narrow the CBD. The stapler should be long enough to divide the duct with one staple load and use 2.5-mm staples. Once the cystic structures are ligated and divided safely, the gallbladder is dissected away from the remainder of the liver bed. Care should be taken to maintain dissection in the appropriate plane and not deviate course into the liver parenchyma unless necessary, as this can lead to bleeding and bile leak complications.

If any of the previously discussed techniques are not successful in aiding dissection, or the anatomy cannot be clearly defined, there should be no hesitation to convert to open cholecystectomy or perform a bailout maneuver. Inadequate exposure and persistent attempts to perform surgery laparoscopically can lead to a severe CBD or vascular injury, the likelihood of which can be minimized in experienced hands by converting to open exposure.

Indocyanine Green Use in Cholecystectomy

ICG is a green dye injected by the intravenous route preoperatively and is excreted exclusively in the bile. The standard dose of ICG at our institution is 7.5 mg administered IV at least 45 minutes, and up to 3 hours, before incision. Protein-bound ICG fluoresces when illuminated with NIR light and allows for FC. FC offers a potential detailed anatomic mapping of extrahepatic biliary structures and can be a useful adjunct to the critical view of safety technique. As the NIR light is built into the laparoscopic or robotic camera and processor equipment, FC can be performed without the need for additional equipment, supplies, or personnel in the operative theater. It has the added benefit of not requiring cannulation of the biliary tree, such as with IOC. No substantial contraindication for use of ICG exists, and it has been used safely in patients with iodine allergy. Anaphylactic reaction has been reported at a rate of 0.003%. Our group avoids use of ICG dye in patients with a history of anaphylactic reaction to shellfish or iodine out of an abundance of caution.

Although current firm recommendations are limited by published sample size, early data suggest both reduced operative time and conversion to open surgery in FC cases for both inflamed and

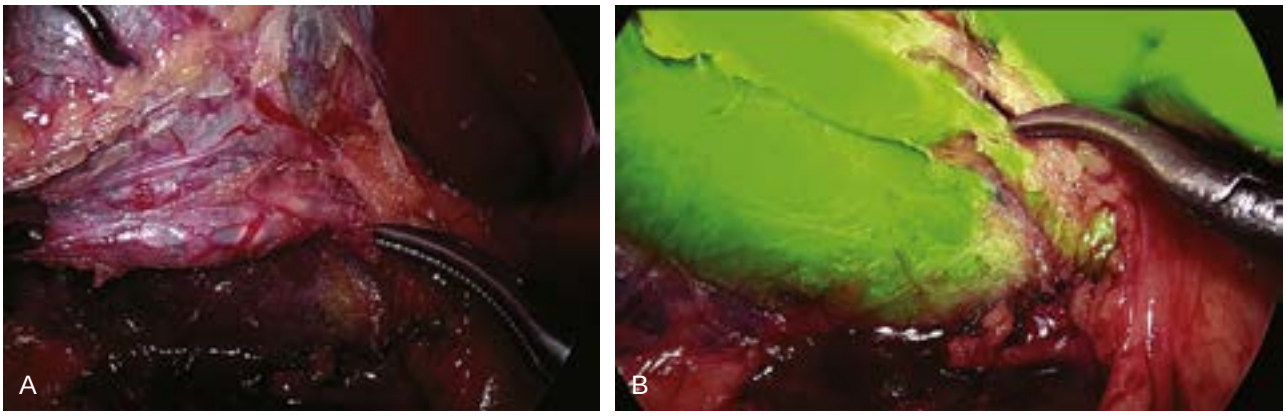


FIG. 1 **(A)** Bright light/traditional laparoscopic view; instrument points to cystic duct. **(B)** Fluorescence cholangiography with "overlay" mode for the same patient as in **(A)**; instrument points to cystic duct with cystic/common duct junction noted inferior to instrument.



FIG. 2 Fluorescence cholangiography with grayscale mode. Grasper is retracting infundibulum while cystic duct and common bile duct are visible before peritoneal dissection.

noninflamed pathology. Whether FC significantly moves the needle on reducing major CBD injury remains to be confirmed with further collation of data and use in practice. Our institution routinely uses ICG in laparoscopic cholecystectomy. Examples of ICG use in practice are seen in Figures 1 and 2.

Open Cholecystectomy

Open cholecystectomy for AC occurs as a conversion from laparoscopic approach and is not a sign of weakness, rather it is a sign of mature surgical decision making. There are several risk factors requiring conversion to open cholecystectomy including prior upper abdominal surgery, obesity, long duration of symptoms, cirrhosis, and male sex. Both upper midline and right subcostal incisions are appropriate; we favor use of right subcostal for exposure and include placement of a wound protection device. A fundus-down technique is used after appropriate abdominal wall and viscera retraction is in place. The fundus and peritoneum at the apex of the gallbladder are grasped and countertraction applied. Electrocautery is used to dissect the posterior wall of the gallbladder off the liver bed. When this plane is too challenging, a plane behind the cystic plate can be taken and developed with an advanced energy device. One can safely be in this plane until halfway down the gallbladder fossa, at which point reentry into a plane superficial to the cystic plate must occur to preclude injury to the adjacent hilar structures. The medial and lateral peritoneum overlying the gallbladder and infundibulum are dissected with cautery again taking a line on the left side of the gallbladder above the node of Calot, if visible. When the infundibulum is exposed, lateral retraction is used to expose the cystic duct and artery to facilitate ligation. It is not uncommon to find substantial inflammation of the fundus, body, and infundibulum, while at the same time the region of the cystic duct is generally normal. In these instances, it may be preferable to begin the procedure at the base of the gallbladder and proceed retrograde. Blunt dissection with the thumb and index finger to thin out the tissue overlying the cystic duct and artery is often useful in patients with marked thickening in the duodenohepatic ligament.

Bailout Options

Some gallbladders cannot be removed safely. Such situations are not reliably predicted on preoperative imaging as some markedly thickened gallbladders are easily removed. In situations where one cannot safely progress, open or laparoscopic bailout options must be considered. As surgical training features fewer open cholecystectomy operations, surgeon comfort with conversion to open is declining. It is becoming more common to see laparoscopic bailout options used in the setting of severely inflamed hepatocystic triangle anatomy. If inability to safely perform dissection is recognized early in an operation and the gallbladder is mostly intact, or if the patient becomes clinically unstable, a cholecystostomy tube is a good option. A pigtail catheter may be placed under direct view from a subcostal location into the gallbladder and secured in place.

If the gallbladder is firmly adherent to the liver with no identifiable tissue planes and dissection results in repeated parenchyma disruption raising concern for bleeding or bile leak, the back wall of the gallbladder may be left in place. The mucosa of the remnant gallbladder is then cauterized extensively to reduce the risk of mucocele. A drain is left in the surgical bed for postoperative monitoring and management.

If the cystic structures cannot be safely dissected from the portal structures but the gallbladder is no longer intact or if it is gangrenous, a partial/subtotal cholecystectomy can be performed. The gallbladder is surgically divided high on the infundibulum, all stones are removed, and the infundibulum left in situ. The infundibulum is then oversewn with permanent suture in full-thickness fashion or the cystic duct is sewn internally through the infundibulum if tissue is friable. Alternatively, suturing can be omitted if this is not feasible. Again, a closed suction drain is placed in the surgical bed due to high risk of bile leak. Such approaches are associated with high rates of subsequent intervention for bile leak (e.g., transampullary stenting). Patients left with substantial gallbladder remnants should be considered for completion cholecystectomy at a later date, especially in relatively young and healthy patients.

Complications and Postoperative Care

Postoperative care should focus on early advancement of diet and discontinuation of antibiotics in most patients. Postoperative antibiotics are discontinued often immediately after surgery, but some patients require longer duration for sustained systemic inflammatory response. For patients in which a drain was placed in the operative bed, bile leak is assessed early. If there no evidence of bile leaks, the drain is often removed on postoperative day 1 or 2; however, high-risk patients may be discharged home with the drain. In cases that had to be converted to open cholecystectomy, pulmonary complications are common as a function of splinting inspiratory effort; pain control is crucial to aid in respiratory mechanics and airway clearance.

The most common intraabdominal complications following laparoscopic cholecystectomy for AC are abscess formation, bleeding, and bile leak. These complications can usually be managed with the assistance of interventional radiology rather than return to the operating room; however, in the setting of a bile leak causing diffuse peritonitis, operative washout and drain placement is indicated. Bile and gallstone spillage are common in cases of acute inflammation. Bile should be irrigated and aspirated, and efforts should be made to retrieve all dropped gallstones. Larger dropped stones can result in abscess formation, so every effort should be made to retrieve them. In the scenario of a patient who returns 1 or 2 weeks after surgery with imaging findings of fluid collection in the surgical bed, one must determine if a drain should be placed. If the patient is having systemic inflammatory response syndrome (SIRS) or presents with concerning lab and imaging findings, a drain should be placed. If the patient appears well, has normal labs, and has simple fluid on CT scan, the fluid may represent seroma and a drain may not be necessary.

Most bile leaks postoperatively are not related to major CBD injury but are due to leakage from the cystic duct or small subcapsular ducts (ducts of Luschka). When a patient is deemed to be higher than average risk of leak, a closed suction drain should be left in the operative field. Examples of when to leave in a drain are a gallbladder that is exceptionally adherent to the liver parenchyma, poor cystic duct quality, or if bailout techniques have been employed. Leaks may not be immediately apparent in many instances. As stated previously, it is our practice to remove the drain before discharge on postoperative day 1 or 2 if there is no evidence of a leak. If a small leak is present, it will usually heal on its own. In patients who return to the ER with an unanticipated biloma, percutaneous drainage by interventional radiology is used. While it is true that many bile leaks following cholecystectomy for AC are cystic stump leaks, the default assumption should be that of a bile duct injury unless clinical findings suggest otherwise. Patients with abnormal liver function test, high volume leaks, upward trending drainage volumes, and those with signs of sepsis should undergo endoscopic retrograde cholangiopancreatography (ERCP) for delineation of the anatomy and possible stent placement (for those patients with leaks whose CBD is still in continuity).

CBD injury is the most feared and morbid complication of cholecystectomy. Identification and management of CBD injury is discussed extensively elsewhere in this book. The key to minimizing the likelihood of an injury is complete dissection of connective tissue so only two structures are seen entering the gallbladder, the lower third of the gallbladder is dissected free from the liver bed, and a hepatocystic window is clearly identified before ligation of these two structures. Judicious use of cholangiogram should be used to help delineate anatomy. If common duct injury does occur, the key is recognizing it. Partially visualized clipping to control bleeding should be avoided, but if it is done, a careful postclip inspection of anatomy is necessary. After completion of cholecystectomy, the area should be examined for any bile leakage and the source identified. Although techniques to repair bile duct injury are discussed elsewhere, if the operative surgeon is not comfortable performing bile duct repair or reconstruction, early identification, wide drainage, and transfer to a center of expertise can limit morbidity. If at a center with expertise, intraoperative consultation should be considered.

MEDICAL MANAGEMENT

Patients with moderate to severe medical comorbidities (ASA>3, CCI>6) and mild cholecystitis may be managed medically with possible interval cholecystectomy. Antibiotics should empirically cover the most common organisms: enteric gram-negatives *(E. coli, Klebsiella, Enterobacter),* anaerobes *(Bacteroides, Clostridium),* enterococci, and streptococci. Duration of antibiotics is generally 7 to 14 days. Analgesia is also needed during the inflammatory response; regimens include aggressive multimodal nonnarcotic medications (acetaminophen, nonsteroidal antiinflammatory drugs) and opiates as needed. Supportive IV fluids are used until pain is controlled, laboratory tests begin to show improving trends, and the patient tolerates a diet. When patients clinically worsen or do not improve within 72 hours, percutaneous drainage should be considered. An 85% response rate to medical therapy is observed in AC, with most patients not experiencing recurrent issues in short term follow-up.

PERCUTANEOUS DRAINAGE

Percutaneous cholecystostomy is reserved for patients who do not respond to medical therapy, are clinically unstable with multiple comorbidities, have comorbidity that precludes general anesthesia, have atypical prolonged duration of symptoms (over 4 days), or already have associated abscess.

Cholecystostomy is 90% effective in alleviating symptoms and is performed under local anesthesia or light sedation by interventional radiology. Minor complications, such as catheter dislodgement or blockage, occur in 15% of cases and may require repeat IR intervention. Serious complications such as bleeding or bile leak are rare. If the patient is a surgical candidate, we leave the drain in place and perform interval cholecystectomy in 6 to 12 weeks. If comorbidities preclude surgery, IR cholecystogram is performed after a minimum of 6 weeks; if there are no stones present and cystic duct is patent, the tube can be removed or sequentially capped, symptoms monitored, and then removed. A more detailed description of cholecystostomy tube management can be found elsewhere in this book.

ENDOSCOPIC THERAPY

Endoscopic management of cholecystitis is rare but can be helpful in highly select patients. There are limited reports of treating AC via ERCP with placement of a transampullary stent into the gallbladder via the cystic duct. Transmural drainage can also be performed by puncturing the gallbladder via the duodenum under endoscopic US guidance, dilation of the tract, and placing a stent. This may be a long-term solution in the case of a patient who is not a surgical candidate, although it is used very rarely.

SPECIAL CONSIDERATIONS

Acalculous Cholecystitis

Acalculous cholecystitis is inflammation of the gallbladder not due to gallstones. It is a result of gallbladder stasis and ischemia from various sources classically seen in the critically ill patient. Duration of cholecystitis is often difficult to ascertain in these critical patients, especially if intubated or mental status is diminished. In this setting, early percutaneous cholecystostomy is advised. This is often definitive therapy as gallstones are not the source of cholecystitis, and the drain can frequently be removed 6 weeks after placement if the cystic duct is patent.

Cholecystitis in Pregnancy

Laparoscopic cholecystectomy is as safe as medical management of cholecystitis in all trimesters of pregnancy. First trimester surgery from general anesthetic may affect fetal organ development, though this is considered low risk. Third trimester surgery may induce

preterm labor or be physically challenging to perform due to size of the fetus. We use same-admission cholecystectomy in first- and second-trimester patients with low risk (short duration of symptoms, limited comorbidity). In the third-trimester patient, we usually attempt medical management followed by percutaneous cholecystostomy tube placement if needed. Subsequent cholecystectomy is performed after delivery.

Suggested Readings

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Proper Use of Cholecystotomy Tubes

Ashwyn K. Sharma, MD, and Jason K. Sicklick, MD

Cholecystostomy tube placement has traditionally been considered for the treatment of acute calculous cholecystitis and acalculous cholecystitis when definitive treatment with cholecystectomy is deemed high risk or contraindicated secondary to high morbidity/mortality potential resulting from patient factors, comorbid conditions, or underlying intraabdominal disease. In these cases, cholecystostomy tube placement is an effective strategy for achieving source control. In recent years, the Tokyo Guidelines were developed to create a classification system for the severity of cholecystitis and to offer consensus recommendations for cholecystostomy tube placement. However, once inserted, recommendations for long-term management of cholecystostomy tubes have not been standardized, although consensus on removal focuses on the presence or absence of cystic duct patency and the patient's surgical risk. For appropriate surgical candidates, definitive treatment with cholecystectomy is recommended following tube placement. However, cholecystectomy rarely occurs in practice, leading to multiple tube-related complications and recurrent gallbladder pathology. Therefore, clearer indications for the use of cholecystostomy tubes and their subsequent management are imperative. This chapter reviews the current literature on cholecystostomy tube placement and provides the most up-to-date recommendations based on current evidence.

INTRODUCTION

Gallstone disease is one of the most common gastrointestinal disorders encountered by general surgeons. Moreover, older patients who have severe cholecystitis and associated physiologic decompensation resulting from comorbidities and gallbladder pathology are increasingly more common. Ultimately, the preferred definitive treatment for patients with acute cholecystitis is laparoscopic cholecystectomy. However, there are situations in which emergent cholecystectomy is not always safe, including when cholecystitis leads to sepsis and hemodynamic instability, when cholecystitis causes acute decompensation of underlying comorbid illnesses, or when underlying comorbid conditions increase the patient's surgical morbidity risk (e.g., severe cardiac disease, severe pulmonary disease, and/or metastatic malignancies). In these cases, cholecystostomy tube insertion should be considered as a less invasive treatment that avoids general anesthesia and provides infectious source control.

INDICATIONS FOR CHOLECYSTOSTOMY TUBE PLACEMENT

Despite moving toward early cholecystectomy in all patients presenting with acute cholecystitis, there remain patients with high surgical risk either because of severe cholecystitis, the advanced nature of their comorbid conditions, or both. It is in these subsets of patients that cholecystostomy tube placement may be indicated.

The decision to forgo cholecystectomy and perform a cholecystostomy tube placement is mainly driven by two factors, namely gallbladder pathology and patient-related factors. Gallbladder pathology is primarily described by (1) the presence or absence of gallstones (calculous or acalculous cholecystitis), (2) the severity of inflammation (with or without gangrene), (3) the duration of symptoms, (4) the presence of sepsis and/or hemodynamic instability, and (5) the presence of underlying intraabdominal malignancy. Patient-related factors are a combination of objective and more subjective factors including, but not limited to, underlying neurologic, cardiac, respiratory, renal, hepatic, and other systemic diseases that increase surgical risk. Such comorbid conditions, in the setting of otherwise manageable acute cholecystitis, may lead to physiologic decompensation. As a result, cholecystostomy tube placement is generally performed in critically ill, debilitated, and/or high–surgical risk patients with acute cholecystitis.

GALLBLADDER PATHOLOGY FACTORS

Calculous or Acalculous Cholecystitis

Acute cholecystitis is most often related to gallstones. Complications from gallstones include acute calculous cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis. The pathophysiology of acute cholecystitis results from obstruction of the cystic duct by an impacted gallstone, which then leads to transmural gallbladder edema and inflammation with potential necrosis. When indicated, cholecystostomy tube placement allows for gallbladder decompression in the setting of cystic duct obstruction and can be performed under ultrasound guidance with local anesthetic and minimal sedation. Decompression of the gallbladder reduces the inflammatory process, allowing the patient to recover from the infection and any underlying systemic inflammatory response. Further, cholecystostomy tube placement may provide a bridge to definitive therapy with interval cholecystectomy in selected patients.

In contrast to cholecystitis associated with cholelithiasis, acalculous cholecystitis primarily occurs in patients who are critically ill and cannot tolerate surgical intervention. Given the lack of gallstones, this is not considered an obstructive process. Numerous studies have

reported cholecystostomy tube placement in patients with acalculous cholecystitis (Table 1). But, given the fact that acalculous cholecystitis often occurs in already critically ill patients, mortality remains relatively high, with 30-day and in-hospital mortality rates ranging from 9% to 21% following percutaneous cholecystostomy tube placement. Despite lower morbidity rates of cholecystostomy tube placement versus cholecystectomy in this patient population, mortality rates were reported to be similar in a large retrospective study of 1725 patients with acalculous cholecystitis undergoing cholecystostomy tube placement or cholecystectomy. Although these data propose cholecystostomy tube placement as definitive treatment for patients with acalculous cholecystitis who cannot tolerate cholecystectomy, one-third of these patients eventually underwent definitive treatment with cholecystectomy (Table 2).

Severity of Inflammation and Duration of Symptoms

In recent years, consensus recommendations have been created to provide formal guidelines regarding the diagnosis and management of cholecystitis. The Tokyo Guidelines (TG) were developed in 2007 (TG07) and subsequently revised in 2013 (TG13) and 2018 (TG18). The TG07 and TG13 created a classification system for the severity of cholecystitis (Table 3). Based on this, an algorithm for cholecystostomy tube placement was derived. Earlier versions of the Tokyo Guidelines recommended utilization of cholecystostomy tubes for (1) patients with grade II cholecystitis who have symptoms lasting more than 72 hours and fail to respond to antibiotic therapy, or (2) patients with grade III cholecystitis (Fig. 1). The updated TG18 guidelines now recommend percutaneous cholecystostomy tube placement in cases of grade II and grade III cholecystitis in high–surgical risk patients following failure of antibiotics and supportive care (Fig. 2).

Sepsis and/or Hemodynamic Instability

In some cases, the degree of inflammation in cholecystitis can worsen and thereby lead to sepsis, septic shock, and hemodynamic instability. For patients who present with severe cholecystitis, mortality rates in some studies have been shown to be as high as 35%. Along with supportive care and broad antibiotic therapy, early source control is crucial and has been demonstrated to be a major factor for reducing mortality in this population. However, hemodynamic instability and/or shock may preclude operative interventions, including cholecystectomy, as a viable option for source control. Cholecystostomy tube placement in patients with severe cholecystitis is easy to perform, effective, and provides adequate source control for patients with cholecystitis.

Underlying Intraabdominal Malignancy Precluding Definitive Surgical Intervention

A small subset of patients with underlying malignancies, such as pancreatic adenocarcinoma or cholangiocarcinoma, may develop acalculous cholecystitis from an obstructive process secondary to either the malignancy or a therapeutic intervention (e.g., biliary stenting to relieve a common bile duct obstruction). In both situations, the tumor and/or stent can occlude the cystic duct leading to cholecystitis. However, the underlying malignancy may preclude a safe cholecystectomy; therefore cholecystostomy tube placement can be offered if antibiotics are insufficient at treating the cholecystitis. Consistent with this approach, multiple case reports and one retrospective series have shown that the use of a cholecystostomy tube allows patients to recover more quickly and potentially proceed or return to their cancer therapy. In these cases, cholecystostomy tube management requires a multidisciplinary approach because patients may not be able to undergo definitive interval cholecystectomy. In contrast, for patients with resectable cancers, the gallbladder can be addressed at the time of definitive surgical intervention.

PATIENT-RELATED FACTORS

Multiple studies in the United States have evaluated the utilization of cholecystostomy tube decompression in the setting of acute calculous cholecystitis (Table 4). As discussed earlier, although gallbladder pathology is an important factor when cholecystostomy tube placement is considered, these studies demonstrated that the primary indications for tube placement are independent of the severity of cholecystitis, and rather are largely based on patient-related factors including patient comorbidities that make the risk of anesthesia and an operation prohibitive (see Table 4). Some studies are nonspecific, simply recommending cholecystostomy in "poor surgical candidates" without clear definition. Others report specific patient-related factors as indications for cholecystostomy tube placement. In a retrospective analysis of 424 cholecystostomy tube patients published

TABLE 1 Studies Primarily Reporting Outcomes in Patients with Acalculous Cholecystitis Who Undergo Percutaneous Cholecystostomy Placement

Study	Total AAC (N)	Study Design	Outcomes
Horn (2015)	278	Retrospective	30-day mortality was 4.7%; 54.7% of patients were definitively treated with PC with a follow-up of 5 years; 23.5% of patients were readmitted for recurrently cholecystitis; 28% underwent an LC at some point in the study period.
Kirkegard (2015)	56	Observational	30-day mortality was 10.7%, with 80.4% being definitively treated with PC; 9% underwent LC at some point in the study period.
Anderson (2014)	4329	Retrospective	Decreased mortality in patients undergoing cholecystectomy versus PC (hazard ratio, 0.29, P < .001).
Simorov (2013)	704	Retrospective	Compared with LC and OC, those who underwent PC had decreased LOS, morbidity, ICU stay, and cost. No difference in mortality.
Chung (2012)	57	Retrospective	In-hospital mortality was 21%, and 49% were managed nonoperatively; 31% underwent cholecystectomy; 7% had recurrent cholecystitis.

ICU, Intensive care unit; *LC*, laparoscopic cholecystectomy; *LOS*, length of stay; *OC*, open cholecystectomy; *PC*, percutaneous cholecystostomy.

TABLE 2 Tube-Related Complications, Readmission, and Cholecystectomy Rates Associated with Cholecystostomy Tube Placement

Study	Total (N)	Tube-Related Complications (%)	Readmission Rates (%)	Recurrent Cholecystitis (%)	Cholecystectomy (%)
Kim (2017)	144	21.4	NR	9.7	27.9
Papis (2017)	39	0	15.4	15.4	30.7
Boules (2016)	380	NR	3.7	NR	32.9
Pang (2016)	71	28	NR	NR	45
Wang (2016)	279	NR	NR	9.2	33
Bala (2015)	257	31	15	NR	63.4
Jang (2015)	93	3.2	NR	19.3	33
Khasawneh (2015)	245	NR	NR	NR	83
Cha (2014)	82	NR	0	0	54.8
Chang (2014)	60	9.8	NR	11.7	5
Al-Jundi (2012)	30	9	NR	NR	36.7
Horn (2014)	278	35.2	23.5	23.5	28.4
Hsieh (2012)	166	16.3	NR	13.8	31.9
Joseph (2012)	106	5	NR	NR	27
McKay (2012)	68	14.7	41	41	30
Kortram (2011)	27	3.7	NR	19.7	16
Nasim (2011)	62	1.6	NR	9.7	37
Saeed (2010)	41	25	NR	NR	22
Wisemen (2010)	86	21	NR	NR	54.6
Paran (2006)	54	33	19*	NR	51.8
Basaran (2005)	18	5.6	NR	NR	42.8
Byrne (2003)	45	2	NR	NR	37.8
Hatzidakis (2002)	63	5	NR	NR	25
Spira (2002)	55	16	19.2	19.2	56.4
Berber (2000)	15	13	NR	NR	80†

*Percent of patients who had a percutaneous cholecystostomy and never underwent surgery because they were deemed unfit
†Unknown denominator.
NR, Not reported.

in 2017, Boules et al. reported that it was at the attending surgeon's discretion whether a patient was considered a high-risk surgical candidate; review of the data identified six risk factors driving cholecystostomy tube placement: (1) cardiac surgery within 2 months of symptom onset, (2) pulmonary infection, (3) end-stage liver disease (ESLD) with cirrhosis, (4) new diagnosis of pulmonary embolism (PE), (5) use of systemic anticoagulation, and (6) hemodynamic instability. Other retrospective reviews have reported cholecystostomy tube indications such as terminal stage IV cancer and coronary artery disease.

The 2018 Tokyo Guidelines (TG18) attempted to further define high-risk patients for early operative intervention by including the Charlson Comorbidity Index (CCI) and American Society of Anesthesiologists' (ASA) Physical Status Classification System. In addition, the TG18 guidelines established predictive factors that have been associated with increased surgical mortality risk on multivariate analyses, including jaundice (total bilirubin ≥2 mg/dL) with coexisting neurologic dysfunction or respiratory dysfunction.

1. For grade II cholecystitis, TG18 recommends cholecystostomy tube placement in patients with CCI ≥ 6 and/or ASA class ≥ III, as well as local inflammation resistant to systemic antibiotic therapy.
2. For grade III cholecystitis, TG18 recommends cholecystostomy tube placement in patients who, (1) fail supportive care with antibiotics, (2) are jaundiced and have neurologic or respiratory dysfunction, and (3) have organ system failure not rapidly reversible with therapy. However, even when antibiotics and supportive care are effective, as well as when cardiovascular and/or renal organ system failure are reversed in grade III disease, a cholecystostomy tube is still recommended if the patient has a poor performance status (CCI > 4 and/or ASA class ≥ III) (see Fig. 2).

ROLE OF CHOLECYSTOSTOMY TUBE PLACEMENT IN COVID-19 PATIENTS

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 pandemic has had a major impact on emergent

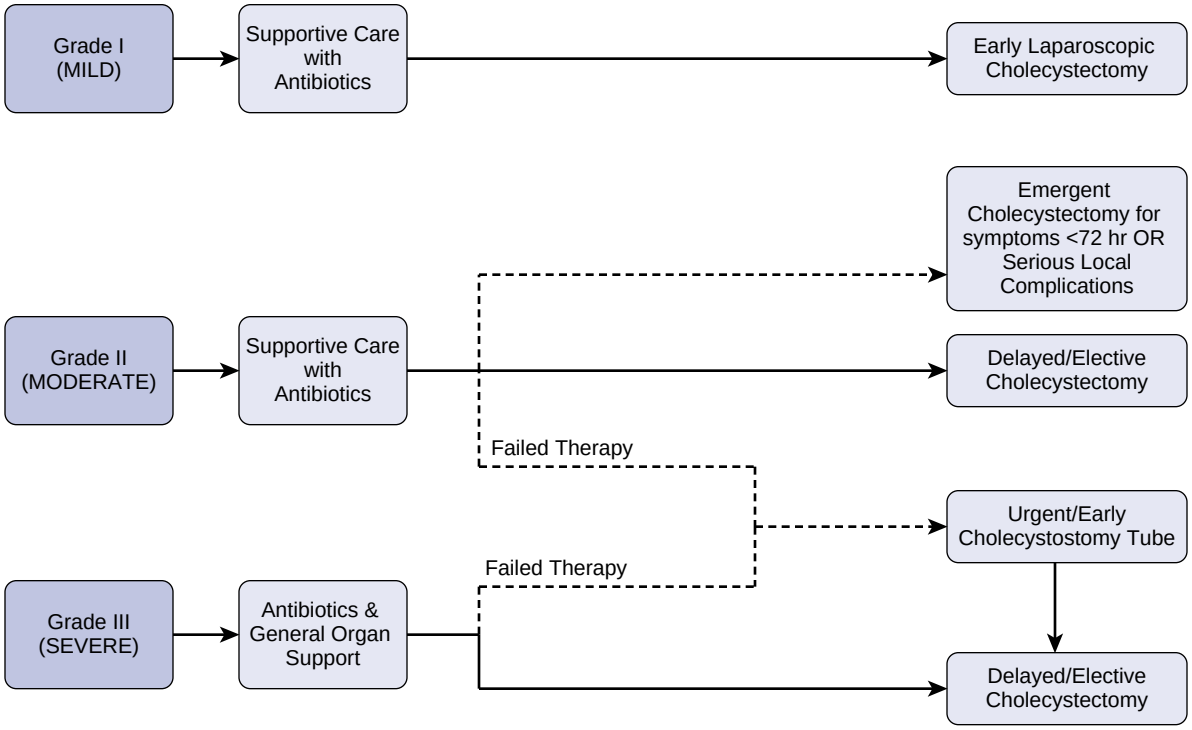


FIG. 1 Tokyo Guidelines 2013 algorithm for the management of acute calculous cholecystitis. Cholecystostomy tube placement is recommended in grades II and III disease when antibiotics and supportive care do not provide source control. Delayed elective cholecystectomy is recommended after tube placement. *(From Miura F, Takada T, Kawarada Y, et al. Flowcharts for the diagnosis and treatment of acute cholangitis and cholecystitis: Tokyo Guidelines.* J Hepatobiliary Pancreat Surg. *2007;14:27–34.)*

TABLE 3 Tokyo Guidelines Definition of Acute Cholecystitis Based on Disease Severity

Grade	Definition
I (Mild)	• No findings of organ dysfunction and acute cholecystitis (does not meet criteria for grades II–III) • Cholecystectomy is deemed low risk and safe • Duration of symptoms <72 hours

II (Moderate)	• Degree of inflammation is likely associated with operative difficulty if cholecystectomy is to be undertaken
	• Associated with any one of the following:
	  • Elevated white blood cell count (>18,000/mm^3)
	  • Palpable tender mass in the right upper quadrant
	  • Symptoms >72 hours
	  • Marked local inflammation (i.e., gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

III (Severe)	• Cholecystitis with associated organ dysfunction to include any of the following:
	  • Circulatory failure (hypotension requiring treatment with dopamine >5 μg/kg/min, or any dose of norepinephrine
	  • Neurologic disturbance (decreased level of consciousness)
	  • Respiratory failure (partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio <300)
	  • Renal failure (oliguria, creatinine >2.0 mg/dL)
	  • Hepatic failure (international normalized ratio >1.5)
	  • Thrombocytopenia (platelet count <100,000/mm^3)

and elective surgical services. Half of patients with perioperative SARS-CoV-2 infection develop pulmonary complications, which are associated with high mortality. In addition, multicenter studies have shown that COVID-19 is associated with an increased risk for serious perioperative morbidity and mortality. Moreover, a substantial number of patients with COVID-19 are not identified until after surgery.

At the start of the pandemic, the American College of Surgeons recommended nonoperative management of surgical diseases, including cholecystitis, when possible, for patients who had

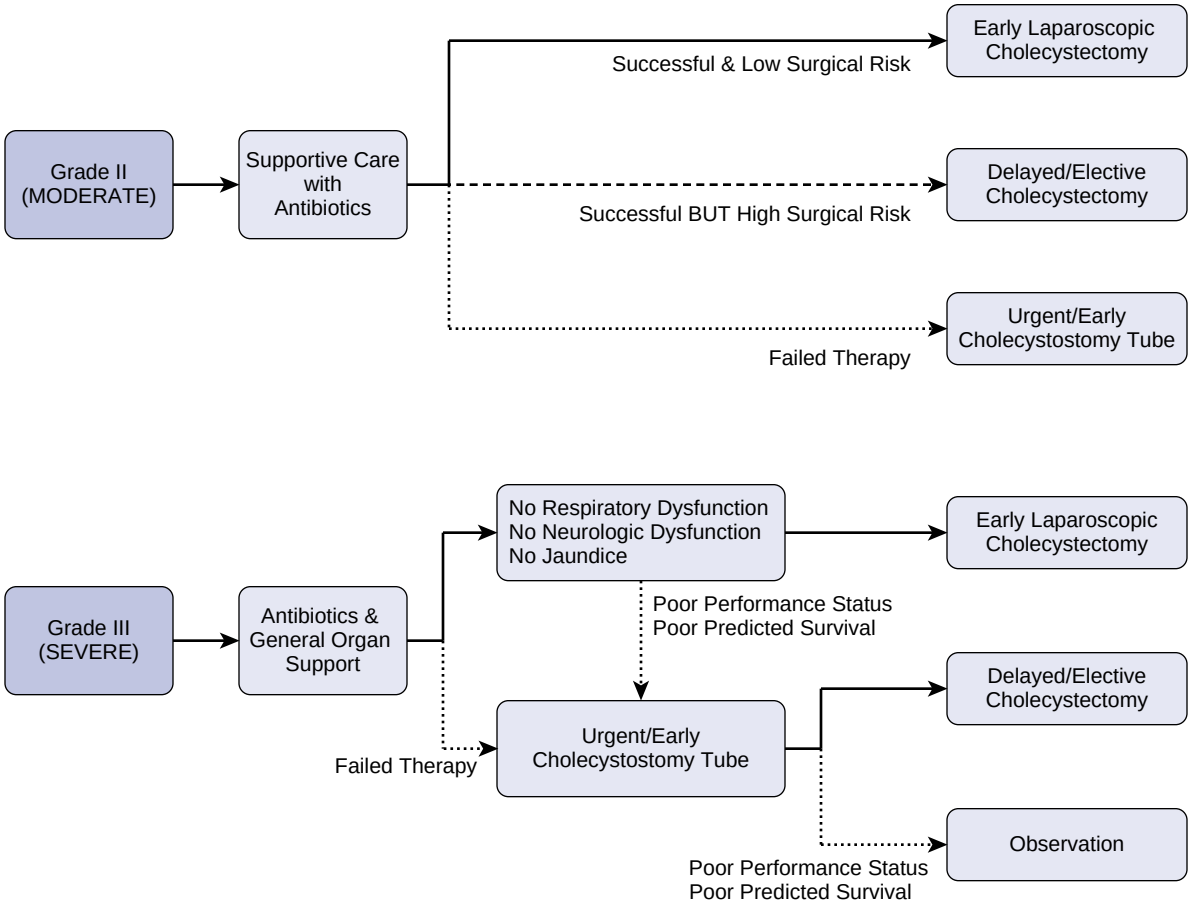


FIG. 2 Tokyo Guidelines 2018 algorithm for the management of patients with acute calculous cholecystitis. Cholecystostomy tube placement is now recommended in patients with grade II disease only if they fail antibiotics and supportive care and are not candidates for cholecystectomy based on poor performance status as measured by a Charlson Comorbidity Index ≥6 or American Society of Anesthesiologists class ≥3. In grade III disease, cholecystostomy is recommended in patients who (1) do not respond to antibiotics and supportive care, (2) have respiratory and/or neurologic dysfunction, and (3) do not rapidly resolve their cardiovascular and renal dysfunction. After cholecystostomy tube placement, cholecystectomy is recommended unless the Charlson Comorbidity Index is ≥4 and life expectancy is short, in which case patients can be observed. These management protocols assume advanced centers that include intensive care unit treatment, appropriate surgical expertise, and advanced endoscopy. *(Modified from Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis.* J Hepatobiliary Pancreat Sci. *2018;25:55–72.)*

confirmed or suspected SARS-CoV-2 infection. Because of the morbidity and mortality risks associated with SARS-CoV-2 infection, the possibility of transmission to hospital staff, and resource shortages caused by the pandemic, many centers transitioned to conservative and nonoperative management of acute cholecystitis. Published data for treatment of SARS-CoV-2–positive patients with acute cholecystitis comes from only a few single-institution retrospective studies. Although based on limited data, some studies suggest that percutaneous cholecystostomy is safe and effective compared with laparoscopic cholecystectomy in the setting SARS-CoV-2 infection. However, other studies have raised concerns about this approach, with approximately 35% of patients who underwent cholecystostomy tube placement experiencing a complication and up to 43% requiring readmission. Thus, each treatment recommendation must be thoroughly discussed with patients with COVID-19 and their other comorbidities in mind.

APPROACHES TO CHOLECYSTOSTOMY TUBE PLACEMENT

The majority of cholecystectomy tubes are placed via a percutaneous approach. However, these tubes can also be surgically placed via an open or laparoscopic approach. Success rates of tube placement exceed 90% in most studies.

Percutaneous Approach

Percutaneous cholecystostomy is most often performed by interventional radiologists but can also be placed by a surgeon trained in the procedure. After localization by computed tomography (CT) or ultrasound (Figs. 3 and 4), the gallbladder is accessed percutaneously with radiologic guidance via either a transhepatic or transperitoneal approach. Traditionally, the transhepatic approach is preferred to prevent bile spillage or bile leakage, especially in the setting of severe cholecystitis and a potentially necrotic gallbladder wall. In practice, however, there is the possibility of hepatic abscess and transient bacteremia with the transhepatic approach because of the direct connection with hepatic sinusoids. The transperitoneal approach is an alternative method that works best when the gallbladder wall is extremely inflamed and thickened because it is more likely to seal and more likely to tolerate a coiling wire without rupturing.

Under image guidance, a long, hollow Yeah sheathed needle is placed through the liver and into the gallbladder until bile is aspirated (Fig. 3C,D). In many cases, the cystic duct is obstructed, and

TABLE 4 Studies Reporting Various Indications for Cholecystostomy Tube Placement

Study	Sample Size	Study Design	Reported Indications
Joseph (2018)	952	Retrospective	Patient's general condition, comorbidities, and fitness for anesthesia, rather than the grading and acute disease process itself
Kim (2018)	144	Retrospective	No specific indications, except for decision for tube placement was in a "multidisciplinary manner"
Boules (2017)	380	Retrospective	Cardiac surgery within 2 months of symptom onset Pulmonary infection End-stage liver disease New diagnosis of pulmonary embolism Use of systemic anticoagulation Hemodynamic instability
Pang (2016)	71	Retrospective	Declined surgery Severe sepsis/shock Gallbladder perforation Multiple comorbidities
Wang (2016)	279	Retrospective	Patient preference Failure to respond to initial medical management Impending rupture of severely distended gallbladder Severe sepsis/septic shock
Bala (2015)	257	Retrospective	Physician discretion and either the presence of comorbid conditions and/or lack of clinical improvement with antibiotic therapy alone
Horn (2015)	278	Retrospective	High burden of comorbidity Prolonged symptom duration reported as >5 days
Khasawneh (2015)	245	Retrospective	Calculous cholecystitis Acalculous cholecystitis Sepsis likely from a biliary source
Cha (2014)	82	Retrospective	Patient comorbidities
Chang (2014)	60	Retrospective	Failure to respond to initial medical treatment in patients with high perioperative risk Impending rupture of a severely distended gallbladder that may cause clinical deterioration Suspected gallbladder necrosis or perforation in patients with severe comorbidities and no other treatments available
Hsieh (2012)	166	Retrospective	Septic shock/severe sepsis Gallbladder rupture Failed conservative treatment after 48 hours
Joseph (2012)	106	Retrospective	Poor surgical candidates
McKay (2012)	68	Retrospective	Surgeon discretion
Kortram (2011)	27	Retrospective	A component of one or more of the following: Age ASA APACHE Comorbidity
Nasim (2011)	62	Retrospective	ASA grade II/IV Significant sepsis resulting in hemodynamic instability Patients deemed moderate or high risk for general anesthesia
Saeed (2010)	41	Observational case series	Calculous cholecystitis Acalculous cholecystitis Gallbladder perforation and/or empyema
Paran (2006)	54	Prospective	Poor surgical candidate secondary to comorbidities and/or symptoms >72 hours
Basaran (2005)	18	Retrospective	Medical comorbidity including terminal cancer, uncontrolled hypertension and diabetes, CAD, HTN, CHF, ARF
Byrne (2003)	45	Retrospective	Medical comorbidities including cardiovascular disease and malignancy

TABLE 4 Studies Reporting Various Indications for Cholecystostomy Tube Placement—cont'd

Study	Sample Size	Study Design	Reported Indications
Hatzidakis (2002)	63	Prospective	Randomized to cholecystostomy tube group, but patients were referred to surgical team for possible tube placement
Spira (2002)	55	Retrospective	Biliary sepsis Septic shock Severe comorbidities
Berber (2000)	15	Retrospective	High risk for general anesthesia secondary to comorbidities and/or chronic illness Inflammation too severe during attempted laparoscopic cholecystectomy

APACHE, Acute Physiology and Chronic Health Evaluation II; *ARF*, acute renal failure; *ASA*, American Society of Anesthesiologists; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *HTN*, hypertension.

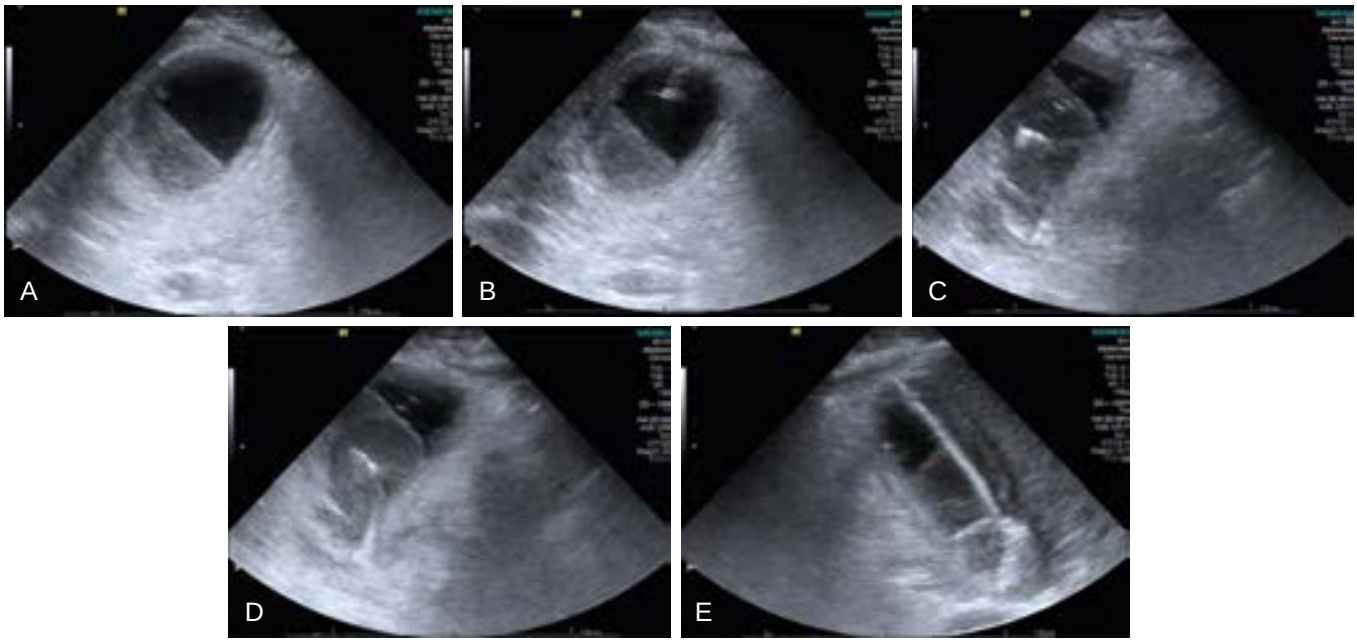


FIG. 3 Ultrasound placement of a cholecystostomy tube. **(A)** Gallbladder is visualized. **(B, C)** Gallbladder is accessed with a Yeah needle. **(D, E)** Pigtail catheter is placed into the gallbladder lumen.

this fluid will be clear secondary to resultant hydrops. Once the gallbladder is accessed, a wire (short 75-cm Amplatz or Rosen curved tip wire) is placed through the needle and into the gallbladder lumen (Fig. 3C,D). A dilator is placed over the wire, and an 8-Fr pigtail catheter is then advanced and coiled in the gallbladder lumen using the Seldinger technique (Fig. 3E and Fig. 4D–F). At the end of the procedure, CT and/or ultrasound should be utilized to confirm the proper position of the drainage tube (Fig. 4D–F). The catheter is then secured to the skin by a suture or proprietary adhesive device.

Operative Approach

A cholecystostomy tube can also be placed surgically via laparoscopic or open approach. These options should be kept in mind when the surgeon begins the operation with the intent of performing cholecystectomy but finds inflammation so severe that the dissection is deemed unsafe or the patient becomes unstable during the operation. In either situation, the gallbladder is visualized by the surgeon and the tube can be inserted under direct vision through a small cholecystotomy made in the gallbladder or transhepatically using the Seldinger technique. If placed directly into the gallbladder, the drain can be secured to the gallbladder wall to prevent bile leakage around the tube. If the gallbladder wall is necrotic, a fenestrating partial cholecystectomy with removal of stones along with wide drainage may be an alternative option if cholecystectomy is deemed unsafe or unfeasible.

COMPLICATIONS OF CHOLECYSTOSTOMY TUBE PLACEMENT

Although cholecystectomy tube placement is often not difficult and allows for poor surgical candidates to avoid an operation, both immediate and long-term complications can occur. Data on complications are largely derived from single-institution retrospective studies.

Immediate Complications

Immediate complications from cholecystostomy placement include continuation/progression of acute cholecystitis, biliary peritonitis, sepsis, bleeding, biliary leak, and tube dislodgement. Overall,

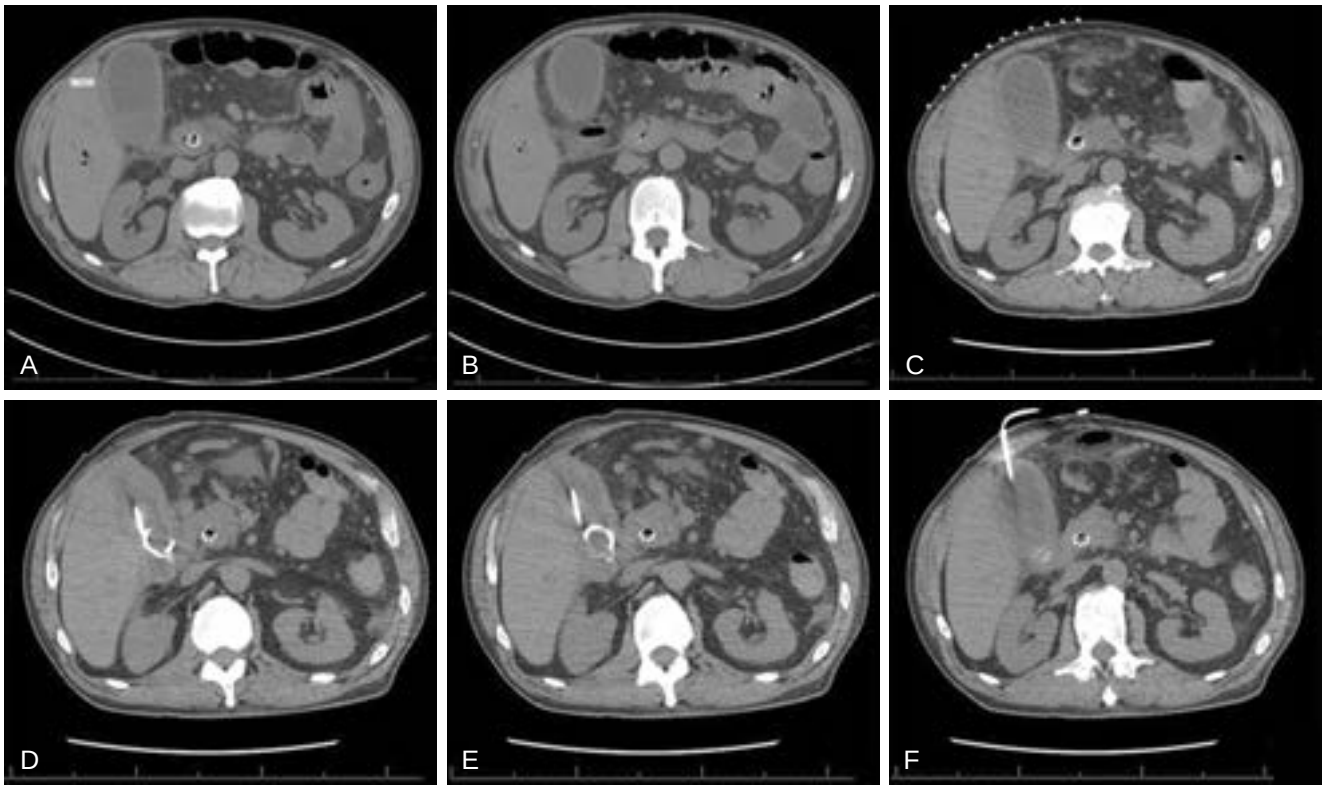


FIG. 4 Computed tomography placement of a cholecystostomy tube. **(A, B)** Gallbladder is visualized. **(C)** Computed tomography markers are placed on the abdominal skin on the right upper quadrant to help with guidance. **(D–F)** Verification of pigtail catheter placement in the gallbladder lumen.

complications specifically related to cholecystostomy tube placement range from 5% to 33% across studies, but most are related to the latter three issues (i.e., bleeding, biliary leak, or tube dislodgement). To prevent bleeding, especially with the transhepatic approach, the interventional radiologist and/or surgeon should ensure that any coagulopathy is corrected before tube placement. Bile leakage can occur if the tube is dislodged or the gallbladder wall is necrotic and the bile leaks around the tube itself. This can lead to sepsis, diffuse biliary peritonitis, and/or a biloma/abscess in the right upper quadrant if the leakage is contained and localized. This should be suspected when a patient's leukocytosis worsens or does not improve after tube placement as well as when symptoms initially improve but the patient subsequently develops sepsis, hemodynamic instability, fever, worsening leukocytosis, or worsening abdominal pain.

Later Complications

In the long-term, both readmission to the hospital and recurrence of acute cholecystitis are common after cholecystostomy tube placement when delayed definitive therapy with cholecystectomy is not performed. There is significant cost associated with frequent hospital visits, radiologic interventions, and overall increased hospital days, stressing the importance of definitive cholecystectomy when at all possible. Recurrence of acute cholecystitis after cholecystostomy tube placement ranges from 9% to 41% in small series, and readmissions rates are as high as 40%. Readmissions are mostly related to inadvertent tube dislodgement or removal, tube occlusion, recurrent cholecystitis, or catheter-site related pain.

Ineffective Placement

Although placement of cholecystostomy tubes is 90% to 100% effective in most studies, some patients will not resolve their cholecystitis as measured by ongoing sepsis, leukocytosis, and/or right upper quadrant pain. Cha and colleagues reported a technical success rate of 100% in 82 patients undergoing cholecystostomy tube placement, and a clinical success rate of 98% with one patient dying of cholecystitis-related complications. But, in a study by Joseph et al., 32% of critically ill patients who had a cholecystostomy tube placed did not improve or declined clinically after tube placement.

LONG-TERM MANAGEMENT OF CHOLECYSTOSTOMY TUBES

The management of cholecystostomy tubes after initial treatment remains somewhat controversial. There are no broadly accepted guidelines regarding definitive tube management. Across studies, 5% to 63% of patients eventually undergo definitive cholecystectomy, but this is not well defined. However, the TG18 recommends delayed cholecystectomy after tube placement, regardless of initial grade of the cholecystitis. In the literature, several authors have proposed different algorithms for the management of cholecystostomy tubes, many of which involve cholangiography to assess the patency of the cystic duct and biliary tree. In a study by Cha and colleagues, patients underwent a cholangiogram through the cholecystostomy tube to evaluate for patency of the cystic duct and biliary tract once the patient's symptoms and clinical status improved. This was done during the index hospitalization. If patency was demonstrated via contrast emptying into the duodenum, the catheter was clamped. If patients developed recurrent cholecystitis after clamping, worsening laboratory values (e.g., leukocytosis, hyperbilirubinemia, transaminitis), or worsening symptoms, the catheter was placed back to external drainage for 7 days, after which patients were reassessed. If the patient tolerated clamping and had continued clinical improvement, the cholecystostomy tube was removed during the initial admission. If the cystic duct was not patent, patients were discharged with the cholecystostomy tube placed to an external drainage bag. Zarour and colleagues reviewed outcomes of 119 patients who underwent

cholecystostomy tube placement for acute cholecystitis. In their study, all patients who underwent tube placement were discharged with the tube in place and draining externally. Follow-up cholangiogram was performed 2 to 3 weeks later; if the duct was patent and the patient was deemed an appropriate surgical candidate, the tube was clamped and left in place, and the patient subsequently underwent interval cholecystectomy. In patients who were not deemed fit but had biliary tract patency, the tube was removed.

In the absence of prospective data, (1) the duration of recommended tube drainage, (2) the need for definitive cholecystectomy, (3) the timing of tube removal, and (4) the timing of cholecystectomy remain topics of debate. The reported median length of time that the tube remained varies widely in the literature and depends on whether definitive cholecystectomy was performed. Times ranged from 10 days in those who eventually underwent cholecystectomy to 70 days in patients who did not undergo definitive treatment with cholecystectomy. Most studies recommend drainage for 3 to 6 weeks because this allows a tract to develop. Others recommend earlier removal and early definitive cholecystectomy. In contrast, separate studies recommend a longer period of tube drainage in patients with uncontrolled diabetes, persistent infection, malnutrition, and/or those on steroids because these conditions may hinder the healing process.

Ultimately, tube removal is dependent on resolution of the patient's symptoms, the presence or absence of cystic duct obstruction, and whether the patient is a candidate for cholecystectomy. This is determined on a case-by-case basis through evaluation of laboratory values, abdominal examination, and the patient's report of resolved abdominal pain.

In our opinion, if the patient's acute cholecystitis has resolved and he or she is a candidate for cholecystectomy, tube evaluation is not necessary. Cholecystectomy should be scheduled, and the tube should be left in situ and draining externally until the operation is performed. This can be done laparoscopically or open, though conversion rates in this setting are higher than normal and should not be unexpected. If the patient's clinical status improves and he or she is not a candidate for cholecystectomy, the patient should undergo a tube cholangiogram, and tube removal should only be considered if there is patency of the patient's cystic duct. This is because the likelihood of recurrent episodes of cholecystitis is extremely high if the cystic duct remains obstructed. The timeline in which a cholangiogram is done in these patients varies in the literature, but we recommend 3 to 6 weeks to allow for a track to form before tube removal. If a cholangiogram demonstrates a patent cystic duct, the next step is clamping of the cholecystostomy tube, with removal in the absence of recurring symptoms after clamping. It is important to note that the criterion of cystic duct patency does not necessarily apply to patients with acalculous cholecystitis as the pathophysiology is different from calculous cholecystitis. But patients should at least undergo clamping trials before removal to reduce the risk of having recurrent symptoms after tube removal that may lead to an additional procedure.

DEFINITIVE TREATMENT WITH CHOLECYSTECTOMY

Cholecystectomy remains the only definitive treatment for patients with acute cholecystitis. In individuals who undergo cholecystostomy tube placement, the TG18 recommend delayed-interval cholecystectomy after tube placement (see Figs. 1 and 2), except for patients with initial grade III disease, poor performance status, and limited predicted life expectancy. These recommendations apply to calculous cholecystitis, but other reports on patients with acalculous cholecystitis agree that cholecystectomy may not be necessary. The recurrence of acute cholecystitis in those who do not undergo definitive therapy ranges from 11% to 41%. Therefore, definitive therapy should be considered if the patient's clinical status allows.

Despite the recommendation for cholecystectomy in the Tokyo guidelines, cholecystectomy rates vary widely, with 15% to 80% of patients undergoing cholecystectomy after cholecystostomy tube placement across many retrospective series. Ideally, cholecystectomy should be performed in the elective setting after the patient's clinical status has improved. Cholecystectomy may be needed more urgently if cholecystostomy tube placement fails to control local inflammation and systemic sepsis or if inflammation recurs acutely. However, data from Medicare beneficiaries undergoing cholecystostomy tube placement for grade III cholecystitis demonstrate that only one-third of these patients undergo definitive treatment with a delayed cholecystectomy.

The timing for delayed cholecystectomy is also a topic of deliberation. In a study by Hung et al., there is some evidence that optimal timing for laparoscopic cholecystectomy is 9 to 10 weeks after placement of a cholecystostomy tube. In another retrospective study by Woodward et al., increased complications occurred when interval cholecystectomy was performed less than 1 month after cholecystostomy tube placement. However, patients with tubes in place for greater than 8 weeks demonstrated higher rates of tube-related complications, leading the authors to suggest that the most favorable timing for interval cholecystectomy is between 4 and 8 weeks after cholecystostomy tube placement. A retrospective analysis of the New York SPARCS database involving 9728 patients suggested that early cholecystectomy (≤8 weeks after cholecystostomy tube placement) was associated with a higher risk of complications and longer hospital length of stay. Ultimately, the timing of delayed cholecystectomy should be delayed at least 4 to 6 weeks after tube insertion, but there are no prospective analyses to determine this timing.

PROPOSED ALGORITHM FOR CHOLECYSTOSTOMY TUBE PLACEMENT AND MANAGEMENT

The proper use of cholecystostomy tubes includes temporary treatment for patients with calculous or acalculous cholecystitis who cannot tolerate surgery according to the TG18 guidelines. The severity of cholecystitis and the duration of symptoms are not absolute contraindications for cholecystectomy, and they do not mandate cholecystostomy tube placement in isolation. Potential reasons for a patient's inability to tolerate surgery include severe systemic disease, including cardiovascular disease, underlying terminal malignancy, and/or any condition that precludes general anesthesia.

The TG18 algorithm for management of patients with acute cholecystitis (see Fig. 2) notes that initial evaluation should include assessment of the patient's clinical status and the severity of the gallbladder disease. If patients are hemodynamically stable and able to tolerate a general anesthetic, cholecystectomy should be performed as soon as possible during the index admission, regardless of the Tokyo grade. Cholecystostomy tubes should be reserved for patients who are not candidates for cholecystectomy because of underlying comorbidity and/or physiologic decompensation resulting from acute illness and for those who do not rapidly respond to antibiotics and supportive care. In cases of grade III disease, if a patient improves with antibiotics and organ support, reevaluation should be undertaken during the index hospitalization for possible cholecystectomy. If not performed on the index admission, then delayed or elective cholecystectomy should be performed in patients who have a life expectancy of greater than 1 year as cholecystitis recurrence rates are high. As with all interventions, surgeons must consider the risks and benefits of this procedure and its long-term consequences with each individual patient in mind.

SUGGESTED READINGS

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Management of Common Bile Duct Stones

Artem Shmelev, MD, Shirali T. Patel, MD, and Steven C. Cunningham, MD

Common bile duct stones (CBDS), or choledocholithiasis, is simply the presence of stones in the common bile duct (CBD) and may present as an incidental finding on imaging or with symptomatic biliary obstruction, including various sequelae, such as acute pancreatitis and ascending cholangitis. Surgeons should maintain a high index of suspicion for CBDS when managing patients with other biliary pathology and should collaborate closely with gastroenterology colleagues for CBD clearance, which is most commonly achieved with endoscopic retrograde cholangiopancreatography (ERCP). However, all general surgeons should be familiar with the operative management of CBDS as well, as ERCP is unsuccessful in as many as 10% to 20% of cases.

EPIDEMIOLOGY

The true incidence of CBDS in the general population is poorly known, as most cases are asymptomatic. CBDS are present in 10% to 15% of patients undergoing evaluation for cholelithiasis and are identified in 10% to 12% of intraoperative cholangiograms (IOC) when performed routinely during cholecystectomy (CCY). Similarly, the incidence of CBDS is approximately 10% to 20% in patients undergoing CCY for symptomatic cholelithiasis or acute cholecystitis.

PATHOPHYSIOLOGY AND PRESENTATION

Classification of CBDS by their point of origin is important for understanding their recurrence. The majority of CBDS in the Western population are secondary stones originating in the gallbladder and indicate the need for CCY to prevent recurrence. Primary CBDS, by contrast, form in bile ducts and are more common in Asian populations and patients with abnormal ducts. Primary CBDS recur after endoscopic CBD clearance in 4% to 24% of patients, and subsequent CCY may, in fact, increase risk of CBDS recurrence in Asian populations, possibly by increasing CBD stasis in the absence of periodic flushing of the CBD from gallbladder contractions.

Symptomatic CBDS typically present with episodes of epigastric or right upper quadrant (RUQ) abdominal pain. CBDS may cause biliary obstruction and subsequent jaundice, typically with pain, unlike neoplastic causes of jaundice. As intraductal pressure increases, disruption of epithelial tight junctions leads to cholangiovenous reflux as bacteria or endotoxins translocate from the biliary to the vascular system. Obstruction resolves with stone passage into the duodenum in more than half of patients but may lead to ascending cholangitis with Charcot's triad of fever, RUQ pain, and jaundice in 15% to 20% of patients or even progress to septic shock with altered mental status, comprising Reynold's pentad, and requiring emergent biliary decompression. In addition, biliopancreatic reflux from impacted distal CBDS or ampullary edema from passing CBDS is a cause of 30% to 50% of cases of acute pancreatitis.

DIAGNOSIS

The initial evaluation of patients with suspected symptomatic cholelithiasis, acute pancreatitis, or cholangitis includes transabdominal ultrasound (TAUS) and a liver panel, but the accuracy of TAUS and a liver panel for the diagnosis of asymptomatic CBDS is low. Factors associated with CBDS include clinical symptoms of cholangitis, dilation of the cystic and CBDs, and elevated serum bilirubin, alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT). A patient with several of these factors has a high pretest probability for CBDS (Fig. 1) and warrants preoperative ERCP or preparedness for intraoperative management with IOC and/or CBDE. A patient with none of these factors and no CBDS seen on imaging has a very low probability of CBDS and can proceed simply to CCY. Patients with intermediate CBDS probability require additional imaging (e.g., magnetic resonance cholangiopancreatography [MRCP] or endoscopic ultrasound EUS]) or IOC/IOUS during CCY. The sensitivity and specificity of common diagnostic tests for CBDS are listed in Table 1.

Liver Panel Changes in Patients with CBDS

A cholestatic pattern in the liver panel (e.g., elevated ALP and bilirubin) may be a useful test in the right clinical settings to support a diagnosis of CBDS. A direct consequence of biliary obstruction is conjugated (direct) hyperbilirubinemia resulting from reflux of bile components into hepatic sinusoids from pressurized bile ducts. Biliary obstruction stimulates the biliary epithelium to release ALP, which has a half-life of 1 week. GGT elevation is also reasonably accurate for biliary obstruction due to CBDS, especially when ALP is also elevated (see Table 1). A low ratio or alanine transferase to ALP (<2.0) also correlates with biliary obstruction and can help to distinguish it from hepatocellular injury.

Useful Diagnostic Imaging Modalities

TAUS is an inexpensive, noninvasive, and common modality for initial evaluation but poorly visualizes CBDS. In the presence of a cholestatic liver panel, CBD dilation on TAUS is very suggestive of CBDS. (The upper limit of normal for CBD diameter is controversial but is approximately 4 mm to 6 mm in middle-aged adults and

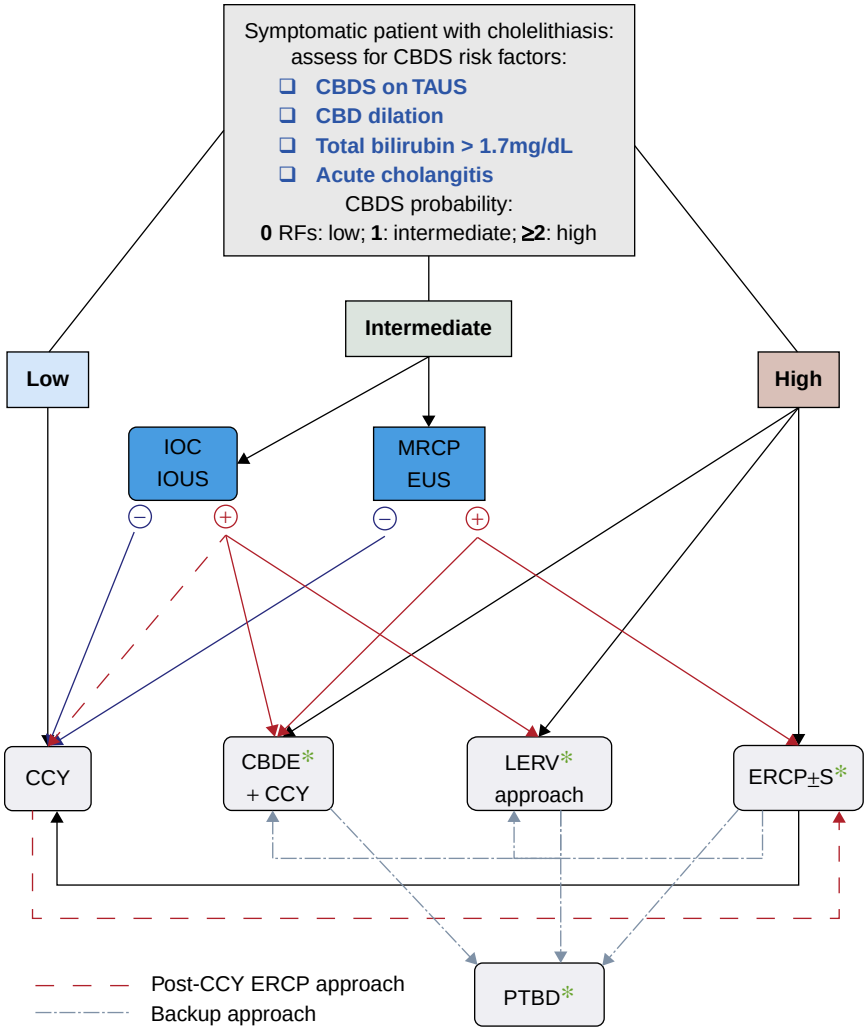


FIG. 1 Management algorithm of suspected CBDS. *Depends on surgeon's expertise and availability. ⊖ no CBDS detected; ⊕ CBDS detected. CBDE, Common bile duct exploration; CCY, cholecystectomy; ERCP±S, endoscopic retrograde cholangiopancreatography ± sphincterotomy; EUS, endoscopic ultrasound; IOUS, intraoperative ultrasound; LCBDE, laparoscopic common bile duct exploration; LERV, laparoendoscopic rendezvous (IOC+ERCP); PTBD, percutaneous transhepatic biliary drainage; TAUS, transabdominal ultrasound. *(Modified from Narula VK et al. 2020: Clinical spotlight review for the management of choledocholithiasis. Surg Endosc. 2020;34:1482.)*

TABLE 1 Performance of Laboratory and Imaging Tests in Diagnosing CBDS

Diagnostic Test	% Sensitivity (95% Confidence Interval)	% Specificity (95% Confidence Interval)	Reference
Total bilirubin >1.3 mg/dL	84 (64–94)	91 (86–94)	Gurusami, 2015 (PMID: 25719223)
Total bilirubin >twice the normal limit	42 (22–63)	97 (95–99)	Gurusami, 2015 (PMID: 25719223)
Alkaline phosphatase (ALP) >125 IU/L	92 (74–99)	79 (74–84)	Gurusami, 2015 (PMID: 25719223)
Alkaline phosphatase >twice the normal limit	38 (19–59)	97 (95–99)	Gurusami, 2015 (PMID: 25719223)
Gamma-glutamyltransferase (GGT) >95.5 IU/L	90.8	83.6	Mei, 2019 (PMID: 30705891)
GGT >95.5 IU/L and ALP >151.5 IU/L	93.5	85.1	Mei, 2019 (PMID: 30705891)
Transabdominal ultrasound (TAUS)	73 (44–90)	91 (84–95)	Gurusami, 2015 (PMID: 25719223)
Magnetic resonance cholangiopancreatography (MRCP)	93 (87–96)	96 (90–98)	Giljaca, 2015 (PMID: 25719224)
Endoscopic ultrasound (EUS)	95 (91–97)	97 (94–99)	Giljaca, 2015 (PMID: 25719224)
Intraoperative cholangiography (IOC)	99 (83–100)	99 (95–100)	Gurusami, 2015 (PMID: 25719223)
Laparoscopic ultrasound (LUS)	90 (87–92)	99 (99–99)	Jamal, 2016 (PMID: 26985813)
Endoscopic retrograde cholangiopancreatography (ERCP)	83 (72–90)	99 (94–100)	Gurusami, 2015 (PMID: 25719223)

increases 0.2 mm to 1 mm per decade of life before CCY; following CCY, it is normal to have a dilated CBD.) Computed tomography (CT) and MRCP are also commonly used to evaluate patients with suspected biliary pathology. CT may overestimate CBD diameter compared with TAUS or MRCP. EUS and MRCP both have high accuracy for revealing CBDS. In patients with an intermediate likelihood of CBDS (see Fig. 1) and a tentative plan for CCY, both IOUS and IOC are acceptable options with high accuracy in skilled hands.

MANAGEMENT

General Considerations

All CBDS that have not passed into the duodenum spontaneously need to be evacuated. Timing is dictated by severity of symptoms. In general, more symptomatic cholangitis warrants more urgent clearance of the obstructing CBDS, and patients with grade II or III cholangitis according to the 2018 Tokyo Guidelines need emergent drainage. Selection of management strategy is largely dependent on availability of local surgical and endoscopic instruments, expertise, and accessible referral centers. ERCP is most commonly used and provides CBD clearance in more than 90% of patients.

Data from recent systematic reviews and meta-analyses comparing a two-stage approach (pre- or postoperative ERCP with CCY) versus single-stage procedure (CCY with CBDE) vary. Both approaches share comparable morbidity (13%–16%), mortality (0.7%–1%), and failure rates. The single-stage approach may have a shorter length of hospitalization, fewer reinterventions, and reduced costs but a higher rate of postoperative bile leak.

Percutaneous transhepatic cholangiogram (PTC) and biliary drainage (PTBD) serve as a last resort when the biliary tree cannot be drained endoscopically or surgically to stabilize the patient with cholangitis, alleviate biliary obstruction, and temporize for transfer to a referral center with available expertise and resources. An alternative to PTBD is endoscopic ultrasound-guided choledochoduodenostomy, which, however, is rarely used in nonmalignant CBD obstruction.

Endoscopic CBD Clearance

Conventional ERCP is performed with a side-viewing duodenoscope and, in expert hands, successfully clears the CBD in 90% of cases. After papilla identification, the CBD is cannulated and cholangiography detects CBDS or sludge, which may be cleared with a sphincterotomy and sweeping of the CBD with a balloon catheter. In cases of distal CBD strictures or hematologic contraindications to sphincterotomy, balloon dilation may be useful. Larger stones may require retrieval by endoscopic basket or fragmentation by lithotripsy.

Factors associated with failure of endoscopic CBD clearance include impacted, large (>15 mm) or multiple (>4) stones, periampullary diverticula, distal CBD strictures, altered gastric or duodenal anatomy, and advanced age.

Recurrence of CBDS, as well as calculous cholecystitis, cholangitis, and biliary colic, are all expected consequences of failure to perform CCY after endoscopic clearance of secondary CBDS, and thus CCY is recommended within 2 to 4 weeks post-ERCP, ideally during the same admission. However, sphincterotomy, especially a generous sphincterotomy, may protect patients from further cholangitis or pancreatitis for several weeks to months, allowing for outpatient elective CCY in reliable patients. In high-risk patients with advanced comorbidities or limited life expectancy, sphincterotomy alone may be considered reasonable destination therapy.

Early complications of ERCP and sphincterotomy include acute pancreatitis (1%–7%), hemorrhage (0.3%–2%), duodenal or biliary perforation (<1%), and mortality (<1%); delayed complications include papillary stenosis. Postprocedure acute pancreatitis is the Achilles heel of ERCP but may be mitigated by temporary pancreatic duct stents and rectal indomethacin. In some instances, retrograde passage of a guidewire through a ductotomy in the cystic duct (CD) in the rendezvous approach may allow for smooth CBD cannulation and significantly reduce the risk of pancreatitis.

ERCP in Patients with Altered Anatomy

Patients with surgically altered anatomy (e.g., Billroth II gastrectomy, Roux-en-Y gastric bypass [RYGB]) preclude standard access to the duodenum. ERCP in this population requires advanced expertise and use of special endoscopic equipment such as single- or double-balloon enteroscopy or spiral enteroscopy. Alternatively, laparoscopically assisted, transgastric ERCP (LATG-ERCP is a useful option. Choledocholithiasis following RYGP is one of the most common such scenarios.

LATG-ERCP may be performed with four ports: three 5-mm ports across the midabdomen (a camera port and two working ports) and a 12- to 15-mm port in the left upper quadrant for the duodenoscope. Retraction of the liver segments 2/3 with a Nathanson retractor or sutures may be needed. After the excluded gastric remnant is identified and dissected from adhesions, two to three stay sutures are placed in the anterior wall and pulled through the abdominal wall with a laparoscopic suture-passer. A purse-string suture may be placed around the area of future gastrotomy, which is made with an energy device. Pneumoperitoneum is then decreased, and a 12- to 15-mm port (one with a balloon tip for better anchoring and seal is useful) is placed through the gastrotomy while pulling on the stay sutures for good apposition of the excluded stomach and abdominal wall. If a CCY is also being performed, a guidewire may be passed through a cystic ductotomy into the duodenum to facilitate smooth CBD cannulation in a laparoendoscopic rendezvous (LERV) approach (see earlier and later discussions). After the ERCP, the gastrotomy is closed with sutures or a stapler.

Laparoendoscopic Rendezvous Approach

LERV is a relatively novel, single-stage approach to CBD clearance, facilitating endoscopic cannulation of the CBD by a guidewire passed through the CD into the duodenum during CCY. According to a recent meta-analysis, the LERV approach is associated with significantly decreased morbidity than a two-stage approach with ERCP then CCY (7.5% vs. 14.5%), decreased incidence of acute pancreatitis (1.5% vs. 6.4%), and shorter hospital stay (mean difference 3.5 days). The LERV and the two-stage approaches were equivalent in CBD clearance (90%–95%), conversion to open (5%–8.4%), postoperative cholangitis (1.6%–2.6%), bleeding (1.2%–1.9%), and bile leak (1.9%–2.1%).

Surgical CBD Clearance

Surgical clearance of CBDS and CCY may also be done with a single- or two-stage approach. Single-stage CBD clearance (CCY + CDBE) offers shorter length of hospitalization and is likely cost-effective, while sharing similar morbidity and mortality with the two-stage approach (isolated CCY with pre- or post-CCY ERCP). The choice is up to the surgeon and based on available resources, expertise, and logistics. A minimally invasive surgery CBDE (MIS-CBDE) shares the same contraindications as any other MIS. CDBE should be avoided in patients with a small (<3 mm) CBD. Additionally, the single-stage approach is contraindicated in patients with suspected malignant process, unless appropriate staging workup has been completed, the case has been discussed in a multidisciplinary tumor-board setting, and the surgeon is prepared for an oncologically sound operation. Otherwise, patients should be referred to a surgeon with the relevant expertise.

Equipment and materials used for IOC/IOUS/MIS-CDBE include a fluoroscopy-compatible operating table, a fluoroscopic system, 3- to 5-Fr cholangiocatheters, Olson or Kumar or similar cholangiography clamps, water-soluble contrast, a hydrophilic 0.035" guidewire, 8-mm × 40-mm over-the-wire dilation balloon

with high-pressure inflation capability, nitinol wire basket, Fogarty balloon catheters, and a choledochoscope (pediatric ureteroscopes and disposable bronchoscopes work well). Depending on available expertise, mechanical, electrohydraulic, or laser lithotripsy may be used for fragmentation of large CBDS.

Intraoperative Imaging

IOC or IOUS is a key step in any patient undergoing CCY and suspected of having CBDS at the time of operation. IOC is particularly useful as part of an MIS-CDBE (Fig. 2). IOUS compares favorably to IOC but is best done before dissection, as dissection may obscure otherwise clear sonographic windows. After obtaining a critical view of safety, IOC may be done via the gallbladder, the CD, or, as a last resort, the CBD. Commonly, the CD is dissected, a locking clamp placed on the gallbladder for retraction, and another locking clamp or clip is placed on the CD cholecystad to the planned ductotomy to prevent filling of the gallbladder with contrast. A transverse 1- to 2-mm ductotomy is performed, and stones and debris are milked from the duct. A cholangiocatheter is passed through midclavicular port or via a 14- to 16-gauge, transabdominal, sheath trocar placed in the RUQ, and secured, ideally with an Olson or Kumar clamp, to the ductotomy. Digital subtraction on the C-arm and holding respirations may both improve image quality. A live, real-time (as opposed to still-image) cholangiogram is ideal. Contrast may be used full-strength, or, more commonly, diluted 50/50 in saline, as full-strength contrast is more likely to obscure small filling defects. The number and size of filling defects should be noted (the 5-mm diameter of the cholangiogram clamp may be used as a size reference). Smaller (≤3 mm) stones have a higher chance of being flushed into the duodenum, which is facilitated by administration of 1 mg to 2 mg intravenous glucagon to relax the sphincter of Oddi. Once the location, number, and size of stones, as well as CBD diameter, are determined, an optimal treatment strategy may be selected. To confirm the biliary tree free of stones by IOC, it is essential to visualize contrast opacification of both the duodenum and the intrahepatic biliary tree, both right and left sides.

Minimally Invasive Surgery CBDE

MIS-CBDE may be performed transcystic and transcholedochal. The transcystic approach is a reasonable initial choice, particularly with a large (>5 mm) nontortuous CD, a lateral insertion into the CBD, and small CBDS. The transcystic approach is contraindicated with multiple (>5–8) or large (>~7 mm) stones or stones hepatad of the CD insertion to the CBD.

Transcystic Approach

In patients with a long and tortuous CD, a ductotomy closer to the CD–CBD junction may be made with care. If CBDS cannot be cleared during IOC by flushing, then MIS-CDBE may proceed by fluoroscopically advancing a soft-tipped, 0.035", hydrophilic guidewire through the CD, the CBD, and well into the duodenum. The introduction catheter is removed and exchanged over the wire for a 12-Fr introducer sheath to provide better support and facilitate instrument exchange.

The CD is dilated to facilitate passage of instruments through the spiral valves and extraction of stones (Fig. 3). This may be performed with an 8-mm × 40-mm (5-Fr), over-the-wire, dilation balloon filled with half-strength contrast under fluoroscopy, over 2 to 3 minutes, using an inflation device. Care should be taken to not overdilate the CD.

Stone clearance can be achieved by nitinol baskets or Fogarty-balloon catheters. The basket is passed collapsed beyond the target stones, deployed, and slowly withdrawn (Fig. 4). Baskets, as opposed to balloon catheters, are less prone to cause inadvertent migration of CBD stones proximally into the common hepatic duct. It is important to advance and withdraw instruments along the CBD axis. If



FIG. 2 Intraoperative cholangiogram showing filling of the common bile duct and the left and right hepatic ducts, but absent filling of the duodenum due to a distal stone obstructing the duct, with a meniscus sign *(arrow)*.



FIG. 3 Balloon dilation of the cystic duct in preparation for transcystic common bile duct exploration and stone extraction. See text for details.



FIG. 4 Transcystic stone extraction with basket. *(From Qandeel H, et al. Basket-in-catheter access for transcystic laparoscopic bile duct exploration: technique and results.* Surg Endosc. *2016;30:1958–64.)*

available, a flexible choledochoscope (see earlier) may be used for direct visualization of CBD and controlled retrieval of stones. The choledochoscope should ideally have video with an integrated light source and picture-in-picture capabilities. With available expertise and equipment, MIS-CDBE may be coupled with mechanical, electrohydraulic, or laser lithotripsy. An endoscopic retrieval bag and/or gauze sponge close to the ductotomy may facilitate collection of debris.

After a satisfactory completion IOC, the CD is transected and closed, preferably with an endoscopic loop. If a transcystic approach fails to achieve CBD clearance or is otherwise inappropriate, the surgeon may proceed with a transcholedochal MIS-CBDE, convert into open CBDE (OCBDE), or plan for postoperative ERCP or PTBD.

Transcholedochal Approach

Unlike a transcystic CBDE, transcholedochal CBDE provides access to both the CBD and the hepatic ducts. However, transcholedochal CDBE is associated with a higher risk of biliary strictures and postoperative bile leaks, and is contraindicated when CBD diameter is <7 mm and with hostile porta hepatis, as may occur with severe inflammation.

After exposing the anterior surface of the CBD, a ~10-mm, longitudinal choledochotomy is made sharply. Fine-needle aspiration or indocyanine green cholangiography may be done to confirm the identity of the CBD if needed. Stay sutures on either side of the choledochotomy are useful to elevate the duct and maintain easy access to the ductotomy but are not used by all surgeons. The CBD is flushed via a cholangiocatheter, and stones are evacuated with a grasper, if possible. If not, CBDS may be retrieved with baskets and balloon catheters.

The choledochotomy is closed longitudinally with interrupted or running fine (4-0 or 5-0), absorbable suture on a tapered needle. An additional 5-mm port may be placed in the right-to-midabdomen to facilitate choledochotomy closure. Historically, it was standard practice to close the choledochotomy over a T-tube, which allows sustained access to the biliary tree, reliable decompression, and stenting of the CBD to possibly reduce risk of stricture. However, recent literature has supported primary closure instead, which has the advantage of avoiding tube-related discomfort and complications, with apparently similarly favorable outcomes. If a T-tube is left (Fig. 5), it should fit loosely, not snugly, and the ductotomy should be closed hepatad of the tube to prevent tension on the suture line upon removal. The T-tube should remain for at least 3 weeks to allow maturation of the tract, to avoid bile leakage upon removal, after a normal tube cholangiogram. Typically, with or without a T-tube, a closed-suction drain is left near, but not touching, the ductotomy and removed after a few days if no bile is present in the drain. Before closure, a completion IOC should be performed.

Because papillary edema is not uncommon after MIS-CDBE, some surgeons prefer to leave a plastic biliary stent across the ampulla before choledochotomy closure to assure decompressed biliary tree and to decrease risk of postoperative bile leak from the choledochotomy.

Open CBDE

The proportion of patients with CBDS managed with OCBDE has decreased over the last decade from 30% to 5%. OCBDE is now performed mainly when less invasive techniques have failed or are not available. OCBDE may also be performed for patients with significant inflammation in Calot's triangle or the porta or when the patient requires open CCY for other reasons. The CBD diameter for OCBDE should be >5 mm, and it is contraindicated if the CBD diameter is ≤3 mm.

The abdomen is entered through an upper midline or right subcostal incision, and the liver is retracted superiorly. An IOC should be performed before CBDE. After IOC and characterization of the CBD and contents, the duodenum is Kocherized and all portions of CBD are gently palpated. IOUS may be useful to identify CBDS. Stay sutures are placed and a stab choledochotomy is made between them with an #11 blade at the level of cystic duct insertion, slightly to the left of the longitudinal CBD midplane. Once the direction of CBD is determined by gentle probing, the choledochotomy is extended to ~15 mm with Potts scissors. The stay sutures are retracted, and CBDS are gently milked or flushed out through the ductotomy. Fogarty balloons and Randall stone forceps are useful to sweep or grasp stones, respectively, in either direction, but care should be taken not to mistake the hepatic duct confluence for CBDS when using forceps. If a balloon is used, it should be passed through the ampulla and seen or palpated in the duodenum, at which point it should be inflated, pulled back until apposed to the ampulla, deflated enough to traverse the ampulla, then reinflated and withdrawn to extract stones and sludge. Evaluation by choledochoscopy is recommended. A completion cholangiogram or choledochoscopy should be obtained. Similar to MIS-CDBE, in OCBDE the ductotomy can be primarily closed with or without transpapillary temporary stent or closed over a T-tube.

Severely impacted stones are best managed with fragmentation by lithotripsy guided by choledochoscopy. If lithotripsy is not available, a biliary stent can be placed across the papilla or the CBD drained via T-tube and the patient transferred to a center with available expertise. Procedures such as transduodenal sphincteroplasty have been used for distally impacted CBDS but are rarely performed currently.

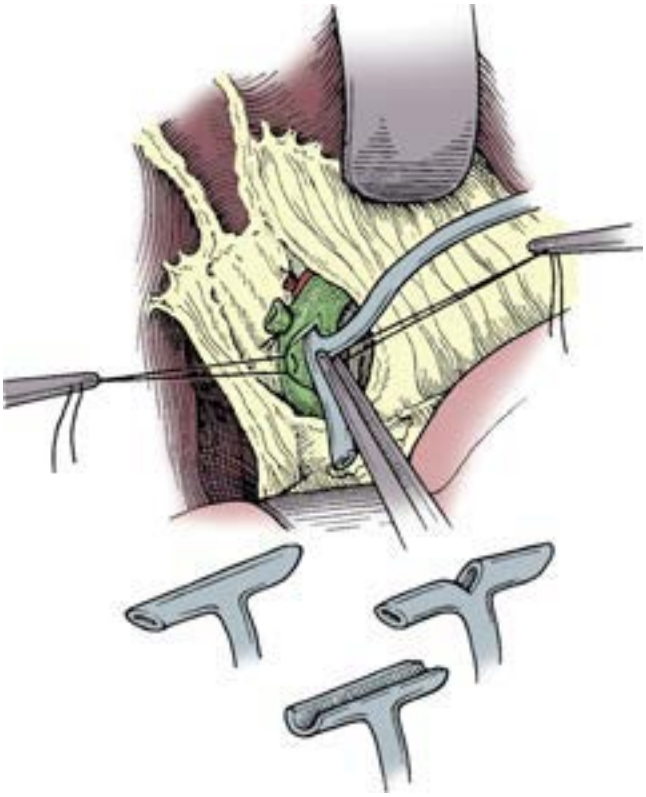


FIG. 5 Closure of the ductotomy over a T-tube. When trimming the T-tube, it is common to excise part or all of the back wall to facilitate extraction. The ductotomy should be closed as described in the text. *(From Zollinger RM Jr, Zollinger RM.* Atlas of Surgical Operations. *7th ed. New York: McGraw-Hill; 1993.)*

Suggested Readings

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Management of Acute Cholangitis

Rebecca Tang, MD, Erica Barnett, BA, and David Berger, MD

INTRODUCTION

Acute cholangitis is a clinical syndrome first described by Jean-Martin Charcot in 1877 characterized by abdominal pain, fever, and jaundice from stasis and infection in the biliary tract. In 2006, the Tokyo International Consensus Meeting consolidated literature about acute cholangitis into evidence-based guidelines, which were most recently updated in 2018.

EPIDEMIOLOGY

Acute cholangitis most commonly occurs in the fifth through seventh decades of life with equal prevalence in men and women. The most common causes of acute cholangitis include choledocholithiasis (40%–70%), malignancy (10%–60%), or benign stricturing (5%–30%). Cholangitis can also occur after instrumentation from either endoscopic retrograde cholangiopancreatography (ERCP) (1%–7%) or placement of biliary stents and indwelling biliary drains.

PATHOPHYSIOLOGY

The primary issue in acute cholangitis is obstruction of the common bile duct. Under physiologic conditions, bile remains sterile due to continuous flow, secretion of immunoglobulin A in the biliary tree, and the presence of bacteriostatic bile salts. In addition, the sphincter of Oddi acts as a barrier against ascending infection from duodenal reflux. The causes of acute cholangitis can therefore be conceptualized as related to stasis from biliary obstruction or to direct seeding of the biliary tree (Table 1).

In the setting of acute inflammation, increased biliary pressure causes increased permeability of biliary ductules and translocation of bacteria from the portal venous system into the biliary tract. As a result, infection in acute cholangitis is typically polymicrobial and most commonly includes gram-negative rods of colonic origin. The most common bacteria identified in biliary cultures are *Escherichia coli* (25%–50%), *Klebsiella* (10%–20%), *Enterococcus* (10%–30%), and *Enterobacter* (5%–10%). Anaerobes such as *Bacteroides* and Clostridia are more commonly seen in patients with recurrent infections or biliary instrumentation.

The underlying permeability of the biliary system facilitates bacterial translocation from the biliary tract to the portal and systemic venous systems, leading to sepsis in severe cases.

DIAGNOSTIC WORKUP

History and Physical Examination

Less than 60% of patients present with the complete Charcot's triad of fever, right upper quadrant pain, and jaundice. The most common presenting symptoms are fever and right upper quadrant pain (80%) and jaundice (60%). Patients may rarely (5%) present with additional altered mental status and hemodynamic instability to complete Reynold's pentad. The differential diagnosis for patients presenting with symptoms of acute cholangitis includes acute cholecystitis, Mirizzi's syndrome, biliary leak, acute pancreatitis, liver abscess, right lower lobe pneumonia, and empyema.

TABLE 1 Causes of Acute Cholangitis

Biliary Stasis	Seeding of Biliary Tree
Intrinsic obstruction	Disruption of sphincter of Oddi
Choledocholithiasis	Endoscopic retrograde cholangiopancreatography
Stricture (benign or malignant)	Sphincterotomy
Tumor (cholangiocarcinoma)	Biliary stent insertion
Stent occlusion	Biliary reconstruction after choledochal surgery
Polyp	Biliary drain placement
Blood clot	
Infectious parasite	
Food impaction	
Extrinsic Obstruction	
Mirizzi's syndrome	
Tumor (pancreatic, ampullary, gallbladder, or duodenal cancer)	
Duodenal periampullary diverticulum (Lemmel syndrome)	
Chronic pancreatitis	

Laboratory Workup

The laboratory workup for suspected acute cholangitis should include CBC, BMP, electrolytes, LFT, PT-INR, β-hCG, blood cultures, and biliary cultures. Leukocytosis is most commonly seen. Liver function tests most often demonstrate a cholestatic pattern of abnormalities, although a mixed hepatocellular pattern may be seen with microabscess formation in the liver. Of note, the tumor marker CA19-9 may be elevated in the setting of biliary obstruction. CA19-9 is not specific for the presence of malignancy in patients with biliary obstruction and should be rechecked in patients after resolution of the obstruction and associated hyperbilirubinemia. Biliary cultures should be obtained if possible and are positive in 60% to 90% of cases. Blood cultures are less sensitive and are positive in 20% to 70% of cases.

Imaging Studies

The initial imaging study of choice is an abdominal ultrasound to evaluate for biliary dilation, cholelithiasis, or gallbladder sludge (Fig. 1). Ultrasound is 40% sensitive but nearly 100% specific for acute cholangitis with findings of common bile duct dilation and choledocholithiasis. Although ultrasound is noninvasive, expedient, and easily accessible, it remains highly operator-dependent. Ultrasound also has difficulty detecting small stones and often results in false-negative reads in the setting of acute obstruction before the bile ducts dilate.

An abdominal CT scan is very effective in identifying the presence of biliary dilation or stenosis and the location of biliary obstruction, as well as local sequelae like liver abscess and portal vein thrombosis. However, it has low sensitivity for detecting choledocholithiasis and exposes the patient to radiation.

Magnetic resonance cholangiopancreatography (MRCP) is the best noninvasive imaging modality for identifying causes of biliary obstruction, characterizing biliary strictures, and detecting choledocholithiasis. MRCP is 90% sensitive and 95% specific in detection of choledocholithiasis, although its sensitivity decreases significantly with small stones <6 mm. As a result, it is increasingly becoming the imaging of choice when available. However, it is an expensive test and requires additional expertise for interpretation. Given its limited accessibility, routine use of MRCP is not universally recommended unless diagnosis is difficult despite abdominal ultrasound and CT.

Endoscopic ultrasound (EUS) is better able to identify bile duct stones and characterize the level of obstruction along the biliary tree. Given its invasive nature, it is only used for workup of cholangitis patients who are high risk for ERCP and cannot undergo MRCP.

Diagnostic Criteria

Based on the clinical presentation, laboratory workup, and imaging studies, a suspected or definite diagnosis of acute cholangitis can be made (Table 2). The 2018 Tokyo Guidelines also provide a severity grading system that should be serially used at time of diagnosis, within 24 hours of diagnosis, and 24 to 48 hours after diagnosis to determine initial management steps (Table 3).

MANAGEMENT

The management of acute cholangitis follows the principles of resuscitation with appropriate antibiotic coverage, early biliary drainage, and definitive management to address the underlying etiology of biliary obstruction. The choice and timing of treatment options depends on the severity of disease (Fig. 2).

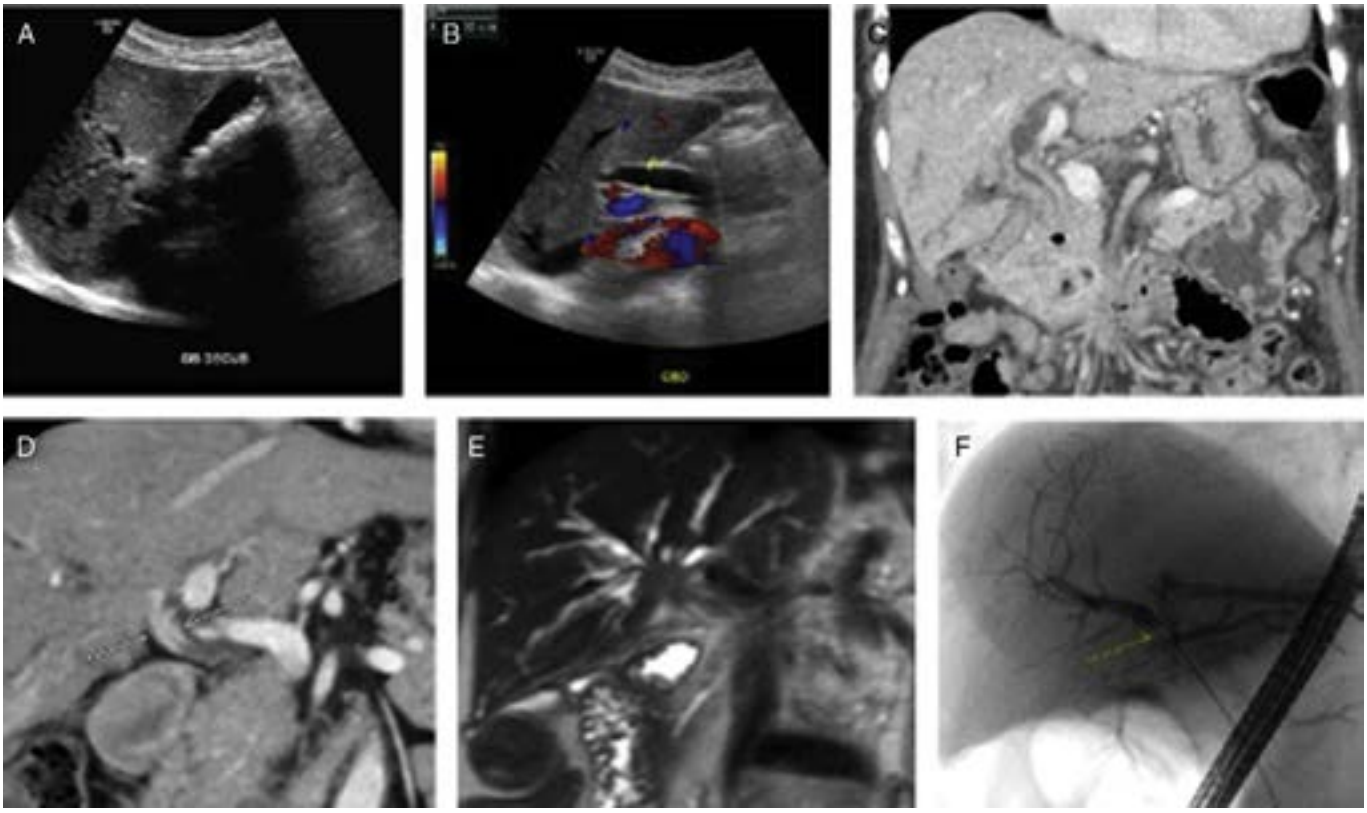


FIG. 1 Imaging findings with cholangitis. **(A)** Cholelithiasis on ultrasound. **(B)** Common bile duct dilation on ultrasound. **(C)** Extrahepatic bile duct dilation on abdominal CT. Common hepatic duct stricture from cholangiocarcinoma seen on abdominal CT **(D),** MRCP **(E),** and ERCP **(F).** *(Images courtesy Mark A. Anderson, MD.)*

TABLE 2 Diagnostic Criteria for Acute Cholangitis (Tokyo Guidelines 2018)

A. Systemic Inflammation	• Fever and/or shaking chills • Laboratory data: elevated WBC or CRP
B. Cholestasis	• Jaundice • Laboratory data: abnormal liver function test (bilirubin ≥2 mg/dL) or abnormal liver chemistries (elevated ALP, GGT, ALT, or AST greater than 1.5 times the upper normal limit)
C. Imaging	• Biliary dilatation • Evidence of etiology on imaging – stricture, stone, stent, etc.
Suspected Diagnosis: one item in A *and* one item in B *or* C Definite Diagnosis: one item in A *and* one item in B *and* one item in C	

TABLE 3 Severity Grading and Initial Management (Tokyo Guidelines 2018)

Severe (Suppurative)	Onset of organ dysfunction • Cardiovascular: hypotension requiring dopamine ≥5 ug/kg/min or any dose of norepinephrine • Neurologic: disturbance of consciousness • Respiratory: P/F ratio <300 • Renal: oliguria, Cr >2.0 mg/dL • Hepatic: PT-INR >1.5 • Hematologic: Plt <100,000	ICU resuscitation Broad-spectrum antibiotics Urgent biliary drainage once stabilized Defer definitive care
Moderate	Two of the following: • WBC >12,000/mm^3 or <4000/mm^3 • Fever (39°C or 102.2°F) • Age ≥75 years • Hyperbilirubinemia (total bilirubin ≥5 mg/dL) • Hypoalbuminemia	Early biliary drainage Delayed definitive treatment
Mild	Does not fulfill above criteria	Antibiotics Biliary drainage if no response to treatment

Management Based on Severity

Antibiotic treatment is sufficient in most cases of mild cholangitis. Biliary drainage should be considered if patients do not respond to 24 hours of antibiotic therapy.

Patients with moderate cholangitis require antibiotic therapy and early biliary drainage, whether endoscopically or percutaneously. Urgent (within 24 hours) and early (within 48 hours) biliary drainage has been shown to significantly decrease 30-day mortality in patients with moderate cholangitis. Definitive treatment of the underlying etiology of obstruction should be undertaken after the patient's general condition improves dependent on the patient's overall condition.

Patients with severe or suppurative cholangitis often present with hemodynamic instability and end organ dysfunction requiring intensive supportive care and resuscitation. Biliary drainage should be considered once the patient is stabilized with definite care deferred until after the acute phase of care.

Resuscitation and Antibiotic Choice

Supportive care of patients with acute cholangitis includes intravenous fluids, correction of electrolyte derangements, and analgesics for pain control. Patients should be closely monitored for signs of septic shock and end organ dysfunction.

The goal of antibiotic therapy is to control inflammation and bacteremia rather than to completely sterilize bile. The antibiotic regimen should cover enteric streptococci, coliforms, and anaerobes. Single-agent coverage can be achieved with piperacillin-tazobactam, which is the first-line antibiotic regimen of choice at the author's institution. Alternatively, a combination of metronidazole and cefepime or ceftazidime can be used, with addition of ampicillin or vancomycin for healthcare-associated cholangitis. Antibiosis should be continued 48 to 72 hours after biliary decompression.

Biliary Drainage

Compared with surgical drainage, endoscopic drainage is associated with significantly lower rates of morbidity and mortality in patients with acute cholangitis and is therefore preferred whenever possible. Percutaneous options may be pursued in cases not amenable to endoscopic drainage. Operative drainage should be considered as a last resort.

ERCP with concomitant sphincterotomy is the procedure of choice for biliary drainage. Stenting, cholangiogram, and brushings can also be performed at the time of the procedure. In coagulopathic patients with high bleeding risk following sphincterotomy, stenting with plastic or metal stents should be considered. Compared with

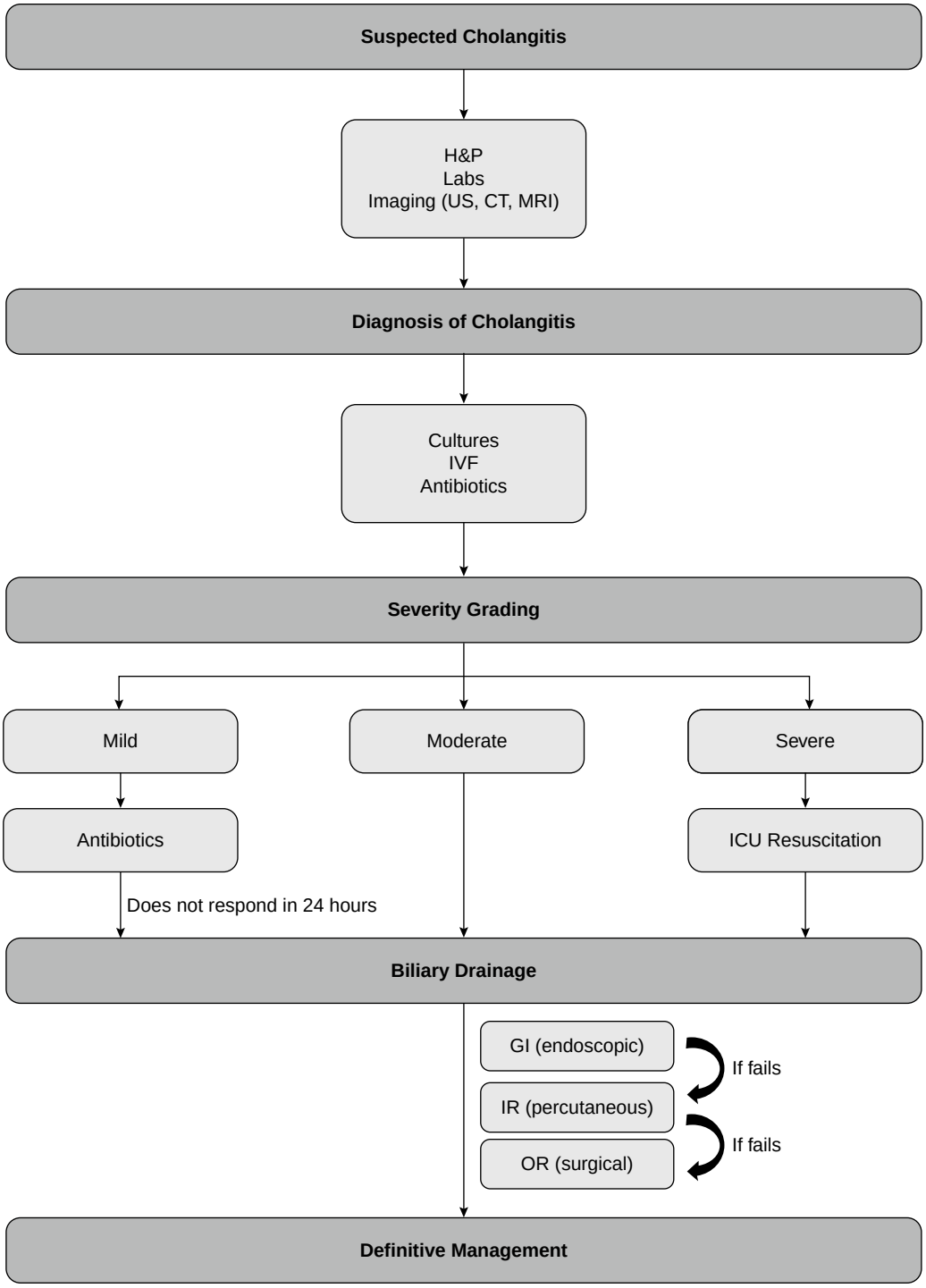


FIG. 2 Algorithm for workup and management of cholangitis.

metal stents, plastic stents are easier to insert and remove, more cost-effective, and less likely to have tumor ingrowth or overgrowth. However, they are also more likely to be occluded with biofilm and sludge.

ERCP successfully clears distal common bile duct obstructions in 90% to 95% of cases. However, ERCP with papillotomy has a 5% to 15% risk of complications including bleeding from the sphincterotomy site, intestinal perforation, pancreatitis, and worsening cholangitis. ERCP is further limited by anatomic considerations, particularly in postsurgical patients who have undergone Roux-en-Y hepaticojejunostomy or gastric bypass, pancreaticoduodenectomy, or gastrectomy. ERCP is also challenging in patients with difficult access to the ampulla and duodenal obstruction, whether intrinsic or extrinsic from severe pancreatitis.

In patients who are poor anatomical candidates for ERCP or who have failed ERCP, percutaneous transhepatic cholangiography (PTC) should be considered second-line treatment. PTC requires a dilated biliary system and patent cystic duct with the obstruction distal to the entry of the cystic duct into the common bile duct. PTC is more invasive than ERCP and carries the additional risk of biliary peritonitis and intraperitoneal bleeding.

Percutaneous transhepatic biliary drainage (PTBD) involves stenting at time of PTC and successfully decompresses the biliary tract in 90% of cases. However, complications of PTBD include biliary fistulas, bleeding, recurrent cholangitis, and hepatic abscesses. Ascites increase the risk of failure of tract maturation and subsequent complications and is therefore a relative contraindication to PTBD. PTBD is also difficult in patients with intrahepatic biliary strictures.

In patients with ascites or hilar strictures, endoscopic ultrasound–guided biliary drainage (EUS-BD) may be considered. In EUS-BD, a covered metal stent is placed through an EUS-guided transgastric or transduodenal approach. In the transgastric approach, an intrahepatic bile duct in the left lobe of the liver is punctured through via the stomach, creating a hepaticogastrostomy. In the transduodenal approach, the common bile duct is accessed via the duodenum, creating a choledochoduodenostomy. EUS-BD requires advanced endoscopy skills, and placement of metal stents can complicate definitive operative management. EUS-BD is therefore most often used in cholangitis patients with unresectable malignancies.

Surgical biliary decompression for acute cholangitis is used as a last resort as it is associated with high morbidity and mortality ranging from 10% to 50% of cases. The goal of operative management is simple biliary drainage. This can be accomplished with laparoscopic or open common bile duct exploration (CBDE), stone removal if applicable and possible, and T-tube placement. Concomitant cholecystectomy is performed if the patient is stable; definitive management is deferred in all other cases.

Laparoscopic CBDE remains an advanced laparoscopic procedure. A transcystic approach with cholecystectomy may be performed for mild to moderate cholangitis. Severe cholangitis requires a 1 cm choledochotomy along the anterior surface of the CBD, removal of stones using a wire basket through a choledochoscope, and placement of a 12Fr or 14Fr T-tube before closure of the CBD.

Open CBDE involves exposure of the anterior surface of the CBD and a 1- to 1.5-cm longitudinal choledochotomy. A 4Fr biliary Fogarty balloon is then passed into the distal CBD and flushed to clear small stones and sludge. Glucagon may be used at this stage to relax the sphincter of Oddi. A choledochoscope is then passed before T-tube placement and choledochotomy closure. A drain should be placed near the choledochotomy site.

Of note, patients undergoing choledochotomy must have CBD dilation to at least 6 mm to prevent future stricture. A cholangiogram may be obtained on postoperative day 4 or 5 after CBD exploration to prove CBD patency before capping the choledochostomy tube. A cholangiogram should be performed 2 to 4 weeks postoperatively before T-tube removal.

Broad antibiosis should be continued 48 to 72 hours after biliary decompression, as manipulation and flushing of the biliary system can cause transient increases in biliary pressure leading to subsequent systemic inflammatory response.

Definitive Management

The goal of definitive management is to address the underlying etiology of the biliary obstruction causing cholangitis after the patient is stabilized with biliary drainage in the acute phase.

Patients with gallstones and choledocholithiasis should undergo elective cholecystectomy, as risk of recurrent cholangitis is high even after sphincterotomy. Impacted stones at the ampulla that are unable to be removed endoscopically may require transduodenal sphincteroplasty, in which the ampulla is selectively incised toward the common bile duct. However, the procedure does risk injury to the distal pancreatic duct, causing recurrent pancreatitis in addition to duodenal leak.

Formal biliary-enteric bypass may be required for patients with strictures or unresectable malignancies. Roux-en-Y hepaticojejunostomy is the preferred technique. Choledochoduodenostomy is an alternative approach but may be complicated by sump syndrome, in which sphincter of Oddi dysfunction causes biliary stasis in the distal common bile duct and leads to recurrent cholangitis. Patients with acute cholangitis arising from resectable malignancies may undergo liver resection or pancreaticoduodenectomy as appropriate.

AREAS OF RECENT INVESTIGATION

Early Cholecystectomy

Although cholecystectomy as definitive management for cholangitis arising from gallstone disease has classically been deferred until resolution of the acute phase of disease, early cholecystectomy during index admission has recently been investigated. Early studies have shown no difference in intraoperative complications, overall complication rates, and length of postoperative hospital stay with cholecystectomy during the index admission compared with delayed cholecystectomy.

Antibiotic Duration

The duration of antibiotic treatment for acute cholangitis is controversial but largely depends on presence of bacteremia. The 2018 Tokyo Guidelines recommend 4 to 7 days of antibiotics after biliary decompression, while the Dutch national sepsis guidelines recommend shorter duration of therapy of 3 days after source control. In patients with bacteremia, the 2018 Tokyo Guidelines recommend 14 days of antibiotic treatment. Institutional retrospective series have suggested noninferiority of shorter antibiotic duration as short as 6 days, with current efforts to undertake randomized controlled trials.

CONCLUSION

Workup and management of acute cholangitis stems from an understanding of its pathophysiology, particularly when related to biliary obstruction. The vast majority of cases (85%) therefore resolve with antibiotic therapy and nonsurgical biliary drainage. With improved techniques for biliary drainage, mortality from acute cholangitis has decreased from 50% to 10% over recent decades. However, morbidity and mortality remain high in vulnerable populations, including the immunocompromised and elderly, as well as in patients with severe cholangitis.

SUGGESTED READINGS

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Management of Benign Biliary Strictures

Heather A. Lillemoe, MD, and Keith D. Lillemoe, MD

Benign biliary strictures are a challenging and serious clinical problem. Furthermore, as most biliary strictures are the result of an iatrogenic injury during laparoscopic cholecystectomy, which can frequently be mismanaged, there are often two "victims" of the complication: the patient and the surgeon. Thus, optimal management and the best short- and long-term outcomes are obtained by early involvement of an experienced hepatobiliary team.

This chapter will review the mechanisms behind and prevention of iatrogenic bile duct injuries, as well as the anatomic classification systems used to describe them. The necessary steps to diagnose and effectively treat iatrogenic bile duct injuries will be discussed, with an emphasis on operative repair. Finally, noniatrogenic benign biliary strictures will be briefly reviewed.

IATROGENIC BILE DUCT INJURY AND STRICTURE

Overview and Incidence

Although benign biliary strictures can arise from inflammatory processes, gallstone disease, or noniatrogenic traumatic injury, by far the most common cause of a bile duct injury or stricture is iatrogenic injury during an operation. Laparoscopic cholecystectomy, the "gold standard" for patients with symptomatic gallbladder disease, is one of the most common operations performed by a general surgeon. With the introduction of the laparoscopic approach in the early 1990s, the incidence of biliary injuries increased. As surgeons gained more experience and confidence with the laparoscopic approach, the incidence has improved, with a current rate of 0.1% to 0.2%. However, it is estimated that one in three general surgeons will create a bile duct injury during their career, and the impact of biliary injuries is substantial. With nearly one million cholecystectomies performed annually, this complication remains a significant cause of patient morbidity, diminished quality of life, financial burden, malpractice claims, and even mortality. Finally, although the incidence of injury during laparoscopic cholecystectomy has improved over time, new data suggest that the rate of injury is increased with robotic cholecystectomy.

Mechanisms of Bile Duct Injury

Iatrogenic injury during laparoscopic cholecystectomy typically results from a perceptual error in identifying biliary anatomy. The most common injury is a complete transection of the common bile duct, which is also the most challenging to manage. Typically, either excessive cephalad retraction of the gallbladder fundus or insufficient lateral retraction on the infundibulum result in an alignment of the cystic and common bile ducts. This results in misperception of the common bile duct as the cystic duct and leads to clipping and complete ductal transection (Fig. 1).

Additional risk factors for biliary injuries include acute or chronic inflammation. Thickened, friable tissue and adhesions can obscure normal anatomy and lead to increased difficulty of the procedure. Aberrant anatomy of the biliary tree, most commonly a low-lying aberrant right hepatic duct, can also lead to biliary injury. Finally, excessive use of electrocautery and surgeon inexperience with the procedure can play a role in these injuries.

Preventing Iatrogenic Bile Duct Injuries

The "Critical View of Safety"

Although the primary goal of this chapter is to discuss the management of bile duct injuries and strictures once they occur, prevention of the injury altogether is preferred. The core tenet to the prevention of bile duct injuries is obtaining the "critical view of safety." During this maneuver, described by Soper and Strasberg in the 1990s, the fundus of the gallbladder is retracted superiorly while the infundibulum is retracted laterally, allowing the surgeon to carefully dissect out Calot's triangle and leave only two structures connected to the gallbladder: the cystic duct and cystic artery (Fig. 2). The "critical view of safety" is the single most effective means of preventing a bile duct injury; however, many factors can complicate its achievement. As previously mentioned, inappropriate traction, inflammation, and scenarios with a short or nonexistent cystic duct or small bile duct can lead to the misidentification of key structures. Thus, the identification of associated regional anatomy is crucial to properly orient the critical structures of interest and proceed with a safe procedure. Given the decreased open operative experience amongst current general surgery trainees, some experts argue that converting to the open approach may no longer be the safest option for a "difficult" cholecystectomy. A partial cholecystectomy with stone evacuation and placement of closed suction drains or placement of a cholecystostomy tube may be a safe and more reasonable option in such scenarios.

Intraoperative Cholangiography

Intraoperative cholangiography can be used to define biliary anatomy. Its role in the prevention of bile duct injuries remains controversial.

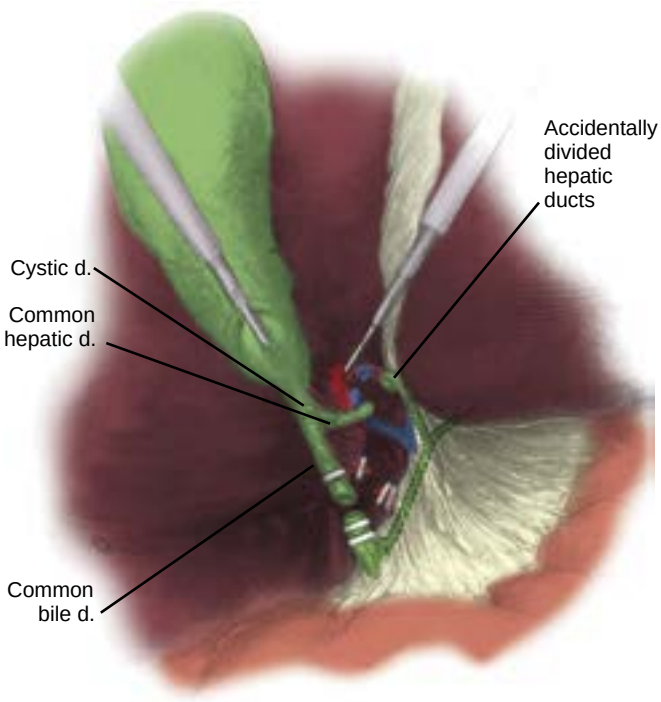


FIG. 1 Classic laparoscopic bile duct injury. The common bile duct is mistaken for the cystic duct and transected. A variable extent of the extrahepatic biliary tree is resected with the gallbladder. The right hepatic artery, in background, also is often injured. *(Adapted from Branum G, Schmidt C, Baillie J, et al. Management of major biliary complications after laparoscopic cholecystectomy.* Ann Surg. *1993;217:532.)*

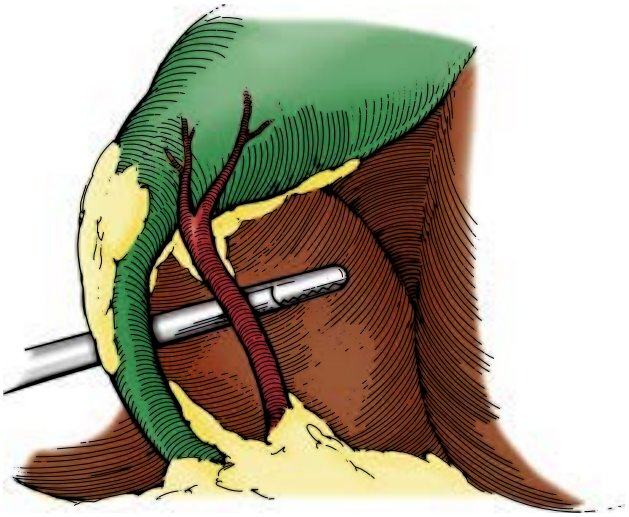


FIG. 2 The critical view of safety includes: the hepatocystic triangle dissected free of all tissue except for putative cystic duct and artery, the lower one third of the gallbladder dissected off of the cystic plate, and two (and only two) structures are seen attached to the gallbladder. *(Adapted from Strasberg SM, Eagon CJ, Drebin JA. The "hidden cystic duct" syndrome and the infundibular technique of laparoscopic cholecystectomy: the danger of the false infundibulum.* J Am Coll Surg. *2000;191:661–667.)*

Many surgeons believe that routine intraoperative cholangiography is technically challenging, adds to the cost and duration of the procedure, and is unnecessary in most patients. Others prefer its routine use so that the operative team is familiar with the procedure. Selective use of intraoperative cholangiography based on preoperative imaging and laboratory values seems to be a well-accepted strategy, given that only approximately one-third of general surgeons in the United States routinely use intraoperative cholangiography. The current literature is mixed, with one large retrospective study of nearly 100,000 patients showing no statistically significant association between intraoperative cholangiography and bile duct injury, with several smaller studies demonstrating decreased rates of bile duct injury when intraoperative cholangiography is performed. Recent prospective data suggest that intraoperative cholangiography can be performed routinely without a significant increase in case duration or morbidity. However, the question of whether intraoperative cholangiography actually prevents bile duct injury remains controversial. Finally, other intraoperative techniques for imaging biliary anatomy, including laparoscopic ultrasonography or near-infrared biliary imaging using indocyanine green or white light technology, have been reported but are not routinely used due to lack of familiarity and high-level evidence.

Classification of Biliary Injuries

There are several anatomic classification systems for describing biliary injuries. The most widely used system in the prelaparoscopic era was described by Bismuth based on the location of the injury in the biliary tract with respect to the hepatic bifurcation. After the popularization of laparoscopic cholecystectomy, when injuries became more common and more complex, Strasberg and colleagues proposed a modified classification system (Fig. 3).

Although not specifically described within a classification schema, it is important to discuss the scenario of concurrent vascular injury at the time of biliary injury, which has been reported in up to 15% of cases. Although biliary injuries are typically caused by direct operative trauma, they can also be ischemic in origin or a combination of both. The right hepatic artery is the most common structure involved in a vasculobiliary injury given its proximity to

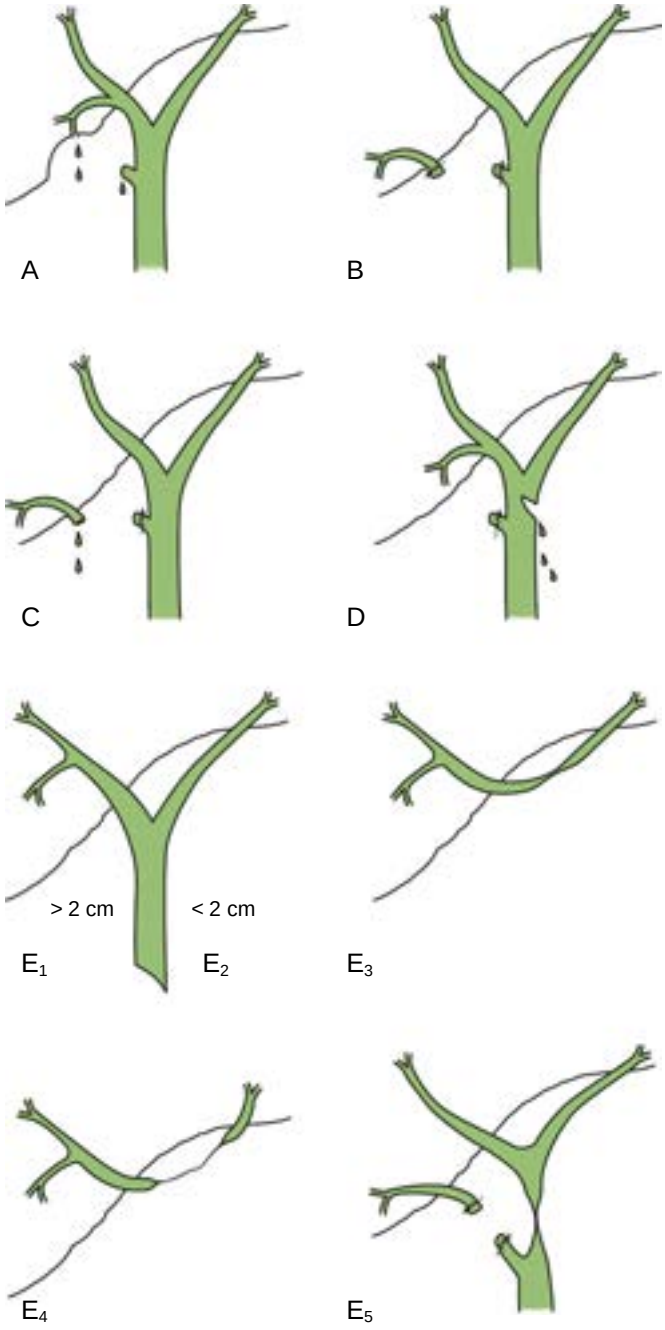


FIG. 3 Classification scheme for benign biliary strictures. *Type A*, Cystic duct leaks or leaks from small ducts in the liver bed. *Type B*, Occlusion of part of the biliary tree, typically clipped and divided right hepatic ducts. *Type C*, Transection (but not ligation) of the aberrant right hepatic ducts. *Type D*, Lateral injuries to major bile ducts. *Type E1*, Common hepatic duct division, more than 2 cm from bifurcation. *Type E2*, Common hepatic duct division, less than 2 cm from bifurcation. *Type E3*, Common bile duct division at bifurcation. *Type E4*, Hilar stricture, involvement of confluence and loss of communication between right and left hepatic duct. *Type E5*, Involvement of aberrant right hepatic duct alone or with concomitant stricture of the common hepatic duct.

the common hepatic duct. Arterial injury can lead to biliary ischemia and may propagate the injury to a higher level than the mechanical injury on the bile duct. Given the impact this can have on successful bile duct repair, it is imperative to assess the hepatic arteries when

investigating any major biliary injury. In the postoperative period, arterial phase contrast computed tomography (CT) can usually provide adequate delineation of the arterial anatomy. Excessive dissection around the bile duct during cholecystectomy or bile duct anastomosis can disrupt the arterial supply of the bile duct that travels in the 3 o'clock and 9 o'clock positions. This can lead to the development of late strictures and should be avoided. Finally, there has been an unfortunate increase in "catastrophic biliary-vascular injuries" seen over the last decade. Such cases involving injury to the bile duct and the arterial and portal venous system result in rapid and progressive clinical deterioration of the patient. Urgent liver transplant often offers the only chance of patient survival.

Recognition of Bile Duct Injuries

Immediate recognition of bile duct injuries can avoid the development of complications in many cases. However, only approximately one-third of biliary injuries are recognized at the time of laparoscopic cholecystectomy. Most bile duct injuries present in a delayed fashion with signs and symptoms of biliary leak or obstruction, and their management depends on the nature of the injury and the mode and timing of the presentation.

Intraoperative Recognition

When a biliary injury is noted intraoperatively during a laparoscopic cholecystectomy, immediate repair should be performed if the surgeon is experienced with these procedures. If not, then consultation with a hepatobiliary surgeon is warranted, even if this requires transferring the patient to another institution. If an experienced team is available, prompt cholangiography should be performed to further characterize the bile duct injury, followed by operative repair as described in the subsequent section. It is appropriate to postpone the repair in some situations even if recognized during cholecystectomy. Examples include a very proximal injury, diminutive bile ducts, significant inflammation, or technical limitations of the surgeon requiring transfer of the patient to another surgical team. In this scenario, the key technical principles are to provide appropriate and effective drainage and avoid propagation of the injury. A catheter (such as a pediatric feeding tube) should be placed into the proximal transected duct and loosely secured if possible without further damage to the duct. This catheter will assist in controlling the bile leak and allow future access for cholangiography. The surgeon should avoid ligation of the bile duct to prevent necrosis and a more challenging definitive reconstruction. Closed-suction drains should be placed in the subhepatic space to control the bile leak and prevent peritonitis or biloma formation.

Most bile duct injuries during laparoscopic cholecystectomy occur during procedures by surgeons who are not experienced with complex biliary reconstruction. Data suggest the best outcomes after iatrogenic biliary injuries occur from centers with experienced hepatobiliary surgeons and interventionalists. Thus, the decision to transfer care to a more experienced surgeon is entirely appropriate, and full disclosure to patients and their families, including the rationale behind a decision for transfer, is paramount.

Delayed Presentation

The majority of patients with an iatrogenic biliary injury present in the early postoperative period with symptoms such as fever, jaundice, abdominal pain, or peritonitis. The management of the injury depends on the timing and character of the presentation; however, in almost all scenarios, immediate return to the operating room is not indicated. In most situations, a CT scan upon arrival is necessary to identify fluid collections, bile ascites, or a vascular injury. Patients with an intraperitoneal bile leak typically present within 72 hours of the initial operation. The bile leak should be controlled with percutaneous drainage of any collections, and then the biliary anatomy should be defined with cholangiography, either endoscopically or percutaneously. In patients with complete transection, percutaneous cholangiography and biliary drainage is necessary. Although this can be difficult in a nondilated biliary system, this step is crucial. Once external catheter drainage is obtained, there is no urgency to intervene operatively. In most cases, 6 to 8 weeks is an appropriate amount of time to allow the inflammation in the area of the transected/leaking duct(s) to resolve. Percutaneous biliary catheters that control the bile leak and associated sepsis are also extremely helpful for the intraoperative identification of the hepatic ducts in a proximal biliary injury. For injuries above the hepatic duct bifurcation, both right and left main hepatic ducts should be stented individually.

In patients with cholangitis, usually a later presentation, biliary drainage to control sepsis is the priority, followed by percutaneous or endoscopic retrograde cholangiopancreatography (ERCP) to define the biliary anatomy. In patients with biliary obstruction without infection, magnetic resonance cholangiopancreatography (MRCP) can be used to define the anatomy noninvasively. In this scenario, repair without placement of a biliary catheter is considered appropriate.

Operative Repair of Bile Duct Injuries and Strictures

The primary goal of operative management for bile duct injuries is to establish biliary flow into the proximal gastrointestinal tract, which is best accomplished with a tension-free anastomosis between healthy tissues. The technique for operative repair depends on the extent and location of the injury. Options for reconstruction include end-to-end repair, Roux-en-Y hepaticojejunostomy, or hepatico- (choledocho-) jejunostomy.

Segmental or Accessory Duct Injuries

For segmental or small accessory duct injuries where cholangiography demonstrates segmental or subsegmental drainage of the injured ductal system, simple ligation of the injured duct is adequate. A larger duct (greater or equal to 4 mm) is likely to drain multiple hepatic segments, thus requires reconstruction.

Partial Injury to the Bile Duct

In some cases, the injury is limited to a lateral injury. These can best be repaired over a T-tube with absorbable suture (typically 5-0) and drained externally. Another scenario involves a patient who has had a clip placed without an injury to the duct or a small hole in the duct from performance of an intraoperative cholangiogram. Such cases, in the experience of the authors, can be managed with removal of the clip, repair of the ductotomy, and external drainage. If stricture develops either early or late postoperatively, endoscopic dilation and stenting will usually manage the condition successfully.

Transection of the Common Bile Duct

The most common ductal injury involves complete transection of the common bile duct or common hepatic duct. For such injuries recognized at the time of laparoscopic cholecystectomy with appropriate expertise available, immediate repair should be performed if ductal length can be maintained without tension. All repairs performed at the time of initial operation should be drained externally.

If the injured bile duct segment is short (less than 1 cm) and the two ends can be opposed without tension, an end-to-end anastomosis can be performed. A generous Kocher maneuver, mobilizing the duodenum out of the retroperitoneum, will help approximate the ends of the bile duct. A T-tube can also be placed through a separate choledochotomy either above or below the anastomosis (Fig. 4). A disadvantage of this approach is that it is associated with a high risk of stricture formation. However, an end-to-end anastomosis is less complex and allows future endoscopic transampullary intervention including balloon dilation and stenting, which have excellent long-term outcomes.

For proximal injuries or those greater than 1 cm in length, the distal bile duct should be oversewn, the proximal bile duct debrided, and an end-to-side Roux-en-Y hepaticojejunostomy performed

(Fig. 5). A Roux-en-Y jejunal limb is preferred over an anastomosis to the duodenum because, in the latter case, an anastomotic leak results in a duodenal fistula. In most cases, a transanastomotic stent should be placed across the anastomosis and certainly in cases when two ducts have been transected. Such catheters can be easily placed retrograde through the duct, exited through the surface of the liver, and then placed through the abdominal wall for external drainage. The anastomosis is typically constructed with interrupted 4-0 or 5-0 absorbable sutures. Closed suction drains are placed near the anastomosis.

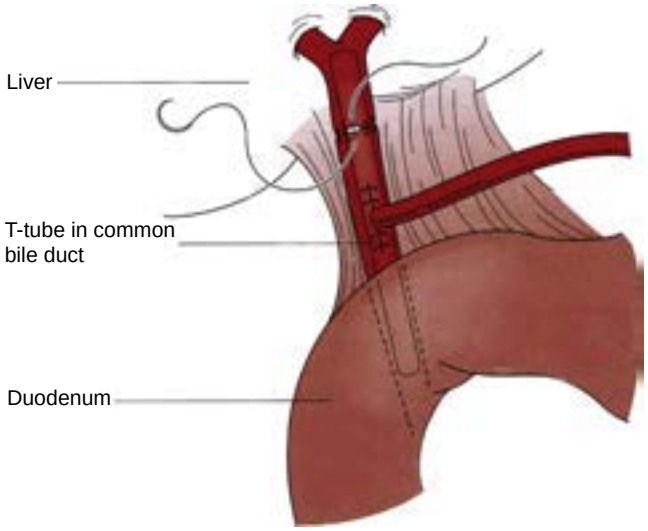


FIG. 4 If the injured segment of the bile duct is short (<1 cm) and the two ends can be opposed without tension, an end-to-end anastomosis can be performed with placement of a T-tube through a separate choledochotomy either above or below the anastomosis. The T-tube should not be brought out directly through the anastomosis.

General Approach to Repair of Bile Duct Injuries Recognized in the Postoperative Period

The definitive repair of a bile duct transection recognized in the postoperative period and controlled by external biliary drainage should not be planned until the patient has fully recovered from any sepsis or significant inflammation associated with a bile leak. In many cases, a period of 6 to 8 weeks is allowed before repair. These patients will have complete bile diversion during this period, so fluid, electrolytes, and hydration must be monitored. If there has been no bile leak, repair can occur at any time postoperatively.

The abdomen is explored through a midline incision. Usually there are significant adhesions in the right upper quadrant. If biliary stents are placed preoperatively, they can be used as a guide to help the surgeon identify the transected duct, which can be difficult in a reoperative field. Catheters should be advanced by the interventional radiologist across the transected segment into the subhepatic space or up to the transected end if the duct was completely clipped. After identification of the injured duct, the surgeon then dissects the bile duct proximal to the injury circumferentially in a cephalad direction for approximately 5 mm. Excessive proximal dissection should be avoided to prevent ischemia to the future anastomosis.

A guidewire is placed in the catheter, and appropriately sized soft Silastic stents can be placed over the guidewires after dilation of the system with a series of Coudé catheters. Silastic stents, sized 12 to 22 French, which have side holes through a portion of their length, can be placed with the perforated aspect of the catheter in the Roux-en-Y jejunal limb and intrahepatic biliary tree and the nonperforated aspect passed through the liver parenchyma and brought out externally through the anterior abdominal wall. Biliary decompression in the early postoperative period can minimize the consequences of an anastomotic leak and provide access for postoperative cholangiography and future therapeutic intervention if indicated. After the stent has been placed, the anastomosis is performed in an end-to-side fashion, typically using interrupted 4-0 or 5-0 absorbable suture. Closed suction drains are placed posterior to the anastomosis.

Postoperatively, the stents are left to gravity drainage for approximately 3 to 4 days. A postoperative cholangiogram is performed, and if there is no evidence of anastomotic leak, the stents are internalized (Fig. 6). Further management and ultimate removal of the stents

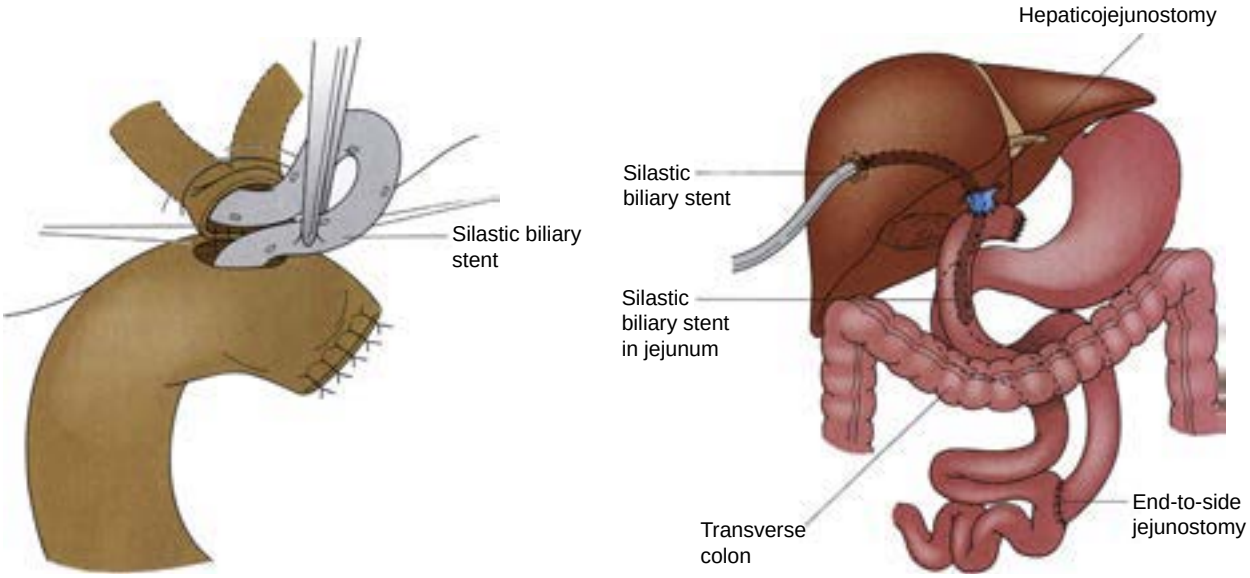


FIG. 5 The Silastic stent is placed through the anastomosis. A completed Roux-en-Y hepaticojejunostomy with transanastomotic stent. *(Adapted from Cameron JL. Resection of benign bile duct stricture with reconstruction utilizing Silastic transhepatic biliary stents and hepaticojejunostomy. In:* Atlas of Surgery. Vol 1. *Ontario: BC Decker; 1990:45, 55, 57.)*

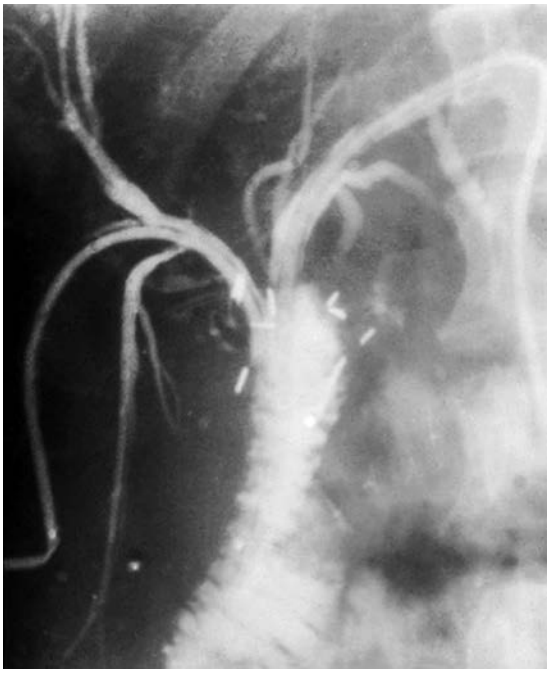


FIG. 6 Postoperative cholangiogram demonstrating completed hepaticojejunostomy to the individual right and left hepatic ducts. Soft Silastic stents are placed across the anastomosis.

depends on the clinical picture of each patient. The senior author's preference usually includes outpatient follow-up cholangiography at 6 to 10 weeks. Based on the cholangiographic appearance, the stents can be removed or, if necessary, balloon dilation can be considered.

Definitive Management of Established Bile Duct Strictures

With recent advancements in endoscopic and percutaneous techniques, there are excellent options for nonsurgical management of biliary strictures. For patients with primary bile duct strictures or stenosis of an end-to-end repair, endoscopic balloon dilation and stenting can be used and has excellent outcomes. Double balloon enteroscopy can now be employed in patients with a Roux-en-Y biliary-enteric anastomoses for the same purposes. In scenarios where the stricture is inaccessible endoscopically, percutaneous access to the proximal biliary tree can be obtained by the interventional radiologist, with subsequent dilation and stent placement across the area of stricture. This technique involves leaving behind a transhepatic stent to prevent cholangitis and for follow-up cholangiography and further intervention, if necessary. Of course, surgical treatment of bile duct strictures is still required in certain scenarios. Outcomes for all three approaches continue to improve over time.

Variable treatment strategies are available depending on the site and extent of the biliary stricture. Typically, strictures related to Strasberg types A, B, and C injuries are managed with endoscopic measures. If a patient with a type B or C injury suffers recurrent sepsis from cholangitis in the undrained sector, a right posterior hepatic sectionectomy is typically the best surgical option given the high failure rate of a posterior sectoral duct-enteric anastomosis. Strictures from Strasberg type D injuries (more than 50% of the common or hepatic bile duct circumference) are managed variably. For short segment stricturing, endoscopic or percutaneous interventional biliary stent placement may be successful. For thermal injuries requiring operative intervention, definitive repair with debridement of the bile duct back to healthy tissue and biliary-enteric anastomosis is preferred. Simple excision of any bile duct stricture with end-to-end ductal anastomosis or repair is rarely technically feasible.

Similar to the principles of repairing an acute biliary injury, the management of established bile duct strictures focuses on the reestablishment of bile flow into the gastrointestinal tract in a manner that prevents sludge, stone formation, cholangitis, restricturing, and cirrhosis. Strasberg type E strictures always require biliary-enteric anastomosis. Strictures that entirely separate the right and left systems require either creating a common back wall by sewing the right and left ducts together or creating distinct right and left biliary-enteric anastomoses. There is utility in performing a "high" hepaticojejunostomy reconstruction to an intact proximal hilar bridge between the right and left ducts as this preserves the crossing arterial anatomy. In very rare cases with failure of all standard surgical techniques of reconstruction for biliary stricture with resultant end-stage liver disease, liver transplantation may offer opportunity for survival. However, most liver transplants are indicated urgently after devastating vasculobiliary injuries caused during open cholecystectomy.

Outcomes after Surgical Reconstruction

Morbidity and Mortality

In a series of 200 patients who underwent surgical repair for biliary injuries after laparoscopic cholecystectomy, the incidence of postoperative complications was 43% and the postoperative mortality rate was 1.7%. Common complications include wound infection, cholangitis, and intraabdominal abscess. Anastomotic leak occurred in 5% of patients; however, no patients required reoperation. In 2013, a retrospective review of 528 patients compared long-term outcomes for endoscopic, surgical, or interventional radiology management of postoperative bile duct injuries over almost 20 years, which showed overall success rates were highest for surgical repair (88%), followed by techniques performed endoscopically (76%), and by interventional radiologists (50%). Success rates, defined as no need for further intervention beyond 1 year after completion of treatment, improved over time.

Quality of Life

Several studies have examined quality of life after surgical repair of iatrogenic bile duct injuries and suggest that patients largely return to baseline functional health. One study compared quality of life scores in patients who underwent surgical repair of a major bile duct injury to age- and sex-matched healthy controls and to those who underwent an uncomplicated laparoscopic cholecystectomy and demonstrated comparable scores in the physical and social domains but significant differences in the psychological domain. Quality of life scores were also significantly lower in patients who pursued a lawsuit compared with those who did not.

NONIATROGENIC BILIARY STRICTURES

Chronic Pancreatitis

Biliary strictures may develop in patients with severe chronic pancreatitis. Patients typically present with jaundice, abdominal pain, and rarely, acute cholangitis. Pancreatic fibrosis leads to stricturing of the intrapancreatic bile duct with dilation of the proximal bile duct. Pancreas-protocol CT can assist in the initial investigation of the process; however, ERCP or MRCP is required for diagnostic purposes and to assist in ruling out malignant processes. Cholangiography will typically demonstrate a long, smooth, gradual tapering of the distal bile duct. Fine-needle aspiration and serum CA 19-9 can be used to assess for periampullary malignancy and IgG4 levels obtained to rule out autoimmune pancreatitis.

There are several therapeutic options, which are driven by the patient's symptoms. Endoscopic therapy with removable stent placement is appropriate in patients without significant pain and in whom malignancy is not suspected. Nearly 90% of patients experience resolution of symptoms after stenting, but for those with persistent

strictures, Roux-en-Y hepaticojejunostomy or choledochoduodenostomy is typically the surgical procedure of choice. For patients with significant pain, concurrent duodenal obstruction, or in whom malignancy cannot be ruled out, operative management must be considered at the onset. The recommended treatment depends on the presence of other sequelae of pancreatitis (i.e., inflammatory mass in the head of the pancreas or pseudocyst) but may require a Frey or Puestow procedure. Pancreaticoduodenectomy is preferred if malignancy is suspected.

Strictures from Gallstone Disease

In Mirizzi's syndrome, gallstones impacted in the gallbladder infundibulum or cystic duct can lead to obstruction of the common hepatic duct. Patients typically present with jaundice and abdominal pain. Before surgical intervention, CT and/or MRCP can be used for diagnostic purposes, with confirmation and stenting provided by ERCP. The impacted stone can cause ulceration, fibrosis, and erosion into the common hepatic duct, thus open cholecystectomy with careful dissection is warranted. Roux-en-Y hepaticojejunostomy is required should a fistula to the common hepatic duct be identified.

Chronic parasitic infections of the biliary tree can lead to inflammation and development of bile duct stones, typically of the brown pigment type. Recurrent infections are common, as is stricture formation. Treatment is aimed at minimizing the long-term consequences of the disease, including biliary cirrhosis and cholangiocarcinoma, and includes a combination of endoscopic, percutaneous, and surgical techniques.

Noniatrogenic Bile Duct Injuries

Although rare, injuries to the biliary tree occur in noniatrogenic trauma, typically nonpenetrating in nature and concurrent with other intraabdominal injuries. Isolated bile duct injury from penetrating trauma is fortunately exceedingly rare but devastating as it is often accompanied by vascular injury to the hepatic artery and portal vein. The principles of management are similar to iatrogenic injuries, but the surgeon must be cognizant of the likelihood of concomitant vascular injury and possible devascularization of the bile duct above the site of mechanical injury.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a destructive autoimmune condition of the bile ducts associated with inflammatory bowel disease. It causes both intrahepatic and extrahepatic biliary strictures that lead to recurrent cholangitis and can progress to biliary cirrhosis and malignancy. For dominant strictures, endoscopic biliary stenting can be of use. Many patients require liver transplantation as definitive treatment for this progressive disease.

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Management of Cystic Disorders of the Bile Ducts

Sean P. McGuire, MD, and Nicholas J. Zyromski, MD

Cystic disorders of the bile ducts include dilation of the extrahepatic biliary tree, intrahepatic biliary tree, or both. Bile duct cysts include simple cysts, biliary cystadenoma, and congenital choledochal cysts (CC). This chapter will focus on the latter process. CC disease is a congenital disease that develops in infancy and childhood, although diagnosis often only occurs in adulthood. Due to the risk of malignancy associated with CC, understanding the diagnosis and proper surgical treatment are critical.

EPIDEMIOLOGY

The incidence of CCs varies widely based on geography. This problem is seen rarely in Western countries, with an incidence of 1 to 1.5 per 100,000 people. CCs are more common in select East Asian countries, with an incidence that may approach 1 per 1000 people. Females are more commonly affected, with a reported female-to-male ratio as high as 8:1.

ETIOLOGY

Several theories have been proposed to explain the etiology and pathophysiology of CCs. Frequent diagnosis in childhood supports a congenital origin of CCs. The most widely accepted etiology posits that CCs originate from a congenitally anomalous pancreaticobiliary duct junction (APBDJ), defined as insertion of the bile duct greater than 15 mm proximal to the ampulla of Vater (Fig. 1). The resultant long common channel permits reflux of pancreatic secretions into the common bile duct (CBD), resulting in increased biliary pressure, inflammatory changes in the biliary epithelium, and ultimately cystic dilation of the biliary tree. An APBDJ has been reported in as many as 90% of CCs; however, recent series have noted lower coincidence of APBDJ, especially in type III CCs (choledochoceles), suggesting multiple etiologies likely underlie cystic disorders of the biliary tree.

CLASSIFICATION

The earliest classification system for CCs was put forth by Alonso-Lej in 1959. This classification system included three types of CC: (1) a segmental cystic dilation of the CBD, (2) a solitary CBD diverticulum, and (3) a bulbous dilation of the distal-most portion of the

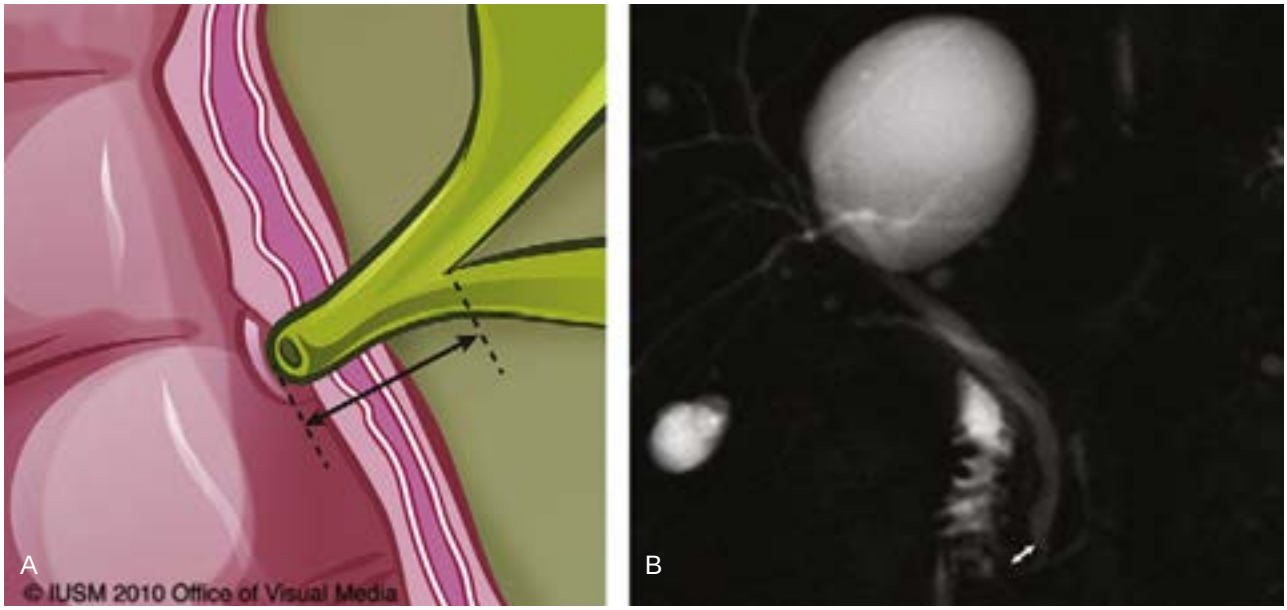


FIG. 1 Anomalous pancreaticobiliary duct junction (APBDJ). **(A)** Artist rendition of long common channel and **(B)** MRCP image demonstrating long common channel; arrow indicates common channel. *(A courtesy IUSM Office of Visual Media; copyright The Trustees of Indiana University.)*

CBD within the ampulla of Vater (choledochocele). In 1977, Todani modified this classification, forming the basis for contemporary description of CC.

The Todani classification consists of five types of CC (Fig. 2). Type I cysts are by far the most common type, making up >70% of all CCs and consisting of dilations of the extrahepatic biliary tree. Type II cysts comprise about 1% to 3% of all CCs and consist of a saccular diverticulum off of the extrahepatic biliary tree. Type III cysts (choledochoceles) consist of biliary ductal dilation within the duodenal wall and make up 1% to 3% of all CCs. Recent evidence suggests that choledochoceles represent a separate entity from the remainder of CCs. Due to the unique demographics, presentation, pancreaticobiliary ductal anatomy, and management of choledochoceles, many authors have suggested they should not be included in the general classification system for CCs (Fig. 3). Type IV cysts are the second most common type of cyst and make up 24% of all CCs. These cysts consist of cystic dilation of the intrahepatic and extrahepatic biliary tract. Type IV cysts are further subdivided into type IVa, consisting of multiple intrahepatic cysts and a single extrahepatic cyst, while IVb consists of multiple extrahepatic cysts. Type V cysts, also known as Caroli's disease, comprise 1% to 3% of CCs and consist of multiple intrahepatic cysts.

CLINICAL PRESENTATION

CCs present most classically in female infants and young children, though presentation in adulthood is relatively common. The classic triad of presenting symptoms includes right upper quadrant pain, jaundice, and abdominal pain. However, this triad is rarely documented in modern series, and perhaps more importantly, presentation differs between children and adults. Children are more likely to present with jaundice and/or abdominal mass, while adults are more likely to present with pain, cholangitis, and malignancy. Acute pancreatitis can also be a presenting symptom, most commonly in the case of choledochoceles.

DIAGNOSIS

Diagnosis of CCs relies heavily on imaging findings, as clinical symptoms overlap with many other pancreaticobiliary and gastrointestinal conditions, and lab markers—including transaminases, amylase, bilirubin, CA 19-9, and CEA—are frequently within normal limits. Modern imaging modalities, including ultrasound (US), computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP) are each used to varying degrees with variable sensitivity and specificity to diagnose cystic disorders of the bile ducts. A CBD diameter of >10 mm in an adult on any imaging modality should alert practitioners to the possibility of CC; however, this guideline should be used with caution in older patients, as bile duct diameter increases with age.

US is the most frequently used imaging modality to diagnosis CC and is the first imaging study recommended in the pediatric population given its high sensitivity in this population, low cost, and avoidance of radiation exposure. Although both US and CT have a sensitivity of >90% for diagnosing CC, these studies are limited in their ability to delineate the exact pathologic anatomy, including identification of APBDJ.

Cholangiography, including ERCP and PTC, represents the most sensitive technique to delineate biliary anatomy. ERCP permits direct visualization of the pancreaticobiliary junction, decompression of jaundice, and sampling of biliary epithelium. PTC is also sensitive in delineating the anatomy of the intrahepatic bile ducts but is more invasive than ERCP and requires extended percutaneous drainage. Both ERCP and PTC are invasive procedures that are operator dependent and may be difficult to perform in the pediatric population.

MRCP is becoming the preferred imaging modality due not only to its noninvasiveness, high sensitivity (70%–100%), and specificity (90%–100%), but also to its superiority in identifying the precise pathologic anatomy, including APBDJ.

WHEN IS A DILATED COMMON BILE DUCT A CHOLEDOCHAL CYST?

A common clinical conundrum is the presentation of a patient with dilated CBD. The natural dilation of the CBD with age and after cholecystectomy may make differentiating true CC pathology from benign biliary dilation challenging. In these settings, MRI/MRCP

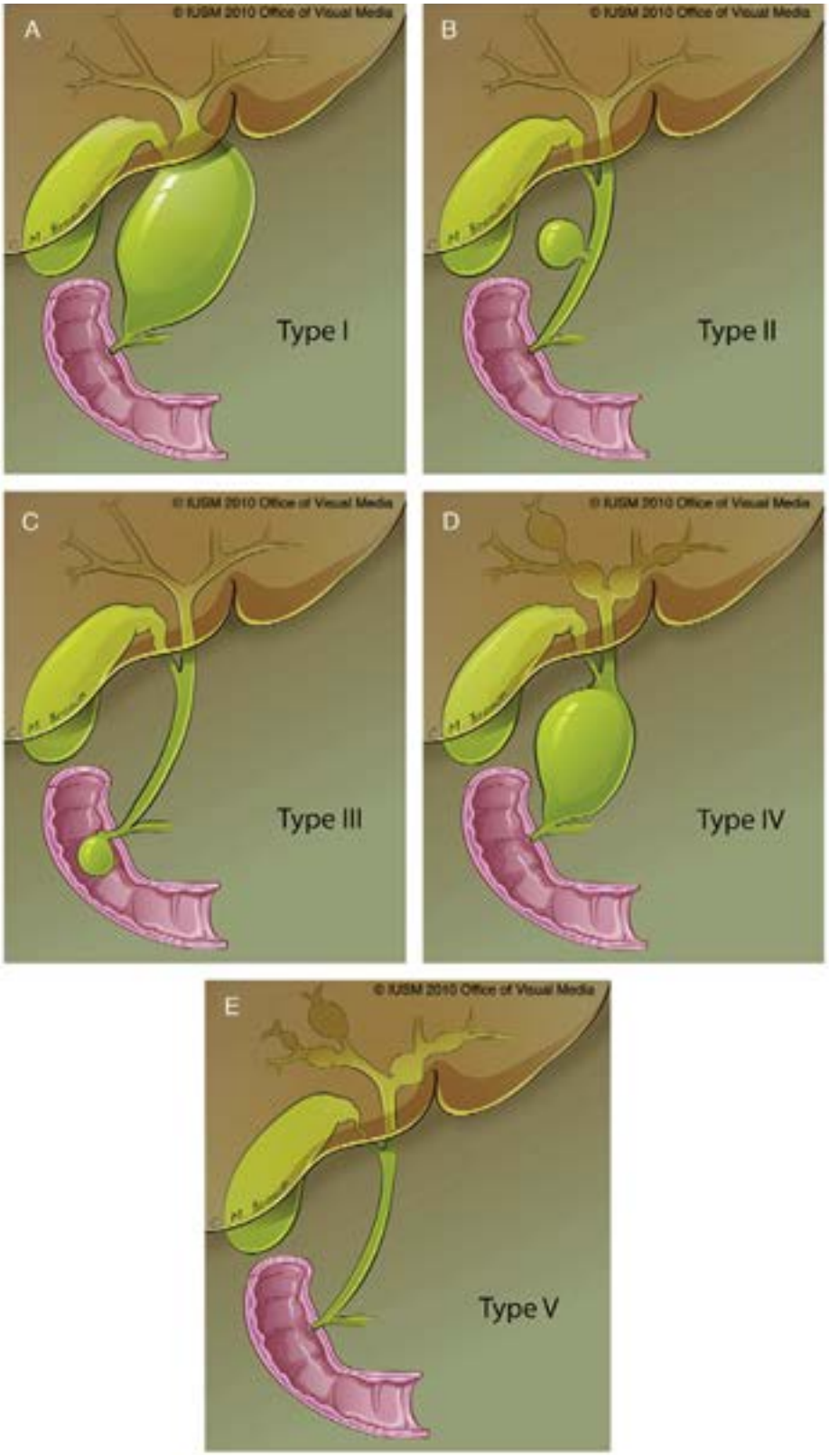


FIG. 2 Todani Classification of choledochal cysts. **A-E,** Types I-V. *(Courtesy IUSM Office of Visual Media; copyright The Trustees of Indiana University.)*

is extremely helpful. In the absence of long common channel, the diagnosis of CC is extremely unlikely.

The differential diagnosis of biliary dilation also includes sphincter of Oddi spasm, most commonly seen in females after gastric bypass. Figure 4 illustrates a case of biliary dilation raising initial concern for CC (Fig. 4A). Subsequent imaging showed no APBDJ, and the bile duct decompressed completely after endoscopic sphincterotomy (Fig. 4B).

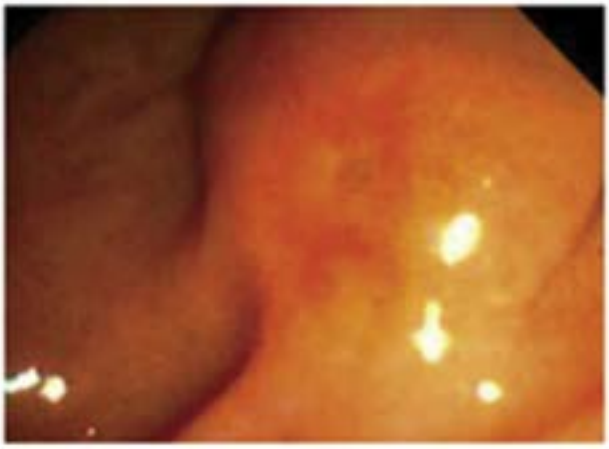


FIG. 3 Endoscopic view of type III choledochal cyst (choledochocele).

MANAGEMENT

The presence of a CC is in itself an indication for surgery. CCs are associated with increased risk of cholangitis, pancreatitis, and malignant degeneration into cholangiocarcinoma. The risk of malignant degeneration is felt to be related to APBDJ; reflux of pancreatic secretions into the biliary tree results in inflammation, dysplasia, and ultimately carcinoma of the biliary epithelium. Stasis of bile within CC also likely contributes to ongoing inflammation and malignant transformation. The incidence of cholangiocarcinoma has been reported to be as high as 75% in certain series from Japan, with higher risk in patients with intrahepatic involvement (Fig. 5). Surgical management is tailored to specific type of CCs but generally includes cholecystectomy, complete resection of the CC, and biliary enteric anastomosis.

Type I: Extrahepatic Bile Duct Cyst

The surgical treatment for Todani type I bile duct cysts begins with cholecystectomy, after which a Kocher maneuver should be performed to allow for visualization of the CBD and CC (Fig. 6A). Dissection follows the CBD distally to the caudal portion of the cyst. The question of how far distally to resect the CBD is an important clinical challenge. The ideal situation includes complete resection of the cyst to its point of insertion into the main pancreatic duct. Intraoperative US may be helpful in identifying the distal most aspect of the cyst and bile duct. Understanding and identifying this anatomic relationship is particularly important should the surgeon operate laparoscopically. All operations for type I CC should involve preoperative counseling regarding the potential need for pancreatic head resection. Following transection of the distal CBD, the superior portion of the cyst should be mobilized to the level of the common hepatic duct bifurcation. Transection of the duct at the level of the confluence is generally recommended (Fig. 6B). However, any abnormality of the hepatic duct above the level of the bifurcation should prompt further dissection until the surgeon is able to identify a normal duct, and transection should occur proximal to this point. The proximal and distal bile duct margins should be sent for frozen section testing to exclude cholangiocarcinoma at the margin. Biliary-enteric anastomosis is accomplished via end-to-side Roux-en-Y hepaticojejunostomy (HJ) (Fig. 6C).

Preoperative percutaneous cholangiography and biliary drainage may be considered in cases of type I cysts. Advantages include preoperative delineation of biliary anatomy and easier intraoperative identification of the hepatic duct confluence. Transhepatic biliary drainage may be continued postoperatively to decompress the HJ during the early healing period.

Type II: Extrahepatic Biliary Diverticulum

Type II CCs are not typically associated with APBDJ and thus carry a relatively lower risk of malignant transformation. For this reason, resection of the CBD during surgical management is not required. Rather, diverticulectomy with CBD closure at cyst neck provides adequate surgical management. Closure of the bile duct over a T-tube may be useful in managing a small (normal-sized) bile duct.

Type III: Choledochocele

Contemporary understanding of this rare condition suggests that choledochocele is a discrete entity from CC. Endoscopic sphincterotomy for choledochoceles was first performed in 1981 and in the decades since has been shown to a be a safe, effective, and durable means of managing choledochoceles. Although no clearly established link between choledochocele and malignancy exists, two case reports have identified ampullary (1) and pancreatic (2) malignancy in association with choledochoceles.

Type IV: Intrahepatic and Extrahepatic Bile Duct Cyst

Like type I cysts, type IV cysts carry a significant risk of malignant transformation, and surgical management is the primary

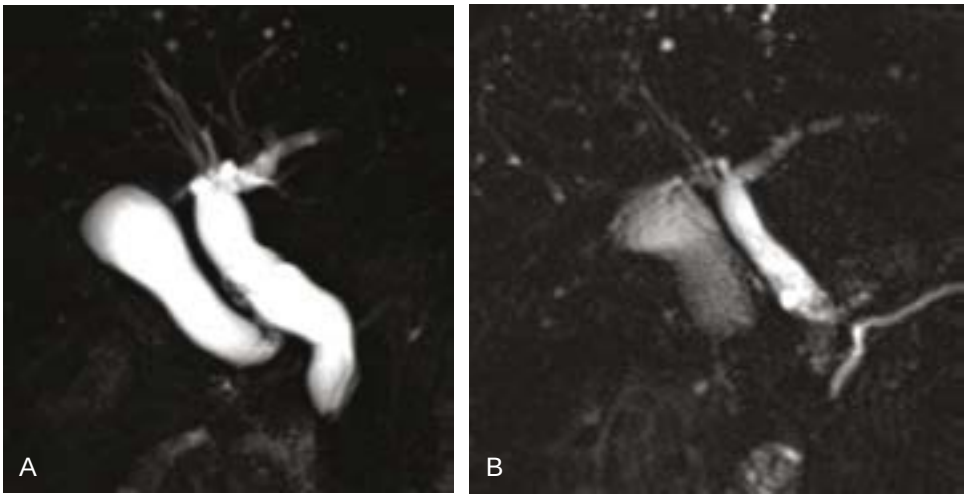


FIG. 4 Magnetic resonance images demonstrating a case of biliary dilation concerning for choledochal cyst **(A)** and subsequent decompression after endoscopic sphincterotomy **(B)**.

treatment. The diffuse nature of type IV CCs, with both intra- and extrahepatic components, presents a somewhat more demanding clinical challenge. The extrahepatic portion can be treated as outlined before when discussing type I CCs: complete cyst resection with biliary-enteric anastomosis. If the disease is unilobar, partial hepatectomy is the appropriate treatment. Bilobar disease should be managed with aggressive surveillance with serial imaging and CA 19-9 levels, understanding that, like Caroli's disease, definitive management of bilobar involvement requires orthotopic liver transplantation (OLT).

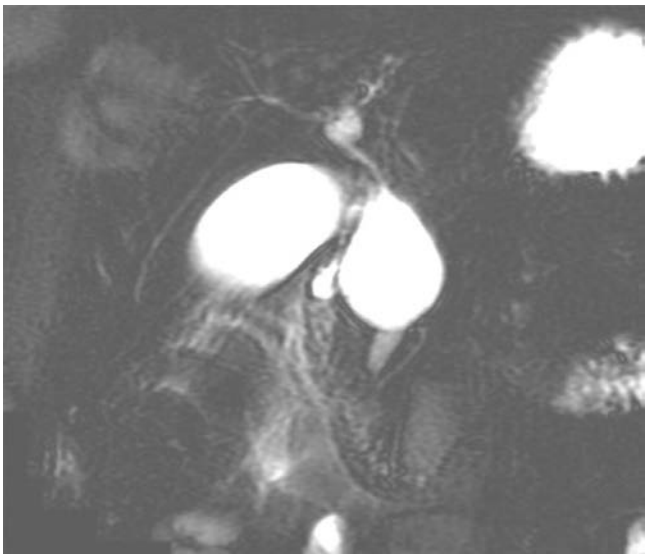


FIG. 5 MRCP image of choledochal cyst containing cholangiocarcinoma.

Type V: Caroli's Disease

Type V CCs also represent a significant clinical challenge. Some authors have suggested managing the asymptomatic patient with aggressive surveillance including serial imaging and CA 19-9 levels. Most patients diagnosed with Caroli's disease will eventually also experience portal hypertension, cholangitis, and cholangiocarcinoma. Cholangitis related to intrahepatic cyst disease can be managed with antibiotics, biliary drainage via large bore stents, and stone extraction. However, these approaches should be considered temporary measures because they do not mitigate the risk of malignancy. OLT is the definitive surgical management for patients with type V CCs. Timing of OLT remains a primary question for the multidisciplinary clinical care team and should be individualized to the specific patient condition.

Morbidity of Surgical Therapy

Short-term morbidities following surgical therapy for CCs include wound infection, intraabdominal infection, postoperative pancreatitis, cholangitis, and bile leak. Of these, wound and intraabdominal

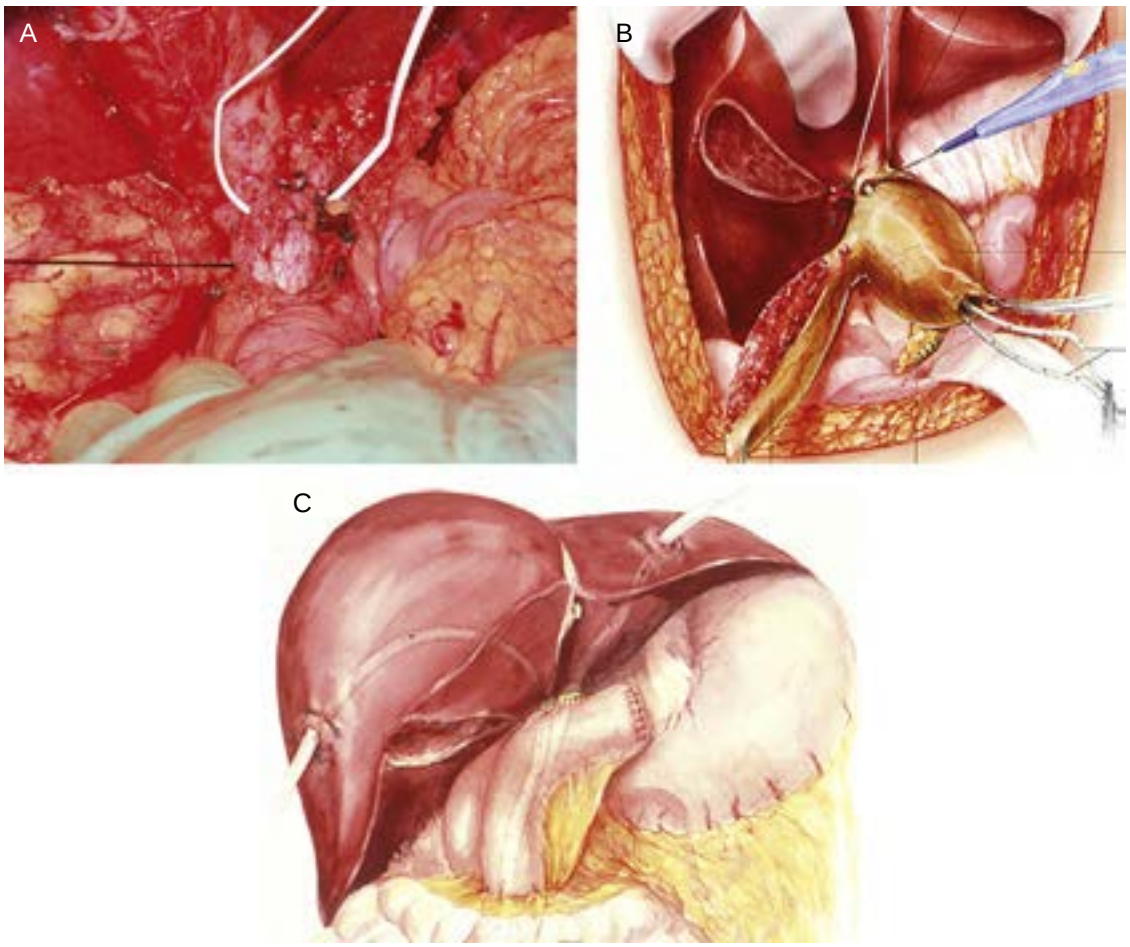


FIG. 6 Surgical management of type I choledochal cysts. **(A)** Intraoperative image of a dissected and exposed CBD with choledochal cyst. **(B)** Schematic of resection margins. **(C)** Schematic of reconstruction. *(B and C from Cameron JL, Sandone C.* Atlas of Surgery, vol. 1. *Philadelphia: BC Decker; 1990.)*



FIG. 7 Over-the-wire cholangiogram showing stricture at hepaticojejunostomy. *(Image courtesy David Agarwal, IU Dept of Radiology.)*

infections are most common, with a rate of 6% to 7% in large series from the United States. The remaining short-term postoperative complications are rare, with incidence generally reported in less than 5% of patients.

Transanastomotic stenting in the perioperative period is controversial. Many experienced biliary surgeons use transhepatic, transanastomotic stents (usually soft silastic Heyer-Schulte type stents between 12 and 20F), especially with very proximal anastomoses. The advantage of decompressing the biliary tree controls the leak potential during the immediate postoperative period. In addition, stenting facilitates cholangiography. The timing of stent removal is individualized based on anatomic findings; over-the-wire cholangiography permits interrogation of anastomotic patency.

HJ anastomotic stricture is rare but is the primary long-term complication after HJ (Fig. 7). Long-term follow-up should include annual serum liver enzyme function tests (LFTs) including alkaline phosphatase and bilirubin. Rising enzyme levels may be the earliest sign of stricture; abnormal or increasing LFTs (particularly alkaline phosphatase) should prompt imaging with MRI/MRCP. Biliary stricture after HJ is treated by percutaneous transhepatic stenting; long-term stenting will resolve most strictures, but surgical revision may be required for refractory stricture.

Cholangiocarcinoma may develop in residual or incompletely resected CCs (Fig. 8). This clinical scenario is difficult and requires

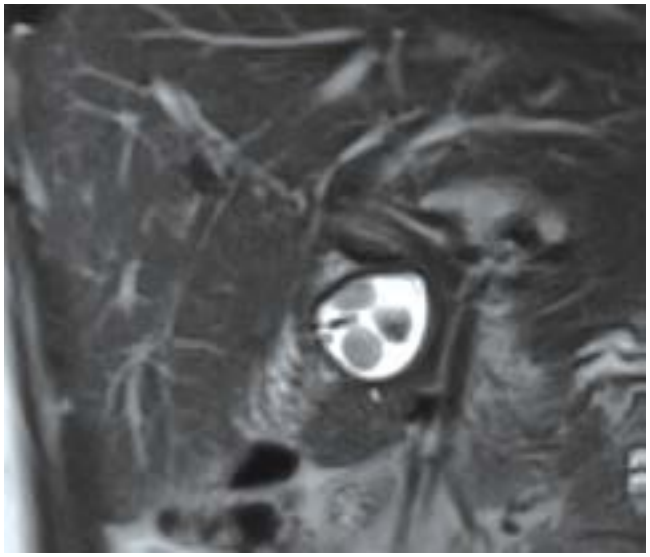


FIG. 8 MRCP image of retained choledochal cyst within the pancreatic head. This patient was managed surgically with pancreatoduodenectomy.

input from an experienced biliary surgeon; however, strong consideration must be given to completion resection of any residual CC left in situ after primary resection.

PROGNOSIS

The overall 5-year survival of patients with CCs managed with resection and biliary reconstruction is 96%. However, the prognosis depends heavily on the development of cholangiocarcinoma, which in turn is related to both the age of the patient as well as the type of cyst. The risk of cholangiocarcinoma is less than 1% if the CC is resected within the first decade of life but rises to 14% if presentation occurs beyond 20 years of age. CCs associated with ABBDJ—types I, IV, and V—carry the highest risk of cholangiocarcinoma. Preoperative diagnosis of cholangiocarcinoma is a harbinger of poor prognosis, as advanced disease is often present. Patients with incidental cholangiocarcinoma discovered at the time of surgical resection have relatively better outcomes. Although proper treatment (i.e., complete surgical resection) decreases the risk of developing cholangiocarcinoma, long-term follow-up for these patients is essential.

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Management of Primary Sclerosing Cholangitis

Gillian M. Ahrendt, MD, and Steven A. Ahrendt, MD

CLINICAL PRESENTATION

Patients present with either abnormal liver function test results or manifestations of cholestatic liver disease. In earlier observational studies, 15% to 40% of patients were found to be asymptomatic at the time of diagnosis. The diagnosis is established in asymptomatic patients typically when persistently cholestatic biochemical tests are discovered. Symptomatic patients usually present with right upper quadrant pain, fatigue, pruritus, and weight loss. Cholangitis is uncommon on presentation in patients who have not undergone biliary surgery or biliary tract manipulation, such as endoscopic retrograde cholangiopancreatography (ERCP). Physical examination findings for symptomatic patients may include jaundice, hepatomegaly, and splenomegaly. Certain biochemical tests are commonly abnormal in patients with PSC. An elevated serum alkaline phosphatase is the "biochemical hallmark" of the disease, although a normal value does not exclude the diagnosis. Serum aminotransferase levels are usually two to three times higher than normal, but again, normal values do not exclude the diagnosis. Total bilirubin level is normal in 60% of cases.

NATURAL HISTORY

A recent meta-analysis of studies from North America and Europe suggests that the incidence and prevalence of PSC is about 1 per 100,000. The disease affects men predominantly, although patients with PSC who do not have inflammatory bowel disease (IBD) are more often women. PSC is most commonly diagnosed in the fourth decade of life.

PSC affects both quality of life and life expectancy. Median survival time in symptomatic patients ranges from 10 to 18 years after diagnosis, with patients dying of complications of PSC, such as liver failure or cholangiocarcinoma (CCA), or of advanced associated disease, such as colorectal carcinoma in patients with IBD. Median survival in asymptomatic patients with PSC is longer than in patients presenting with symptoms, although survival is decreased when compared with matched, healthy individuals. The course of PSC is highly variable among individual patients; some patients have rapid progression to liver failure or development of a biliary malignancy early in their course, whereas others remain asymptomatic for years. Mathematic prognostic models have been developed to help determine when a patient should be considered for liver transplant and to help evaluate the response to certain therapies. The revised Mayo Model, which considers age, total bilirubin level, serum aspartate transferase (AST) value, serum albumin value, and history of variceal bleeding, has been developed to estimate survival over 4 years.

ASSOCIATED DISEASES AND COMPLICATIONS

Primary sclerosing cholangitis (PSC) has been associated with several diseases and potential complications. The strongest association is with IBD, usually ulcerative colitis (UC). Although as many as 80% of patients with PSC have IBD, only 3% to 8% of patients with IBD have PSC. Patients with both PSC and IBD are much more likely to have pan colitis than more limited colonic involvement. PSC has also been shown to be an independent risk factor for colon cancer in patients with UC. In addition, the risk of development of colorectal cancer in patients with PSC and UC appears to increase further after liver transplant. Colonoscopy is warranted in all patients with PSC either to exclude the diagnosis of IBD in patients without a history or for cancer surveillance in patients with UC or Crohn's disease.

An increased frequency of autoimmune disease has been found in patients with PSC. This includes disorders unrelated to the liver and colon, such as type I diabetes mellitus and thyroid disease. Autoimmune hepatitis (AIH) has also been seen in up to 17% of patients with PSC and has been designated separately as PSC-AIH overlap syndrome.

PSC is also associated with an increased frequency of hepatobiliary malignancies, including CCA, gallbladder cancer, and hepatocellular carcinoma (HCC). PSC is considered a risk factor for CCA, which is one of the most feared complications of this disease. In population-based studies, CCA has been shown to occur in 7% to 14% of patients with PSC. It is common (30%–42% incidence rate) in autopsy series of patients with PSC, and it has been diagnosed in up to 10% of patients undergoing liver transplant despite an extensive preoperative evaluation to exclude this diagnosis. CCA is often diagnosed early in the clinical course of PSC, with up to half of patients diagnosed within 1 year of a PSC diagnosis. The subsequent annual incidence rate is 0.5% to 1.5%. Unfortunately, CCA is usually not an operable lesion once discovered because it is diagnosed either at an advanced stage or because the background liver disease precludes resection as an option. Strong suspicion for malignancy should be maintained for patients with PSC and a dominant stricture (defined as a stenosis with a diameter of ≤1.5 mm in the common bile duct or ≤1 mm in the hepatic duct) and for patients who have clinical signs of rapidly increasing jaundice, abdominal pain, and weight loss. Cytologic examination of biliary brushings and biopsies may be helpful, but they generally have low sensitivity for diagnosis of CCA. Periodic testing for carbohydrate antigen 19-9 (CA 19-9) has been recommended by some investigators to evaluate for an elevated level, particularly a sustained elevation, although a high false-positive rate exists because of factors such as bacterial cholangitis.

Patients with PSC are predisposed to gallbladder disease, both benign and malignant. Gallstones have been found in 25% of patients with PSC. Gallbladder polyps are commonly seen on ultrasound scan in patients with PSC (4%–6%), and more than half of these contain an invasive cancer. Cholecystectomy should be performed in patients with PSC with gallbladder polyps regardless of lesion size. Annual ultrasound scan screening of the gallbladder has been recommended for patients with PSC.

HCC is a risk among patients with PSC with end-stage liver disease. Between 2% and 4% of explanted livers from patients with PSC were found to have concomitant HCC.

DIAGNOSIS

The diagnosis of PSC is normally supported with typical findings on cholangiogram. Magnetic resonance cholangiography (MRC) is the diagnostic procedure of choice when PSC is suspected. The diagnosis can usually be established noninvasively with MRC with a sensitivity and specificity exceeding 80%. The diagnosis may also be established with endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography (PTC). The typical cholangiographic findings in PSC include multifocal strictures with a resultant and characteristic beading pattern in both the intrahepatic and extrahepatic bile ducts (Fig. 1). The hepatic duct bifurcation is often the most severely strictured segment of the biliary tree. Isolated involvement of the intrahepatic ducts and proximal extrahepatic ducts occurs in approximately 20% of patients. Conversely, only 5% to 10% of patients have sclerosing cholangitis involving just the extrahepatic duct without intrahepatic duct involvement. Visualization of the entire biliary tree is critical to avoid missing a CCA.

The role of liver biopsy for the diagnosis of PSC has evolved. A liver biopsy often shows nonspecific findings in patients with PSC and rarely adds additional diagnostic information in patients with



FIG. 1 Typical characteristic primary sclerosing cholangitis on cholangiography, showing stricturing and beading.

typical findings of the disease on cholangiography. However, a liver biopsy is warranted in patients with a cholestatic liver function panel and a normal cholangiogram to diagnose small duct PSC. Liver biopsy can also help diagnose patients suspected to have PSC-AIH overlap syndrome in whom immune suppressive therapy should be used for treatment.

PSC must be distinguished from secondary sclerosing cholangitis (SSC) that results from identifiable causes of biliary tree injury and stricture such as chronic obstruction, infection, chemical agents, drugs, and ischemia. Other diagnostic possibilities that are important to consider when pursuing a diagnosis of PSC are small duct PSC, PSC overlap syndromes, and immunoglobulin G4 (IgG4)–associated cholangitis. A cholestatic pattern to liver function studies supports the diagnosis of PSC and is useful for monitoring the course of the disease. Serum bilirubin is not commonly elevated early in the course of the disease but does increase as the disease progresses. The serum tumor marker CA 19-9 may also be elevated in patients with PSC and CCA.

Occasionally, surgical resection may be necessary to make the diagnosis. For example, differentiation of localized sclerosing cholangitis from CCA can be difficult, especially when the stricture is in the perihilar region. Also, the combination of CCA and bacterial cholangitis may mimic sclerosing cholangitis. In cases like these, resection of the dominant stricture may be necessary to establish a diagnosis.

THERAPY

The overall goals of treatment of PSC are to slow progression of the disease and reduce the risks for cancer and end-stage liver disease. A management algorithm is pictured in Figure 2. In general, asymptomatic patients should not be treated. No currently available medical therapy has shown any effect on disease progression. Symptomatic patients with persistently elevated liver function tests, pruritus, pain, or fatigue; evidence of significant extrahepatic or hilar strictures; and no clinical or imaging signs of cirrhosis are candidates

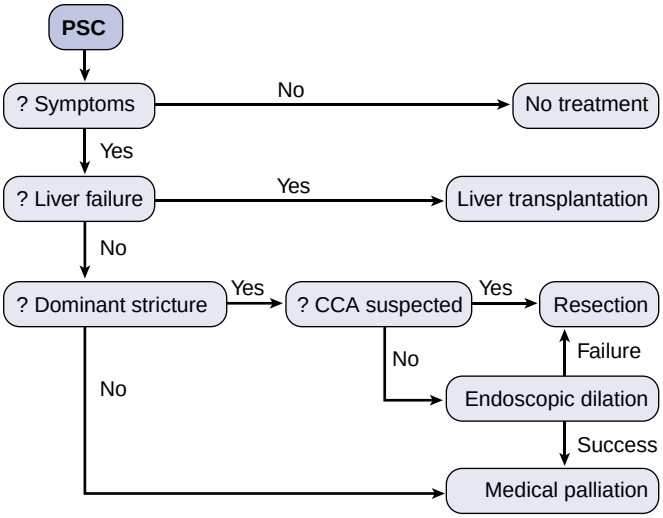


FIG. 2 Management algorithm for primary sclerosing cholangitis (PSC). *CCA*, Cholangiocarcinoma.

for an endoscopic or surgical approach to improve biliary drainage. In addition, patients with dominant biliary strictures suspicious for CCA should undergo surgical exploration and resection of the extrahepatic bile ducts rather than prolonged efforts to establish a tissue diagnosis. When cirrhosis is present, liver transplant is the only reasonable therapy.

Medical Therapy

Ursodeoxycholic acid (UDCA), which is used to treat primary biliary cirrhosis, initially showed promise as patients experienced improvement in liver function tests over time. However, in randomized studies that compared UDCA with placebo, the rates of treatment failure, including death, liver transplant, progression to cirrhosis, worsening of fatigue or pruritus, inability to tolerate the drug, or voluntary withdrawal from the study, were similar among the two treatment arms. Currently, the American Association for the Study of Liver Diseases (AASLD) recommends against use of UDCA as medical therapy for patients with PSC.

Antiinflammatory and immunosuppressive drugs, such as corticosteroids, penicillamine, azathioprine, colchicines, and anti–tumor necrosing factor (TNF) antibodies, have been tried in small studies. None of these drugs have proved to be beneficial in patients with classic PSC.

Symptoms of PSC are managed individually. Pruritus, for example, is managed with cholestyramine or UDCA and possibly antihistamines. Fatigue is managed symptomatically after hypothyroidism is ruled out. With advanced disease, fat malabsorption and steatorrhea may be present with subsequent deficiency of fat-soluble vitamins, such as vitamins A, D, E, and K. This can usually be treated with oral replacement of these vitamins.

Nonoperative Interventional Therapy

Dominant hilar and extrahepatic strictures occur in 15% to 20% of patients with PSC. They are defined as stenoses with a diameter of 1.5 mm or less in the common bile duct or of 1 mm or less in the hepatic ducts. The initial approach to patients with a dominant stricture is endoscopic balloon dilation with or without stenting. The endoscopic approach avoids dissection of the porta hepatis before the need for hepatic transplant, allows treatment of both the right and left hepatic ducts simultaneously, and is associated with fewer

complications than percutaneous or surgical procedures. Endoscopic therapies to treat dominant strictures include balloon dilation and stenting. Endoscopic stents are associated with a higher risk of complications, including cholangitis, and should be reserved for strictures that recur after balloon dilation. Endoscopic intervention can result in clinical improvement, and studies show that patients need fewer annual hospitalizations and have a short-term decrease in serum bilirubin and cholestatic symptoms after treatment. However, PSC is characterized by fluctuations in symptoms and degree of cholestasis, and to date, no controlled data show that endoscopic therapy alters the natural history of the disease.

The possibility of an existing CCA should be considered in all patients with a dominant stricture. Up to 9% of patients with dominant strictures managed endoscopically are ultimately diagnosed with CCA. Brush cytology or biopsy should be obtained at the time of dilation in all patients.

Dilation of biliary strictures also can be performed percutaneously in patients in whom an endoscopic approach has been unsuccessful. These strictures may be approached more easily via the percutaneous route than via the endoscopic route. In addition, the percutaneous approach may also be beneficial before surgery to aid in the intraoperative placement of large-bore Silastic transhepatic stents. Morbidity for the percutaneous approach is higher when compared with endoscopic methods.

Operative Therapy

Surgical Resection

Surgical resection of the extrahepatic biliary tree is less commonly used now with the application of endoscopic therapy. In appropriately selected patients, resection of the extrahepatic biliary tract and hepatic duct bifurcation, which is frequently involved with a dominant stricture, may provide lasting relief from jaundice, may be used to exclude or diagnose CCA in a dominant biliary stricture, and may postpone the need for liver transplant.

Operative management entails resection of the extrahepatic biliary tree, including the hepatic duct bifurcation, which is frequently involved with a dominant stricture (Fig. 3). A cholecystectomy is performed if the gallbladder is still in place, and the distal common bile duct is divided at the level of the superior edge of the pancreas. Frozen sections are taken of each margin and of any suspicious areas to exclude the presence of CCA. If stents are planned for reconstruction, percutaneous stents can be placed before surgery to aid in the dissection of the hepatic bifurcation and to guide the exchange with larger Silastic stents at the time of surgery. Bilateral Roux-en-Y hepaticojejunostomies are created over these transhepatic stents, which are intended for removal approximately 1 year after placement if no obstruction exists at the anastomosis.

The overall morbidity rate after Roux-en-Y hepaticojejunostomy in PSC is 35%. Common complications include cholangitis, hemobilia, bile leak, and wound infection. Rarely, hepatic arterial bleeding related to the transhepatic stent has necessitated embolization for control. In a series of 40 patients without cirrhosis undergoing biliary reconstruction, the operative mortality rate was 2.5%.

Although used less frequently over the past decade, resection of the extrahepatic biliary tree in selected patients may delay the need for liver transplant. In a series of 77 patients followed for more than 5 years, the overall 3-year, 5-year, and 10-year survival rates after bile duct resection were 85%, 76%, and 53%, respectively. Patients without cirrhosis fared better with 1-year, 5-year, and 10-year survival rates of 95%, 83%, and 60%, respectively (Fig. 4). Furthermore, in comparison of outcomes of surgical resection with endoscopic intervention, overall survival for patients without cirrhosis managed with bile duct resection was significantly longer than for a group of 35 concurrent patients without cirrhosis managed with endoscopic balloon dilation (Fig. 5). Survival free of liver transplantation for the 40 patients who did not have cirrhosis at the time PSC was diagnosed was 95%, 92%, and 82% at 1, 3, and 5 years, respectively, after resection. This was also significantly better than transplant-free survival in patients undergoing endoscopic intervention. None of the patients with surgical resection developed CCA, with long-term follow-up exceeding 10 years, and only one patient (2%) needed a second operation for focal extrahepatic biliary obstruction and cholangitis.

Liver Transplant

Once cirrhosis develops, nonoperative biliary dilation or operative resection has little role in patient management because of the high morbidity. Complications of portal hypertension (e.g., variceal bleeding, ascites, hepatic encephalopathy, and recurrent cholangitis) are clear indications for liver transplant. Survival after hepatic transplant for PSC is similar to that for other end-stage liver disease. In several

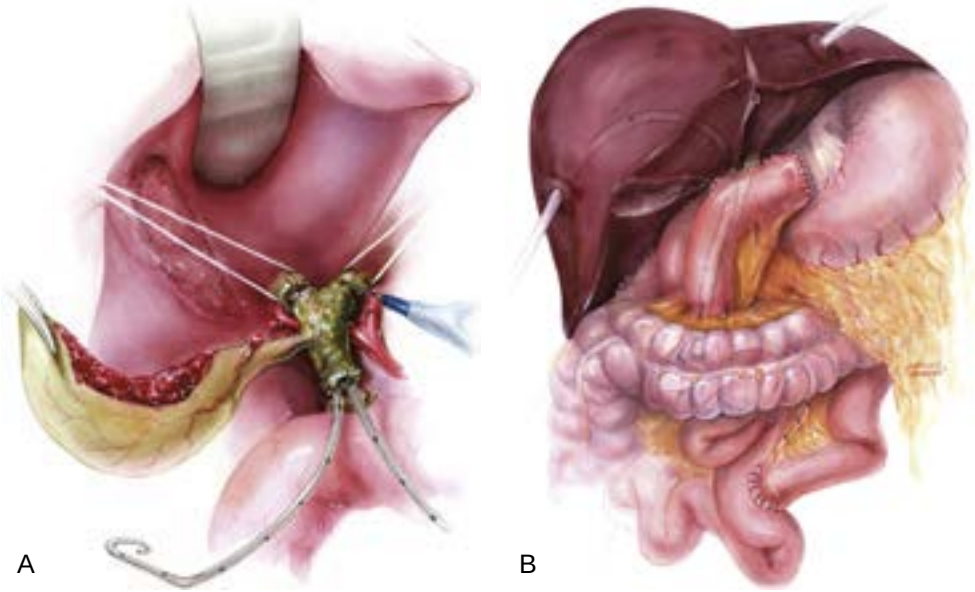


FIG. 3 **(A)** Resection of extrahepatic biliary tree with **(B)** reconstruction by Roux-en-Y hepaticojejunostomy over transhepatic biliary stents. *(Courtesy Corrine Sandone. From Cameron JL, Sandone C.* Atlas of Gastrointestinal Surgery, Vol 1, 2nd ed. *People's Medical Publishing; 2007.)*

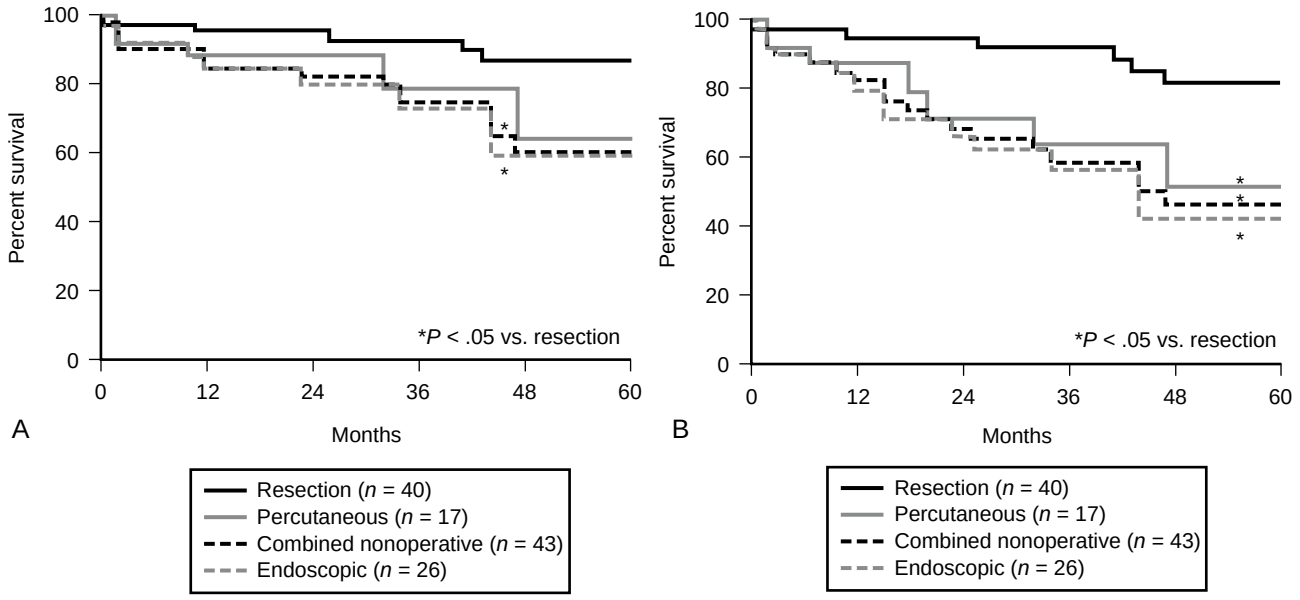


FIG. 4 **(A)** Overall and **(B)** transplant-free survival curves for noncirrhotic patients undergoing resection, endoscopic, and percutaneous treatment for dominant biliary strictures. *(From Ahrendt SA, Pitt HA, Kalloo AN, et al. Primary sclerosing cholangitis: resect, dilate, or transplant?* Ann Surg. *1998;227:412–423.)*

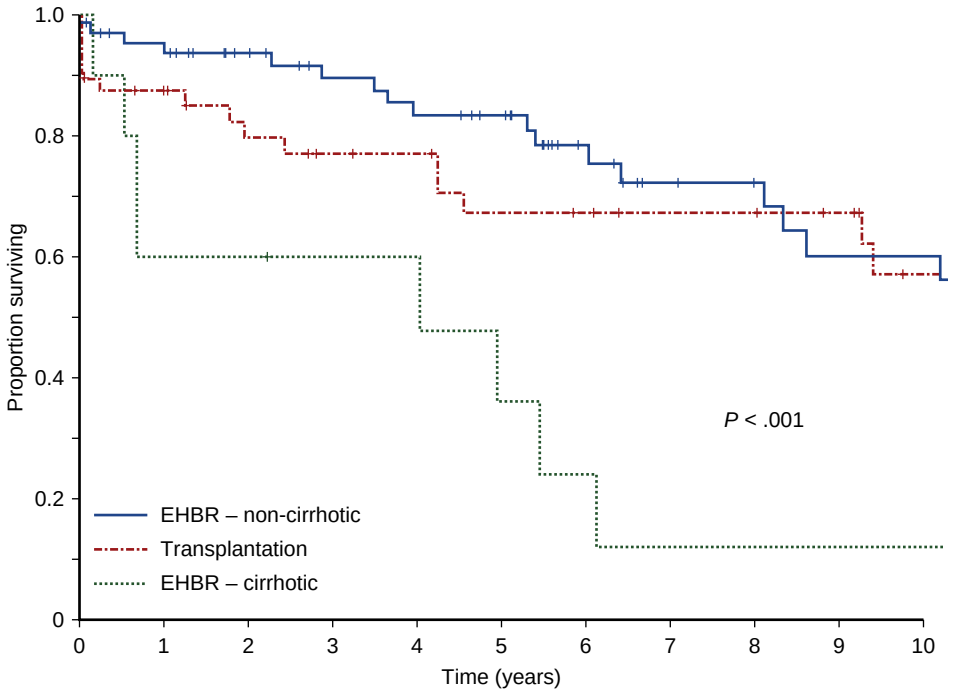


FIG. 5 Survival rates for noncirrhotic primary sclerosing cholangitis patients treated with extrahepatic biliary resection (EHBR) were similar to those treated with transplantation, whereas cirrhotic patients treated with EHBR has significantly worse survival. *(From Pawlik TM, Olbrecht VA, Pitt HA, et al. Primary sclerosing cholangitis: role of extrahepatic biliary resection.* J Am Coll Surg. *2008;206:822–832.)*

large series, 5-year patient and graft survival rates are approximately 70% to 80% and 60%, respectively. Patients with prior biliary tract or portal venous surgery do not appear to have increased hospital mortality after liver transplant. The development of CCA before liver transplant significantly affects the long-term outcome. In the combined University of Pittsburgh and Mayo Clinic experience, 11 of 216 patients had an unsuspected CCA, and the survival rate was only 47% at 2 years. Preoperative diagnosis of CCA before transplant remains difficult. Long-term survival has been reported with a neoadjuvant regimen of external and bile duct luminal radiation therapy with concurrent chemotherapy before liver transplant for perihilar CCA.

Another potential problem after transplant is recurrent sclerosing cholangitis. Nonanastomotic biliary strictures are more

common after liver transplant for PSC than for other diseases and have been diagnosed in up to 20% to 25% of patients within a median follow-up of 5 to 10 years after transplant. Male gender and the presence of intestinal inflammation after transplant in patients with IBD have been strongly associated with recurrent PSC in the transplanted liver.

SUMMARY

Medical therapy can improve liver function tests in patients with PSC but has not been proven to delay progression of disease to cirrhosis and the need for liver transplant, the development of CCA, or survival. Thus, patients managed medically should be included in clinical trials. Balloon dilation or stenting of dominant strictures has provided short-term symptomatic relief but has not been proven to improve survival and may, in fact, delay the diagnosis of CCA. Surgical resection of hilar and extrahepatic strictures in patients without cirrhosis may postpone or prevent the need for transplant in carefully selected patients. Surgical resection should be considered in patients particularly if CCA is suspected. Liver transplant is the treatment of choice for patients with PSC and cirrhosis. However, liver transplant has significant short-term and long-term morbidity and should not be used too early in the natural history of the disease.

Suggested Readings

Ahrendt SA, Pitt HA, Kalloo AN, et al. Primary sclerosing cholangitis: resect, dilate, or transplant?. *Ann Surg*. 1998;227:412–423.

Ahrendt SA, Pitt HA, Nakeeb A, et al. Diagnosis and management of cholangiocarcinoma in primary sclerosing cholangitis. *J Gastrointest Surg*. 1999;3:357–368.

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Management of Intrahepatic, Perihilar, and Distal Extrahepatic Cholangiocarcinoma

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INTRODUCTION

Cholangiocarcinomas, or bile duct cancers, originate from the epithelial lining of the biliary tree and encompass a diverse set of malignancies. Clinically, these are grouped according to anatomic location within the biliary tree: intrahepatic, perihilar (often referred to as *Klatskin tumors*), or distal extrahepatic; gallbladder cancer is commonly classified separately. Intrahepatic cholangiocarcinoma (ICC), which arises within the liver parenchyma, is the second most common primary liver tumor in the United States after hepatocellular carcinoma (HCC). Perihilar extrahepatic cholangiocarcinomas include tumors arising from the extrahepatic biliary tree proximal to the cystic duct. When gallbladder cancers are excluded, perihilar cholangiocarcinomas account for 60% to 70% of extrahepatic cholangiocarcinomas. Tumors involving the confluence of the right and left hepatic ducts are commonly termed *Klatskin tumors*. Distal extrahepatic cholangiocarcinomas include tumors centered in the extrahepatic biliary tree below the cystic duct. These are less common than perihilar tumors (account for approximately 30% of extrahepatic cholangiocarcinomas) and can be difficult to distinguish from other periampullary malignancies such as pancreatic ductal adenocarcinoma or ampullary adenocarcinoma. Lastly, cholangiocarcinomas commonly propagate longitudinally along the bile ducts, resulting in disease that can overlap these anatomic landmarks.

The overall incidence of cholangiocarcinoma has been increasing, though incidence varies by geographic location, reflecting the environmental and genetic risk factors. Incidences range from 113 per 100,000 person-years in Thailand, where liver flukes are endemic, to 0.5 to 1.5 per 100,000 person-years in the Western Hemisphere. Cholangiocarcinomas typically affect patients in the sixth or seventh decade of life and have a slightly higher predominance in men than in women. Most cholangiocarcinomas in Western populations are likely sporadic in nature. There have been several risk factors recognized across populations, including biliary tract disorders (such as primary sclerosing cholangitis), parasitic infections (such as liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* endemic in Southeast Asia), hepatic toxins, and hepatitis B or C infection. In addition, genetic polymorphisms, inflammatory bowel disease, choledochal cysts, cirrhosis, diabetes, obesity, hepatolithiasis, choledocholithiasis, and alcohol abuse have all been linked to cholangiocarcinoma. Some genetic syndromes that increase the risk of cholangiocarcinoma include Lynch syndrome, *BRCA*-associated protein-1 (BAP1) tumor predisposition syndrome, cystic fibrosis, and biliary papillomatosis.

The dominant histopathology is adenocarcinoma (90%), while the rest are squamous cell carcinomas and rarely adenosquamous cancers. Adenocarcinomas are graded as well, moderately, or poorly differentiated. The most common morphologic subtype is sclerosing cholangiocarcinoma, which is thought to extend in a subepithelial plane and cause thickening of the duct without an obstructing intraductal mass. These tumors can develop and grow without causing clinical symptoms, such that they are often detected at a stage that precludes curative-intent resection. Nodular cholangiocarcinoma also results in thickening of the duct, but the radial growth pattern of these tumors can lead to clinical symptoms of biliary obstruction and allow for diagnosis at an earlier stage for some patients. Papillary cholangiocarcinomas typically arise in the distal bile duct, characteristically forming a polypoid lesion that expands the lumen of the duct. In all subtypes, perineural and lymphovascular invasion of the locoregional structures are frequently seen.

The best chance for long-term survival and cure is surgical resection with negative margins. Like many solid tumors, both the radial margin around the tumor mass and the longitudinal margin of the biliary tree must be considered in surgical planning. Unfortunately, many patients with a cholangiocarcinoma are diagnosed at a late stage. It is estimated that only one-third of patients qualify for curative-intent resection. Even after surgical resection, disease recurrence is common, with 5-year survival ranging from 10% to 50% depending on anatomic location and disease stage.

INTRAHEPATIC CHOLANGIOCARCINOMA

Presentation and Preoperative Evaluation

Similar to other liver tumors, ICCs can develop in the absence of clinical symptoms. Therefore, some patients are diagnosed with ICC following incidental discovery of a liver mass during the workup of an unrelated problem. On the other hand, patients can also present with a variety of symptoms including abdominal pain, fatigue, weight loss, poor appetite, and fever. Similarly, physical examination can range from unremarkable findings to identification of a palpable abdominal mass, signs of jaundice, or other evidence of chronic liver disease. Rarely, patients may develop paraneoplastic dermatologic syndromes such as Sweet's syndrome, erythema multiforme, or porphyria cutanea tarda. Laboratory evaluation includes a liver chemistry panel, which may reveal elevated liver enzymes with an obstructive (direct) hyperbilirubinemia and an elevated alkaline phosphatase. Cancer antigen 19-9 (CA19-9) is the most likely tumor marker to be elevated, but it is neither highly specific nor sensitive for cholangiocarcinoma and can be falsely elevated in cholangitis or cholestasis. Workup should also include tumor markers that are associated with primary liver and gastrointestinal tumors such as alpha-fetoprotein (AFP) for HCC, carcinoembryonic antigen (CEA) for colorectal liver metastasis, and chromogranin-A for neuroendocrine tumors; immunoglobulin profiling is also warranted in patients with findings suspicious for autoimmune disease.

Cross-sectional imaging with liver-protocol magnetic resonance imaging (MRI) or liver-protocol multidetector computed tomography (CT) is the mainstay of diagnostic evaluation. These multiphase, contrast-enhanced imaging studies can aid in differentiating ICC from other primary liver lesions such as HCC, hepatic adenoma, or focal nodular hyperplasia. It is also useful for operative planning by identifying aberrant liver or biliary anatomy. Radiographic features of ICC vary depending on tumor type: mass-forming, periductal-infiltrating with intrahepatic ductal dilation, or mixed type. On liver-protocol CT imaging, ICC can appear as a well-defined or infiltrative hypodense lesion; other potential findings are upstream biliary dilation, capsular retraction, and rim enhancement throughout both arterial and venous phases. On liver-protocol MRI, ICC can appear as a hypointense lesion on T1-weighted images and a heterogeneously hyperintense lesion on T2-weighted images. Primary liver cancers can also exhibit a mixed histologic subtype with features of ICC and HCC. These mixed tumors, which are considered a subtype of ICC for staging and treatment, often appear as an irregular mass with rim enhancement on gadoxetic acid–enhanced MRI, whereas mass-forming ICCs appear as lobulated lesions with a weak rim and a target appearance.

Although percutaneous biopsy is commonly used to establish a diagnosis of ICC, patients with "classic" history, physical examination, laboratory, and diagnostic imaging findings of ICC may not require biopsy. It is also critical to consider whether a liver mass suspicious for ICC represents metastatic disease from a gastrointestinal or other malignancy. In these instances, a search for the primary tumor can include upper and lower endoscopy, chest imaging or bronchoscopy, and mammography in female patients. Positron emission tomography (PET) may also be helpful in staging, although it is not necessary for all patients. Surgeons should consider staging laparoscopy during the workup or at the time of planned surgical resection to evaluate for radiographically occult peritoneal metastasis.

Surgical resection is the primary treatment modality for patients with localized disease, as summarized by guidelines from the National Comprehensive Cancer Network (NCCN). Characteristics of disease that preclude resection include metastatic disease on preoperative staging, lymph node metastasis beyond the porta hepatis, or identification of radiographically occult metastasis at the time of surgical exploration. Although disease spread to locoregional (porta hepatis) lymph nodes is not a contraindication to resection, the prognosis of patients with gross disease in this location is generally poor. Likewise, patients with multifocal hepatic disease are at increased risk for systemic disease and should be considered for systemic therapy before undergoing curative-intent surgery. Other adverse prognostic factors include identification of satellite lesions and the presence of portal hypertension. Lastly, tumors should be classified as unresectable when the mass involves the vascular inflow or outflow of the future liver remnant (FLR).

An assessment of liver volume and hepatic function should be performed as part of preoperative planning. Technical resectability is defined as the ability to completely remove the disease while preserving FLR. The volume of the FLR may be estimated from cross-sectional imaging in patients undergoing minor hepatectomy, whereas more quantitative volumetrics should be considered when major hepatectomy is planned to aid in preoperative risk assessment. An FLR of at least 20% to 40% of normal hepatic parenchyma (two consecutive Couinaud segments) should be maintained postresection with an intact arterial and portal inflow, hepatic venous outflow, and biliary enteric drainage. If cirrhosis is present or suspected, the FLR needed is increased, with most surgeons targeting 40% to 50%. The Child-Turcotte-Pugh score and the Model for End-Stage Liver Disease (MELD) score are commonly used to indirectly assess liver function and degree of cirrhosis. Direct hepatic functional assessment using a variety of techniques, including indocyanine green kinetics, is also selectively used when considering major hepatectomy.

In preparing for surgical resection, preoperative global functional assessment is ideal given the morbidity (20%–40%) and mortality (2%–5%) of major hepatic resections in this patient population. Common tools used for functional assessment include the Eastern Cooperative Oncology Group performance status (range: 0–5), the G-8 geriatric screening tool (range: 0–17; score of 14 or less identifies at-risk individuals), and the American College of Surgeons Surgical Risk Calculator (http://riskcalculator.facs.org).

Staging

Historically, staging systems for ICC were identical to those used for HCC. These systems were based on tumor size, number of tumors, tumor invasion into major vessels or other structures, and metastasis. However, the American Joint Committee on Cancer (AJCC) introduced a separate tumor-node-metastasis (TNM) staging system for ICC in 2010. In the most recent version, the eighth edition released in 2017, there is improved prognostic capacity, particularly in the ability to separate survival between patients with T1 and T2 disease from those with T3 disease. The T1 category is for solitary tumors without vascular invasion, whereas the T2 category now accounts for the prognostic values of vascular invasion and tumor multifocality. Patients with tumors perforating the visceral peritoneum are classified as T3, and those with tumors involving extrahepatic structures by direct invasion are classified as T4. Despite the refinement in the setting for ICC, it is important to note that survival across several intermediate stages (e.g., stage IB, II, and IIIA) are similar.

Management

Surgical Resection

Liver resection achieving negative margins offers the only chance for cure and should be attempted in the cohort of patients who are otherwise healthy and share goals of care that are in line with aggressive surgical management. Historically, curative resection with negative margins was achieved in less than 30% of patients. This number appears to be improving as advances in preoperative imaging,

intraoperative ultrasound, and resection techniques continue to evolve. Portal lymphadenectomy is recommended, as these lymph nodes are positive in approximately one-third of patients. The therapeutic benefit of lymphadenectomy is controversial, but it provides important prognostic value. Therefore, guidelines from the NCCN and the Americas Hepato-Pancreato-Biliary Association (AHPBA) recommend the removal of hilar lymph nodes as part of the radical surgery for ICC; the AJCC guidelines recommend a minimum of six lymph nodes for staging. There is at least one ongoing randomized controlled trial evaluating the role of extended lymphadenectomy (stations 12, 8, and 13 for right-sided tumors; stations 12, 1, 3, 7, and 8 for left-sided tumors) versus portal lymphadenectomy (station 12 only) in ICC.

Extent of resection depends on tumor size and location as well as the anticipated volume and function of the liver following surgery. Therefore, the procedure can range from minor hepatectomy such as nonanatomic "wedge" resection or anatomic segmental resection for small or peripheral tumors to major hepatectomy such as lobar resection or even extended hepatectomy for large or central tumors. In patients in whom the FLR is felt to be inadequate, preoperative percutaneous embolization of the ipsilateral portal vein can result in compensatory hypertrophy of the contralateral liver. Potential benefits of portal vein embolization include a reduced risk of perioperative morbidity related to post-hepatectomy liver insufficiency and decreased rate of mortality related to post-hepatectomy liver failure. Likewise, surgeons should avoid major hepatectomy in patients who do not respond to the portal vein embolization. Similarly, a two-stage surgical procedure termed *associating liver partition and portal vein ligation for staged hepatectomy* (ALPPS) can be considered. In this approach, the ipsilateral portal vein is ligated, and the liver parenchyma is transected at the first-stage operation. This technique can result in rapid hypertrophy of the liver remnant, such that a second-stage operation to complete the liver resection can be performed within 2 weeks. Major liver resection combined with portal vein and/or vena cava resection and reconstruction has been performed safely in highly selected patients who are otherwise healthy, but these operations should only be performed in high-volume or liver transplantation centers.

The technical aspects of liver surgery vary based on patient factors and surgical experience. For example, diagnostic laparoscopy should be considered if there is concern for advanced cancer. Even when localized cancer is suspected, it is prudent to assess for peritoneal carcinomatosis or multifocal disease before proceeding with liver resection. Major liver surgery is commonly performed in a traditional "open" approach. In an open surgical approach, the surgeon should select an incision to provide adequate exposure of the entire liver. This is commonly achieved with a right subcostal incision, which can be extended vertically along the midline or continued transversely across to the left subcostal region. The liver can also be exposed via a midline incision, especially when there is a prior midline incision or when liver resection is combined with another abdominal procedure. It is important to acknowledge, however, that interest in minimally invasive (i.e., laparoscopic or robot-assisted) approaches is growing as experienced, high-volume surgeons report safe outcomes. Whichever the preferred approach, the principles of liver surgery are similar. We outline a common approach for open hemi-hepatectomy.

As discussed earlier, surgery should begin with evaluation of the peritoneum and liver to assess for advanced malignancy. The liver is then mobilized by dividing the ligamentum teres and incising the Falciform, coronary, and triangular ligaments. The right liver can then be mobilized along its diaphragmatic and retroperitoneal attachments. When right hemi-hepatectomy is planned, the hepatocaval ligament is ligated and divided. In addition to visual inspection and manual palpation, intraoperative ultrasound is useful in defining the liver anatomy, localizing the tumor mass, and detecting additional liver lesions. If the tumor is amenable to surgical resection, cholecystectomy is performed to better expose the cystic plate and liver hilum. Lymph nodes within the porta hepatis are excised. Whenever possible, the surgeon should strive for extrahepatic vascular control before performing parenchymal transection. The ipsilateral hepatic artery and portal vein branches are encircled, test-clamped to confirm perfusion to the contralateral liver, and divided once ischemia is noted in the ipsilateral liver. A Rumel tourniquet can be positioned around the hilar vasculature in preparation for temporary vascular inflow occlusion, often termed a *Pringle maneuver,* should it become necessary. Although this technique varies among surgeons, a common strategy is to compress the vascular inflow to the liver for up to 15 minutes followed by reperfusion for at least 5 minutes. The ipsilateral hepatic vein can also be isolated, although this is typically not ligated before parenchymal transection.

Following extrahepatic vascular control, the liver parenchyma is scored along the plane of transection, which should coincide with the liver demarcation or ipsilateral border of the middle hepatic vein. The liver can then be divided using a variety of techniques including ultrasonic dissection, the clamp-crush method, or stapled transection. From a practical standpoint, surgeons often use a combination of these approaches based on the specific situation. The ipsilateral hepatic duct is exposed during transection of the liver parenchyma; this is often divided with a linear stapler. Lastly, the ipsilateral hepatic vein is ligated, and the liver specimen is submitted for pathologic evaluation (Fig. 1).

Once the liver resection is completed, hemostasis can be achieved with direct pressure, thermal devices, Prolene sutures, or topical hemostatic agents, as needed. The liver should be assessed for bile at the hepatic duct staple line or along the parenchymal surface; bile leaks can be managed with surgical clips or Prolene sutures. Following right hemi-hepatectomy, the left liver should be resuspended

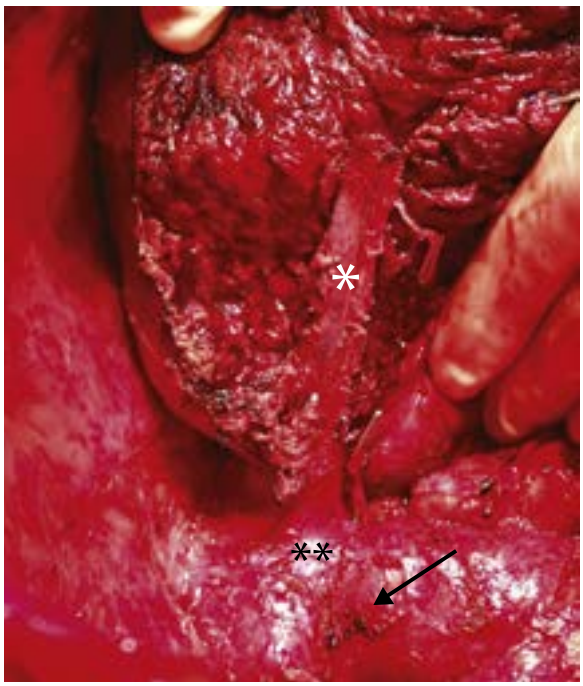


FIG. 1 Liver remnant following right hemi-hepatectomy for intrahepatic cholangiocarcinoma. Parenchymal transection is performed along the right side of the middle hepatic vein *(white asterisk)* until its insertion into the inferior vena cava *(black asterisks);* the right hepatic vein is ligated *(arrow)*.

along the Falciform ligament to decrease the risk of postoperative torsion of the hepatic veins. Lastly, placement of a closed-suction drainage catheter should be considered, especially when there is significant concern for postoperative bile leak (e.g., persistent leak despite attempts to repair, biliary-enteric reconstruction) or severe complications related to a bile leak are anticipated (e.g., diaphragm reconstruction, inability to place a percutaneous drain postoperatively).

Other Treatments

Many patients with ICC present with unresectable tumors, and a large subset of patients who undergo curative-intent surgical resection will develop local recurrence within the liver. These patients should be considered for systemic therapy but may also benefit from liver-directed therapy. Whether a patient is deemed to have an unresectable tumor based on poor functional status, severe chronic liver disease, inadequate FLR, or anatomic factors, the patient may still be a candidate for external beam radiotherapy, transarterial therapy, or ablation. In this setting, radiation is often administered with a fluoropyrimidine radiosensitizer. Options for arterially directed therapies include transarterial chemoembolization (TACE) with either lipiodol or doxorubicin-eluting beads and selective internal radiation therapy (SIRT) with transarterial delivery of yttrium-90-tagged microspheres. These approaches are appealing as the tumor derives most of its blood supply from the hepatic artery, whereas the liver parenchyma is largely perfused by the portal vein. On occasion, large unresectable tumors become amenable to surgical resection following TACE or SIRT. Ablative techniques for ICC include thermal ablation (i.e., radiofrequency, cryoablation, or microwave), percutaneous ethanol injection, and irreversible electroporation. Several limited studies have demonstrated the safety and efficacy of these local therapies, but there are no high-quality data to support the use of one approach over another in ICC.

Despite interest in liver transplantation for patients with unresectable ICC, this approach is not as widely accepted as it is for patients with HCC. However, transplantation may be considered in the context of a clinical trial for highly selected patients with severe liver disease or primary sclerosing cholangitis. These protocols usually require patients to receive chemotherapy and undergo comprehensive testing to rule out metastatic disease before transplantation. Reports of long-term survival in these cohorts of patients are encouraging, although generalizability is limited because of the restrictive selection criteria and inclusion of patients with perihilar extrahepatic cholangiocarcinoma.

Following curative-intent surgery, long-term survival rates generally range between 25% and 50% depending on stage. Even patients who undergo margin-negative resection without evidence of lymph node or distant metastasis have at least a 40% risk of recurrence. Therefore, adjuvant therapy should be considered following surgery. This is especially true for patients with incomplete resection or with lymph node metastasis as these features are associated with poorer prognosis. The BILCAP study was a randomized phase III trial of single-agent capecitabine versus placebo that identified clinically meaningful benefit in overall survival in the per-protocol analysis, although the benefit was not statistically significant in an intention-to-treat analysis. Other options for adjuvant therapy include fluoropyrimidine- and gemcitabine-based chemotherapy regimens or fluoropyrimidine-enhanced chemoradiation. Although high-quality data are lacking, the ongoing ACTICCA-1 trial is comparing single-agent capecitabine to multi-agent gemcitabine plus cisplatin to better define the optimal adjuvant chemotherapy regimen for resected biliary tract cancers. Similarly, there is ongoing research in the use of neoadjuvant (or perioperative) chemotherapy for cholangiocarcinoma, especially in clinical situations in which surgical resection may not be feasible or early postoperative recurrence is suspected.

HILAR CHOLANGIOCARCINOMA

Presentation and Preoperative Evaluation

Patients diagnosed with hilar cholangiocarcinoma most commonly present with obstructive jaundice, as a classic sign or symptom of hyperbilirubinemia (e.g., jaundice or pruritus) is present in up to 90% of patients. Other common symptoms at presentation include abdominal pain, fatigue, weight loss, and anorexia, although these are nonspecific. Less commonly, patients have abnormal laboratory results or experience vague symptoms and undergo testing that identifies hilar cholangiocarcinoma. Despite the potential for "early" diagnosis based on clinically apparent symptoms, the anatomic proximity of critical vascular structures within the liver hilum may still preclude resection.

Once hilar cholangiocarcinoma is suspected, a thorough evaluation is essential. This typically includes high-quality cross-sectional imaging with CT of the chest, abdomen, and pelvis. MRI is also commonly used to assess the liver, while magnetic resonance cholangiopancreatography (MRCP) can provide anatomic details of the biliary tract malignancies. In the absence of a need for biliary decompression or tissue biopsy, MRCP has been shown to be equivalent to endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of hilar cholangiocarcinoma. Chest imaging is used to rule out distant spread (i.e., pulmonary or mediastinal lymph node metastasis), whereas abdominal imaging aids in determining the extent of the primary tumor, assessing the regional lymph nodes, and evaluating for peritoneal, liver, or extraregional lymph node metastasis. In terms of the primary tumor, it is important to note the intrahepatic and extrahepatic sequelae of the tumor including biliary ductal dilation, hepatic atrophy, invasion and/or occlusion of hilar vessels, and portal lymphadenopathy. These tumors are more likely to invade the right hepatic artery than the left hepatic artery based on the anatomic proximity of the right hepatic artery and the ductal confluence.

Laboratory testing should include assessment of the patient's liver function and tumor markers. Abnormal liver function tests or viral hepatitis panel should be considered in treatment planning. Serum CA19-9 and CEA are the most useful tumor markers, but their sensitivity and specificity can vary widely. Therefore, these tests should not be used to diagnose cholangiocarcinoma as they can be elevated in patients with non-malignant biliary strictures and normal in patients with biliary cancers. Nonetheless, markedly elevated tumor markers may denote more advanced disease in patients with cholangiocarcinoma. Tissue diagnosis via endobiliary or percutaneous biopsy is the standard for diagnosis of cholangiocarcinoma. However, it is often difficult to obtain sufficient material for diagnosis, and negative biopsies cannot rule out malignancy. For these reasons, biopsy is not necessary if other clinical data are highly suggestive of hilar cholangiocarcinoma.

The approach to disease in the hilum mimics that for ICC, with resection as a primary modality when technically achievable. Clinical factors that should preclude resection include severe chronic liver disease (e.g., cirrhosis, primary sclerosing cholangitis) and the presence of distant metastasis. Furthermore, several features of the primary tumor are classified as unresectable including (1) main portal vein involvement not amenable to reconstruction, (2) bilateral hepatic artery and/or portal vein branch involvement, (3) bilateral tumor extension to secondary biliary radicals, and (4) unilateral tumor extension to secondary biliary radicals with contralateral hepatic artery and/or portal vein branch involvement (Box 1). Likewise, insufficient volume of the anticipated FLR may prevent safe resection. Therefore, surgeons must carefully review these clinical factors to guide patient selection for curative-intent surgical resection.

Preoperative preparation for patients undergoing resection of hilar cholangiocarcinoma is often complex and requires careful planning. The underlying principle of curative-intent surgery is to

BOX 1 Anatomic Criteria of Unresectability for Perihilar Cholangiocarcinoma

- Hepatic duct involvement up to secondary biliary radicals bilaterally
- Encasement or occlusion of the main portal vein proximal to its bifurcation*
- Atrophy of one hepatic lobe with contralateral encasement of portal vein branch
- Atrophy of one hepatic lobe with contralateral involvement of secondary biliary radicals
- Tumor extension to secondary biliary radicals with contralateral portal vein encasement or occlusion

*Relative criterion; Portal vein resection and reconstruction may be possible. Modified from Jarnigan WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg.* 2001;234:507.

completely remove all tumor with negative margins, often termed *R0 resection.* As historical data have demonstrated that R0 rates are improved with radical resection including concomitant hepatectomy, the standard of care is for liver resection in conjunction with removal of the extrahepatic biliary tree and bilioenteric reconstruction. For patients with hyperbilirubinemia undergoing surgery for hilar cholangiocarcinoma, preoperative biliary drainage is felt to facilitate postoperative liver regeneration. This practice has been associated with a reduction in overall surgical complications, although preoperative biliary drainage is associated with increased perioperative infection. Currently, there is debate regarding optimal preoperative management of hyperbilirubinemia. Surgeons frequently favor biliary drainage for patients with bilirubin levels greater than 7 to 10 mg/dL with a goal of achieving a bilirubin level less than 2 to 3 mg/dL, especially when a major hepatectomy is planned or the FLR is anticipated to be less than 30%; in these patients, improving regenerative capacity of the liver outweighs the associated infectious complications. Both endobiliary stents and percutaneous transhepatic biliary drainage catheters can be used to relieve hepatic congestion. Although debate over the optimal approach continues (especially with advancement in endoscopic biliary intervention), percutaneous transhepatic biliary drainage remains a reasonable choice for patients with resectable hilar cholangiocarcinoma.

Before surgery, all patients should undergo a thorough assessment of their general functional status and careful review of any chronic medical conditions to stratify their perioperative risk. Patients judged to be at increased risk may benefit from preoperative optimization to improve their likelihood of tolerating a major surgical procedure, whereas patients at prohibitive risk should be considered for nonsurgical treatments. Likewise, surgeons should plan for major hepatectomy as part of the operative approach to hilar cholangiocarcinoma because of frequent intrahepatic or vascular involvement. Therefore, both the size and function of the FLR should be carefully assessed. Portal vein embolization, as described earlier in the discussion of the management of ICC, should be considered for patients who are estimated to have an FLR less than 20% to 30%.

Staging

The three most commonly used staging systems for hilar cholangiocarcinoma are the Bismuth-Corlette classification, AJCC TNM staging, and the Blumgart system. Bismuth and Corlette published one of the first anatomic classification systems for hilar cholangiocarcinoma. Based on tumor location and ductal infiltration, tumors are classified into four categories with type I confined to the common hepatic duct, type II involving confluence of the right and left hepatic ducts, type III extending into either the right hepatic duct (type IIIA) or the left hepatic duct (type IIIB), and type IV involving both the right and left hepatic ducts (Fig. 2). This system is useful for stratifying patients based on the extent and location of tumor involvement within the biliary tree, but it does not provide other useful information (such as vascular involvement, extent of liver disease, or sites of metastasis) to determine resectability or inform survival. The 8th edition of the AJCC staging system has several advantages over the Bismuth-Corlette classification and is used most widely. It considers factors of the primary tumor (T category) such as depth of tumor invasion and involvement of adjacent structures, the regional lymph nodes (N category), and metastasis to distant sites (M category). This system provides valuable prognostic information and can guide treatment planning, but it is limited in its ability to determine resectability. Conversely, the modified Blumgart system can better predict resectability by expanding the anatomic features of the Bismuth-Corlette classification to include the tumor's radial involvement of hilar vascular structures and presence or absence of hepatic atrophy (Table 1). Increased stage across this three-tier system has been associated with decreased likelihood of R0 resection and poorer survival.

Management

Surgical Resection

Surgical resection is the best chance of cure and long-term survival. However, these procedures are technically challenging as resection of the extrahepatic biliary tree with en bloc hepatectomy is typically required. Occasionally, pancreaticoduodenectomy is also necessary to enable R0 resection. Liver transplantation is even considered for select patients in whom surgical resection is unlikely to achieve negative margins. Studies have shown that up to 40% of patients may have metastatic or unresectable disease at the time of exploration, such that some surgeons routinely perform a diagnostic laparoscopy before proceeding with laparotomy.

Exposure can be achieved via a variety of approaches ranging from right subcostal incision (often with midline extension), bilateral subcostal incision, or midline incision depending on surgeon preference and/or patient body habitus. Even if a diagnostic laparoscopy

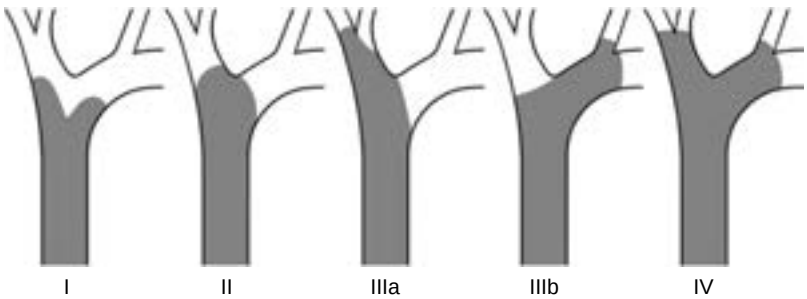


FIG. 2 Bismuth-Corlette classification of perihilar cholangiocarcinoma. Type I, tumors located distal to hepatic confluence. Type II, tumors involving the confluence. Type IIIa, tumors involving the confluence and right hepatic duct. Type IIIb, tumors involving the confluence and the left hepatic duct. Type IV, tumors involving both right and left hepatic ducts. *(From DeOlveria ML, Schuluck RD, Nimura T, et al. New staging system and a registry for perihilar cholangiocarcinoma.* Hepatology. *2011;53:1363–1371.)*

TABLE 1 Modified Blumgart Clinical Staging System for Perihilar Cholangiocarcinoma

T1	Tumor involving the biliary confluence ± unilateral extension into second-order biliary radicals
T2	Tumor involving the biliary confluence ± unilateral extension to second-order biliary radicals and ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving the biliary confluence with bilateral extension to second-order biliary radicals; or unilateral extension to second-order biliary radicals with contralateral portal vein involvement; or unilateral extension to second-order biliary radicals with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement

From Jarnigan WR, Fong, Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg*. 2001;234(4): 507–519.

has been performed, it is advisable to inspect the peritoneal surfaces and palpate the liver to assess for metastatic disease. Suspicious lesions should be submitted for biopsy and intraoperative pathologic evaluation. If there is no evidence of disseminated cancer, the surgeon may proceed with the operation according to preference and the specific aspects of the patient's tumor. One common approach is outlined briefly herein.

The dissection begins along the hepatoduodenal ligament to expose the portal structures in keeping with the principles of an anatomic regional lymphadenectomy. The lymph nodes and other extravascular soft tissue may be left en bloc with the eventual surgical specimen throughout this portion of the procedure. A Kocher maneuver is used to mobilize the duodenum and pancreatic head out of the retroperitoneum, such that the surgeon can assess for extraregional lymph node metastasis along the aortocaval space and for direct tumor extension into the pancreatic head. If surgical resection is to be performed, the distal common bile duct is divided at the level of the pancreas with a margin sent for frozen section. This assists in operative planning by determining if a pancreaticoduodenectomy is necessary to achieve negative margins. Next, the bile duct is reflected anteriorly, and the portal vein and hepatic artery are dissected free and assessed for tumor involvement. The gallbladder may be removed at this time or maintained for use in retraction. Resectability is determined by evaluating the hepatic artery, portal vein, and branches of these vessels. As previously mentioned, tumors are deemed unresectable in the event of nonreconstructible main portal vein involvement, bilateral hepatic artery involvement, unilateral involvement of the hepatic artery or portal vein with anticipated tumor extension into the contralateral biliary tree, or tumor involving the distal common bile duct at the level of the pancreas (if the patient would not tolerate concomitant pancreaticoduodenectomy with liver resection). It must be stated again that preoperative risk stratification, surgical planning, patient counseling, and intraoperative judgment are all critical to achieving optimal outcomes. This is particularly true as the surgical risks increase as more advanced technical maneuvers are required of the operating surgeon, who is often unable to accurately predict whether the tumor extends bilaterally to the secondary biliary radicals before committing to operative extirpation.

If the tumor is deemed unresectable, local excision of the bile duct should be completed at this time (if feasible) with creation of a Roux-en-Y hepaticojejunostomy for palliation. However, if the tumor is deemed resectable, the surgeon should proceed with hilar resection in the context of hepatectomy. The choice of hepatectomy (right vs. left, standard vs. extended) is informed by preoperative staging but ultimately dictated by intraoperative findings. Caudate resection is typically performed for all patients with hilar disease. Once the extent of liver resection is determined, the ipsilateral hepatic artery and portal vein branches are ligated extrahepatically, and the liver specimen should demarcate. The liver parenchyma is transected using any of the various techniques mentioned earlier. Many surgeons divide the liver and ligate the ipsilateral hepatic vein before they transect the contralateral hepatic duct. As mentioned earlier, the intrahepatic bile duct margin is typically not assessed until after the majority of the procedure is completed. The bile duct margin should be assessed by frozen section if there is an option to excise additional tissue in an attempt to achieve negative margins.

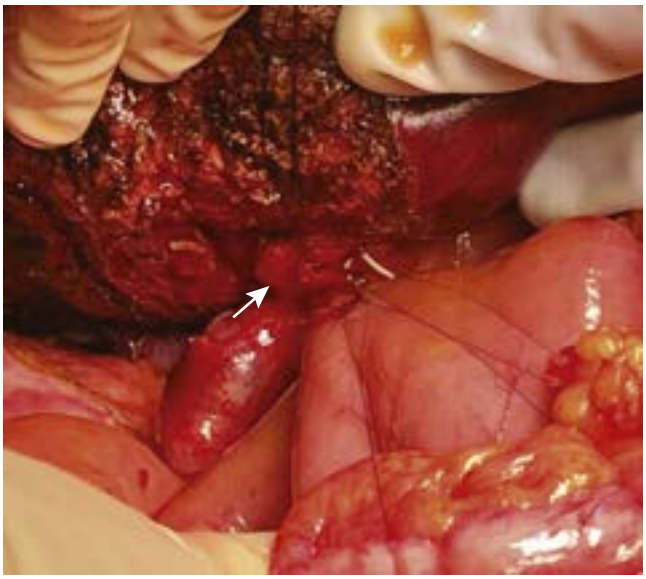


FIG. 3 Biliary-enteric reconstruction following resection of perihilar cholangiocarcinoma. Tension-free reconstruction of the liver remnant via Roux-en-Y hepaticojejunostomy *(arrow)* following resection of the extrahepatic biliary tree and involved liver for perihilar cholangiocarcinoma.

There are reports of extrahepatic biliary tree resection without hepatectomy (or with limited liver resection), although this is for select cases of hilar cholangiocarcinoma without vascular involvement and tumor extension into the secondary biliary radicals. When such an attempt at limited resection is performed, both the right and left hepatic duct margins should be assessed by frozen section to ensure complete resection of the patient's tumor before leaving the operating room as data suggest an increased risk of incomplete resection (higher R1 resection rate) with this approach.

Following resection, a portion of jejunum is selected for biliary-enteric reconstruction. This often requires Roux-en-Y reconstruction to allow adequate length for tension-free hepaticojejunostomy (Fig. 3). When more than one biliary radical requires reconstruction, the surgeon may consider joining two adjacent lumens with sutures to make a common wall and enable creation of a single anastomosis. If the patient underwent preoperative biliary decompression with a percutaneous transhepatic biliary drainage catheter, this may be placed across the anastomosis into jejunum. Given the risk of bile

leak from the liver parenchyma or biliary-enteric reconstruction, surgical drains are commonly used.

Additional Treatments

Following curative-intent resection, patients should be reviewed by a multidisciplinary team or evaluated by a medical oncologist. Adjuvant chemotherapy is typically recommended for patients following R0 resection with options ranging from single-agent capecitabine to multi-agent fluoropyrimidine- or gemcitabine-based regimens (similar to those used for ICC). On the other hand, concurrent chemoradiation (or multi-agent chemotherapy followed by radiation) is typically offered to patients with positive margins, as per the 2019 American Society of Clinical Oncology (ASCO) guidelines; a similar approach is considered for patients with lymph node metastases. Neoadjuvant or perioperative chemotherapy is now being considered for patients with hilar cholangiocarcinoma, especially those with high-risk features (e.g., markedly elevated tumor markers, suspicious portal lymph nodes) or imaging findings suggestive of close margins. Enrollment in clinical trials should be encouraged for these patients.

There are several treatment options for patients with unresectable hilar cholangiocarcinoma. Therefore, patients should be encouraged to undergo multidisciplinary evaluation at a high-volume center that offers a range of therapies. Although studies are limited, there is a growing experience with liver transplantation for patients with hilar cholangiocarcinoma. This approach is typically considered for patients with unresectable, localized cancer following neoadjuvant chemoradiation. Initial data demonstrate that long-term survival is possible in this highly selected cohort. In fact, the most recent consensus-based guideline from the NCCN includes that referral to a transplant center should be considered for patients with unresectable tumors without evidence of intrahepatic, lymph node, or distant metastasis. Other treatment options include systemic chemotherapy, chemoradiation, clinical trials, and supportive care. These patients often require biliary decompression and subsequent stent or catheter exchanges to prevent recurrent hyperbilirubinemia. Lastly, there are several emerging nonsurgical local therapies for patients who are not candidates for surgical resection or are awaiting liver transplantation. Delivery of intraluminal thermal energy, most commonly radiofrequency ablation administered via either percutaneous or endoscopic approaches, is being explored as an option to treat the tumor and palliative biliary obstruction. Similarly, photodynamic therapy has gained popularity at some centers. This method of brachytherapy involves intravenous administration of a photosensitizing agent, which accumulates in cancer cells. Next a nonthermal laser is used to deliver light of an appropriate wavelength within the biliary tree, thereby generating free oxygen radicals that lead to tumor cell death. Photodynamic therapy has been shown to palliate malignant biliary strictures and may improve survival in patients with hilar cholangiocarcinoma.

DISTAL CHOLANGIOCARCINOMA

Presentation and Preoperative Evaluation

Patients with distal cholangiocarcinoma commonly present with painless jaundice and other associated abdominal symptoms including nausea, anorexia, fatigue, and weight loss. It is not surprising that these tumors centered below the cystic duct lead to similar symptoms as the perihilar tumors centered above the cystic duct. On physical examination, a markedly distended gallbladder may be palpable, often termed *Courvoisier's sign.* Laboratory testing typically reveals elevated liver enzymes and hyperbilirubinemia; a total bilirubin greater than 10 mg/dL is highly suggestive of a malignant process. When an autoimmune process is considered, serum IgG4 testing can be useful. Tumor markers, most notably serum CA19-9 and serum CEA, should also be evaluated.

Initial workup may include abdominal ultrasonography, which typically reveals both intrahepatic and extrahepatic biliary ductal dilation as well as a distended gallbladder. This contrasts with the intrahepatic biliary ductal dilation and nondilated extrahepatic biliary tree seen in patients with hilar cholangiocarcinoma. In addition, a periampullary mass may be seen on ultrasound examination. Whether or not an ultrasound examination is performed, cross-sectional imaging with CT or MRI is critical to determine the extent of the tumor, identify invasion of surrounding structures, and assess for metastasis. These studies should include both arterial and venous phases to evaluate the adjacent vascular structures and reveal any anatomic variants. Chest imaging should also be performed to assess for pulmonary or mediastinal metastases. It can be challenging to distinguish distal cholangiocarcinoma from other periampullary malignancies, especially those arising from the pancreas or ampulla of Vater. Pancreatic atrophy or pancreatic ductal dilation may be present based on location of the tumor, although these findings are more commonly suggestive of pancreatic cancer.

Though not always necessary, invasive studies such as ERCP with endoscopic ultrasound may be utilized to further characterize the tumor and obtain a tissue diagnosis. These tumors can be very small and difficult to characterize on imaging, such that patients may not have a definitive diagnosis until after undergoing surgical resection. In cases of cholangitis or severe hepatic congestion, placement of an endobiliary stent can provide therapeutic biliary decompression. However, preoperative instrumentation of the biliary tree increases the risk of perioperative infectious complications. As major liver resection is very rare in the surgical management of distal cholangiocarcinoma (in contrast with hilar cholangiocarcinoma), routine biliary stenting is discouraged. Preoperative assessment should evaluate the patient's ability to tolerate a pancreaticoduodenectomy (Whipple procedure) as isolated resection of the extrahepatic biliary tree with biliary reconstruction is rarely feasible.

Staging

Distal cholangiocarcinoma is most often staged using the AJCC TNM system. As with hilar cholangiocarcinoma, the AJCC 8th edition classifies the primary tumor (T category) based on depth of invasion and involvement of adjacent vascular structures, the regional lymph nodes (N category) based on number of lymph nodes with metastasis, and the presence or absence of distant metastasis (M category). Surgeons should strive to remove at least 12 lymph nodes, in line with guidelines for pancreatic cancer.

Management

Surgical Resection

The goals of surgery include removal of the tumor, palliation of biliary obstruction, and accurate pathologic staging. As with cholangiocarcinoma in other locations, surgeons should begin with a thorough assessment to rule out metastatic disease. Although the risk of radiographically occult metastasis is low (typically less than 10%) in patients with distal cholangiocarcinoma, some surgeons routinely perform diagnostic laparoscopy, whereas others use it selectively for patients with high-risk features (e.g., indeterminate radiographic findings, markedly elevated serum tumor markers). Any suspicious lesions are submitted for biopsy and intraoperative pathologic evaluation. Next, resectability is assessed by evaluating for tumor invasion into the hepatic artery or the superior mesenteric vein–portal vein axis; if the tumor involves these structures, vascular reconstruction can be considered in select patients if technically feasible. As mentioned earlier, surgeons should plan to perform pancreaticoduodenectomy in the majority of cases. The procedure may be performed using a traditional open approach via midline incision or a minimally invasive approach using laparoscopic and/or robotic instrumentation. Surgeons often perform the critical steps of a pancreaticoduodenectomy in different ways, but one common approach is detailed in the following text.

After ruling out metastatic disease, the distal common bile duct, duodenum, and pancreatic head are evaluated by entering the lesser sac and completing a wide Kocher maneuver. The superior mesenteric artery is assessed by palpating the structure posteriorly, whereas the superior mesenteric vein is exposed along the inferior border of the pancreatic neck. If there is no evidence of tumor involvement along these mesenteric vessels, the common hepatic artery and portal vein are exposed within the porta hepatis. Lymph nodes and other extravascular soft tissue may be mobilized for inclusion with the eventual specimen. The gallbladder is mobilized out of the gallbladder fossa to expose the common hepatic duct, which is then encircled. If the tumor mass does not extend into the liver hilum, the surgeon may proceed with exposing the gastroduodenal artery and assessing the portomesenteric venous confluence. Many advocate for "test clamping" the gastroduodenal artery to ensure sufficient arterial perfusion to the liver, thereby ruling out celiac artery stenosis or misidentification of the hepatic artery, before doubly ligating this vessel. The portal vein dissection is continued along the superior border of the pancreatic neck, and a tunnel is created between the posterior surface of the pancreas and the anterior surface of the portomesenteric venous confluence. At this point, if the critical structures are uninvolved by the tumor mass, the surgeon may proceed with pancreaticoduodenectomy. In situations in which the tumor is suspected to involve the superior mesenteric vein–portal vein axis, the surgeon may still proceed with surgical resection if the operative team has experience with venous reconstruction and believes the patient will benefit from this aggressive surgical approach. As with other periampullary malignancies, arterial resection and reconstruction remain controversial in the treatment of distal cholangiocarcinoma.

The bile duct is transected sharply with the margin submitted for intraoperative pathologic evaluation. The proximal bile duct can be gently occluded to minimize spillage of bile into the operative field. The distal stomach (in a classic Whipple procedure) or proximal duodenum (in a pylorus-preserving Whipple procedure) is then divided with a linear stapler. A Penrose drain is placed through the previously established tunnel behind the pancreatic neck, and the pancreas is divided. This margin may also be submitted for frozen-section analysis, especially when there is still concern for pancreatic cancer. The proximal jejunum is then divided with a linear stapler distal to the ligament of Treitz. The peritoneal attachments between the proximal bowel and the transverse mesocolon are then incised, and the bowel is mobilized away from the root of the mesentery. The proximal jejunum can then pass into the right upper quadrant and allow the surgeon to complete the dissection from a supracolic exposure.

Resection of the Whipple specimen is achieved by separating the head of the pancreas from the portal vein–superior mesenteric vein axis and then incising the attachments between the uncinate process of the pancreas and the superior mesenteric artery. Much of the dissection along the portomesenteric venous confluence can be performed bluntly as this is a largely avascular plane. However, surgeons should ligate the vein of Belcher along the right posterolateral aspect of the portal vein and identify the first jejunal vein arising from the superior mesenteric vein and passing posterior to the superior mesenteric artery. Once the specimen is separated from these venous structures, the portomesenteric venous confluence can be retracted to the left and expose the superior mesenteric artery. The arterial dissection should be performed along the periadventitial plane to facilitate clearance of the lymphatic tissues as this is a common location for local recurrence. In fact, there is growing support for complete removal of all soft tissue bordered by the superior mesenteric artery, portomesenteric venous confluence, and hepatic artery (Fig. 4), which is sometimes referred to as the *Heidelberg triangle*. During the uncinate dissection, the inferior pancreaticoduodenal artery is ligated and divided to allow removal of the Whipple specimen.

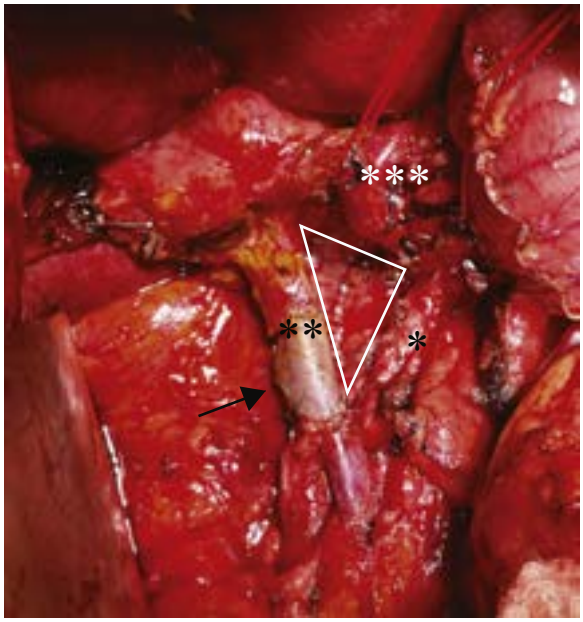


FIG. 4 Vascular structures after resection of distal extrahepatic cholangiocarcinoma. The pancreaticoduodenectomy specimen and soft tissue along the superior mesenteric artery *(black asterisk)*, the portomesenteric venous confluence *(black asterisks)*, and hepatic artery *(white asterisks)* were removed to clear lymphatic tissue within the Heidelberg triangle *(white triangle)*. In this case, the portomesenteric venous confluence was reconstructed *(arrow)* with ligation of the splenic vein.

There are many techniques to perform the pancreatic, biliary, and gastrointestinal reconstruction. We prefer to close the ligament of Treitz defect and deliver the proximal jejunum through a defect created in the transverse mesocolon to the right of the middle colic vessels, although others prefer to bring the jejunum through the ligament of Treitz defect itself. Once the jejunum is mobilized, an end-to-side pancreaticojejunostomy is typically performed. There are many variations of this anastomosis without clear superiority of any technique. In our center, a two-layer technique is commonly employed. The outer layer approximates the serosa of the bowel with the capsule of the pancreas, whereas the inner "duct-to-mucosa" layer completes the anastomosis; a pancreatic duct stent is often placed through this anastomosis. The biliary reconstruction is performed via an end-to-side hepaticojejunostomy using interrupted absorbable sutures. The jejunum is secured to the transverse mesocolon to minimize tension and reduce the risk of internal hernia. Lastly, gastrointestinal continuity is restored with a Billroth II-type gastrojejunostomy. This can be antecolic or retrocolic in orientation using a hand-sewn or stapled technique. Closed-suction drainage is still routinely employed, although some advocate for selective use of surgical drains based on the anticipated risk of postoperative pancreatic fistula.

Other Treatments

Patients with unresectable or metastatic distal cholangiocarcinoma are considered for palliative chemotherapy. Common treatment regimens include gemcitabine-based doublets (i.e., gemcitabine plus cisplatin or gemcitabine plus nab-paclitaxel) or the triplet regimen of gemcitabine, cisplatin, and nab-paclitaxel. These combinations have shown efficacy in randomized, controlled trials such as the ABC-02 study, which demonstrated an improvement in disease-free survival and overall survival without substantial added toxicity in patients receiving gemcitabine plus cisplatin compared with patients receiving

gemcitabine alone. More recent studies have shown the benefit of gemcitabine, cisplatin, and nab-paclitaxel, although patients may have additional toxicity with this triplet regimen. Alternatively, patients may receive a fluoropyrimidine-based regimen such as FOLFOX. Palliative radiation is often recommended for patients with unresectable but non-metastatic distal cholangiocarcinoma. As with hilar cholangiocarcinoma, photodynamic therapy may also be considered for these patients.

Choices for adjuvant therapy following surgical resection of distal cholangiocarcinoma are akin to those following resection of hilar cholangiocarcinoma, as most studies have included patients with these two subsets of extrahepatic cholangiocarcinoma. The aforementioned BILCAP trial included patients with distal cholangiocarcinoma (as well as ICC, hilar cholangiocarcinoma, and gallbladder cancer), leading many centers to offer adjuvant capecitabine following resected distal cholangiocarcinoma. Alternatively, patients may receive multi-agent gemcitabine- or fluoropyrimidine-based regimens (similar to those used for metastatic or unresectable distal cholangiocarcinoma). For patients with positive margins or lymph node metastasis, concurrent chemoradiation (or multi-agent chemotherapy followed by radiation) should be considered. Lastly, neoadjuvant or perioperative chemotherapy is being considered for patients with distal cholangiocarcinoma, just like the approach used in patients with pancreatic cancer.

SUMMARY

Cholangiocarcinoma encompasses a diverse group of malignancies arising from the biliary tract, which are grouped as intrahepatic, perihilar, and distal extrahepatic based on anatomic location. Although their clinical presentation, initial evaluation, and therapeutic options differ, surgical resection is the cornerstone of curative-intent treatment for each subset of cholangiocarcinoma. Multidisciplinary review is useful as patient performance status, tumor stage, and anatomic factors all factor into treatment decisions. Patients with localized cholangiocarcinoma should be considered for surgery if their tumor is amenable to complete resection and they can tolerate the planned operation. Neoadjuvant therapy may be considered in situations in which surgical resection may not be feasible or high-risk features are present. For patients requiring liver resection, the FLR should be carefully estimated before surgery, and preoperative biliary decompression should be considered. The technical approach to extirpation of the tumor differs based on location: ICCs are removed with liver resection, perihilar cholangiocarcinomas require resection of the extrahepatic biliary and involved liver with biliary reconstruction, and distal extrahepatic cholangiocarcinomas are treated with pancreaticoduodenectomy. Regional lymphadenectomy is recommended, and intraoperative pathologic evaluation of surgical margins can improve the likelihood of achieving negative margins. Though the use of adjuvant chemotherapy and radiation is common, the optimal treatment regimen and magnitude of benefit are areas of active investigation. Unfortunately, many patients present with advanced disease that precludes curative-intent surgery. There are a range of options to palliate symptoms and prolong survival. Therefore, patients often benefit from multidisciplinary evaluation at a high-volume center to consider systemic chemotherapy, chemoradiation, liver-directed therapy, or liver transplantation. Enrollment in clinical trials should be encouraged as there is growing promise of targeted therapy and immunotherapy.

Suggested Readings

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Biomarker Guided Surgical Management of Hepatobiliary and Pancreatic Tumors

Mahip Grewal, BA, Joseph R. Habib, MD, and Ammar A. Javed, MD

INTRODUCTION

Hepatobiliary and pancreatic tumors remain some of the most lethal malignancies known to mankind. Compared with other cancers, their incidence is on the rise and despite improvements in the operative management and development of systemic therapies, long-term survival remains dismal. This is in part driven by a paucity of biomarkers which are tools that can provide insight into disease biology and guide personalized therapy for patients (Table 1). Traditionally, because of the complex nature of these operations, resectability was based on anatomic criteria. However, clinical evidence, recently reinforced by molecular evidence, dictates that we must also consider and address the systemic component of disease to truly affect patient survival. Recently, liquid biomarkers (discussed subsequently) that are more representative of systemic burden of disease have been identified and are being integrated into patient care. This chapter outlines the concept of a liquid component of a solid tumor; summarizes current clinically available biomarkers, highlighting their strengths and weaknesses; and introduces the role of evaluating *tumor biomarker portraits* for the surgical management of patients.

LIQUID COMPONENT OF A SOLID TUMOR: DEFINING ANATOMIC AND BIOLOGIC RESECTABILITY

Historically, malignancies were measured as isolated disease processes, and emphasis was placed on determining "anatomic" resectability. Moreover, given the complex nature of surgical procedures required to successfully resect hepatobiliary and pancreatic tumors,

TABLE 1 Biomarkers in Clinical Use for Hepatobiliary and Pancreatic Tumors

Disease	Biomarker	Clinical Utility	Current Limitations
Pancreatic ductal adenocarcinoma (PDAC)	CA 19-9	Diagnosis Prognosis Assessment of response to therapy Surveillance for recurrence	Poor sensitivity and specificity
	CEA	Diagnosis Assessment of response to therapy	Poor sensitivity and specificity
Pancreatic neuroendocrine tumor (PNET)	CHGA	Assessment of response to therapy	Nonspecific, associated with all neuroendocrine tumors Can be elevated as a result of other malignancies, endocrine disorders, or medication use
	Ki-67 expression	Prognosis Prediction of response to therapy	Variation within subgroups
Hepatocellular carcinoma (HCC)	Elevated AFP	Screening Prognostication Transplant eligibility Detection of recurrence	Lack of consensus on threshold level (i.e., 200 ng/mL vs. 400 ng/mL) Low sensitivity (50%–60%)
	Molecular subtyping	Prognostication	Classification does not inform treatment decisions
Colorectal cancer liver metastases (CRLM)	CEA	Prognostication Detection of recurrence	Poor sensitivity and specificity
Cholangiocarcinoma (CCA)	CA 19-9	Diagnosis	Poor sensitivity and specificity
	CEA	Diagnosis	Poor sensitivity and specificity
	MSI, MMR, TMB	Prediction of response to therapy (i.e., pembrolizumab)	
	FGFR2 fusion	Prediction of response to therapy (i.e., pemigatinib)	Available to patients with previously treated, unresectable locally advanced or metastatic CCA Overall response rate (ORR): 36%
	IDH1 mutation	Prediction of response to therapy (i.e., ivosidenib)	Available to patients with previously treated, locally advanced or metastatic CCA Compared with placebo, significant improvement in progression-free-survival (PFS) but not overall survival (OS)
	NTRK fusion	Prediction of response to therapy (i.e., entrectinib, larotrectinib)	
	BRAF V600E mutations	Prediction of response to therapy (i.e., dabrafenib, trametinib)	
Gallbladder carcinoma (GBC)	CA 19-9	Diagnosis Detection of recurrence	Poor sensitivity and specificity
	CEA	Support diagnosis Detection of recurrence	Poor sensitivity and specificity

AFP, Alpha-fetoprotein; *CA 19-9*, carbohydrate antigen 19-9; *CEA*, carcinoembryonic antigen; *CHGA*, chromogranin; *FGFR2*, fibroblast growth factor receptor 2; *IDH1*, isocitrate dehydrogenase-1; *MMR*, mismatch repair; *MSI*, microsatellite instability; *NTRK*, neurotrophic tyrosine kinase receptor; *ORR*, overall response rate; *OS*, overall survival; *PFS*, progression-free-survival; *TMB*, tumor mutational burden.

the associated morbidity and mortality was substantial. However, with improvement in both surgical techniques and perioperative care, these procedures are now considered safe when performed by well-trained surgeons at high-volume centers. Furthermore, patients previously deemed to be anatomically unresectable can now undergo curative surgery involving complex vascular resection and reconstruction after administration of neoadjuvant chemotherapy and/or radiotherapy. With more patients surviving postoperatively, it is becoming increasingly evident that it is the systemic component of disease that drives long-term survival, with most patients having distant progression of disease resulting in treatment failure. As hepatobiliary and pancreatic surgeons, we are now faced with a unique challenge of factoring in the systemic tumor biology when selecting appropriate care for these patients. Anecdotally, we have all observed patients who presented with large locally advanced cancers that remained localized without metastatic spread over time and others who presented with a hardly perceptible primary tumor and had extensive metastatic disease. Thus, it has become clear that significant improvement in survival will only be observed with effective treatment of both local and systemic components of the tumor.

On a biological level, the behavior of these tumors is complex. Numerous processes are at play including interaction among tumor cells and surrounding stroma, resulting in an ideal tumor microenvironment, changes in tumor cell characteristics permitting escape to the bloodstream, immune evasion, development of a premetastatic niche to prime distant organs for tumor deposits, intravasation into these distant sites, and dormancy or activation of micrometastatic disseminated disease. These mechanisms are driven by multiple factors such as tumor genetics and biomolecules including proteins, miRNA, and exosomes. Studying these processes in detail has allowed us to identify clinically actionable biomarkers that can be harnessed for a precision approach to managing disease, both locally and systemically.

INTEGRATING ANATOMIC AND BIOLOGIC RESECTABILITY IN HEPATOBILIARY AND PANCREATIC SURGERY

Previously, anatomic complexity represented the key barrier for surgeons operating on these tumors. Whereas the mortality rate associated with hepatectomies was 15% to 20% through the 1970s, surgeons have since successfully implemented laparoscopic and robotic approaches as well as pioneered innovative vessel reconstruction techniques such as microvascular anastomoses, yielding single-digit mortality rates. Similarly, until the 1980s, pancreatoduodenectomies were associated with a 25% to 30% mortality rate, which now is less than 2% at high-volume centers. Furthermore, the use of neoadjuvant chemotherapy for locally advanced disease has expanded surgical candidacy.

Despite tremendous improvements in short-term outcomes, long-term survival rates remain blunted. The 5-year recurrence rate of hepatocellular carcinoma (HCC) is upward of 70%. Comparably, the postoperative 5-year survival rate after surgery for pancreatic ductal adenocarcinoma (PDAC) is approximately 20%, with most patients succumbing to metastatic disease. Therefore, although advancements in surgical techniques have facilitated great strides in overcoming localized disease, there is an urgent need to improve treatment of systemic disease. Altogether, the high rates of recurrence underscore the importance of assessing biologic resectability in addition to anatomic resectability when determining surgical candidacy. By harnessing biomarkers to establish a portrait of each patient's tumor biology, surgeons will be better equipped to optimize patient selection and incorporate multimodal therapies.

DEFINING A BIOMARKER

Biomarkers in oncology were originally defined as biomolecules produced by tumors that can be measured in bodily fluids (proteins, circulating tumor DNA [ctDNA], circulating tumor cells [CTCs]) and tissue (tumor mutational profile) to characterize disease. The concept has since grown to encompass substances produced by host cells in response to the tumor (proteomic dysregulations, exosomes, miRNA) and epigenetic alterations. Ongoing research efforts are further expanding the definition to include quantifiable clinical, pathologic, and radiologic features (i.e., radiomics). Underpinning the rise of precision medicine, biomarkers have been utilized for (1) **screening** (e.g., prostate-specific antigen [PSA], prostate cancer); (2) **diagnosis** (e.g., stool circulating tumor DNA [ctDNA], colorectal cancer); (3) **prognostication** (e.g., *BRCA1* mutation, breast cancer); (4) **prediction of response to therapy** (e.g., HER2 receptor– positive targeted therapy, breast cancer); (5) **assessment of response to therapy** (e.g., serial measurement of ctDNA, colorectal cancer); and (6) **early detection of recurrence** (e.g., prostate-specific antigen [PSA], prostate cancer) (Fig. 1). Considering these six potential

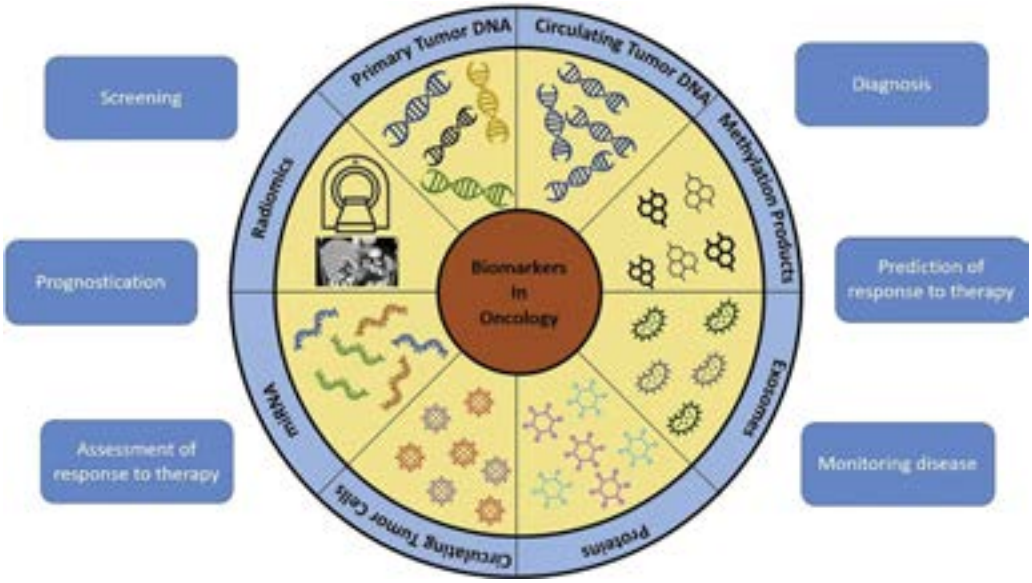


FIG. 1 Traditionally defined as measurable molecules in bodily fluids (e.g., proteins, circulating tumor cells, primary tumor DNA, etc.), biomarkers characterize disease and can accordingly serve an array of clinical utilities. Ongoing investigations are underway to potentially expand the concept of biomarkers to include markers derived from radiomics and exosomal analysis.

applications in hepatobiliary and pancreatic tumors, biomarkers can be used to provide precision patient management in various phases of care.

TUMOR BIOMARKER PORTRAIT IN HEPATOBILIARY AND PANCREATIC SURGERY

Identification of reliable, accessible, and scalable biomarkers to enhance the development of tools for the aforementioned applications would allow oncology teams to paint a portrait of each patient's unique tumor biology and accordingly tailor optimal therapy. For example, biomarker portraits could facilitate assessment of whether a patient with locally advanced pancreatic cancer has "favorable" tumor biology and thus would respond to induction chemotherapy and subsequently be a candidate for surgery (Fig. 2). Currently, surgical pathology reports are the most reliable source of prognostic information. Additionally, preoperative sequencing of tumors could reveal genomic/transcriptomic signatures associated with varying degrees of metastasis, providing earlier prognostic estimates. By the same token, liquid biopsy approaches to serially monitor blood-based biomarkers (ctDNA, CTCs, proteins) could provide a window into the presence and behavior of micrometastatic disease and inform toward the necessity of systemic therapies and their efficacy on administration. Recent data suggest that each biomarker represents a unique aspect of tumor biology and has its limitations (low sensitivity or specificity). Development of multiomic (multianalyte) tests by integration of multiple biomarkers can overcome these limitations and provide a more global assessment of tumor biology. When this multiomic approach is applied, the resulting *tumor biomarker portraits* (see Figure 1) represent a powerful tool that can help surgeons tailor patient management and improve long-term survival. This approach includes choosing up front versus neoadjuvant surgery; determining the duration, selection, and sequencing of systemic therapies; and offering early detection and treatment of recurrent disease (Fig. 3).

CURRENT BIOMARKERS TO GUIDE SURGICAL MANAGEMENT OF HEPATOBILIARY AND PANCREATIC TUMORS

Pancreas

Pancreatic Ductal Adenocarcinoma

The most common pancreatic cancer, PDAC is a highly fatal disease with a 5-year overall survival (OS) of 10%. Not only do most patients present with unresectable disease, but recurrence occurs in the majority of those who do undergo surgery. Carbohydrate antigen 19-9 (CA 19-9), considered representative of tumor burden, is the principal biomarker in clinical use for PDAC. Although routine screening for asymptomatic individuals is not recommended, EUS and/or MRI/MRCP is recommended for high-risk individuals (i.e., two or more first-degree relatives with pancreatic cancer, carriers of *p16/BRCA2* mutations, Peutz-Jeghers syndrome, or Lynch Syndrome). For high-risk individuals, CA 19-9 has shown promise

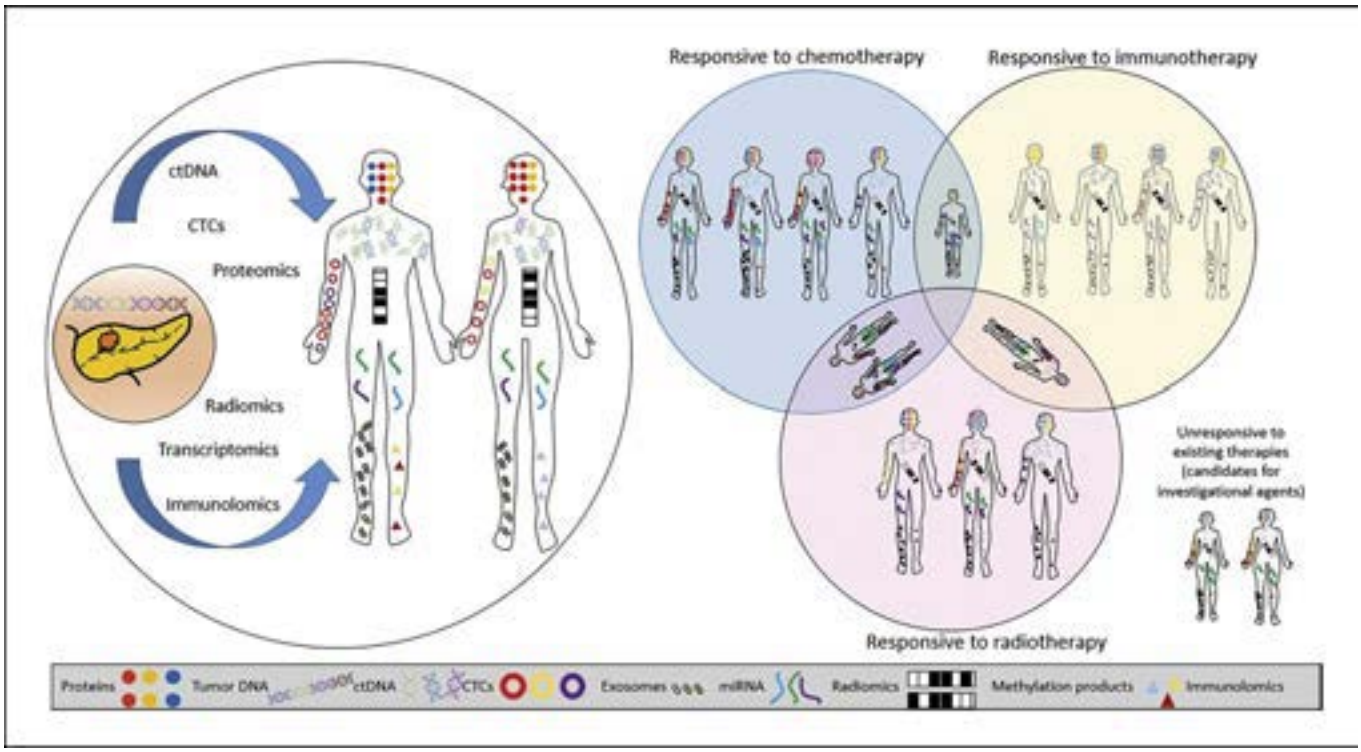


FIG. 2 Multiomic tumor biomarker portraits (TBPs) to guide therapy selection. Integrative analysis of multiple biomarkers could yield a multiomic "tumor biomarker portrait" for each patient to predict treatment sensitivities and guide therapy selection. For example, patients responsive to immunotherapy would have similar TBPs, with characteristics distinct from those of TBPs of patients unlikely to respond to existing therapeutic options.

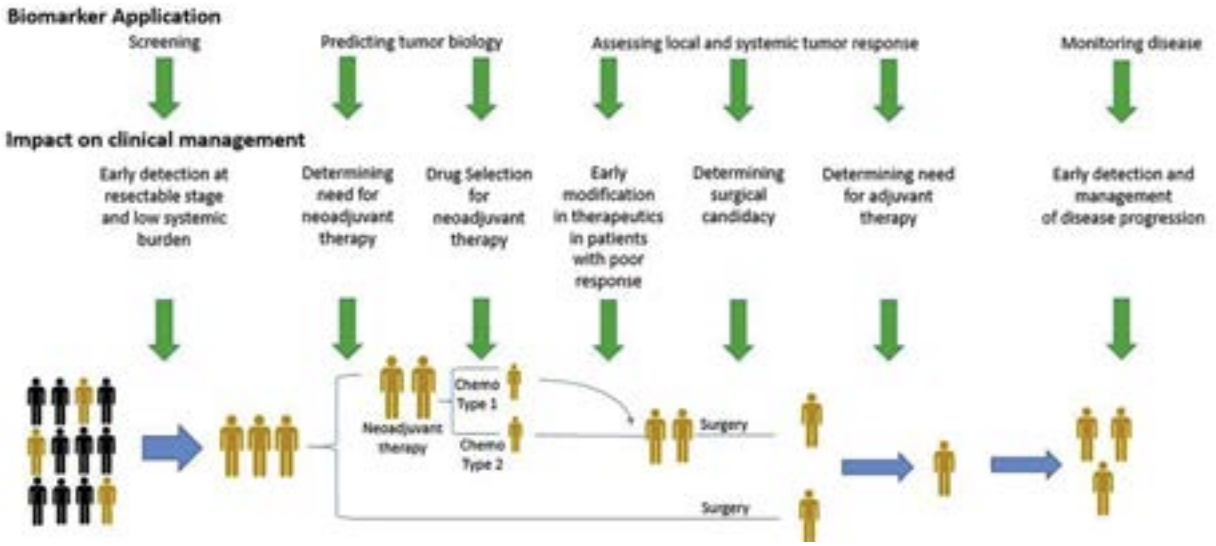


FIG. 3 Integration and serial assessment of tumor biomarker portraits (TBPs) for precision surgical oncology. Providing insight into multiple, dynamic aspects of tumor biology, TBPs could be serially assessed during each step of clinical management in surgical oncology. For example, particular changes in a patient's TBP following resection could guide the need for adjuvant therapy.

in screening as it can be elevated years before PDAC diagnosis. As a diagnostic marker, CA 19-9 has a sensitivity and specificity of approximately 80%. Although there is a lack of consensus with respect to exact cutoff levels and relative percent differences to apply in clinical practice, the National Comprehensive Cancer Network (NCCN) recommends measuring CA 19-9 before intervention and conducting serial measurements following therapy. Preoperative CA 19-9 levels correlate with resectability; lower to normalized CA 19-9 confers improved prognosis, and decreasing CA 19-9 is associated with a favorable response to therapy.

Patient performance status currently guides administration of FOLFIRINOX and Gemcitabine nab-paclitaxel, but high recurrence rates underscore a need for predictive biomarkers to fine-tune patient selection for these systemic therapy regimens. Germline and microsatellite instability (MSI)/mismatch repair (MMR) testing is recommended for locally advanced and metastatic PDAC to appraise the utility of larotrectinib or entrectinib, targeting NTRK fusions, and pembrolizumab, targeting programmed cell death protein 1 (PD-1), as subsequent or maintenance therapeutics. Beyond these, ctDNA and exosomal analysis may pinpoint more targetable mutations and be subsequently examined to identify treatment resistance.

Some biomarkers with potential diagnostic value under investigation include *ctDNA* mutations, *miR-21 and miR-155,* methylation of genes such as *NTPX2,* and glypican-1 *(GPC-1)* expression. In terms of improving prognostication, meta-analyses suggest that the presence of CTCs is associated with poorer progression-free survival (PFS) and OS, and multiple studies have found ctDNA *KRAS* positivity to be correlated with poorer OS and recurrence-free survival (RFS). Emerging evidence also bolsters the potential of radiomic features and protein expression levels to inform prognosis. Moreover, as various groups are beginning to link decreasing levels of ctDNA and CTCs to treatment response in PDAC patients, serial assessment of these markers could be used to gauge micrometastatic disease and guide patient selection for resection, efficacy, the necessity of neoadjuvant/adjuvant therapy, and detection of recurrence. Altogether, it is likely that a composite biomarker incorporating ctDNA, CTCs, proteomic profiling, and radiomic features will facilitate improved patient stratification and personalized therapeutic strategies.

Cystic Disease of the Pancreas

Premalignant cystic lesions include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). These cysts must be distinguished from those that are benign such as serous cystadenomas (SCAs), which often do not require surgical intervention. Existing pancreatic cyst management guidelines rely heavily on imaging, but studies report diagnostic accuracies of experienced radiologists in distinguishing pancreatic cysts to range from 50% to 70%. As such, there is an urgent need for more sensitive and specific diagnostic and prognostic biomarkers to balance the risk of progression to cancer with the morbidity and mortality of pancreatic surgery. Carcinoembryonic antigen (CEA) and amylase levels in cyst fluid are clinically used to determine whether a cyst is mucinous and exhibits duct communication, respectively. When stratifying likelihood of progression to PDAC among the most common pancreatic cystic neoplasm (PCN), IPMNs, the 2017 Fukuoka Consensus Guidelines recommend resection for patients with "high-risk stigmata:" dilation of the main pancreatic duct >10 mm, jaundice, and enhanced solid component (MN). Unfortunately, the performance of these guidelines is suboptimal, as retrospective studies have demonstrated a high rate of unnecessary surgery (e.g., resection of IPMNs with low-grade dysplasia) and a similarly high rate of delayed intervention (e.g., resection of IPMNs with invasive carcinoma).

Cyst fluid analysis represents a source of more nuanced diagnostic biomarkers. Studies have linked mutation in *VHL* to SCAs, and mutation in *CTNNB1* but a lack of mutations in *KRAS*, *GNAS,* or *RNF43* to solid pseudopapillary neoplasms (SPNs). Mutations in *KRAS* and *GNAS,* which are also present in PDAC, are highly specific for IPMNs. There have also been growing efforts to validate radiomic features and markers of systemic inflammation, such as neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein–to–albumin ratio (CAR) to better predict high-grade dysplasia/invasive carcinoma in IPMNs.

Pancreatic Neuroendocrine Tumors

Increasing in incidence, pancreatic neuroendocrine tumors (PNETs) account for 3% of pancreatic malignancies and can occur sporadically or as part of hereditary syndromes such as VHL or MEN1. Surgical and/or endoscopic biopsy of PNETs and immunohistochemical analysis represents the most reliable diagnostic modality. Chromogranin-A (CHGA) is the most commonly used biomarker for neuroendocrine tumors and is associated with disease progression, response to therapy, and systemic metastasis. However, CHGA is not specific to PNETs and can be elevated in other malignancies, endocrine conditions, and in association with medication use. Regarding prognosis, the World Health Organization (WHO) classifies PNETs based on Ki-67 index, mitotic rate, and grade of tumor differentiation. Currently, WHO grade is the most accurate predictor of tumor biology, however, its preoperative assessment via EUS-FNA remains challenging. Furthermore, tumor heterogeneity results in atypical tumor behavior, with small grade 1 tumors presenting with metastases at diagnosis, while some large tumors display indolent behavior.

Circulating tumor DNA and miRNAs are under investigation for prognostic, diagnostic, and recurrence detection, and further studies are warranted. Greater insight into the pathogenesis of various PNETs via genetic and molecular characterization could allow for tailored management via identification of subpopulations that could be candidates for surveillance, those that would benefit from systemic therapies in the resectable cohort, or debulking surgery for metastatic disease.

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) can often present as a diagnostic challenge, typically mimicking PDAC (i.e., elevated CA 19-9 and radiologic features). Management of these patients typically entails administration of glucocorticoids. Type 1 AIP is characterized by high levels of serum immunoglobulin G4 (IgG4) and presents as lymphoplasmacytic sclerosing pancreatitis (LPSP) histologically, whereas type II AIP is not associated with high IgG4 levels and presents as idiopathic duct-centric pancreatitis (IDCP). Because IgG4 does not detect type II AIP, and IgG4 also can be elevated in PDAC, additional biomarkers could improve diagnostic accuracy of AIP. Some markers under investigation include HSP10 and trypsinogen antibodies. Predictive biomarkers, specifically IgG4 levels and serum autotaxin, are being explored to address the fact that a minority of AIP patients relapse despite receiving glucocorticoid therapy.

Periampullary Cancer

Accounting for about 2% of gastrointestinal malignancies, periampullary cancers have typically been classified based on location of origin: pancreas, duodenum, distal common bile duct, or ampulla. However, in 1994, Kimura and colleagues proposed categorizing these cancers into pancreatobiliary and intestinal histologic subtypes, with the latter associated with improved survival. On immunohistochemical staining, the intestinal subtype exhibits MUC2, CDX2, and CK20 expression, whereas the pancreatobiliary subtype exhibits MUC1, MUC5AC, and CK7 expression. These immunohistochemical differences can be used as potential diagnostic and prognostic biomarkers in periampullary cancers.

Liver

Hepatocellular Carcinoma

The sixth most common cancer worldwide, HCC has a 5-year survival rate of less than 20%. Currently, the main biomarker in clinical use for HCC is alpha-fetoprotein (AFP). Biannual screening consisting of abdominal ultrasound and serum measurement of AFP is recommended for those at high risk for HCC (i.e., patients with cirrhosis and patients with HBV without cirrhosis). Although numerous studies have found that combined ultrasound and AFP testing is superior to ultrasound alone, it is important to note that AFP is often normal in early-stage disease, limiting its use as an independent screening biomarker. In fact, at the commonly used cutoff of 20 ng/mL, its sensitivity is only 50% to 60%, and AFP can be elevated in pregnancy, chronic liver disease, and other malignancies, undermining its specificity. Notwithstanding, if a nodule >10 mm and/or AFP is positive on screening, abdominal multiphasic CT or MRI is indicated to direct further workup for HCC. Although imaging is the main modality for diagnosis and there is no validated AFP cutoff value associated with HCC, an increasing AFP can support the diagnosis. Furthermore, AFP has shown promise as a prognostic biomarker and is used to determine transplant eligibility by the United Network for Organ Sharing (UNOS). Preoperative AFP levels have been associated with long-term outcomes, and postoperative serial AFP levels can surveil for recurrence, but there is similarly a lack of consensus with respect to cutoffs. In addition to AFP, the MELD score, utilized to assess liver function and determine candidacy for transplant and prognosis, is essentially a composite biomarker as it encompasses measurement of several serum biomarkers (protein) including creatinine, bilirubin, and INR. Fibrolamellar HCC is a unique entity that has neuroendocrine features and secretes characteristic hormones and proteins such as neurotensin and vitamin B_{12}-binding protein, which can be used to diagnose it.

With the suboptimal sensitivity and specificity of AFP for screening purposes and the lack of robust biomarkers to guide systemic therapy selection, assess response, and detect recurrence, other biomarkers are needed. The molecular categorization of HCC has identified subtypes. The proliferative class is characterized by activation of pathways involving AKT, RAS, and IGF-2 and associated with poorer prognosis. Contrastingly, the nonproliferative class characterized by activation of the WNT pathway is associated with a more favorable prognosis. Assessment of this biomarker represents another prognostic tool in HCC that can potentially guide treatment; however, this remains to be translated into clinical practice. Other potential biomarkers including AFP-L3, DCP, miRNAs, cell differentials, and ctDNA have shown promise. Advancements in high-throughput proteomic techniques will likely accelerate the pace at which additional candidates can be studied.

Colorectal Liver Metastases

Over 50% of patients with colorectal cancer (CRC) develop liver metastases, and surgical resection represents the leading option for cure. CEA is the biomarker used to surveil for CRC recurrence. The sensitivity and specificity of elevated CEA levels are suboptimal, particularly closer to the normal range (i.e., <2.5 ng/mL). CEA can be elevated in response to more indolent influences such as smoking, infections, pancreatitis, and cirrhosis, and not all patients with colorectal liver metastases (CRLM) exhibit CEA elevations. Candidacy for resection of liver metastases is currently based on preoperative CEA level, along with anatomic considerations, number and size of metastases, and lymph node positivity. Recurrence occurs in two-thirds of patients following resection. CEA has demonstrated good performance as a biomarker for surveillance for recurrent disease after treatment of CRLM. It is recommended that it be assessed every 3 months following resection, with an increasing CEA being indicative of recurrent disease.

Biomarkers to guide patient selection and timing of surgical resection are urgently needed, and there are many avenues

under investigation. Quantification of the degree of primary tumor genomic heterogeneity could also serve as a multipurpose biomarker. Studies suggest that *KRAS* and *BRAF* mutations could be predictive of response to anti-EGFR therapies, while degree of microsatellite instability is currently being used for immunotherapies. Further research is warranted to validate associations between mutations in single genes, combinations of genes, and proteomic profiles, such as Ki-67 expression.

Cystic Disease of the Liver

Cystic diseases of the liver are typically diagnosed incidentally and encompass simple cysts, polycystic liver disease, cystadenomas, and intraductal papillary mucinous neoplasms of the bile duct (IPMN-B). Although no biomarkers are currently available for diagnosis, given the low yet real risk of malignancy, appropriate workup should be performed. Imaging features suggestive of malignancy include thickening or nodule of the cyst wall, presence of a multilocular lesion, septations, papillary projections, or debris within the cyst. Furthermore, presence of mucin on aspiration with atypical cells is suggestive of cystadenoma or cystadenocarcinoma. In these cases, cyst fluid CA19-9 and CEA can be used to elevate the lesion.

Gallbladder and the Biliary Tree

Cholangiocarcinoma

Though cholangiocarcinoma (CCA) is a rare gastrointestinal tumor, its incidence is increasing. CCAs can arise throughout the biliary tree and are categorized into intrahepatic (iCCA) and extrahepatic (eCCA) subtypes. Patients with iCCA typically present later with nonspecific symptoms, and workup is initiated for an intrahepatic mass identified on incidental imaging. Measurement of CEA and CA 19-9 can be considered to aid in the diagnosis of iCCA in the context of radiologic, clinical, and histologic findings, but their sensitivity and specificity are low. AFP can also be measured to distinguish HCC from iCCA. Patients with eCCAs often present with jaundice, biliary obstruction, and/or pain; in addition to CEA and CA 19-9, serum IgG4 should be measured to rule out IgG4-associated cholangitis. MSI/MMR, tumor mutational burden (TMB), and additional molecular testing for targeted therapies are indicated for patients with unresectable or metastatic disease. Pembrolizumab, targeting programmed cell death protein 1 (PD-1), can be used as the first-line or subsequent-line (i.e., disease progression, no prior checkpoint use) for MSI-High, dMMR, and TMB-High CCAs. More than 40% of CCAs exhibit predictive biomarkers in the form of genetic alterations suitable for targeted therapies. The US Food and Drug Administration recently approved two therapies for subsequent line use for unresectable or metastatic CCA: pemigatinib, a fibroblast growth factor receptor (FGFR) inhibitor for patients with *FGFR2* fusions, and ivosidenib, an isocitrate dehydrogenase-1 (IDH1) inhibitor for patients with *IDH1* mutations. For patients with unresectable or metastatic disease, the NCCN supports use of entrectinib and larotrectinib to target *NTRK* fusions and dabrafenib and trametinib for *BRAF V600E* mutations. Although not yet targetable therapeutically, molecular testing can identify alterations with prognostic implications; *HER2* gene amplification, *ALK, ARID1A, PIK3C2G, STK11,* and *TGFBR2* are associated with poor prognosis.

Gallbladder Carcinoma

Gallbladder carcinoma (GBC) has a 5-year OS rate ranging from 4% to 60% based on stage. Although surgical resection is the mainstay of treatment, most patients present with unresectable disease and are diagnosed on imaging or during interventions for symptomatic cholelithiasis. Therefore, discovery of diagnostic and prognostic biomarkers is critical. For patients who present with jaundice or a mass on imaging, measurement of CEA (>4.0 ng/mL), which has the higher sensitivity, and CA 19-9 (>20.0 units/mL), which has the higher specificity, can be considered and are supportive of the presence of GBC, but these markers are not recommended for diagnostic use. Measurement of CEA and CA 19-9 can also be utilized, in addition to imaging, for the purpose of surveillance following resection. Among those with unresectable or metastatic disease, testing for MSI, MMR, and TMB is indicated, as these features represent predictive biomarkers. Patients with MSI-H, dMMR, and/or TMB-H are more likely to respond to pembrolizumab. The utility of liquid biopsy approaches (i.e., assessing ctDNA, CTCs, exosomes, miRNAs) and serum cytokeratins are under investigation for diagnosis. Further, studies suggest that miRNAs, inflammatory indices such as NLR, CA19-9/CEA, and tyrosine kinase receptors could serve as prognostic biomarkers.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a rare, chronic, inflammatory disease of unknown etiology affecting intrahepatic and/or extrahepatic bile ducts, and liver transplantation is the sole curative treatment. With respect to diagnosis, the gold standard is a "string and bead" appearance (i.e., multifocal strictures and adjacent dilations) on MRCP or ERCP, along with negative antimitochondrial antibody (AMA) and IgG4 to rule out primary biliary cholangitis (PBC) and IgG4-associated cholangitis, respectively. Liver fibrosis markers, namely the serum-based enhanced liver fibrosis (ELF) test and ultrasound-based liver stiffness measurements (LSMs), have shown promise in predicting transplant-free survival. With early evidence for the utility of assessing levels of the bile protein, calprotectin, and cytokine IL-8 in characterizing disease stage and transplant-free survival, comparisons of proteomic and inflammatory profiles across various stages of PSC could also yield prognostic and predictive biomarkers amenable to serial assessment.

THE FUTURE OF BIOMARKERS: PRECISION HEPATOBILIARY AND PANCREATIC SURGERY

Having advanced techniques to conquer the anatomic complexity of hepatobiliary and pancreatic resections, surgeons must now also focus on identifying and harnessing biomarkers to better appraise and target the biology of individual tumors. Current biomarkers in clinical use for diagnosis, prognostication, therapeutic selection, and assessment of response to therapy, such as CA 19-9, CEA, AFP, and imaging features have suboptimal specificity and sensitivity. Additionally, there is an urgent need for screening biomarkers to facilitate earlier detection and intervention. Promisingly, efforts are being directed toward establishing and validating liquid biopsy approaches and composite tests incorporating multiple biomarkers (i.e., molecular, radiomic, clinical features, pathologic), which could facilitate dynamic assessment of tumor biology and serve multiple clinical utilities. Complementing such tests, three-dimensional cell cultures sourced from biopsies and/or surgical specimens could facilitate ex vivo testing of therapies, further personalizing treatment.

To advance hepatobiliary and pancreatic surgery to the next level, it is imperative that surgeons remain up to date on the current knowledge of biomarkers so they can assess both the local and systemic component of disease. It is only through this biomarker-driven personalized approach to management that long-term survival will finally be achieved in these patients.

Suggested Readings

Boilève A, Hilmi M, Delaye M, et al. Biomarkers in hepatobiliary cancers: what is useful in clinical practice? *Cancers (Basel)*. 2021;13(11):2708.

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Surgical Management of Gallbladder Cancer

Anthony Sorrentino, MD, and Christopher L. Wolfgang, MD, PhD

OVERVIEW

Gallbladder cancer (GBC) is a rare but aggressive malignancy that affects approximately 4000 people per year in the United States. An oncologic resection of patients with localized disease is the only potentially curative therapy. Optimal outcomes require careful patient selection and performance of a tailored operation that depends on the stage and extent of local involvement. Even though GBC is a rare condition, the general surgeon in both the community and academic center will diagnose nearly half of all cases because of a commonly performed operation—laparoscopic cholecystectomy. It is therefore important for the general surgeon to understand the full range of this rare disease, as they will often be involved in making the initial diagnosis and will be responsible for determining next steps in treatment. This chapter will focus on information regarding GBC pertinent to surgical management. The first portion of the chapter will provide background information on GBC. The remainder of the chapter will provide details on the surgical management of GBC in context of the three most common clinical scenarios: (1) the incidental finding of GBC on final pathology following a cholecystectomy, (2) the intraoperative finding of suspected GBC, and (3) the preoperative diagnosis of GBC.

EPIDEMIOLOGY

GBC accounts for around 80% to 95% of cancers of the biliary tract and ranks sixth most common among gastrointestinal (GI) tract tumors. Overall incidence of GBC in the United States has been shown to be 1.1 cases/100,000 patients, with the incidence steadily increasing over a 40-year time span. Mortality incidence yearly is 0.6/100,000. Although it is diagnosed only in 0.2% to 3% of cholecystectomies, 40% to 70% of GBC are found incidentally, either intraoperatively or after pathologic review of gallbladder specimens following cholecystectomy. The majority of GBC arise within the fundus of the gallbladder, followed by the body, and then neck/infundibulum (60%, 30%, and 10%, respectively). The majority of GBC are adenocarcinoma, accounting for up to 90% of identified tumors, although squamous cell, adenosquamous, neuroendocrine, undifferentiated tumors exist.

The median age at diagnosis is middle to late 60s, which follows the theoretical 5 to 15 years it takes to progress through the metaplasia, dysplasia, and carcinoma sequence of chronic inflammation. GBC is more likely to develop in women than men, with a predominance of 2–3:1. The incidence increases with age and varies with location. Within the United States, the incidence is higher in Native Americans individuals, with an incidence of 3.15/100,000. Globally, the highest incidences of GBC are seen in northern India, Chile, Poland, Ecuador, Pakistan, Korea, and Japan. The incidence in Northern Indian women has been cited to be as high as 21.5/100,000, 10 times that of the general US population.

RISK FACTORS

The common denominator in the risk of development of GBC is persistent chronic inflammation. The principal risk factors for developing GBC include cholelithiasis, gallbladder polyps, porcelain gallbladder, anomalous pancreaticobiliary duct junction, salmonella species infection, primary sclerosing cholangitis (PSC), obesity, and carcinogens (tobacco, arsenic).

Gallstones are the most significant risk factor for development of GBC, as they are present in approximately 85% of all GBCs. The size of the stone is directly proportional to the risk of developing cancer, with the relative risk increasing from 2.4 to 9.2–10.1 if the stones are 2 to 2.9 cm or >3 cm, respectively. Anomalous pancreaticobiliary duct junction (APBDJ) refers to the abnormal junction of the pancreatic duct and the common bile duct that occurs outside the duodenal wall and is seen in 10% to 17% of GBC patients. These patients are typically younger and have a lower incidence of gallstones. Obesity lends a twofold increased risk to the development of GBC. Chronic *salmonella* typhi and *paratyphi* infection, both as chronic infection and carrier states, have a positive association with GBC development, with a relative risk of 10.2 in one systematic review. Patients with PSC have a higher incidence of gallstones that can predispose these patients to the development of GBC. Porcelain gallbladder is a radiographic finding initially described on plain films of the abdomen and is characterized by a thin rim of calcium within the wall of the gallbladder. The calcifications of a porcelain gallbladder are thought to be the result of chronic inflammation, particularly in the setting of gallstones. Historically, porcelain gallbladder was associated with an underlying incidence of GBC quoted around 60%; however, recent studies cite this incidence to be around 6%. The calcifications can arise either as small plaques within the mucosal layer or as full thickness involvement and replacement of the muscularis layer. This distinction is important, because recent studies have shown that the focal mucosal calcifications are at higher risk for developing carcinoma.

Similar to colon cancer, GBC is thought to arise from premalignant polyps in an adenoma to carcinoma sequence. Although not the focus of this chapter, the findings of enhancing gallbladder polyps are often referred to surgeons and require careful evaluation. The malignant risk of gallbladder polyps is dependent on size. For those smaller than 10 mm, the malignant potential is 0% to 5%, whereas for 10 to 15 mm, it is 11% to 13%, and >15 mm, it is 46% to 70%. Due to their malignant potential, gallbladder polyps should be resected if (1) >10 mm, (2) growth of >2 mm within observation period (6 months), (3) symptomatic polyps, or (4) polyps 6 to 9 mm with high-risk features (>50 years old, Indian ethnicity, inflammatory bowel disease history, sessile polyp).

Xanthogranulomatous cholecystitis (XGC) and gallbladder adenomyomatosis can often be confused with true gallbladder polyps but are not neoplastic or premalignant. XGC is a benign, inflammatory disease of the gallbladder that is characterized by diffuse gallbladder wall thickening. The presence of elevated CA 19-9 with XGC in one small study showed association with underlying GBC. Gallbladder adenomyomatosis is a benign acquired condition of the gallbladder that poses diagnostic confusion on radiography.

STAGING

The staging of GBC is based on the eighth edition of the American Joint Commission for Cancer (AJCC) TNM cancer staging system. T-stage is the strongest prognostic factor for patients with GBC, and most of the survival data and management recommendations centers around the depth of invasion of the primary mass. The most significant change in the update from the seventh edition was the implementation of segregating perimuscular invading lesions as peritoneal (T2a)- or hepatic (T2b)-sided as the result of a study showing improved survival in patients with peritoneal- compared with hepatic-sided tumors (Fig. 1). The T component describes the depth of invasion into the gallbladder wall and is based on the wall anatomy, which consists of an inner mucosal layer, lamina propria, muscular layer, perimuscular connective tissue, and either serosa or

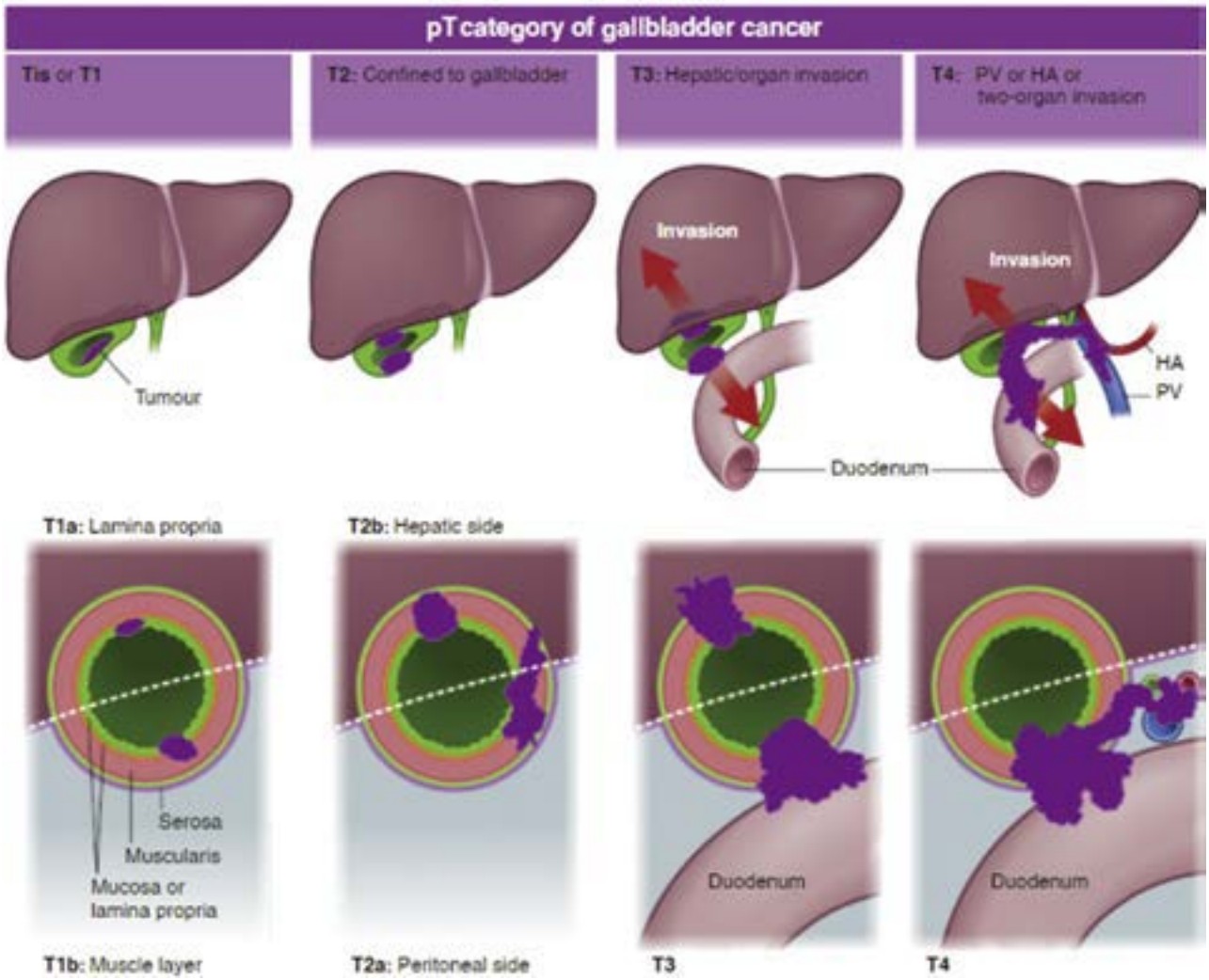


FIG. 1 Depth of invasion of gallbladder cancer and relation to hepatic and peritoneal sides. ***PV***, Portal vein; ***HA***, hepatic artery. *(From Søreide K, Guest RV, Harrison EM, Kendall TJ, Garden OJ, Wigmore SJ. Systematic review of management of incidental gallbladder cancer after cholecystectomy.* Br J Surg. *2019;106:32-45.)*

hepatic parenchyma. This depth of invasion is a main driver for the type of operation performed, ranging from simple cholecystectomy to extended cholecystectomy with resection of segment IVb and V along with portal lymphadenectomy.

N-stage represents the nodal staging, which is measured as number of lymph nodes involved (no lymph nodes, 1–3 lymph nodes, 4 or more lymph nodes). The differentiation made between the seventh and eighth AJCC staging system was that lymph node location can be local or metastatic, depending on where it is located, with celiac and aortocaval nodes being classified as distant metastasis. M-stage denotes the presence or absence of metastatic disease, the most common of which being the liver or peritoneum. Prognostic staging is primarily driven by T-stage.

BRIEF ANATOMY AND PHYSIOLOGY OF THE GALLBLADDER

The gallbladder is a saccular organ that is attached to the inferior surface of the liver through the cystic plate. It consists of a fundus, body, infundibulum, and neck. The free margin is peritonealized and contacts the peritoneal surface of the lateral wall of the duodenum and the hepatic flexure of the colon. Posteriorly, it rests on Gerota's fascia of the right kidney. The gallbladder attaches to the extrahepatic bile duct through the cystic duct. This connection defines the transition from the common hepatic duct to the common bile duct. The blood supply to the gallbladder is through the cystic artery that runs through the triangle of Calot. As the cystic artery approaches the neck of the gallbladder, it bifurcates into anterior and posterior branches. The cystic artery typically originates from the right hepatic artery but can be variable depending on variations of the hepatic arterial anatomy. Moreover, anomalous junctions of the cystic duct with the common bile duct are common. The venous drainage of the gallbladder through the cystic vein initially follows the course of the cystic artery until it deviates and directly enters the cystic plate connecting within the intrahepatic parenchyma to the middle hepatic vein. The gallbladder receives both sympathetic and parasympathetic innervation. Sympathetic fibers that innervate the gallbladder originate from the ninth thoracic segment and the celiac plexus. In addition, the right phrenic nerve contributes further sympathetic innervation. Parasympathetic innervation originates

from the hepatic branch of the anterior vagus nerve. The function of the gallbladder is to store bile that is produced at a constant rate. In the fasting state, closure of the sphincter of Oddi promotes filling of the relaxed gallbladder on the basis of pressure. Cholecystokinin release is stimulated with enteral feeding and causes relaxation of the sphincter of Oddi and contractions of the gallbladder, which then provides a bolus of bile delivered through the common bile duct into the duodenum. The main function of bile is the emulsification of ingested fats that allows pancreas-derived lipase to break these compounds into triglycerides and fatty acid chains that can be absorbed through the intestinal tract.

The understanding of the lymphatic drainage of the gallbladder is pertinent to the rationale behind nodal dissection and staging of GBC. The gallbladder has various routes of lymphatic drainage and does not form a predictable drainage pattern. In general, the cholecystic-retropancreatic pathway is the major and most consistent route of drainage. This pathway drains along the cystic duct, through the node of Calot, and then into the pericholedochal nodes, portal vein nodes, and superior retropancreatic nodes to the periaortic lymph nodes. In addition, the cholecystic-celiac pathway also exists less commonly. This route of drainage includes cystic duct channels to Calot's node to lymphatic channels medial along the hepatoduodenal ligament followed by channels along the common hepatic artery to the celiac trunk lymph nodes. According to the eighth addition of the AJCC staging manual, involvement of periaortic, pericaval celiac, and superior mesenteric artery lymph nodes are considered to be distant metastases. Therefore, when performing a potentially curative oncologic resection for GBC, a lymphadenectomy beyond the porta hepatis and the hepatoduodenal ligament is not routinely performed.

PRESENTATION, WORKUP, AND MANAGEMENT

Incidental GBC

A common scenario is the incidental finding of GBC on the final pathology report. The next steps in the surgical management of such a patient depend primarily on the T-stage and absence of disseminated disease. Patients found to have any T-stage of GBC other than T1a should undergo a formal staging workup as described next for preoperatively diagnosed GBCs. The specific treatment algorithm based on T-stage for incidental GBC is as follows.

For T1a lesions, a simple cholecystectomy is potentially curable. Residual disease on reresection is negligible, and 5-year overall survival approaches 100% across multiple reviews. Per National Comprehensive Cancer Network (NCCN) guidelines, if a T1a or Tis lesion is identified postoperatively after laparoscopic cholecystectomy for a presumed benign condition, expert pathologic review should be undertaken to ensure no missed lesions and proper T-stage. Review should also include evaluation of tumor location and margin status both at the lesion and cystic duct. No further workup is required beyond surgical resection if these remain negative.

Patients with invasion of the muscular layer of the gallbladder, a T1b lesion, after initial cholecystectomy should undergo formal staging followed by reexploration with resection of the gallbladder fossa, a portal lymph node dissection, and assessment of the cystic duct. If the cystic duct margin is negative for carcinoma, then the extrahepatic bile duct does not need to be resected. This recommendation is based on literature showing that patients with stage T1b will benefit from a more radical resection than cholecystectomy alone. In addition, some studies have demonstrated a median survival advantage of a more radical resection over cholecystectomy alone.

Invasion of the perimuscular connective tissue of GBCs is associated with a high risk of residual disease. Several multiinstitutional studies have reported residual disease in these T2 lesions in 50% to 60% of patients who underwent reexploration and radical resection. In addition, the nodal metastatic rate has been reported to be at least 30% in these patients. Based on these results, the recommendation for patients who are found to have an incidental T2 lesion is to undergo formal staging followed by reexploration and oncologic resection as described for T1b lesions. T2 GBCs can be further characterized into two categories dependent on the predominant location of the primary tumor. Those present on the peritoneal surface are classified as T2a, while those on the hepatic interface are considered T2b. Some controversy exists as to whether T2a patients should undergo reexploration. T2b lesions have been reported to have higher rates of lymph node metastasis, hepatic metastasis, and perineural invasion than T2a tumors. However, the standard of care remains exploration and oncologic resection for all T2 patients.

T3 lesions have approximately an 80% chance of residual disease including approximately one-third of patients who have disease within the hepatic parenchyma and about 40% who have regional lymph node metastases. This cohort benefits from formal staging followed by reexploration and oncologic resection. By definition, T4 lesions have extensive local invasion of surrounding major vascular structures and adjacent organs that is evident at the index operation and are seldom found as incidental GBCs on final pathology report.

Perforation of the gallbladder during a difficult laparoscopic or open cholecystectomy at the index operation is a common scenario in the incidental finding of GBC. GBC has a known propensity for local seeding of tumor. No consensus exists on the management of incidental GBC in patients who had perforation of the gallbladder at the index operation. There are very little data in the literature to formulate an evidence-based approach in this setting. Several retrospective studies have demonstrated a worse overall survival in this cohort. In these patients, our preference is to perform a staging workup and present the case at a multidisciplinary tumor board. Most commonly, our approach is to administer neoadjuvant therapy and, in the absence of progression, perform an exploratory laparoscopy followed by the appropriate resection dictated by T-stage.

Intraoperative Suspicion of GBC

The presentation and imaging characteristics of benign gallbladder disease and GBC overlap significantly. Moreover, the risk factors for an incidental GBC are of limited use in the definitive preoperative diagnosis of GBC. This must be kept in mind for all patients undergoing cholecystectomy, and one must be prepared to alter the planned operation based on certain findings. If a malignant lesion is suspected based on operative findings for presumed benign gallbladder, it is best to not take intraoperative biopsies, violate the gallbladder wall or biliary tract, or perform a subtotal cholecystectomy due to the risk of tumor dissemination.

If one is experienced in complex hepatobiliary surgery, the operation should proceed with modifications toward an oncologic approach. This includes assessing for extraregional spread within the abdomen and, if absent, performing an intraoperative ultrasound (US) to assess for invasion into the liver parenchyma followed by a radical cholecystectomy with *en bloc* resection of the appropriate extent of parenchyma to achieve a margin negative resection. The cystic duct should be divided flush with its insertion of the common bile duct. The specimen should be sent to pathology for an intraoperative frozen test, and if the determination of GBC is made, the cystic duct margin should be assessed. If the cystic duct margin is negative,

a periportal lymph node dissection should be performed. On the other hand, if the cystic duct margin is positive, an extrahepatic bile duct resection with Roux-en-Y reconstruction and periportal lymph node dissection should be performed. After surgical resection, radiographic evaluation of the chest should be performed to complete the staging workup and rule out distant metastatic spread. Additionally, for any lesion other than a T1a, a referral to medical oncology should be made.

For surgeons with less experience in complex hepatobiliary procedures, intraoperative consultation should be made with a hepatobiliary surgeon if possible. If this is not possible, then the operation should be terminated without a biopsy and the patient should be referred to an experienced center.

Preoperatively Diagnosed GBC

Only a few patients with preoperatively diagnosed GBC have localized disease that is amenable to surgical resection. One study reported that out of 435 patients with GBC, 37% were diagnosed as stage IV and 47% were diagnosed incidentally. The delay in presentation of GBC may be due to several factors, including lack of specific symptoms and low incidence making it typically lower on a physician's differential. The typical symptoms of GBC are nonspecific and include abdominal pain, nausea and vomiting, jaundice, anorexia, and weight loss. The presence of jaundice portends a sign of advanced disease.

US is often the initial imagining test in the evaluation of GBC as it is the standard test used to evaluate suspected benign gallbladder conditions. Certain findings on US should raise the suspicion of GBC and elicit a more complete workup. These include a loss of a normal plane between the hepatic parenchyma and the gallbladder (Fig. 2) and symmetric and irregular wall thickening or wall thickness >1 cm. US has a high sensitivity in detecting masses or focal wall thickening but low sensitivity in reporting cancer (44%) since early lesions may be subtle or flat.



FIG. 2 Ultrasound image showing gallbladder cancer *(arrow)*, with enlarged mass, loss of plane between liver and gallbladder wall, and lack of acoustic shadowing. *(From Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review.* J Gastrointest Surg. *2007;11:671.)*

Preoperative staging and surgical planning in patients with localized GBC depends on high-quality cross-sectional imaging. The goal of staging is the determination of extraregional spread of disease to sites such as liver or lung, peritoneal surface, or distant lymph nodes. The determination of resectability in localized patients is made based on the relationship of the tumor to major vascular and biliary structures. CT is the imaging modality of choice for the workup and staging of GBC. A triple-phase CT is recommended, as this will not only allow identification of potential masses but also will give additional information regarding the associated anomalous vessels, quantify liver volume should hepatectomy be recommended, and identify local structures that may be involved (portal vein, biliary tract, etc.). Dual-energy CT uses an iodine map that can more easily discern GBC from benign conditions like XGC or adenomyomatosis. Reported sensitivity, specificity, positive predictive value, and negative predictive value of a triple-phase CT in detecting GBC preoperatively is 90%, 59% to 60%, 52% to 53%, and 92%, respectively.

MRI can be used as an adjunct to CT scan. It is particularly useful in characterizing indeterminate liver lesions. Moreover, magnetic resonance cholangiopancreatography (MRCP) is helpful in operative planning to assess the extent and location of bile duct involvement in jaundiced patients. To complete the anatomic workup, either a chest CT or chest x-ray should be performed to rule out thoracic spread. The additional benefit of 18-FDG PET/CT in the workup of GBC is limited to further assessing potential distant spread and is not routinely used. Finally, serum tumor marker levels should be obtained to assess the potential for high micrometastatic burden and for use in monitoring response to treatment. A CA 19-9 is most useful for this purpose; however, up to 20% of individuals do not express the Lewis antigen. In addition, the CA 19-9 may be spuriously elevated in the presence of biliary obstruction and jaundice. In these instances, CEA serves a similar role.

Contraindications to surgical resection include distant disease as defined by celiac, aortocaval lymph nodes, distant organ metastases (most commonly liver and lung), malignant ascites, and carcinomatosis. Local factors that preclude oncologic resection include invasion of major vascular structures that would not be resected as the result of a hemihepatectomy/central hepatectomy or the predicted inability to achieve a margin-negative resection on the contralateral bile duct. Jaundice or multiorgan involvement (stomach, duodenum, colon, head of pancreas) is considered a *relative* contraindication, since outcomes are poor in patients with this as an initial presentation. Before entertaining resection of this cohort, a multidisciplinary review should be performed.

A planned oncologic resection of GBC should begin with an exploratory laparoscopy when feasible based on the patient's previous operative history. A careful assessment is made for carcinomatosis and liver metastases. A detailed assessment of the liver parenchyma is made possible by the addition of intraoperative US. Once localized disease is confirmed, the oncologic portion of the operation should commence.

The general approach is through a right subcostal incision (Kocher incision) with the superior midline extension, a Makuuchi incision, or Chevron incision. In the first step of the operation, the hilar plate is lowered and the entire hepatoduodenal ligament is skeletonized along with the common hepatic artery, and all of the soft tissue and regional lymph nodes are sent for specimen. Since they are now considered distant metastasis, the lymph node stations of the celiac trunk and aortocaval groove should be assessed only if they are of preoperative or intraoperative clinical concern. The common hepatic duct is dissected free from the portal vein and the proper hepatic artery. If there is no obvious involvement of the common hepatic or common bile duct, the cystic duct is ligated flush

with its insertion on the bile duct and the cystic duct margin is sent for frozen section. If the cystic duct margin is negative, the extrahepatic biliary tree is not routinely resected. Common duct resection and reconstruction was previously encouraged with resection; however, it is no longer routinely recommended unless there is a positive cystic duct margin. If there is involvement at the confluence of the cystic duct with the common bile duct, an extrahepatic bile duct resection should be performed from the level of the confluence of the right left hepatic ducts distally to the area where the bile duct enters the pancreatic parenchyma. These margins should be assessed intraoperatively. Reconstruction should be performed with a Roux-en-Y hepaticojejunostomy.

The extent of resection of liver parenchyma is determined by the extent of invasion of the GBC into the liver and involvement of the right portal pedicle. If there is minimal invasion or the tumor exists on the free wall of the gallbladder, we recommend taking at least a 2-cm rim of liver parenchyma *en bloc* with the gallbladder. A more formal resection may be required if the level of invasion into the liver is more extensive or the tumor involves the right portal pedicle with preservation of the left portal pedicle and main portal triad. In this case, a formal right hepatectomy with a segmental or subsegmental resection of segment 4B should be performed. The need to perform more than the limited resection of the hepatic parenchyma is often evident on preoperative imaging but can also be confirmed or assessed using intraoperative US.

For surgeons skilled in laparoscopic or robotic oncologic surgery, specifically in hepatic resection, regional lymph node dissection, and advanced GI techniques, the operation can be performed using minimally invasive techniques. The resection of previous port sites used to be routinely recommended. Given the variable nature of the entrance and exit of the port site in relation to the abdominal wall and the relatively low incidence of abdominal wall recurrence, this is no longer recommended as a routine. Retrospective reports have failed to demonstrate a survival benefit in the resection of port sites.

SURVIVAL

Across all stages, the 5-year survival for GBC ranges between 0% and 10%, with median overall survival 12.9 months for those with stage Ia–III disease and 5.8 months for stage IV disease, although there has been a decline in national GBC mortality rates in all countries, most notably in the female population. For those with incidentally discovered tumors at laparoscopic cholecystectomy, median survival is 15.7 months, 14.6 months if they underwent re-resection and residual disease was present, and 72 months if no residual disease was noted. For patients with T1a lesions or less, 5-year survival is reported to be 90% to 100%, with standard cholecystectomy considered curative for these patients. The median survival time in T1a was significantly higher than that of T1b lesions in incidentally found GBC: 96.1 and 32.6 months, respectively. Survival overall is made difficult by rapid growth and early dissemination of the tumor, with local lymph node involvement, penetration of hepatic parenchyma, and peritoneal spread. The lack of a serosal layer between the gallbladder and liver may facilitate early spread and allow early invasion of the liver with metastatic progression because of the shared blood supply. Debate still persists regarding the number of nodes necessary to achieve a survival benefit, with some studies showing a benefit with 5 or 6 nodes.

ADJUVANT THERAPY

Given the rarity of the conditions, biliary tract cancers are typically studied together in regard to chemotherapy regimens. The first major study looking at the effect of adjuvant therapy looked at mitomycin and 5FU; gemcitabine was the first recognized chemotherapy for treatment of advanced biliary tract cancers. The advanced biliary cancer (ABC) phase 3 trial randomized gemcitabine plus cisplatin compared with gemcitabine alone with improvement in survival within the GBC arm of the study. A National Cancer Database (NCDB)-based study looking at T2 and T3 lesions revealed that only 31.8% of patients received adjuvant therapy, and 48.3% of those received radiation therapy as well. Adjuvant therapy had a survival benefit in node-positive and T2 or locally advanced disease. The most frequently used chemotherapy regimens are gemcitabine-cisplatin, gemcitabine-oxaliplatin, or gemcitabine monotherapy, with FOLFOX as second-line therapy. The addition of radiation therapy with chemotherapy also was shown to improve survival, particularly in T2-4 or N+ or R1 resected GBC.

SUMMARY

Overall, GBC is a rare disease in comparison to other cancers and benign gallbladder conditions. The general surgeon in both academic and community settings may encounter patients with malignant gallbladder disease mainly as an incidental finding at operation for presumed benign disease or as an incidental finding on the pathology report. Making the next appropriate steps in the management of these patients has the potential to profoundly impact survival. The incidental finding of a T1a lesion on the pathology report has an excellent chance of being cured with the index operation. Later T-stage lesions in patients with localized disease have the potential to significantly benefit from reexploration and oncologic resection. In all cases, the best outcomes are achieved with the involvement of an experienced hepatobiliary surgeon. In patients who are diagnosed with GBC that is not incidentally found, a careful staging workup should be performed to assess for localized, resectable, and potentially curable disease. Patients with GBC greater than a T1a lesion should be evaluated by a multidisciplinary team that includes medical oncology.

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Management of Gallstone Ileus

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Gallstone ileus is a rare disease involving the biliary and intestinal tract that has an incidence of 0.3% to 3% among all cholelithiasis cases. The name "gallstone ileus" is somewhat misleading as this condition is actually a mechanical bowel obstruction due to an impacted intraluminal gallstone. As with the majority of biliary stone diseases, gallstone ileus occurs more frequently in women compared with men (3:1 ratio) and tends to affect older adults. This disease should be on the differential diagnosis when evaluating an older woman with a small bowel obstruction who has no history of abdominal surgery or hernias on physical examination. Though a rare disease, it has historically been associated with significant morbidity and mortality (35% and 7%, respectively), which demonstrates the need for diligent surgical management. This chapter will address the evaluation and management of this unusual presentation of bowel obstruction.

PATHOGENESIS

Gallstone ileus is caused by migration of gallstones from the biliary tract to the bowel. Gallstones typically migrate into the intestinal tract via a cholecystoenteric fistula created from persistent pressure of an impacted stone in the neck of the gallbladder. The resulting pressure and inflammation cause necrosis that leads to erosion into an adjacent hollow viscous. The offending fistula most frequently forms between the gallbladder and duodenum but can form anywhere along the intestinal tract. Fistulas to the stomach can result in a stone becoming lodged in the pylorus and causing gastric outlet obstruction (Bouveret's syndrome). Prolonged stone impaction may cause concomitant obstruction of the common hepatic or common bile duct (Mirizzi's syndrome) and associated fistula formation between the gallbladder and bile duct. Gallstone ileus has also been described after endoscopic sphincterotomy, which can allow larger stones to traverse the sphincter of Oddi.

Larger stones (>2.5 cm) are more likely to cause gallstone ileus as they have a diameter capable of obstructing the intestinal lumen. The most common intestinal sites of stone impaction are the ileocecal valve, sigmoid colon, ligament of Treitz, and the second portion of the duodenum. As previously described, stones that enter the lumen of the stomach can become impacted in the pylorus and cause gastric outlet obstruction. Any site of bowel stricture from Crohn's disease or malignancy is an additional point of potential obstruction by a passing gallstone.

PRESENTATION

Patients afflicted with gallstone ileus will present with symptoms typical of bowel obstruction: nausea, vomiting, obstipation, constipation, abdominal distension, and diffuse, colicky abdominal pain. They may report a prior distant history consistent with biliary stone disease; however, these symptoms are rarely elicited. Physical examination may demonstrate a distended abdomen that is tympanic to percussion. Jaundice is rarely present. Fever and peritonitis are suggestive of bowel necrosis or bowel perforation and are not typically associated with gallstone ileus.

DIAGNOSIS

Laboratory values in this setting are consistent with those expected of bowel obstructions but are not specific for gallstone ileus. The classical finding on abdominal plain film or abdominal computed tomography (CT) is called Rigler's triad, consisting of (1) pneumobilia and (2) dilated bowel with a transition point at (3) an ectopic gallstone (Box 1). Detecting gallstones on plain film is notoriously difficult as only 10% of stones are radiopaque. Pneumobilia may not be present if the cholecystoenteric fistula has spontaneously closed, which happens in 80% of cases of gallstone ileus. If oral contrast is given, visualization of the cholecystoenteric fistula may be possible on imaging as well (Fig. 1). CT is more sensitive for detecting gallstone ileus than plain film or ultrasonography, as the multiplanar reconstructions best visualize intraluminal stones and gallbladder inflammation (Fig. 2). Magnetic resonance cholangiopancreatography (MRCP) can more accurately detect intraluminal stones that are isodense with fluid than CT, as well as define the anatomy of the biliary tract and any associated fistulae. However, this study can be time consuming and requires a stable patient, thus making MRCP use in gallstone ileus limited.

PREOPERATIVE MANAGEMENT

Severe dehydration and electrolyte derangements are often present in patients with gallstone ileus due to prolonged volume losses from distended bowel and emesis. Patients will also typically have a history of poor oral intake in the days before diagnosis. These physiologic abnormalities can be challenging to manage in gallstone ileus as many patients are older and have significant comorbidities such as

BOX 1 Rigler's Triad for Diagnosing Gallstone Ileus

Pneumobilia
Dilated bowel
Transition point at location with ectopic gallstone

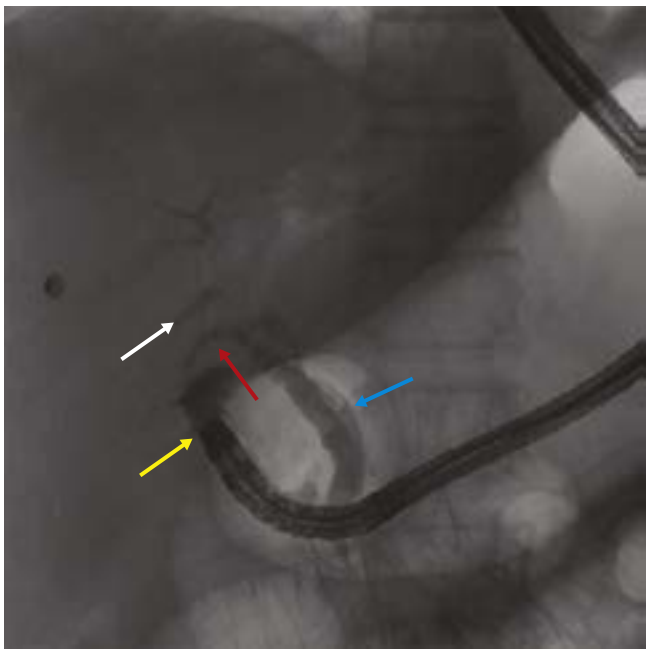


FIG. 1 Endoscopic retrograde cholangiopancreatography image of contrast injection into cholecystoenteric fistula *(yellow arrow)* filling the cystic *(red arrow)*, common *(blue arrow)*, and hepatic bile ducts *(white arrow)*.

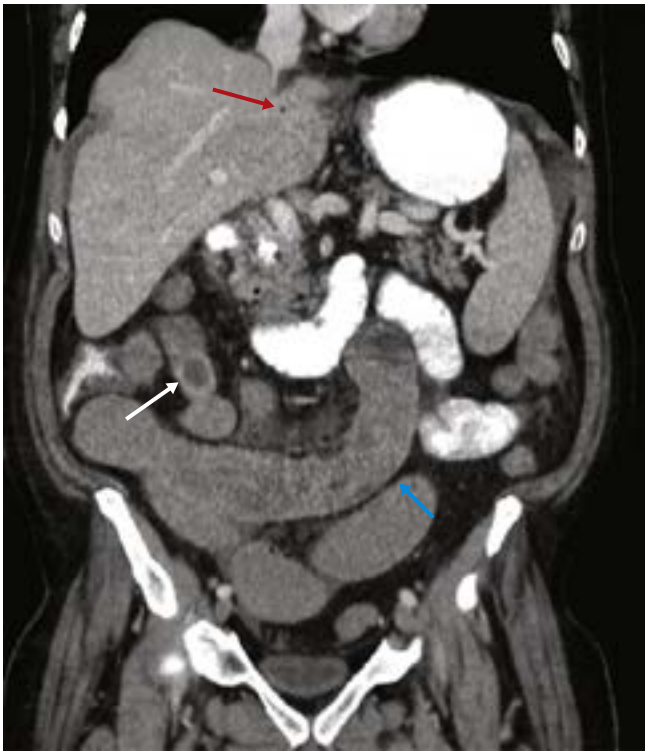


FIG. 2 CT coronal image of Rigler's triad. Pneumobilia from the bilioenteric fistula *(red arrow)*, dilated small bowel (*blue arrow*), and obstructive ectopic gallstone (*white arrow*).

chronic renal failure, congestive heart failure, or pulmonary diseases that are sensitive to fluid shifts.

Initial management should focus on fluid and electrolyte resuscitation. Depending on the associated comorbidities, it is often prudent to resuscitate gallstone ileus patients in the intensive care unit. A Foley catheter may be necessary to assess adequacy of resuscitation. A nasogastric tube should be placed to decompress the proximal gastrointestinal tract and reduce bowel edema. Once enteral decompression has occurred, the care team should take time to optimize comorbid conditions and fluid derangements for general anesthesia because emergent operation is rarely necessary, unless peritonitis or sepsis is present.

SURGICAL MANAGEMENT

Two separate pathologies must be present to develop gallstone ileus: cholecystoenteric fistula/inflammatory biliary disease and mechanical bowel obstruction. The surgeon must be aware that addressing the obstruction and preventing future obstruction is the priority at the initial surgical intervention. Attempting to definitively take down the bilioenteric fistula is associated with higher morbidity and mortality, especially in patients with severe inflammation at the fistula site or patients who are unstable. This is attributed to the challenging nature of taking down fistulas to the duodenum and prolonged operative times.

The site of obstruction in the majority of gallstone ileus cases is the ileum, with the ileocecal valve being the most susceptible location. Operative correction of gallstone ileus includes the following steps: (1) abdominal exploration, (2) identification of obstruction point, (3) longitudinal enterotomy proximal to the ileocecal valve, (4) milk stone back to enterotomy and remove, (5) assess the entire bowel for additional stones, (6) transverse closure of the enterotomy, and finally (7) evaluate the gallbladder for possible cholecystectomy (Box 2). Enterotomies near a competent ileocecal valve should be avoided as increased intraluminal pressure can result in failure of enterotomy repair. Longitudinal enterotomy is recommended to allow for removal of stones with a large diameter, and transverse closure is done to prevent stricture (Fig. 3). In some cases, the impacted stone is not amendable to being moved proximally or has caused full thickness small bowel injury requiring bowel resection as the best management option in these situations. The entire length of bowel should be examined for additional ectopic gallstones to prevent recurrent obstruction from retained stones. Additional stones are found in 5% of cases. Examining the entire small bowel is

BOX 2 Critical Steps in Surgical Management of Gallstone Ileus

1. Explore the abdomen
2. Identify point of obstruction
3. Make longitudinal enterotomy proximal to site of obstruction
4. Milk stone to enterotomy and remove
5. Assess remaining bowel for additional stones
6. Close enterotomy transversely
7. Inspect gallbladder and assess feasibility of cholecystectomy or cholecystolithotomy

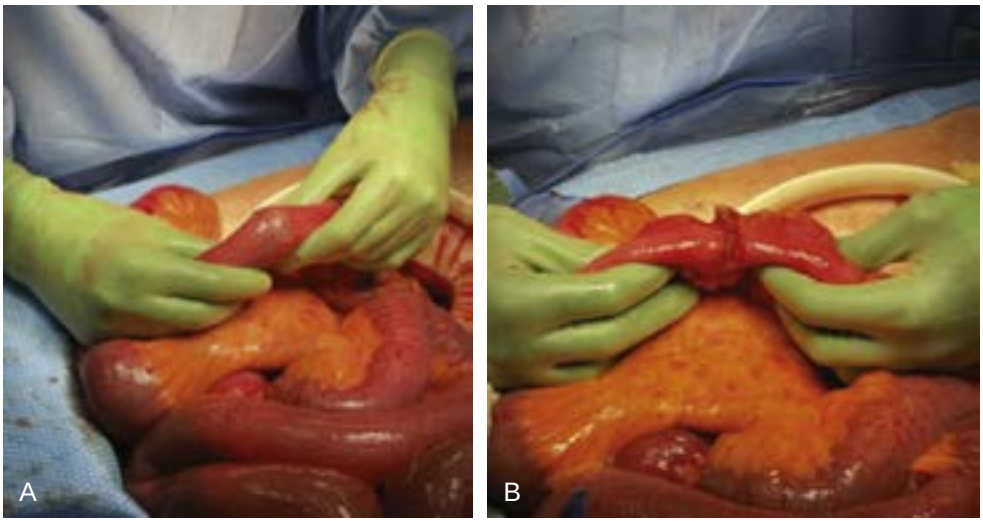


FIG. 3 **(A)** Gallstone within the terminal ileum. **(B)** Transverse closure of longitudinal enterotomy after removal of gallstone.

also indicated because there may be areas of transmural injury and bowel trauma from the passing of the stone upstream, which requires evaluation and possibly repair. Evaluation of the gallbladder for additional stones is done for the same reason. The described approach can be applied to stones impacted anywhere between the ligament of Treitz and the rectum.

Stones impacted in the duodenum can be more challenging to manage. If the gallstone is impacted in the ligament of Treitz, it can often be removed as previously described through a longitudinal enterotomy. However, most stones obstructing the duodenum are impacted near the site of the cholecystoenteric fistula secondary to associated inflammation. The combination of inflammation and adjacent critical structures can make removing a stone impacted in the duodenum difficult. These rare, complicated cases of gallstone ileus should be approached in a multidisciplinary fashion to avoid additional morbidity.

Although laparotomy has historically been the approach for managing gallstone ileus, minimally invasive techniques have been described. Patient comorbidities may be a contraindication for minimally invasive surgery if insufflation would exacerbate their condition. Severe bowel distension can limit visualization on minimally invasive platforms. A direct visualization approach for entering the abdomen is recommended if attempting laparoscopic or robotic management of gallstone ileus to avoid inadvertently injuring dilated bowel loops. Some surgeons use laparoscopy to locate the impacted gallstone and then externalize the affected loop of bowel via minilaparotomy, whereas others approach the entirety of the case using minimally invasive techniques. Regardless of the approach, the steps in Box 2 should be observed.

Endoscopy is an additional treatment option for gallstone ileus. This approach is particularly effective for ectopic stones impacted in the pylorus, duodenum, and colon. Endoscopy can be a useful tool in relieving stone obstruction in the duodenum that is associated with the severe inflammation of cholecystoenteric fistula and not easily amendable to surgical options. Different forms of lithotripsy (endoscopic mechanical, electrohydraulic, laser) can be used to fragment stones, making endoscopic disimpaction feasible. Generally, an endoscopic approach is reserved for patients who will not tolerate surgery from an anatomical or physiologic standpoint because it does not allow evaluation of the entire bowel for additional stones.

Finally, we turn to the question of management of the biliary portion of gallstone ileus. Addressing the gallbladder requires taking down the cholecystoenteric fistula, which may require complicated enteric reconstruction, especially if the duodenum is involved. The fistula take down can result in a large defect in the second portion of the duodenum requiring a complex closure. In addition, this portion significantly increases the morbidity and mortality of the operation. There is a general consensus that attempting cholecystectomy and fistula ligation should be avoided at the initial operation if the patient is not completely resuscitated, has significant comorbidities, or if there is any ongoing inflammation present in the right upper quadrant. Approximately 80% of these fistulae will close spontaneously after the large, offending stone has passed from the gallbladder. There is long-term evidence that nonoperative management of the biliary disease is safe for patients with gallstone ileus. Many surgeons forgo the biliary portion and only deal with the right upper quadrant if there are persistent symptoms. Recurrent gallstone ileus has been reported from stones left in the gallbladder, generally within 60 days of initial presentation. Cholecystolithotomy at the initial procedure is an option to reduce the risk of disease recurrence without the added risk associated with fistula take down. This involves making an incision in the fundus of the gallbladder, removing stones from within the gallbladder, and closing the gallbladder incision with absorbable sutures.

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Transhepatic Interventions for Obstructive Jaundice

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INTRODUCTION

Management of biliary obstruction requires a multidisciplinary approach, which is essential for proper diagnosis, treatment, management, and follow-up. Outcome optimization relies on a coordinated combination of minimally invasive percutaneous transhepatic techniques and/or endoscopic techniques, before definitive surgical intervention, if required. A dialogue between gastroenterologists trained in advanced endoscopy, interventional radiologists, and surgeons is often necessary to optimize treatments for patients with this condition.

Beyond the requisite history, laboratory workup, and physical exam, appropriately selected cross-sectional imaging is necessary. The three main noninvasive imaging modalities used to evaluate the biliary system are ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Table 1 details the pros and cons of the three cross-sectional imaging modalities in the setting of biliary obstruction.

Endoscopic retrograde cholangiopancreatography (ERCP), performed by gastroenterologists, is often the first invasive procedure that patients with obstructive jaundice undergo. During an ERCP, biliary, duodenal, and central pancreatic ductal anatomy can be evaluated and biopsies from suspected malignant lesions can be obtained. Limitations of ERCP include the inability to cannulate the biliary system due to altered anatomy (such as a bilioenteric anastomosis or Roux-en-Y anatomy) and difficulty treating intrahepatic or high hilar lesions. ERCP and endoscopically guided interventions are detailed elsewhere within this text.

The focus of this chapter is percutaneous transhepatic interventions performed by interventional radiologists, such as percutaneous transhepatic cholangiogram (PTC) and percutaneous

TABLE 1 Cross-Sectional Imaging for Obstructive Jaundice*

	Pros	Cons
Ultrasound	Real-time information No radiation exposure Sensitive to biliary pathology	Operator dependent Difficult to compare between studies
CT	Very sensitive to biliary dilation or other pathology Sensitive to incidental pathology	Requires IV contrast to evaluate for biliary dilation
MRI	Very sensitive to biliary dilation or other pathology Best modality for liver lesion characterization	Not great for bowel pathology Long study time Motion sensitive

*A triple-phase, contrast-enhanced CT (with angio) is the go-to study for identifying or following up on intra- or extrahepatic biliary pathology.

biliary drainage (PBD). These minimally invasive procedures remain important options in the management of benign and malignant biliary strictures, biliary ductal injuries, and cholangitis. Additionally, biliary duct biopsy, stone removal, and palliation of malignant biliary obstruction with endoprostheses are important percutaneous options available for management of these conditions (Table 2). The only absolute contraindication to percutaneous transhepatic interventions is significant coagulopathy that cannot be corrected. Relevant guidelines recommend that platelets should be above 50,000/mL and international normalized ratio (INR) should be below 1.7. Correction of the coagulopathy with blood products can be performed before percutaneous intervention. Although not an absolute contraindication, the presence of ascites can present a challenge for transhepatic drainage and result in ascitic leaks around an external catheter. Table 3 summarizes the contraindications to percutaneous biliary interventions.

TABLE 2 Causes for Obstructive Jaundice

Malignant (80%–90%)	Benign (10%–20%)
Cholangiocarcinoma	Choledocholithiasis
Pancreatic cancer	Pancreatitis
Gallbladder cancer	Primary sclerosis cholangitis
Ampullary adenocarcinoma	Iatrogenic injury
Metastatic disease	Cholangitis
Hepatocellular carcinoma (rare)	Secondary sclerosing cholangitis (radiation, ischemia, chemotherapy)
	Biliary cystic disease
	Cystic fibrosis

PERCUTANEOUS CHOLANGIOGRAM TECHNIQUE SUMMARY

Regardless of whether the cause of biliary obstruction is benign or malignant, evaluation of the intrahepatic and extrahepatic bile duct system with contrast-enhanced cross-sectional imaging (CT or MRI) is a must (Fig. 1). This will delineate the location of obstruction and dictate PBD access site and trajectory to ensure adequate drainage. The steps of performing a PTC/PBD are shown in Figure 2. The procedure can be performed with the patient under conscious sedation or, if necessary, with general anesthesia. Premedication with antibiotics is recommended, even if there are no signs of cholangitis, as the increase in biliary pressure with the contrast injection can precipitate sepsis. Figure 3 shows the various cholangiogram findings in obstructive jaundice patients.

COMPLICATIONS OF TRANSHEPATIC PERCUTANEOUS BILIARY INTERVENTIONS

Even though the technical and clinical success of PTC/PBD is high, both minor and major complications of the procedure can occur. Being cognizant of the potential complications, mitigating actions, and treatment options is crucial in optimizing outcomes. Table 4 summarizes the main types of complications of percutaneous biliary interventions.

Hemobilia. The presence of blood in the bile ducts/PBD is usually the result of the PBD transgressing a hepatic vessel. Branches of the portal or hepatic vein are the most commonly injured vessels. Because these are low-pressure systems, upsizing and/or

TABLE 3 Contraindications to Percutaneous Biliary Interventions

	Absolute/Relative	Notes	Complication	Mitigating Action
Coagulopathy	A	Platelets <50k INR >1.7	Significant risk of life-threatening hemorrhage	Correct
Ascites	R		Hemorrhage, technical failure, liver rend	Drain
Cholangitis	R		Sepsis	Antibiotics, allow drainage after biliary access
Polycystic liver disease	R		Biliary leak	
Hypervascular liver mass	R		Hemorrhage if must transgress	Select parenchymal access

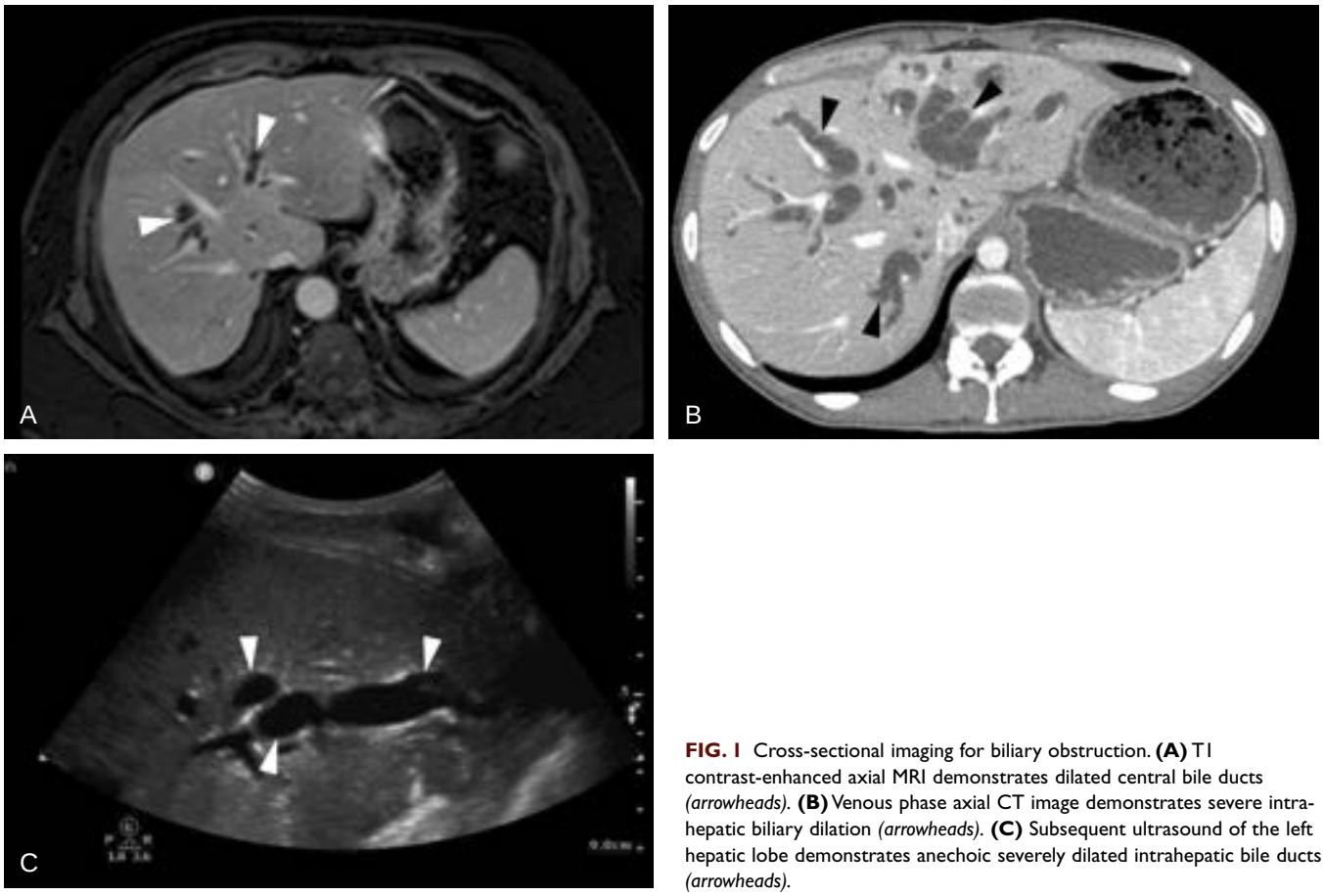


FIG. 1 Cross-sectional imaging for biliary obstruction. **(A)** T1 contrast-enhanced axial MRI demonstrates dilated central bile ducts *(arrowheads)*. **(B)** Venous phase axial CT image demonstrates severe intrahepatic biliary dilation *(arrowheads)*. **(C)** Subsequent ultrasound of the left hepatic lobe demonstrates anechoic severely dilated intrahepatic bile ducts *(arrowheads)*.

repositioning the PBD will tamponade and address the hemobilia. Care should be taken to avoid a PBD side-hole being positioned in the hepatic or portal vein branch because this would result in significant hemobilia via the PBD.

Hemorrhage. There are two ways to diagnose arterial hemorrhage post-PBD placement. The first occurs when removal of the PBD over a wire results in pulsatile, bright red blood in/through the tract. In this situation, a new PBD is inserted to tamponade the hemorrhage and an emergency angiogram + embolization is performed. The second scenario involves a patient with clinical signs of active hemorrhage without an obvious arterial hemorrhage from the percutaneous drain including hypotension, pressure support requirement, decreasing hemoglobin level, or transfusion requirement. In this case, a CT angiography is the diagnostic study of choice because it can delineate the exact site of hemorrhage and help the operator plan embolization. The most commonly injured arterial vessels during PTC/PBD are branches of the hepatic artery or an intercostal artery.

Sepsis. Another complication is cholangitis, which can be seen in up to 20% of patients during biliary interventions or as a result of PBD occlusion. If a patient with an indwelling PBD or biliary stent develops fever, rigors, and hypotension, sepsis secondary to cholangitis should be suspected. Immediate externalization of the biliary system (i.e., connecting back to an external drainage bag) in the case of capped internal-external biliary drains is important for patients to be able to perform at home in the event they become febrile. Sepsis can develop even with prophylactic antibiotic treatment and can be treated with intravenous antibiotics, volume resuscitation, and biliary decompression. In a patient where there is clinical concern for cholangitis without another identified source for sepsis, cholangiography to evaluate for tube clogging usually followed by percutaneous drain exchange is performed.

Pericatheter Leakage and Tube Dislodgement. The major drawback of transhepatic access is the presence of a drain outside the patient; similar to any surgically placed drain, minor complications of leakage and dislodgement can develop. Biliary drains are sutured to the skin to prevent dislodgement. Nonetheless, PBD retraction or clogging can result in pericatheter bile leakage. Although this does not represent a clinical risk, the PBD should be replaced/repositioned for patient comfort.

Biloma. The formation of a bile-containing collection can occur in the liver or around it. This occurs when the PBD is occluded or malpositioned and bile cannot drain into the bowel. Aggressive catheter/wire manipulations during PTC/PBD placement can cause a liver rent and a subsequent biloma. Positioning of the PBD to drain the biloma (if intrahepatic) or placement of a percutaneous drainage catheter (if extrahepatic) usually resolves the biloma without consequences.

Pneumo-, hemo-, bilothorax. These conditions occur when initial percutaneous access is inappropriately high and the pleura are transgressed. Initial access should thus be as low as safely achievable, directed cephalad with entry to the biliary system as peripheral as possible.

MANAGEMENT OF BENIGN CAUSES OF BILIARY OBSTRUCTION

Benign biliary postoperative stenoses, biliary leaks, and fistulae most commonly occur after injury to the common bile duct during laparoscopic cholecystectomy. However, biliary obstruction is also commonly seen after the creation of any bilioenteric anastomosis, including during pancreaticoduodenectomy and liver

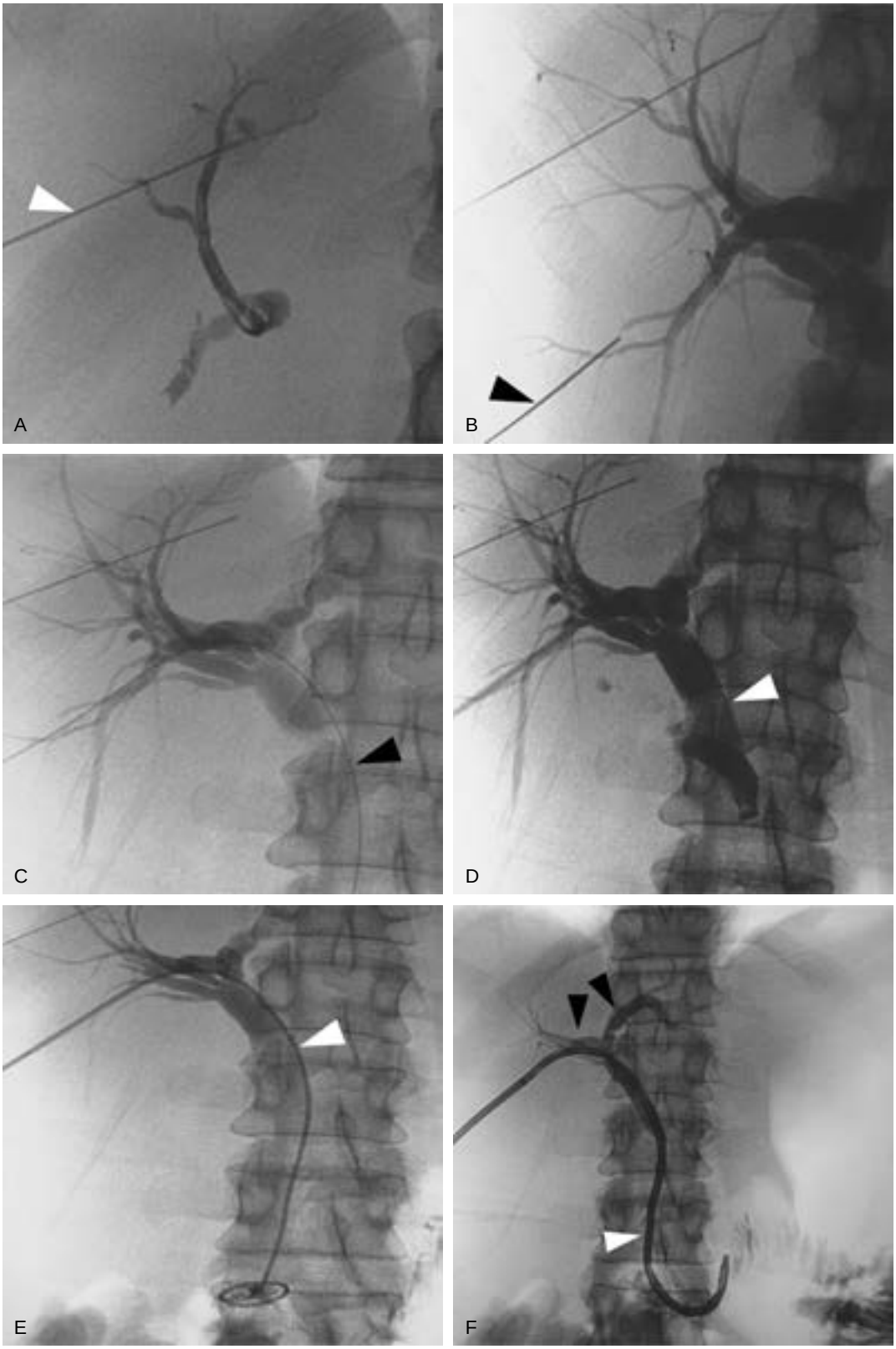


FIG. 2 Steps of placing a percutaneous biliary drain. **(A)** After preparation and local anesthesia at the midaxillary line at the diaphragm, a 22-g needle is used to opacify a dilated biliary system *(arrowhead)*. Multiple random passes may be necessary, especially in a nondilated system. **(B)** Once the system is opacified, a second needle *(black arrowhead)* is used to access a peripheral duct *(arrowhead)*. **(C)** Wire *(arrowhead)* is advanced via the needle into the biliary system or duodenum if possible. A sheath is placed over the wire after the needle has been removed to provide secure access. **(D)** Glide wire–catheter combination *(arrowhead)* is then used to cross the obstruction into the small bowel. **(E)** The wire is exchanged for a stiffer one, and a biliary catheter *(arrowhead)* is finally advanced over it into the duodenum. **(F)** In this case, the obstructive lesion is a pancreatic cancer occluding the distal common bile duct. Final cholangiogram shows both the left and right biliary ducts *(black arrowheads)*, now decompressed by a percutaneous biliary drain *(white arrowhead)*.

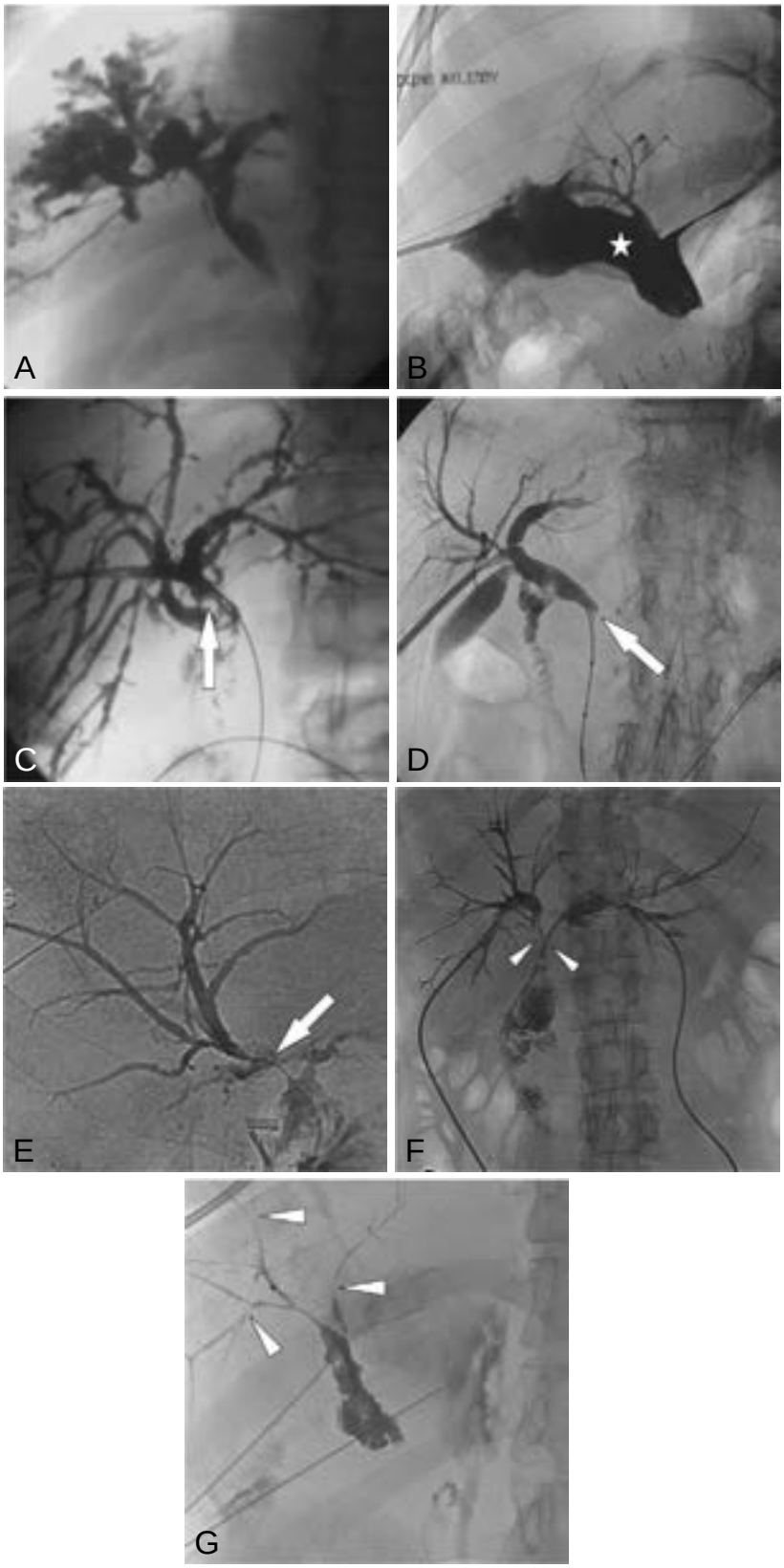


FIG. 3 Cholangiogram findings in obstructive jaundice patients. **(A)** Intrahepatic cystic biliary dilation indicative of Caroli's disease, which often leads to cholestasis and jaundice. **(B)** Large subhepatic contrast leak *(star)* from a nondilated biliary system due to laparoscopic cholecystectomy related common bile duct injury Such leaks are often associated with an underlying hepatojejunostomy stricture. **(C)** Bile stone seen as a filling defect *(arrow)* in bile duct after Whipple's resection. **(D)** Distal CDB obstruction *(arrow)* due to pancreatic cancer. **(E)** Benign HJ anastomotic *stricture (arrow)* after Whipple procedure. **(F)** Klatskin-type cholangiocarcinoma; *arrowheads* point at the malignant strictures at the biliary bifurcation. **(G)** Sclerosing cholangitis indicated by multiple segmental biliary strictures *(arrowheads)*.

TABLE 4 Complications of Percutaneous Biliary Interventions

Complication	PTC (%)	PBD (%)	Risk Factor	Mitigating Actions
Hemobilia	<1	5–10	Central access	If venous, upsize PBD If arterial, embolize
Hemorrhage	<1	2–5		CT angiogram ± embolization
Biliary sepsis	1.8	2.5	Marked dilation	Allow bile drainage before PBD placement
Bile leak	1	3	Difficult access	Upsize PBD to seal leak
Death	<1	<1	Usually arterial hemorrhage related	See above
Biloma/Abscess	0	<1	Difficult anatomy	Antibiotics
Pneumo-, hemo-, bilo-thorax	0	<1	High access	Select low skin access site
Sedation complications	<5	<5	Usually oversedation, apnea	Titrate to pain, reverse sedation, trained in ACLS

ACLS, advanced cardiac life support; *PBD*, percutaneous biliary drainage; *PTC*, percutaneous transhepatic cholangiogram.

transplantation. Additional benign causes of biliary obstruction include choledocholithiasis, papillary stenosis, choledochal cystic disease, postsurgical stricture, Mirizzi's syndrome, pancreatic pseudocyst, sclerosing cholangitis, and parasitic disease. Treatment of benign biliary stenosis is generally initially attempted by ERCP. However, postsurgical anatomy and very tight, low biliary strictures often make ERCP difficult. Percutaneous treatment of a benign biliary stricture is the first-line treatment choice when a patient presents with sepsis from cholangitis, requiring emergent decompression.

If the initial attempt to cross the stricture in a dilated system fails, an anchor drain is placed, and the distended biliary system is allowed to drain. After 24 to 48 hours, a second attempt at crossing the stricture can be attempted with the goal of crossing the biliary stricture with an internal-external PBD, which is usually successful.

The care of internal-external biliary drains, after placement, involves an understanding from the treating physicians, nurses, and the patient. After the initial placement of an external or internal-external drain, the percutaneous biliary drain should be set to external drainage. Biliary drainage catheters are generally flushed twice a day; this is of particular importance in patients with viscous bile to maintain tube patency. In the patient with an external-internal biliary drainage catheter, the importance of gently flushing the tube, forward flushing, and being cautious not to aspirate fluid back into the syringe must be emphasized. Forceful aspiration with a syringe may rapidly transfer bacteria from the gastrointestinal tract into the biliary system, potentially resulting in sepsis. Additionally, forceful forward flushing of the tube can raise biliary pressure and cause pain and discomfort in the patient. Pain management after initial placement of a percutaneous biliary drain is important and should not be overlooked; initial placement can be painful, and patients may complain of radiating chest and right upper quadrant pain. Management with oral pain medications and/or patient-controlled analgesia (PCA) pumps are standard at many institutions after initial PBD placement.

Benign Biliary Strictures

Understanding the long-term management of benign biliary strictures after placement of a percutaneous biliary drain is of particular importance for surgeons and interventional radiologists. While institutional preferences regarding optimal drainage catheter size, number, size of balloon dilation, and treatment duration vary, there are several general principles followed interventional radiologists. The overall goal of treatment is to upsize from an initial 8 to 10Fr hard tube to a large bore flexible silastic (16–20Fr) drainage catheter (Heyer-Schulte; Bentec Medical, Woodland, California), which is achieved through serial dilation occurring over several visits to the interventional radiology department. In general, a catheter needs to remain in place for a minimum of 3 months (preference for at least 6–12 months at our institution) to allow for scar healing around the larger tube. Subsequent cholangioplasty of the stenosis can then be performed and is ideally reserved for final upsizing to maximize the stent-implanted diameter. Periodic exchange of catheters on a 2-month basis is required, which can take place in an outpatient setting if no unplanned event necessitating exchange has occurred.

The decision to remove a biliary drain also follows a general set of principles. Before removing a biliary drain, an over-the-wire cholangiogram is performed by pulling the indwelling biliary drainage catheter back over a guidewire. If the site of the stented stricture looks patent based on injection of contrast through the tube, the decision to initiate a clinical trial is made. A shortened biliary drainage catheter will be reintroduced over the guidewire with the tip placed above the biliary stricture. This functions as an insurance policy; it maintains percutaneous access and can be externalized while allowing bile to flow across a nonstented, previously dilated stricture. The tube is capped for 2 weeks, and any signs of cholangitis, right upper quadrant pain, fever, jaundice, or leakage around the biliary drainage catheter indicates a probable failure of the trial. If needed, the stricture can be redilated with another percutaneous biliary drain and surgical revision with creation of a new biliary anastomosis is considered.

If the patient remains asymptomatic during the clinical trial and there is documented evidence of flow across the stricture on follow-up angiography, a biliary manometric perfusion test may be performed. Dilute contrast is infused in a stepwise manner via the shortened PBD. Biliary pressures are measured, with a normal biliary pressure considered less than 20 cm of H_2O. In patients with an asymptomatic clinical trial and normal pressures during the biliary manometric perfusion test, the positive predictive value of biliary duct patency at 1 year approaches 90%. Patients are followed with laboratory testing of their bilirubin and liver function tests at periodic intervals to ensure patency.

Choledocholithiasis

A complete discussion of choledocholithiasis management is discussed elsewhere in this book; however, percutaneous transhepatic options for stone removal plays a niche, yet important role in management. Percutaneous transhepatic cholangioscopy (PTCS) provides direct visualization of the biliary system and allows for endoscopically guided biopsy. PTCS-guided removal of biliary stones is highly successful, with complete stone removal occurring in up to 90% of cases; it is of particular use in patients in whom

ERCP fails due to altered postsurgical anatomy and for removal of high, peripheral biliary stones. After an approximately 2-week period with external drainage through a PBD to prevent cholangitis, as detailed earlier, an initial cholangioscopy can be performed. Stones can be directly removed in indirect cholangioscopy, which uses a catheter with an optical probe and a push balloon. More commonly used is direct cholangioscopy, which uses a very thin upper endoscope percutaneously and transhepatically positioned within the biliary system. For stones small enough to be removed through the sheath, a stone retrieval basket can be used. Open-ended graspers can also be used but can be technically challenging for larger stones and risk dropping the stone before removal in the sheath.

For stones too large to be removed through the sheath or basket, which is common in patients with chronic biliary obstruction, lithotripsy is often required (Fig. 4). Mechanical lithotripsy, which involves manually crushing stones by forceps or other devices, has several technical limitations. Mechanical lithotripsy is less effective in stones >2 cm, stone composition, or anatomic location (high within the hepatic parenchyma). Electrohydraulic and laser technologies have been used successfully for lithotripsy in cholangiography. Electrohydraulic lithotripsy, which creates a small shockwave capable of stone fragmentation through creation of an electric high-voltage spark between two isolated electrodes, has a higher risk of duct damage because of poor targeting. Laser lithotripsy is more expensive but has several advantages including greater precision in targeting stones and smaller caliber probes. Recurrence is reported in up to one-third of patients with intrahepatic stones and is most common when intrahepatic strictures are present. Multiple sessions of cholangioscopy with lithotripsy are often required in cases with multiple biliary stones for complete clearance.

Malignant Causes of Biliary Obstruction

The most common causes of malignant biliary obstruction are pancreatic adenocarcinoma and cholangiocarcinoma (including Klatskin tumor), among others (see Table 2). The initial management of cholangitis with a suspected malignant etiology is the same as for a benign stricture—prompt treatment with intravenous antibiotics, resuscitation in the setting of sepsis, and prompt placement of a percutaneous biliary drain to decompress the biliary system. Most

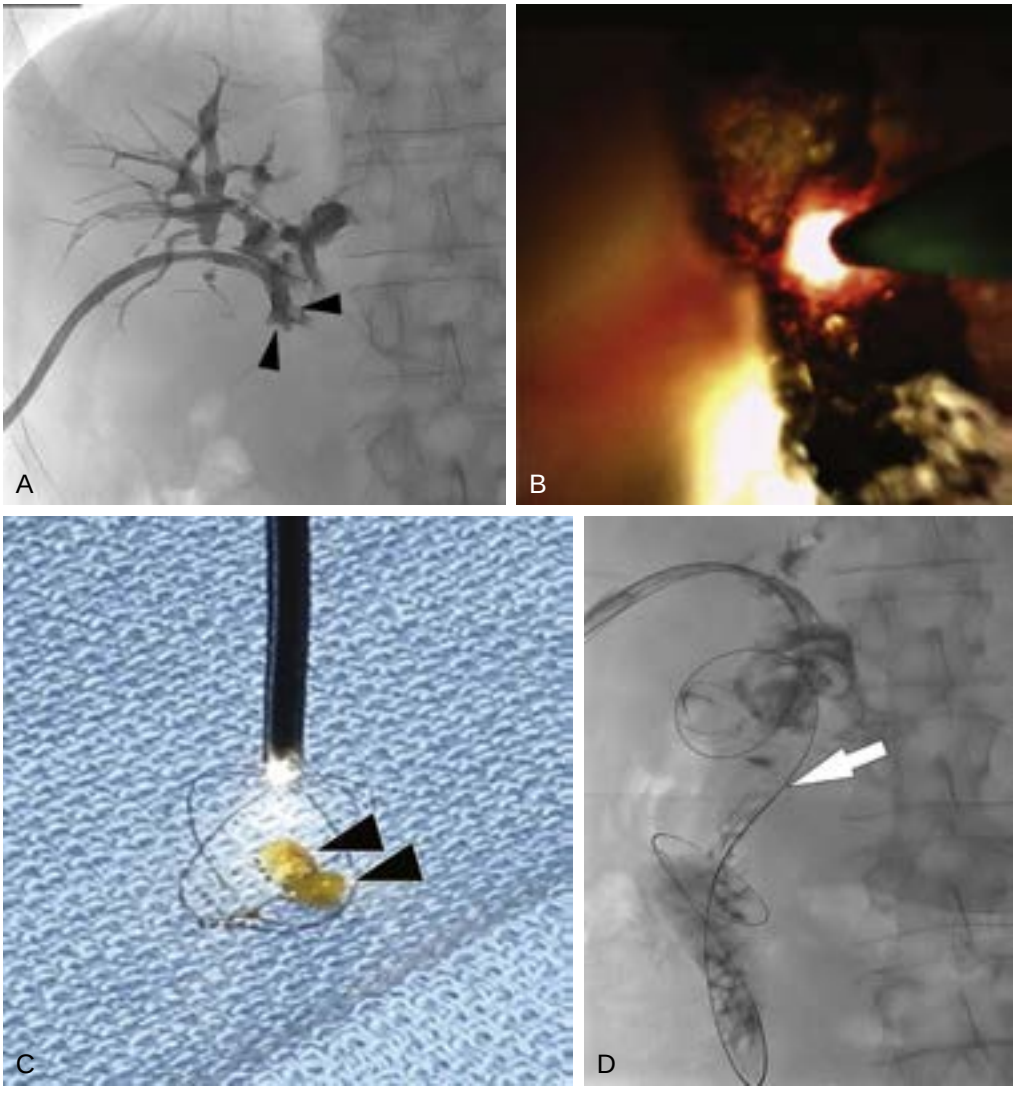


FIG. 4 Images from percutaneous lithotripsy, stone removal, basket. Patient status post-Whipple with obstructing stones at hepaticojejunostomy stricture. **(A)** Cholangiogram through percutaneous anchor biliary drain shows failure of contrast to move past the stricture, with multiple filling defects representing stones *(arrowheads)*. **(B)** Laser lithotripsy of large stone. **(C)** Multiple stone fragments *(arrowheads)* after being removed percutaneously using a basket. **(D)** Wire *(arrow)* able to be passed beyond the stricture after stone removal with contrast free flowing in the jejunal loop.

patients with malignant biliary obstruction, thankfully, are more likely to present with painless jaundice, and in this scenario, initial evaluation with ERCP is generally preferred.

Management of biliary obstruction due to a malignant etiology is often more complicated than treating benign causes of biliary obstruction. Thus, consideration of the patient's underlying malignancy, stage, the patient's functional status, and importantly whether the tumor is deemed resectable or unresectable is necessary. For patients who meet (or are believed will eventually meet) criteria for surgical resection, either ERCP or transhepatic percutaneous interventions can be performed for biliary decompression. Occasionally placement of a Flexima (Boston Scientific, Natick, USA) biliary catheter is indicated, which can act as a bridge between early intervention and definitive surgical management.

In patients deemed unfit for surgery due to comorbidities or unresectable tumors, biliary stenting is performed. After cholangioscopy, endobiliary biopsy with brush probes and endoscopic forceps (Table 5) is performed to provide definitive diagnostic pathology, which is particularly important in patients who will proceed to chemotherapy or radiotherapy (Fig. 5). Following biopsy, the obstructing lesion is crossed using a combination of a catheter and a wire system. After the lesion is crossed, a stent can be placed. In patients who are deemed unresectable with a limited life expectancy (generally <12 months), an internal stent is placed with the distal end optimally across the ampulla. Hilar strictures may require placement of stents from both the right and left hepatic ductal systems. These uncovered metal stents are considered permanent in the sense that the patient's tumor is expected to grow into the stent, which is why they are only indicated in patients with a limited lifespan. Covered stents have a longer patency rate and are preferred over uncovered stents (Fig. 6).

Once a patient is deemed unresectable, involvement of the surgical team ceases, and management is primarily driven by medical oncologists and palliative care physicians. Nonetheless, surgical oncologists may become aware of complications of either endoscopic or percutaneously placed metal or biliary stents. Stents can occasionally block due to either biliary sludge or tumor recurrence; in the case of tumor recurrence, the tumor can grow through the biliary stent struts or overgrow into the proximal or distal ends. In such cases, either a new, longer stent can be inserted into the blocked one, with or without balloon dilation (cholangioplasty), or into a percutaneous catheter.

SUMMARY

Transhepatic access for obstructive jaundice provides several therapeutic options for patients with biliary obstruction. A range of therapeutic options is available including emergent drainage, endoluminal biopsy, biliary stricture dilation, long-term stenting, and endoprosthesis for palliation. Direct visualization with cholangioscopy may assist in the treatment of retained intrahepatic stones. Recognition and management of complications of percutaneous biliary drains are important for both the surgeon and interventional radiologist. The multidisciplinary approach to treating patients with both benign and malignant etiologies of biliary obstruction is central to management.

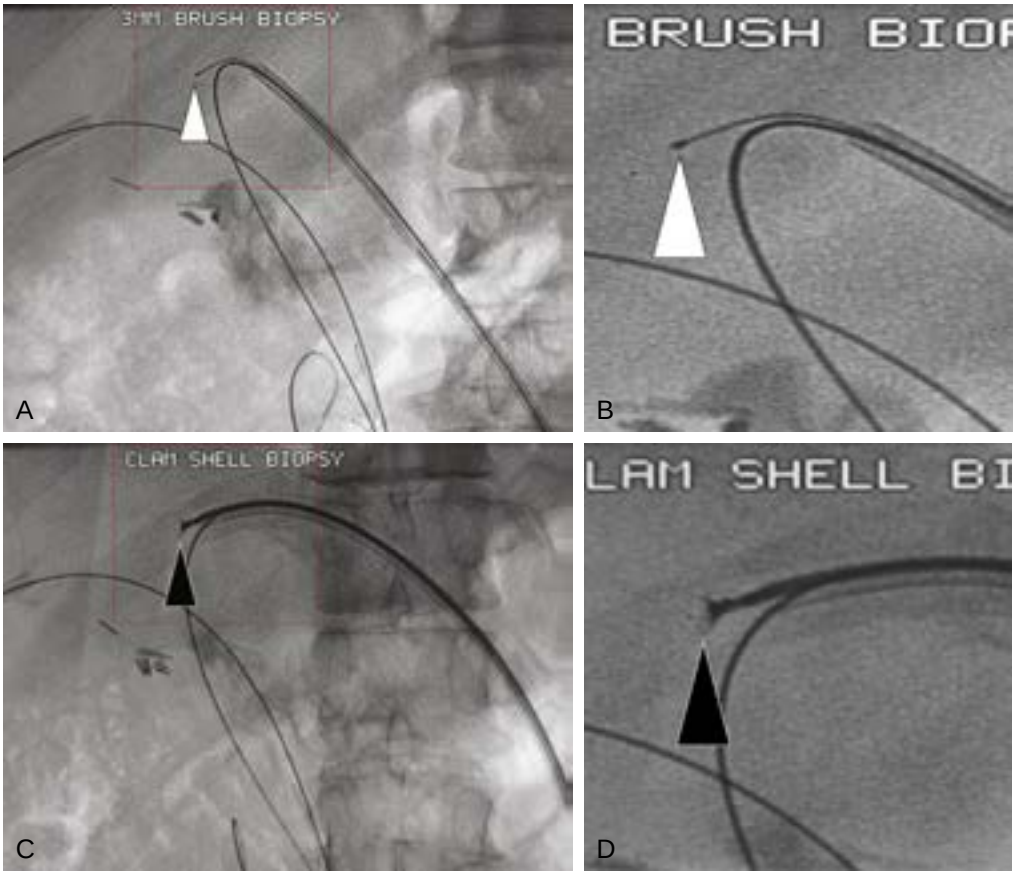
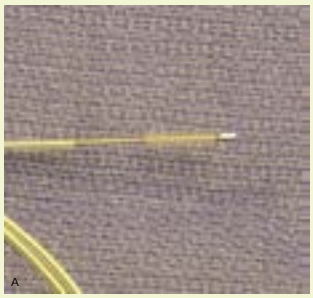


FIG. 5 Endobiliary biopsy. Percutaneous endobiliary biopsy. After the biliary catheters are removed over wires, a sheath is placed with its tip at the suspect lesion site. **(A** and **B)** Through the sheath, the operator first obtains three brush biopsy samples *(arrowheads)*. **(C** and **D)**. Three clamshell biopsy samples *(arrowheads)* are then obtained. Clamshell biopsies result in mild bleeding and may obscure the results of the brush biopsy if done first.

TABLE 5 Endobiliary Biopsy

		Sensitivity (%)	Negative Predictive Value (%)	Specificity (%)
	Brush biopsy (× 3)	70	50	45
	Clamshell biopsy (× 3)	90	80	95

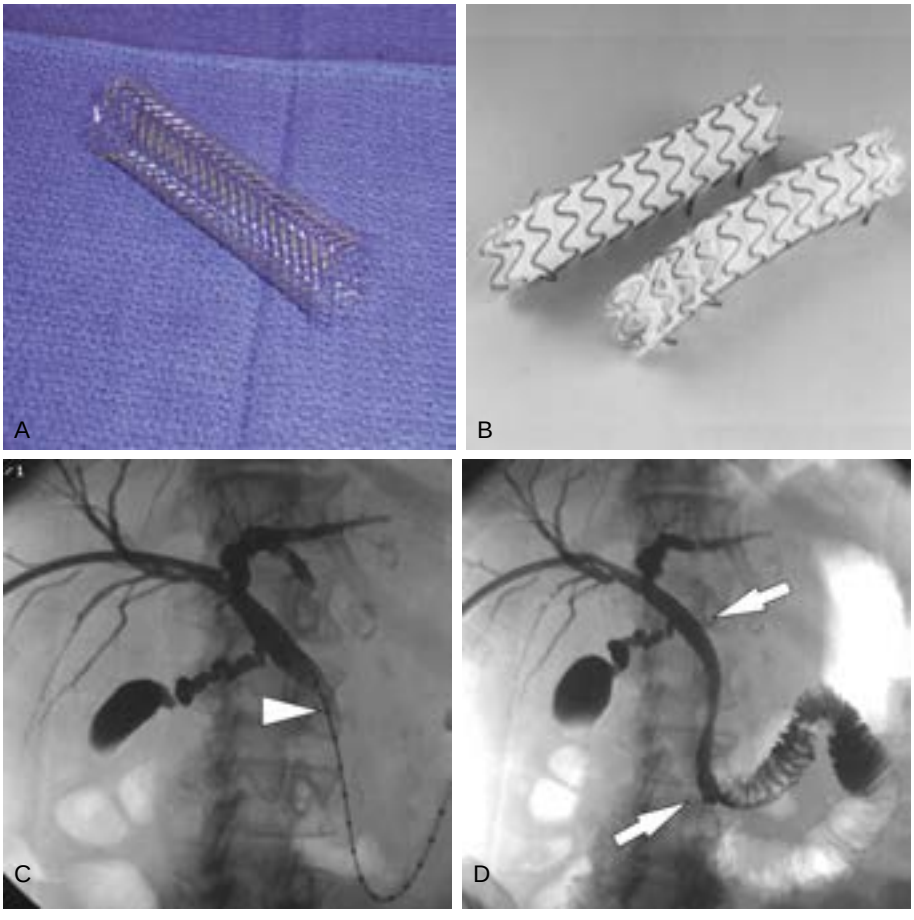


FIG. 6 Internal biliary stents. Both bare **(A)** and covered **(B)** biliary stents can be used. However, the patency rate of covered stents is more than double that of the uncovered ones and should be the default device. Because all stents eventually occlude, stents are reserved for unresectable malignant strictures with a patient life expectancy of less than 1 year. **(C)** Percutaneous cholangiogram in a patient with unresectable pancreatic cancer shows complete occlusion at the distal CBD *(arrowhead)*. **(D)** Cholangiogram after placement of a covered internal stent (*between arrows*); contrast is noted freely flowing into the duodenum.

Suggested Readings

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Obstructive Jaundice: The Role of Endoscopic Intervention

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CLINICAL PRESENTATION

Obstructive jaundice is the clinical manifestation of impaired flow of conjugated bilirubin through the biliary tree and into the duodenum. Cholestasis impairs clotting and immunologic responses, which may lead to an increased risk for cholangitis. Some of the more common symptoms of cholestasis can include fatigue, pruritus, darkened urine, and clay-colored stools. The presence or absence of abdominal pain is an important part of the clinical history as it may allude to the underlying cause of disease. The most common causes of painful obstructive jaundice are biliary duct stones, whereas painless obstructive jaundice is most often due to malignancy. A history of fever is critical to identify as it significantly raises concern for cholangitis. The main causes of extrahepatic cholestasis are summarized in Box 1.

The evaluation of a patient with obstructive jaundice depends largely on the pattern of liver biochemical test abnormalities.

BOX 1 Causes of Extrahepatic Cholestasis

Malignant

Cholangiocarcinoma
Pancreatic carcinoma
Gallbladder carcinoma
Ampullary carcinoma

Benign

Choledocholithiasis
Primary or secondary sclerosing cholangitis
Benign biliary strictures
Choledochal cyst
Parasites
Hemobilia
Pancreatic pseudocysts
Pseudotumoral chronic pancreatitis
Duodenal diverticulum
Ampullary scars
Heterotopic gastric mucosa

Congenital

Biliary duct atresia
Caroli's disease

Alkaline phosphatase (AP) is a serum enzyme primarily derived from the liver and bone. A threefold to fourfold elevation in AP is seen in up to 75% of patient with cholestasis. In cases of diagnostic uncertainty, a 5'-nucleotidase (5NT) and gamma-glutamyl transpeptidase (GGT) may correlate well with hepatobiliary disorders as they are not elevated in disorders of bone. As a disorder of conjugated bilirubin, obstructive jaundice is associated with a rise in direct bilirubin, which accounts for more than 50% of the elevation in the total bilirubin. Depending on the duration of symptoms and severity of obstruction, coagulation as measured by the prothrombin time (PT) can be altered. Elevations can be observed in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In choledocholithiasis, it is common to observe an ALT greater than three times the upper limit of normal. However, the typical AST and ALT elevation seen in the setting of obstructive jaundice is well below levels seen in viral or ischemic hepatitis, which can easily be in the thousands. Finally, serum lipase enzyme elevation can be common in the setting of obstructive jaundice. Small bile duct stones are more prone to cause acute pancreatitis compared with larger stones. Obstructing masses may also compress the pancreatic duct, causing dilation, which can be used to differentiate malignant from benign masses.

EVALUATION OF OBSTRUCTIVE JAUNDICE

Several different noninvasive imaging techniques can be performed to identify the cause of obstructive jaundice with variable sensitivities and specificities. Transabdominal ultrasound (US) is the initial imaging modality of choice for suspected common bile duct (CBD) stones. The presence of biliary dilation and the level of obstruction can be reliably demonstrated with US; however, the exact cause can be determined in only two-thirds of patients. The sensitivity for intraductal stones falls significantly to roughly 21% to 63%.

Further imaging tests such as computed tomography (CT), endoscopic US (EUS), or magnetic resonance cholangiopancreatography (MRCP) are usually needed to detect the level and cause of obstruction. The utility of the CT scan in the evaluation of a dilated bile duct depends on the cause. It is highly sensitive for the detection of pancreatic tumors, especially those greater than 2 cm. MRCP is an excellent noninvasive imaging modality for evaluation of the biliary ducts and has an overall sensitivity rate of 95% in detecting biliary obstruction. Furthermore, in choledocholithiasis, MRCP is the noninvasive test of choice for the detection of CBD stones with a high sensitivity and specificity; however, it lacks the therapeutic advantage offered by endoscopic retrograde cholangiopancreatography (ERCP).

The differentiation of a benign from a malignant biliary stricture on MRI/MRCP can be challenging. EUS can be used to detect tumors at the hepatic hilum, along the biliary ducts, in the ampullary region, and the pancreatic head. This modality also helps in staging by identifying vascular invasion, local tumor spread, and lymph node metastases, although distant lymph node and hepatic metastases are better seen on CT imaging. EUS also has a diagnostic advantage in

that fine-needle aspiration samples from tumors can be collected during the procedure. The efficacy of EUS examination in distal biliary strictures is further augmented with the addition of fine-needle aspiration to provide a sensitivity of 84% to 91% and a specificity of 71% to 100%.

OVERVIEW OF ENDOSCOPIC APPROACHES TO THERAPY AND MAJOR ADVERSE EFFECTS

Endoscopic Retrograde Cholangiopancreatography

ERCP is primarily a therapeutic procedure effective in the nonsurgical management of several pancreatic and biliary disorders, most commonly removal of bile duct stones and relief of malignant obstructive jaundice. During ERCP, a specialized side-viewing endoscope is advanced to the descending duodenum to identify the major papilla. Different accessory instruments including sphincterotomes, guidewires, balloon or catheter dilators, extraction balloon, baskets, and stents (plastic vs. metallic) can then be advanced into either or both the bile and pancreatic ducts depending on the cause of obstructive jaundice. The ducts are opacified by injection of an iodinated contrast permitting their radiologic visualization and therefore allowing for a variety of therapeutic interventions. Selective cannulation of the ducts can usually be accomplished in more than 90% of the cases. Furthermore, the study can be accurate in establishing the location, character, and length of strictures in the bile and/or pancreatic ducts, as well as facilitating drainage in the same session. The main indications for when to consider ERCP and when not to are included in Box 2.

The American Society for Gastrointestinal Endoscopy (ASGE) recommends preprocedure testing in the following settings:

1. Pregnancy testing for women of childbearing potential who provide an uncertain pregnancy history or who have a history suggestive of a current pregnancy.
2. Coagulation studies for patients with active bleeding, known or suspected bleeding disorder, and increased risk of bleeding from medication use.
3. Chest radiograph for patients with new respiratory symptoms or decompensated heart failure.
4. Blood typing and hemoglobin/hematocrit for patients with preexisting significant anemia or active bleeding, or in case of high risk of significant blood loss during the procedure.
5. Serum chemistry testing for patients with significant endocrine, renal, or hepatic dysfunction.

BOX 2 Indications for ERCP

Indications

Biliary drainage of jaundice from biliary obstruction
Bile duct stone removal (Choledocholithiasis/cholangitis)
Biliary stenting for strictures and leakage
Pancreatitis of unknown etiology
Biliary or pancreatic duct tissue sampling
Sphincter of Oddi manometry
Balloon dilation of the duodenal papilla or ductal strictures
Choledochocele involving the major papilla
Sphincterotomy

Not Indicated

Evaluation of abdominal pain of obscure origin in the absence of objective findings that suggest biliary or pancreatic disease
Evaluation of suspected gallbladder disease without evidence of bile duct disease
As further evaluation of proven pancreatic malignancy unless management will be altered

Contraindications

Unstable patient
Relative depending on alteration of anatomy and severity of coagulopathy

Endoscopic Ultrasound with Biliary Drainage

In cases where bile duct access cannot be obtained with ERCP due to challenging cannulation, altered gastrointestinal anatomy, ampullary distortion or diverticulum, gastric outlet obstruction, or in situ duodenal stents, endoscopic ultrasound with biliary drainage (EUS-BD) is an alternative nonsurgical therapeutic option. EUS-BD is performed by using either: (1) rendezvous (RV) technique, (2) transluminal (TL) stenting, or (3) EUS-guided antegrade transpapillary (or transanastomotic) biliary stent placement. These different approaches are outlined in Figure 1.

In EUS-BD, an echoendoscope is positioned within the gastric fundus to access the intrahepatic ducts or in the extrahepatic bile duct. A 19-gauge fine-needle aspiration needle is used to puncture the bile duct, and then access is confirmed with EUS or with contrast injection and fluoroscopic confirmation. In the RV technique, a guidewire is advanced into the bile duct and, under fluoroscopic guidance, is advanced transpapillary into the duodenum allowing for stent placement in a standard ERCP approach over the wire. In the TL technique, the guidewire is advanced more proximally into the intrahepatic ducts and a puncture site is chosen to create a fistula allowing for a choledochoduodenostomy (CDS) or hepaticogastrostomy (HG). Typically, covered self-expandable metal stents (cSEMS) are used in this process (Fig. 2). The anterograde technique is similar in the initial steps as the previously described techniques with the stent being advanced through the echoendoscope over a guidewire to traverse the stricture and then either the papilla (transpapillary) or anastomosis (transanastomotic). An illustration of the different techniques to achieve biliary access can be seen in Figure 1.

Adverse Events

As it relates to ERCP, post-ERCP pancreatitis (PEP) as defined by the Atlanta classification is characterized by abdominal pain with an elevated amylase or lipase three times the upper limit of normal and is the most common serious adverse event attributed to the procedure. Serum amylase or lipase elevation can be seen in up to 75% of patients post-ERCP. In a systematic review of 108 randomized control trials, the average rate of true PEP was 9.7%. The majority of cases were mild; however, some patients may develop severe pancreatitis. Patients deemed to be at high risk for PEP should receive aggressive intravenous hydration using lactated Ringer's solution, rectal indomethacin, and pancreatic stenting.

Bleeding is a serious adverse event after ERCP and can be the result of endoscopic biliary and/or pancreatic sphincterotomy. The rate of postsphincterotomy bleeding after ERCP is estimated to be 0.3% to 2%. Most of the time, treatment is supportive; however, endoscopic therapy can be indicated with interventions including epinephrine injection at the sphincterotomy site, argon plasma coagulation, and clipping at the sphincterotomy site among others.

Cholangitis is the most common infectious adverse event associated with ERCP, occurring in 0.5% to 3% of cases. The risk of cholangitis is highest in patients with incomplete biliary drainage (hilar cholangiocarcinomas [CCA] and primary sclerosing cholangitis [PSC]) and a history of liver transplantation; therefore, periprocedural antibiotics and meticulous biliary drainage techniques are essential in these patients. Perforations associated with ERCP are rare and can occur in 0.08% to 0.6% of patients. ASGE guidelines

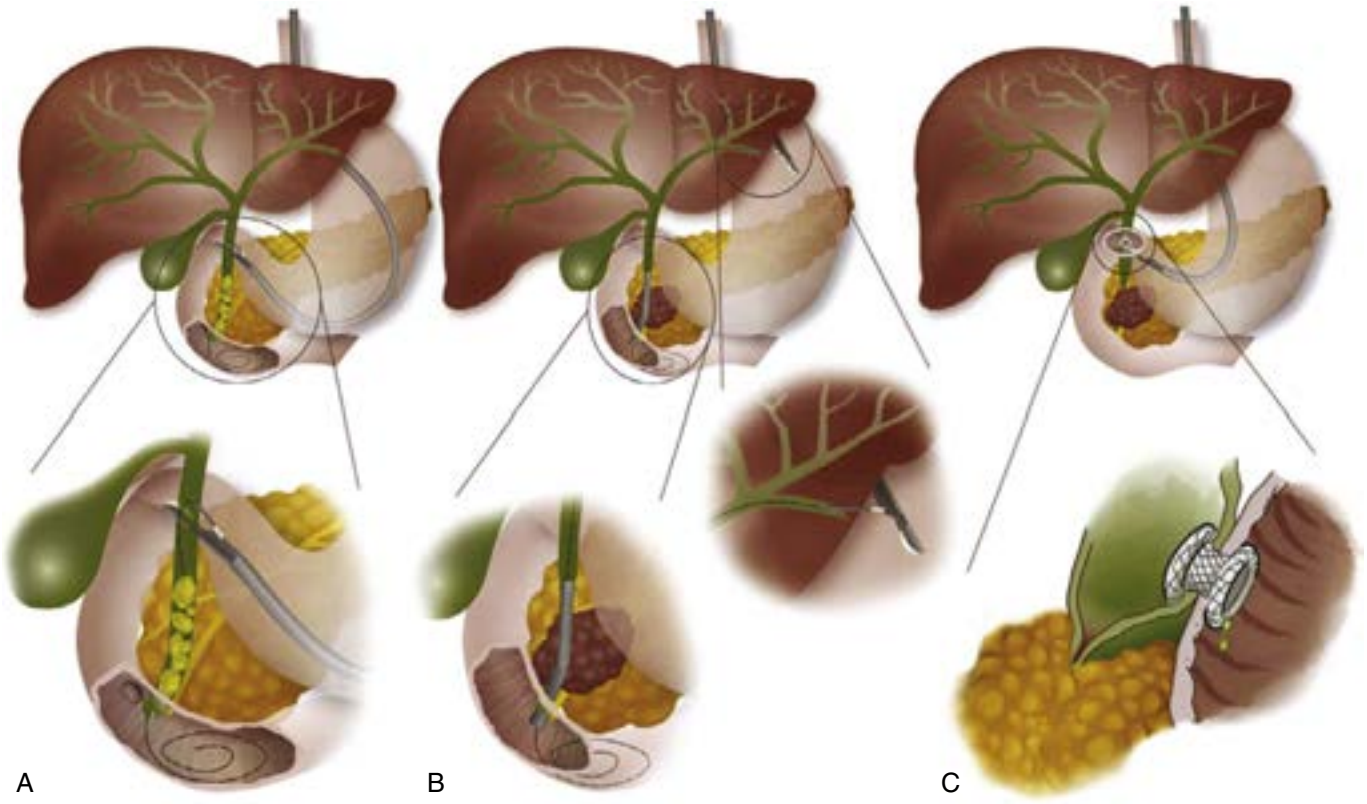


FIG. 1 Illustrations of therapeutic endoscopic ultrasound (EUS) interventions of the pancreaticobiliary and gastrointestinal tract. **(A)** EUS-assisted rendezvous (biliary). **(B)** EUS-guided antegrade stenting. **(C)** EUS-guided choledochoduodenostomy. *(From Martha Meisen, European Society of Gastrointestinal Endoscopy [ESGE].)*

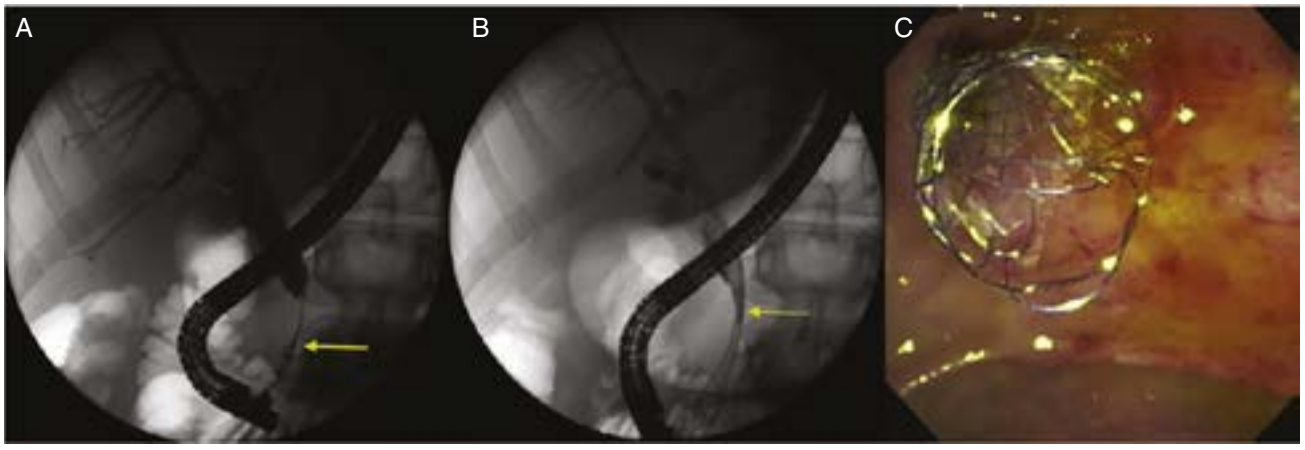


FIG. 2 **(A)** Fluoroscopic image of a guidewire placed across a distal common bile duct stricture in a (*arrow*). **(B)** Fluoroscopic (*arrow*, distal CBD stricture). **(C)** Endoscopic views of metal biliary stent. *(Courtesy Mouen Khashab. Preoperative biliary drainage.* Dig Endosc. *2015;27:265–77.)*

state that in case of suspected periampullary or instrument-related perforations from ERCP without evidence of peritonitis or systemic inflammatory response syndrome, these can be managed nonoperatively.

EUS-BD can achieve high rates of therapeutic success but can be associated with a 10% to 20% risk of adverse events, most of which are mild to moderate in nature. Many endoscopists favor the RV technique because it avoids the creation of a permanent bilioenteric fistula and fistulous tract dilation, which may result in bleeding, pneumoperitoneum, or pneumomediastinum. Data directly comparing EUS-BD with PTBD are limited, but EUS-BD may offer more safety at a significantly lower cost with fewer reinterventions.

APPROACHES IN COMMON CAUSES OF OBSTRUCTIVE JAUNDICE

Choledocholithiasis and Cholangitis

The most common cause of biliary obstruction is choledocholithiasis. In fact, 5% to 10% of those undergoing laparoscopic cholecystectomy for symptomatic cholelithiasis and 18% to 33% of patients with acute pancreatitis will have choledocholithiasis. The ASGE has published a risk stratification scoring system for patients with suspected choledocholithiasis based on age, liver function tests, and abdominal ultrasound findings as seen in Table 1. Similarly, for acute cholangitis, the Tokyo 2018 guidelines utilize clinical predictors to diagnose acute cholangitis as seen in Table 2.

TABLE 1 ASGE Strategy to Assign Risk of Choledocholithiasis in Patients with Symptomatic Cholelithiasis Based on Clinical Predictors

Clinical Predictors of Choledocholithiasis	Clinical Signs	Probability
Very strong	CBD stone on transabdominal US Clinical ascending cholangitis Bilirubin >4 mg/dL	If any, then high probability (>50%)
Strong	Dilated CBD on US (>6 mm with gallbladder in situ) Bilirubin 1.8–4 mg/dL	If both, then high probability (>50%)
Moderate	Abnormal liver biochemical test other than bilirubin Age older than 55 years Dilated CBD on US/cross-sectional imaging	Intermediate to low (10%–50%)

TABLE 2 Tokyo 2018 Criteria for Diagnosing Acute Cholangitis

	Tokyo 2018 Clinical Predictors	Diagnosis
Systemic inflammation	A1) Fever (>100.4°F) and/or shaking chills	*Definite diagnosis*
	A2) Laboratory evidence of inflammatory response	One item in A
	WBC <4000 or >10,000, increased CRP	One item in B
		One item in C
Cholestasis	B1) Jaundice (T. bili ≥2 mg/dL)	*Suspected diagnosis*
	B2) Laboratory evidence of cholestasis	One item in A
	ALP >1.5 STD, GGT >1.5 STD, AST 1.5 STD	One item in either B or C
Imaging	C1) Biliary dilatation	
	C2) Evidence of etiology on imaging (i.e., stent, stricture, stone, etc.)	

ERCP with biliary decompression is the procedure of choice for the treatment of acute cholangitis. A recent systematic review and meta-analysis by Iqbal et al. compared performance of ERCP <48 hours and at >48 hours for cholangitis. ERCP with biliary decompression within 48 hours was associated a nearly twofold reduction in mortality. Khashab et al. demonstrated that a delay >72 hours was associated with an increased composite outcome of death, organ failure, or intensive care unit admission. The role and timing of ERCP in acute biliary pancreatitis remains controversial. The literature suggests there is no evidence that early routine ERCP significantly affects mortality and local or systemic complications of pancreatitis, regardless of predicted severity. Nevertheless, several studies have favored early ERCP in patients with acute biliary pancreatitis and cholangitis concurrently.

Endoscopic sphincterotomy and stone extraction with extraction balloon catheters or wire baskets are successful in more than 90% of cases in achieving bile duct stone clearance. There are other techniques that can be used for stone extraction of difficult bile duct stones such as mechanical lithotripsy using a basket and the digital single operator cholangioscopy system with electrohydraulic lithotripsy or laser lithotripsy, the latter with more than 95% rate of stone clearance with low rate of adverse events. If stone removal is unsuccessful, which usually occurs if stones are large or numerous, then biliary decompression should be accomplished by placement of a biliary stent or nasobiliary drain. In most cases, endoscopic intervention should be followed by cholecystectomy. Biliary symptoms recur twice as commonly in patients whose gallbladder remains in situ with a 5-year risk of significant biliary adverse events leading to cholecystectomy as high as 15%.

Benign Biliary Strictures

ERCP is indicated in the evaluation and treatment of benign biliary strictures, congenital bile duct abnormalities, and postoperative adverse events such as anastomotic strictures and biliary leaks. Biopsies and brushings can help define the etiology of benign biliary strictures and diagnostic yield may increase with cholangioscopy directed biopsies. Benign biliary strictures may be dilated with hydrostatic balloons (maximum biliary dilator diameter 10 mm) or graduated catheters passed over a guidewire. Benign biliary strictures amenable to endoscopic dilation include those secondary to chronic pancreatitis, dominant strictures in PSC, postoperative strictures, and strictures caused by stone disease. Single or multiple plastic stents may be used to maintain patency after initial dilation. Serial endoscopic dilation and maximal caliber stent placement can be used to achieve prolonged ductal patency in most benign postoperative strictures. Fully covered self-expandable metal stents (FCSEMS) are an alternative approach in benign biliary strictures. The cSEMS expand to lumen sizes larger than those of plastic stents, without the risk of tissue ingrowth and embedding such as in uncovered and partially covered metal stents, allowing an indwell time up to 12 months if necessary, and without compromising the ease of removal.

Chronic pancreatitis accounts for 10% of all CBD strictures. Treatment is indicated for patients with jaundice and/or cholangitis, those with significant biliary dilation (12–15 mm) proximal to the stricture, and with abnormal liver function tests (AP >3 times the normal value for 6 months or longer). In patients with bile duct strictures resulting from chronic pancreatitis the use of multiple plastic

stents over a long period (14 months) compared with a single stent increases the chance of long-term overall success to 65.2% with a high risk of restenosis (17%). The FCSEMS has been associated with high levels of success (97%–98%).

In patients with PSC, MRCP is a noninvasive imaging test with comparable diagnostic accuracy to ERCP in the diagnosis of dominant strictures. A dominant stricture is defined as a lumen diameter of 1.5 mm or less in the CBD and 1 mm or less in the common hepatic duct and is seen in 45% to 58% of patients with PSC. In case of unclear results of an MRCP or clinical deterioration of a patient with prior diagnosis of PSC (worsening cholestasis, jaundice, or cholangitis), ERCP can aid in the diagnosis of a dominant stricture. Benign strictures in PSC patients respond well to endoscopic therapy with balloon dilation with or without stent placement. Limited data suggest that balloon dilation is often sufficient and that the use of stents may be associated with an increased risk of adverse events and cholangitis.

Postsurgical strictures occur after orthotopic liver transplantation and laparoscopic cholecystectomy in 3% to 13% and 0.2% to 0.7%, respectively. Strictures recognized early in the postoperative/operative period are often associated with a bile leak caused by direct trauma, whereas delayed presentation is commonly associated with ischemic injury and resultant fibrosis. A commonly used classification for postoperative strictures is the Bismuth classification, based on location of the stricture within the bile tree seen in Table 3. Clinical presentation (elevation of liver function tests, pain, or jaundice) depends on the degree of bile duct obstruction.

Endoscopic treatment usually involves serial placement of large bore plastic stents with exchange every 3 to 4 months. Balloon dilation is high risk in the first 4 weeks of surgery and is typically not performed. Success rates for this approach range from 74% to 90% with recurrence rates as high as 30% within 2 years of stent removal. Distal postoperative biliary strictures (Bismuth I and II) are associated with better success rates compared with proximal hilar strictures (Bismuth III). cSEMS may have a potential benefit in the management of refractory benign biliary strictures due to their large caliber and longer duration of patency allowing them to be left in place longer, resulting in fewer procedures for serial dilations and placement of multiple plastic stents.

TABLE 3 Bismuth Classification for Benign Biliary Strictures

Type	Criteria
I	Low common hepatic duct stricture with a length of common hepatic duct stump greater than 2 cm
II	Proximal common hepatic duct stricture with a common hepatic duct stump less than 2 cm
III	Hilar stricture, no residual common hepatic duct, but the hepatic ductal confluence is preserved
IV	Hilar stricture with involvement of hepatic ductal confluence and loss of communication between right and left hepatic duct
V	Involvement of an aberrant right sectorial duct alone or with concomitant stricture of the common hepatic duct

Malignant Biliary Strictures

The most widely recognized cause of malignant distal biliary obstruction is pancreatic head cancer. Other causes of malignant obstructive jaundice are CCAs, gallbladder cancer, and metastatic tumors compressing the biliary system. ERCP can help identify distal biliary malignancies and enable diagnosis through either brush cytology samples or biopsies of directly visualized ampullary lesion. Only 25% to 30% of the liver volume is necessary to be drained for resolution of jaundice. The right hepatic duct drains 50% to 55%, the left hepatic duct drains 30% to 35%, and the caudate lobe drains 10% of the liver parenchyma. ERCP is the first-line method for biliary decompression.

Only 20% of periampullary cancers are deemed resectable at the time of presentation. Several studies have shown evidence that argue against preoperative biliary drainage in patients with resectable disease. In patients with nonresectable malignant biliary obstruction, effective biliary decompression improves symptoms and enables patients to undergo palliative therapies. With the advent of neoadjuvant chemotherapy used to downstage potentially unresectable tumors in the hope of improving the outcome, preoperative biliary drainage has become even more clinically relevant.

The most common method of achieving biliary drainage is by ERCP and stent placement (plastic or self-expandable metallic stent [SEMS]). In a comparison of stent types, plastic stents have a risk for bacterial biofilm formation increasing risk for cholangitis and stent occlusion. SEMS have a significantly wider diameter and higher patency rate in comparison to plastic stents. A retrospective study in patients of 272 patients who received preoperative drainage showed stent patency was significantly greater in the SEMS versus plastic stent group (125 days vs. 43 days, $P < 0.001$). Covered SEMS are designed to prevent tumor ingrowth into the stent through the stent interstices. They are also removable as the covering prevents embedding of the stent. A meta-analysis comparing cSEMS compared with uncovered SEMS involving eight studies concluded that the group of patients with cSEMS had lower incidence of adverse events, with no significant difference in dysfunction.

Malignant hilar strictures are categorized according to the Bismuth-Corlette classification (Fig. 3). At the time of presentation, only a minority (<30%) of patients with hilar CCA are candidates for resection or transplantation. In patients with predicted survival greater than 3 months, uncovered cSEMS are superior to plastic stents for palliation with respect to outcome and cost-effectiveness. Adequate biliary drainage can be achieved with unilateral, bilateral

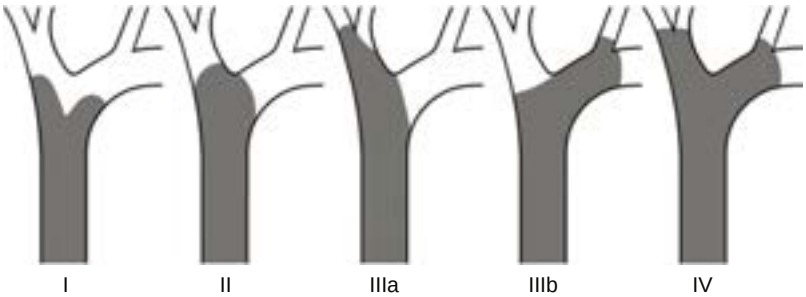


FIG. 3 Bismuth-Corlette classification of hilar cholangiocarcinoma. *HDC*, Hepatic duct confluence; *LHD*, left hepatic duct; *RHD*, right hepatic duct *(From DeOlveria ML, Schuluck RD, Nimura T, et al. New staging system and a registry for perihilar cholangiocarcinoma.* Hepatology. *2011;53:1363–1371.)*

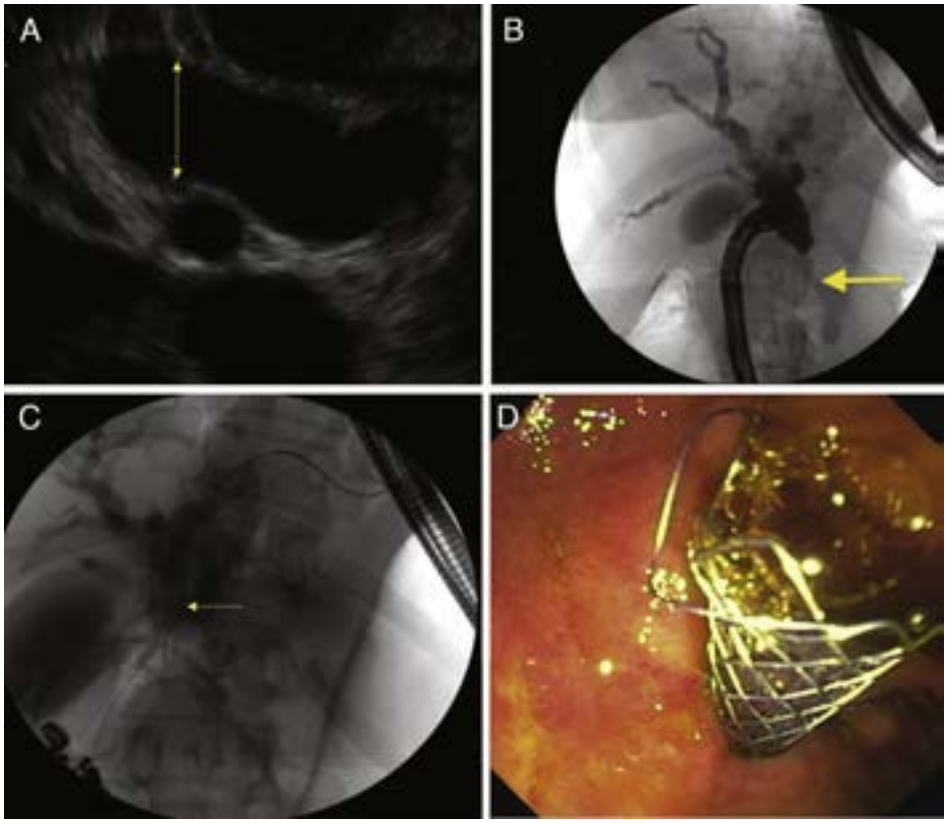


FIG. 4 **(A)** Endoscopic ultrasound image of a dilated common bile duct (CBD). **(B)** Cholangiogram obtained after EUS-guided bile duct puncture and contrast injection demonstrating a distal CBD stricture *(arrow)*. **(C)** Fully covered metallic stent is placed over a wire across the bile duct and duodenal bulb (choledochoduodenostomy). **(D)** Endoscopic view of stent. *(Courtesy Mouen Khashab. Preoperative biliary drainage.* Dig Endosc. *2015;27:265–77.)*

side-by-side, or bilateral stent-in-stent approaches, with evidence currently lacking as to which of these approaches is optimal. The Asian-Pacific consensus suggests that for patients with low-grade hilar obstruction (Bismuth I and II), endoscopic stenting is considered a less invasive approach with acceptable outcome. In contrast, in patients with advanced hilar obstruction (Bismuth III and IV), endoscopic stenting had a lower success rate of cholestasis palliation and a higher rate of post-ERCP cholangitis, making percutaneous stenting a better approach for these patients. In patients with potentially resectable hilar CCA, the Asia-Pacific consensus recommendations are to not perform routine preoperative biliary drainage. Nevertheless, in case of hepatectomy or hepatic vein embolization, some experts prefer to achieve drainage via percutaneous approach.

EUS-BD can play an important role in biliary decompression in patients who are not deemed candidates or fail ERCP (Fig. 4). Transluminal stents can be placed by CDS or HGS. Transpapillary stents can be placed using the EUS-rendezvous technique (retrograde) or EUS-antegrade approach described earlier. The overall success rate is high at 81% with complication rates of approximately 15%, but this can be highly operator-dependent.

Suggested Readings

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Management of Acute Necrotizing Pancreatitis

Ryan B. Morgan, MD, and John C. Alverdy, MD

Acute pancreatitis is the leading cause of gastrointestinal-related hospitalization in the United States, with an estimated incidence of 15 to 45 per 100,000 per year. The severity of acute pancreatitis varies widely among patients, ranging from self-limited episodes to prolonged hospitalization and death from infected necrotizing pancreatitis. The most common causes of pancreatitis include excess alcohol use, the presence of gallstones, hypertriglyceridemia, post–endoscopic retrograde cholangiopancreatography (ERCP), hypercalcemia, genetic disorders, and autoimmune disease; in many cases, there is no clear etiology. Acute pancreatitis occurs across gender and age, though it is more common in older patients and in African Americans. In this chapter, we will discuss the evaluation and management of patients with acute necrotizing pancreatitis, with a particular focus on endoscopic and surgical approaches to infected necrotizing pancreatitis.

DIAGNOSIS AND EVALUATION

The diagnosis of acute pancreatitis requires two of the following three criteria: (1) acute-onset epigastric abdominal pain, often radiating to the back; (2) serum lipase or amylase levels greater than at least three times the upper limit of normal; (3) findings on imaging suggestive of acute pancreatitis, most commonly on computed tomography (CT) but potentially on magnetic resonance imaging (MRI) or abdominal ultrasonography. For patients who meet clinical and serologic criteria for acute pancreatitis, diagnostic imaging is optional. Early CT is best used when pancreatitis is suspected but there is diagnostic uncertainty because of atypical symptoms or nonelevated serum enzyme levels. It may also be appropriate in hemodynamically unstable patients to rule out other life-threatening diagnoses such as mesenteric ischemia or bowel perforation.

As part of the initial evaluation, the etiology of acute pancreatitis should be fully investigated (Box 1). Many of these pathologies, including alcohol use, trauma, recent instrumentation, and hereditary pancreatitis, can be quickly determined by taking a thorough history. Suspected gallstone pancreatitis should be evaluated with right upper quadrant ultrasonography or MRI. Hypercalcemic pancreatitis should be evaluated with serum calcium and parathyroid hormone (PTH) levels to evaluate for underlying hyperparathyroidism. Similarly, hypertriglyceridemia-related pancreatitis can be evaluated by collecting serum lipid levels. It is important to note that serum triglyceride levels may be elevated secondary to pancreatitis as well; persistent elevation after the resolution of acute pancreatitis in the absence of other clear etiologies would support a diagnosis of hypertriglyceridemia-related pancreatitis.

For many patients, the workup for underlying etiologies is unrevealing, leading to the diagnosis of idiopathic pancreatitis. Recurrent idiopathic pancreatitis should prompt further workup for rarer causes. A CT of the abdomen should be obtained in all cases of recurrent pancreatitis. Endoscopic ultrasound (EUS) can also be considered to evaluate for neoplasm and microlithiasis. Magnetic resonance cholangiopancreatography (MRCP) with secretin stimulation can detect neoplasms as well as uncommon anatomic abnormalities. If none of these measures reveal a diagnosis after a patient's second episode of acute pancreatitis, then genetic counseling should be provided.

Multiple scoring systems have been applied to acute pancreatitis patients to predict severe episodes. Currently, the recommended system for evaluating severity both at presentation and at 48 hours post-admission is the systemic inflammatory response syndrome (SIRS) criteria. Persistent SIRS lasting >48 hours is associated with a 25% mortality rate compared with 8% for SIRS that resolves within 48 hours. Other measures of severity have not been shown to be superior to SIRS; these include single serum markers such as C-reactive protein and procalcitonin as well as multifactorial scoring systems such as APACHEII, Ranson's Criteria, Balthazar's CT Severity Index, and the modified Glasgow score.

INITIAL MANAGEMENT

Fluid Resuscitation

Many patients with acute pancreatitis present in a hypovolemic state resulting from both their symptoms (i.e., anorexia, vomiting) and fluid sequestration/extravasation secondary to inflammation. Intravenous fluid resuscitation should be tailored to each patient, though most cases will require large-volume resuscitation (2500–4000 mL) within the first 24 hours. Traditional teaching suggested that patients should remain on rates of isotonic fluid as high as 20 mL/kg/hour with no enteral nutrition until their acute symptoms resolve; however, more recently these practices have been shown to increase the risk of morbidity and mortality. The most recent guidelines from the International Association of Pancreatology/American Pancreatic Association (IAP/APA) recommend goal-directed resuscitation with a starting rate of 5 to 10 mL/kg/hour. Metrics to guide resuscitation include noninvasive measurement of heart rate, mean arterial pressure, and urinary output. Invasive measurement of stroke volume or pulse pressure variation and central venous pressure can also be used as well as repeated hematocrit levels. Ringer's lactate is the preferred fluid for initial resuscitation. Though challenging, every effort should be made to avoid both over-resuscitation and under-resuscitation. Over-resuscitation can lead to acute lung injury, abdominal compartment syndrome, and increased mortality, whereas inadequate resuscitation increases the risk of end organ damage and pancreatic necrosis from hypoperfusion.

BOX 1 Etiologies of Acute Pancreatitis

Gallstones
Alcohol use
Instrumentation (i.e., ERCP)
Hypertriglyceridemia
Hypercalcemia
Hereditary (e.g., *PRSS1* mutation)
Autoimmune
Neoplasm
Toxins
Anatomic anomalies (e.g., pancreatic divisum)
Infection
Ischemia
Idiopathic

ERCP, Endoscopic retrograde cholangiopancreatography.

Nutrition

Traditionally, patients with acute pancreatitis were kept nil per os until their symptoms resolved and lipase levels normalized. This strategy assumed that enteral nutrition would further stimulate the inflamed pancreas. Newer evidence shows significant benefits to early feeding, however, and current guidelines recommend oral feeding within 24 hours of admission, even if lipase levels have not normalized. Patients with mild to moderate acute pancreatitis who can tolerate a diet should be started on a low-fat or normal solid diet without a trial of a liquid or soft diet. In severe cases or in patients who do not tolerate an oral diet, nasogastric or nasojejunal feeds should be attempted once the patient is hemodynamically stable. Early feeding has been associated with decreased length of stay as well as decreased rates of infected pancreatic necrosis, multiple organ failure, and total necrotizing pancreatitis. This is likely caused, in part, by the fact that early feeding improves gut mucosal integrity and stabilizes the gut microbiome. Parenteral nutrition should be reserved for patients who do not tolerate oral or nasoenteric feeding within 5 to 7 days of admission; compared with enteral feeding, parenteral nutrition is associated with an increased risk of infected necrosis and multiorgan failure.

Antibiotics

Prophylactic antibiotics are not indicated in acute pancreatitis without evidence of infection, even in severe cases or in the setting of sterile peripancreatic collections. Historically, pancreatitis patients were given prophylactic antibiotics because of concern that sterile collections could become contaminated and develop into infected pancreatic necrosis. Multiple randomized trials have now shown no benefit to prophylaxis with antibiotics from multiple classes. There are risks to indiscriminate antibiotic prophylaxis as well, including an increased risk of fungal infection and multi–drug-resistant organism development.

Antibiotic administration should be limited to patients with either a diagnosed or suspected infection. The diagnosis of infected pancreatic necrosis can be difficult to make as patients with severe, noninfected pancreatitis and persistent SIRS can develop fever, hemodynamic instability, and leukocytosis, all of which raise concern for infection. If there is any suspicion for infected necrosis, a CT scan should be performed. Gas bubbles within a peripancreatic collection on CT are diagnostic for infected necrosis. Infected necrosis can also be diagnosed using percutaneous fine-needle aspiration of the necrotic collection; this was previously a widespread practice for all suspected cases of infected necrosis but is no longer routinely recommended because of a high false-negative rate (12%–25%) and the risk of contaminating sterile collections. In patients with persistent symptomatic illness without radiographic evidence of infection, there is a 40% rate of occult infection, and fine-needle aspiration may aid in the decision to start antibiotics. Lastly, septic patients with no other likely sources of infection may benefit from empiric antibiotics as most of the pathogens responsible for the septic physiology of acute pancreatitis originate from among the gut microbiota.

When antibiotics are prescribed for suspected or confirmed infected pancreatic necrosis, they should initially provide broad-spectrum coverage including antifungal coverage. The penetration of most antibiotics into necrotic pancreatic tissue is not fully understood, though there is evidence that carbapenems achieve high concentrations within pancreatic tissue after a single dose. In the absence of culture results, broad-spectrum coverage is essential because of the wide range of bacteria implicated in infected pancreatic necrosis. Infections are often polymicrobial, with enteric bacteria most often identified on culture; in a recent study of 137 intensive care patients with infected pancreatic necrosis, the most common bacterium on culture was *Escherichia coli,* though over 100 different species were identified.

Biliary Tract Management

Routine ERCP is not indicated for all patients with gallstone pancreatitis. Most stones will pass through the ampulla into the duodenum without intervention. Retained gallstones in the common bile duct can lead to severe complications, however, and should be removed by ERCP. Patients with evidence of acute cholangitis should undergo ERCP as soon as possible to decompress their biliary system. If choledocholithiasis is suspected without cholangitis, it is reasonable to wait up to 24 to 48 hours to see if the biliary obstruction spontaneously resolves without ERCP. Patients with diagnosed or suspected mild biliary pancreatitis should undergo cholecystectomy during their index admission; cholecystectomy during the patient's initial admission has been shown in a single randomized trial to decrease gallstone-related complications, readmission for recurrent pancreatitis, and mortality.

INTERVENTIONAL MANAGEMENT

Pancreatic Fluid Collections

Patients with acute pancreatitis are at risk for developing a variety of peripancreatic fluid collections, each with distinct characteristics. There are four main categories of pancreatic and peripancreatic fluid collections related to pancreatitis, which are defined broadly by their location, the timing of their formation, and whether they occur in the setting of interstitial edematous pancreatitis or necrotizing pancreatitis.

Most patients with pancreatitis experience interstitial edematous pancreatitis, characterized by enlargement of the pancreas caused by edema with homogenous parenchymal enhancement on CT (Table 1). Fluid collections in the setting of interstitial edematous pancreatitis are defined as *acute peripancreatic fluid collections* (APFC) when they occur within 4 weeks after the onset of symptoms. APFCs are nonencapsulated and generally confined by normal tissue planes. Organized, encapsulated collections that persist past 4 weeks are termed *pseudocysts*. Both APFCs and pseudocysts are fluid-filled and extrapancreatic, though in many cases there is communication with the pancreatic ductal system.

Necrotizing pancreatitis involves necrosis of either the pancreatic parenchyma, surrounding pancreatic tissues, or both. Necrosis occurs in 5% to 20% of pancreatitis cases and most commonly involves breakdown of both the pancreas and surrounding tissues. Nonencapsulated fluid collections within the first 4 weeks after diagnosis of necrotizing pancreatitis are defined as *acute necrotic collections* (ANCs). ANCs may appear homogenous early in their course, similar to APFCs, but over time they adopt a heterogeneous appearance on imaging with both fluid and solid components. Mature, encapsulated collections noted more than 4 weeks after the onset

TABLE 1 Classification of Pancreatic Fluid Collections

	Collection Type	Timing after Onset of Symptoms (wk)	Imaging Appearance (CT or MRI)
Interstitial edematous pancreatitis	Acute peripancreatic fluid collection (APFC)	<4	Homogenous Fluid-filled Nonencapsulated Extrapancreatic
	Pancreatic pseudocyst	≥4	Homogenous Fluid-filled Encapsulated Extrapancreatic
Acute necrotizing pancreatitis	Acute necrotic collection (ANC)	<4	Homogenous (early) or heterogeneous (late) Fluid and solid components Nonencapsulated Extrapancreatic and Intrapancreatic
	Walled-off necrosis (WON)	≥4	Heterogeneous Fluid and solid components Encapsulated Extrapancreatic and Intrapancreatic

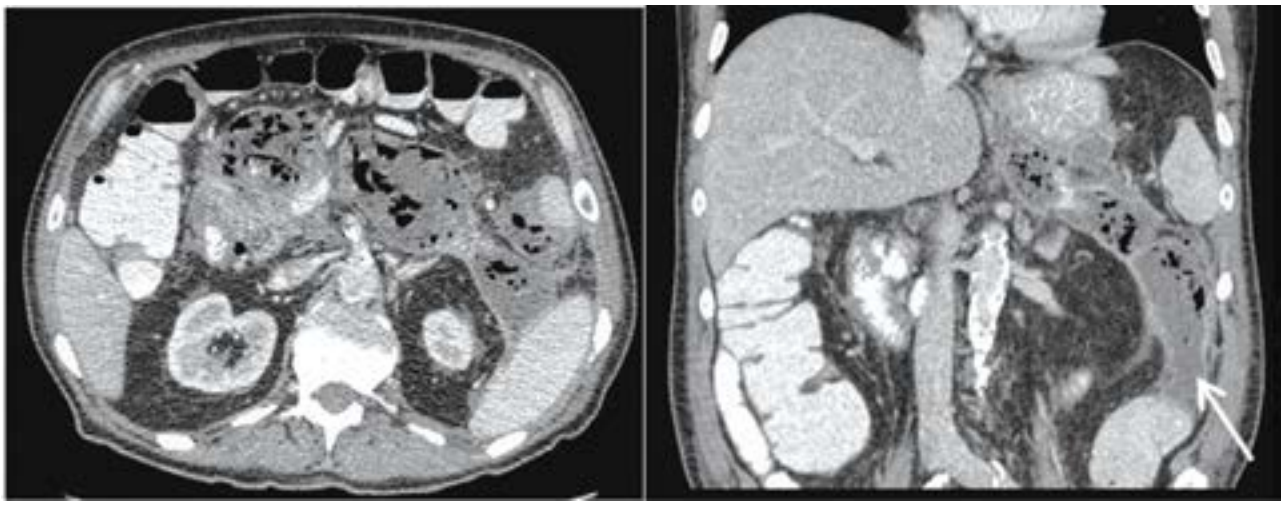


FIG. 1 Infected walled-off pancreatic necrosis.

of necrotizing pancreatitis are called *walled-off necrosis* (WON). As with ANCs, the appearance of WON on CT is usually heterogenous with both intrapancreatic and extrapancreatic components.

Indications for Intervention in Sterile Collections

In general, sterile peripancreatic fluid collections do not require surgical or radiologic intervention. Notable exceptions include larger collections with mass effect leading to gastric outlet obstruction, small bowel obstruction, or biliary obstruction. Concern for bowel ischemia secondary to mass effect may prompt operative intervention as well, and patients who develop abdominal compartment syndrome resulting from their initial resuscitation may require decompressive laparotomy if noninterventional measures (e.g., sedation, paralysis, nasogastric and rectal tube decompression, prokinetics, diuretics) fail to reduce intraabdominal hypertension. Longer-term sequalae that may trigger a surgical or radiologic intervention include pseudoaneurysms, disconnected pancreatic duct syndrome (DPDS), and select patients with persistent failure to thrive. It is important to note that the type of operative or other intervention should be tailored to each indication and will not necessarily follow the paradigm we describe next for infected collections. Percutaneous drainage and necrosectomy should be avoided for sterile collections if possible because of the risk of contamination.

Management of Infected Pancreatic Necrosis

The most common indication for intervention in necrotizing pancreatitis is known or suspected infected pancreatic necrosis. Each type of fluid collection, as discussed earlier, may become infected and require drainage. As described earlier, the diagnosis of an infected collection should be based on the presence of gas within the collection on CT or positive culture results from fine-needle aspiration (Fig. 1). Suspected infections may be based on the presence of sepsis or a condition in which failure to thrive without a clear underlying etiology is present.

Infected necrosis was historically managed with open necrosectomy, though this procedure was complicated by excessively high

rates of morbidity (34%–95%) and mortality (11%–39%). Following the Dutch PANTER trial, there has been a paradigm shift to a step-up approach to infected pancreatic necrosis that begins with minimally invasive interventions. Current alternatives to open necrosectomy, in order of invasiveness, now include endoscopic cystgastrostomy, percutaneous drainage, direct endoscopic necrosectomy (DEN), sinus-tract endoscopic (STE) debridement, video-assisted retroperitoneal debridement (VARD), and surgical transgastric necrosectomy. In broad terms, the step-up approach involves percutaneous or endoscopic drainage followed by minimally invasive or endoscopic necrosectomy for patients who do not improve with drainage alone. Endoscopic and minimally invasive techniques can also be used together for dual-modality drainage (DMD). Although 25% to 55% of patients will improve with drainage only, many will require a "step up" to completely remove their infected necroma. There are no established criteria for when to perform additional procedures; this decision should be tailored to each patient's clinical picture. In the following sections, we will discuss an algorithm to determine the optimal intervention for each patient.

Traditional teaching has held that intervention for infected pancreatic necrosis should be delayed until a minimum of 4 weeks after onset of symptoms. This timing allows for maturation and encapsulation of the collection, demarcating the borders for drainage or debridement. This strategy developed when open necrosectomy was the preferred first-line treatment because of poor outcomes with early debridement and the theoretical risk of a proinflammatory "extra hit" from open surgery in this critically ill patient population. More recent data have suggested that encapsulation is not necessary for safe drainage and that immediate catheter drainage may be feasible. Randomized prospective trials are ongoing to more clearly determine whether early drainage is a safe alternative. For now, delayed intervention remains the standard of care.

Endoscopic Step-Up Approach

Endoscopic drainage is increasingly used as a first-line treatment modality for infected pancreatic necrosis (Fig. 2). Eligibility for endoscopic drainage depends on individual anatomy and the size of the infected collection. Endoscopic ultrasound-guided drainage via a transgastric or transduodenal route requires that the collection be adjacent to these structures. Collections must also be smaller for endoscopic drainage, as larger collections with extension into the paracolic gutters or pelvis are not amenable to endoscopic drainage.

Endoscopic drainage is performed under ultrasound or fluoroscopic guidance. After accessing the collection with a needle, double-pigtail stents can be placed over a guidewire into the collection, draining its contents into the gastrointestinal lumen. Typically, two small-bore (7–10Fr) double-pigtail stents are placed at the time of drainage as well as a nasocystic catheter to perform routine postprocedural lavage. Transgastric drainage is the preferred route, however transduodenal drainage may be necessary for select collections at the head of the pancreas without a clear transgastric window.

Lumen-apposing metal stents (LAMS), a type of self-expanding metal stent, have grown increasingly popular as an alternative to double-pigtail stents. LAMS have a larger diameter and shorter length, hypothetically facilitating increased drainage. LAMS have been associated with decreased number of required procedures and decreased hospital stay, which is significant as a main detractor from endoscopic drainage has been the increased number of required procedures relative to a surgical approach. There are also safety concerns with LAMS as they have been associated with increased pseudoaneurysm bleeding and other stent-related complications. Given this concern for delayed adverse events with LAMS, a CT should be performed at three weeks after placement to assess whether the pancreatic collection has resolved. If the collection has resolved, the LAMS should be removed. For those that do not improve clinically after drainage with either pigtail stents or LAMS drainage, DEN can be performed via the created cystgastrostomy (Fig. 3).

Eligible patients should likely undergo endoscopic drainage as their initial intervention based on multiple recent randomized controlled trials. The Dutch PENGUIN trial initially showed that endoscopic necrosectomy did not provoke as large of an inflammatory reaction as VARD (as judged by IL-6 levels); although this study involved a limited number of patients, the trial also showed decreased mortality and rates of major complications with an endoscopic necrosectomy. The TENSION trial from the same group more recently showed that patients randomized to an endoscopic step-up approach had similar morbidity/mortality but significantly lower rates of pancreatic fistula formation (5% vs. 32%). An endoscopic approach also avoids creation of problematic pancreatico-cutaneous fistulae. Results from the American MISER trial also supported an endoscopic step-up approach, showing similar mortality but significantly fewer major complications than a surgical step-up approach. This study reaffirmed that endoscopic management leads to decreased fistula formation (0% vs. 28%) and showed improved physical quality of life with lower total costs for an endoscopic approach. In this most recent trial, 67% of patients undergoing endoscopic drainage did not require necrosectomy, possibly caused in part by partial use of the LAMS that were not available in previous trials.

Percutaneous Drainage

If endoscopic drainage is not feasible or is not likely to resolve infected pancreatic necrosis, then a surgical step-up approach should be pursued. The initial procedure in this approach is percutaneous drainage. Simple drainage alone will successfully resolve 25% to 55% of infected pancreatic collections, obviating the need for any necrosectomy procedures. In some patients, multiple drainage procedures are required to upsize or otherwise replace drains with diminishing

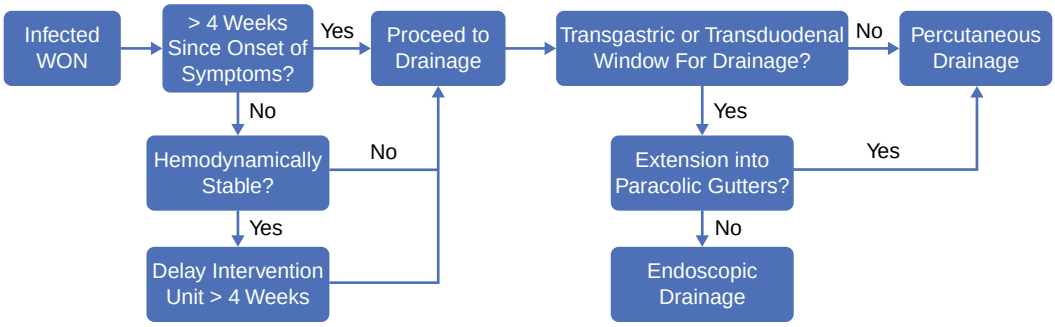


FIG. 2 Decision algorithm for initial intervention in infected pancreatic necrosis.

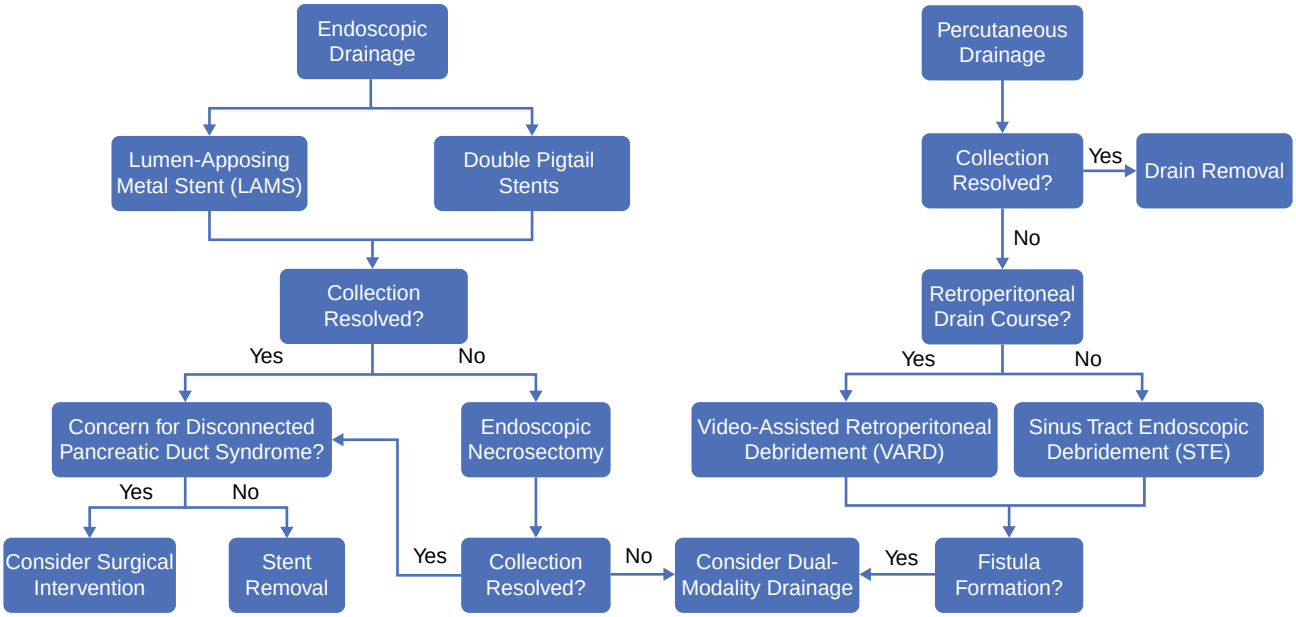


FIG. 3 Endoscopic versus surgical step-up approaches.

output despite continued symptoms or a persistent collection on imaging.

Video-Assisted Retroperitoneal Debridement

If percutaneous drainage is not sufficient, then the next procedure in the step-up approach is a minimally invasive necrosectomy (see Fig. 3). It is important to keep in mind that the route and location of the patient's initial percutaneous drains may dictate further interventions, and a step-up strategy should be in place before initial drain placement. One technique for minimally invasive necrosectomy is VARD, which requires drain placement along a left retroperitoneal course.

This initial drain will serve as a guide for the surgeon performing a VARD in the operating room. For this procedure, the patient is placed in a partial lateral decubitus position with the percutaneous drain prepped into the field. A 5-cm lateral flank incision is made over the percutaneous drain, and electrocautery is used to carry this incision through the retroperitoneum to the necrotic collection. Given the proximity of most collections to critical structures such as the spleen, kidney, and colon, the patient's most recent CT should be carefully studied before dissection to avoid injuries.

Once access to the necrotic collection has been established, suction and irrigation should be used to clear any liquid debris within the cavity. A ring forceps may be used to clear solid necrotic material in superficial collections. For deeper collections, a laparoscope and long, rigid retractors are used for visualization, and laparoscopic graspers can facilitate debridement (Fig. 4). Both free and lightly adherent necrotic material may be removed bluntly, however overly aggressive debridement of the necrosis increases the risk of bleeding. If densely adherent necrotic material is encountered, it can be left in place with a plan for postoperative lavage and potential repeat necrosectomy. Following debridement, drains are placed in the cavity and brought out through stab incisions adjacent to the initial incision. This allows for multilayer closure of the initial incision with decreased risk of wound complications.

Complete debridement is often achievable after a single VARD procedure, and surgeons can use familiar equipment, which is an advantage over STE debridement. Disadvantages include an increased rate of wound complications given the larger initial incision, as well as a relatively high rate of external pancreatico-cutaneous fistulae compared with endoscopic procedures.

Sinus Tract Endoscopic Debridement

An alternative technique for minimally invasive debridement of infected pancreatic necrosis is STE debridement. Like VARD, this procedure follows percutaneous drainage and uses the drain tract as a guide for debridement. Unlike VARD, STE debridement is not limited to a retroperitoneal approach. Collections that require transperitoneal, intercostal, or other less common courses are accessible by STE debridement. This difference in approaches emphasizes the importance of discussing drain placement in detail with the interventional radiologist and developing a strategy for eventual debridement at the time of initial drainage. If possible, the drain should also access the collection at one end; this will facilitate the debridement described in the following sections using a rigid nephroscope.

For STE debridement, the patient may be placed in either a supine or lateral decubitus position depending on the drain location. As with VARD, the drain is prepped into the field. Under fluoroscopic guidance, a guidewire is placed through the drain and into the necrotic collection. After the drain is removed, a nephrostomy balloon dilator catheter is placed over the wire and inflated with contrast to a pressure of 20 psi for 1 minute. After tract dilation, a rigid nephroscope is advanced into the cavity through a 30-Fr working sheath with continuous irrigation to assist with visualization. Graspers are then introduced through the nephroscope to begin debridement. As necrotic material is removed, a working space develops, and the sheath may be advanced. After debridement, a large-bore drainage catheter is placed over the wire and into the cavity. STE debridement with a flexible endoscope has been described as well, though it does not allow for as rapid debridement as a rigid nephroscope. If flexible endoscopy is planned either for debridement or to assess residual necrosis in the cavity, the tract will require additional dilation.

Debridement should be continued until all loose or nonadherent necrosis has been removed. Even more so than in VARD, overly aggressive debridement should be avoided in STE debridement given the difficulty of stopping bleeding during this procedure. If bleeding does occur, direct pressure with gauze packing should be attempted. Alternatively, the working sheath may be advanced past the point of

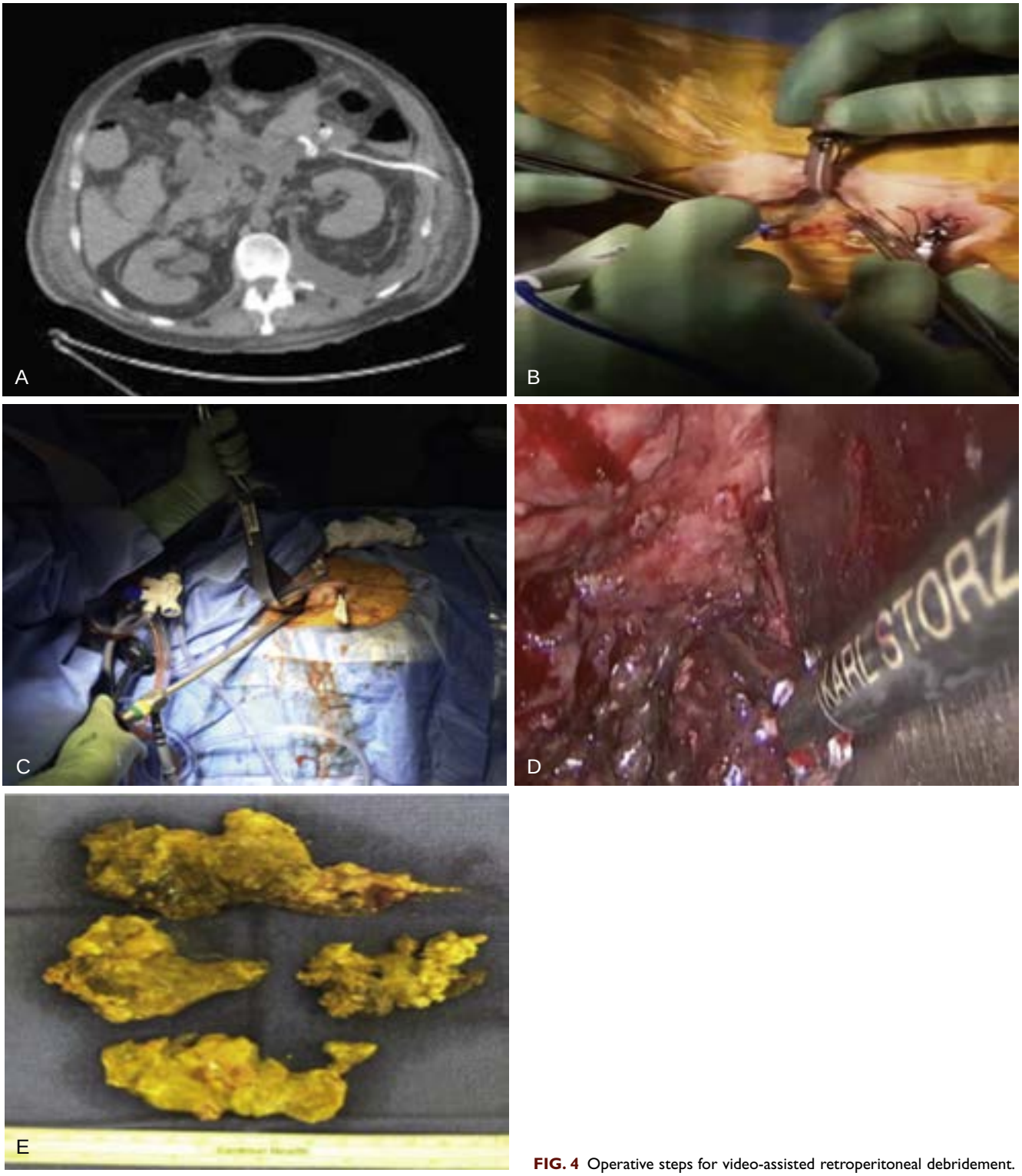


FIG. 4 Operative steps for video-assisted retroperitoneal debridement.

bleeding to "jail" the bleed while the debridement continues distally. The best strategy, however, is to err on the side of caution and avoid bleeding by leaving densely adherent necrosis in place with a plan for repeat debridement after a period of irrigation. If the patient requires irrigation, then a smaller catheter should be placed next to the above-mentioned drainage catheter at the end of the procedure to allow for lavage. This can be accomplished by suturing the drains together and advancing them simultaneously over the guidewire.

Dual-Modality Drainage

DMD is a combination of percutaneous drainage and transgastric endoscopic drainage. This approach combines the advantages of both approaches. Namely, it reduces the formation of external pancreatic fistulae seen in percutaneous drainage while also facilitating drainage of larger collections that cannot be resolved easily by endoscopic drainage alone. With a purely endoscopic approach, multiple necrosectomies are often required for complete resolution; if patients

are slow to resolve, then additional drainage with a percutaneous catheter may shorten their duration of treatment. Similarly, if a patient develops external fistulae after percutaneous drainage, then additional transgastric endoscopic drainage can be used to relieve pressure on the tract.

Surgical Transgastric Necrosectomy

Laparoscopic or open transgastric necrosectomy is an option for surgical drainage of collections limited to the lesser sac. This approach provides the benefit of durable internal drainage while avoiding the risk of external fistula formation. It also allows for complete debridement in one procedure, an advantage over endoscopic procedures that create a similar cystgastrostomy. This operation can be performed through a small upper midline incision or laparoscopically with a 12-mm port at the umbilicus and additional ports in each upper quadrant. A second 12-mm port is generally placed in the right upper quadrant to facilitate use of both a laparoscopic stapler and ultrasound. An anterior gastrotomy is created, and the collection is identified using ultrasonography. A posterior gastrotomy is created, allowing for drainage and debridement with laparoscopic graspers. After adequate debridement, the cystgastrostomy is created between the posterior gastric wall and the cyst capsule using either monofilament nonabsorbable suture or a laparoscopic stapler. Nasocystic catheters for irrigation can be placed under direct visualization as well as postpyloric feeding tubes. At the end of the procedure, the anterior gastrotomy is closed either with a stapler or a two-layered suture closure.

Open Transperitoneal Necrosectomy

Despite the paradigm shift to a step-up approach to infected pancreatic necrosis, there remains a role for open necrosectomy in select patients. Open transperitoneal necrosectomy was first described in 1988 by Beger and is performed via laparotomy through bilateral subcostal incisions. The lesser sac is opened, and necrotic material is removed bluntly. At the end of the procedure, two large bore drains are left in place for postoperative irrigation and drainage. When counseling patients on this operation, it is useful to keep in mind that often-quoted high mortality rates are generally from studies in which open necrosectomy was performed as the initial intervention instead of the final intervention in a step-up approach. A more recent series of 68 well-selected patients undergoing open necrosectomy at a high-volume center showed a more favorable in-hospital mortality rate of 8.8%.

Postprocedural Irrigation

Following both endoscopic and minimally invasive necrosectomy procedures, catheters may be left within the necrotic cavity to facilitate irrigation. This is particularly useful if the surgeon or endoscopist anticipates the need for a second necrosectomy procedure. Successful irrigation requires separate catheters for inflow and outflow. Following endoscopic procedures, this involves a nasocystic catheter for inflow with double-pigtail stents or a LAMS for outflow. Following surgical drainage, irrigation is performed through percutaneous catheters. Irrigation protocols vary by institution. Irrigation may be either continuous or intermittent every 4 to 6 hours. Normal saline is used as the irrigant, and volumes in described protocols range from 1 L total per day to 200 mL/hour (4.8 L/day).

KEY PANCREATITIS-RELATED COMPLICATIONS

Chronic Pancreatitis and Pancreatic Insufficiency

Many patients who survive episodes of necrotizing pancreatitis develop chronic pancreatitis with repeated pain episodes and potential exocrine and endocrine pancreatic insufficiency. A recent review of patients with necrotizing pancreatitis estimated that 16% to 45% will be diagnosed with either chronic pancreatitis, insufficiency, or both on long-term follow-up. Endocrine and exocrine insufficiency can be either coincident or diagnosed individually, and both may be diagnosed up to several years after the index episode of pancreatitis. Exocrine insufficiency may be treated with enzyme replacement therapy, while endocrine insufficiency requires insulin supplementation.

Splanchnic Vein Thrombosis

Thrombosis of the portal, splenic, and superior mesenteric veins is common in acute necrotizing pancreatitis, occurring in 16% to 36% of patients. These thromboses form as a result of inflammation surrounding the splanchnic vasculature, compression from pancreatic fluid collections, and likely altered coagulation during acute pancreatitis. Symptoms range broadly from asymptomatic thromboses to more severe complications such as bowel ischemia, chronic portal hypertension, gastric variceal bleeding, symptomatic splenomegaly, and hepatic failure. Treatment typically involves anticoagulation, though there are little data on the ideal length and timing of anticoagulation. Limited retrospective data suggest that there may be a benefit to prophylactic anticoagulation in acute necrotizing pancreatitis to prevent splanchnic thromboses, however this is not currently recommended in any guidelines because of the risk of hemorrhage.

Disconnected Pancreatic Duct Syndrome

Disconnected pancreatic duct syndrome (DPDS) may also be noted either early or intermediately in pancreatitis patients. DPDS results from necrosis of a central portion of the pancreas, disconnecting a functional pancreatic tail from the main duct leading to the ampulla. If DPDS is identified before any intervention, then the patient's initial intervention should include endoscopic drainage with a soft pigtail stent that can be left in place indefinitely. Use of a LAMS should be avoided. If percutaneous drainage is used, the continuous reaccumulation of pancreatic secretions from the viable tail segment will place the patient at high risk of prolonged drainage and external fistula formation. In select patients, endoscopic stenting may be feasible to reconnect the tail to the ampulla. Up to 80% of patients with diagnosed DPDS will eventually require operative intervention, with the two most common procedures being cystojejunostomy for internal drainage or distal pancreatectomy. The two operations have comparable success rates, though distal pancreatectomy has a higher rate of endocrine insufficiency and usually requires splenectomy.

Pseudoaneurysm

A less common but potentially life-threatening complication from necrotizing pancreatitis is pseudoaneurysm-related bleeding. Pseudoaneurysms form as pancreatic and visceral arteries are bathed in enzyme-rich pancreatic fluid, weakening the vessel walls. Estimates of the incidence of pseudoaneurysm formation in necrotizing pancreatitis range from 1% to 10%, with the splenic and gastroduodenal arteries most commonly involved. Pseudoaneurysms are usually asymptomatic and diagnosed incidentally on imaging. Any pseudoaneurysm occurring in the setting of pancreatitis should be angioembolized as soon as possible to prevent massive hemorrhage from rupture. Patients with undiagnosed pseudoaneurysms may present with a small volume "sentinel" bleed from initial rupture. Sentinel bleeds precede a short window of hemodynamic stability in which angioembolization can be performed before life-threatening hemorrhage occurs from complete rupture of the pseudoaneurysm. In patients with external drains, any new-onset bloody output should be treated as a potential pseudoaneurysm until proven otherwise. In this scenario, either CT angiography or formal angiography in the interventional suite should be performed based on the patient's

hemodynamic stability. Given the difficulty of surgically controlling pseudoaneurysm-related bleeding in the setting of pancreatic necrosis, operative intervention should only be pursued when angiography has failed or is not immediately available for hemodynamically unstable patients.

RECURRENCE PREVENTION

Strategies to prevent recurrent episodes of pancreatitis are dependent on their etiology. All patients who present with gallstone pancreatitis should undergo cholecystectomy. Ideally this should occur during the patient's index admission, though timing may be variable based on the presence of peripancreatic collections. If any collections are present, current recommendations are to delay cholecystectomy until the collections resolve or until 6 weeks after the initial onset of symptoms. This strategy is based on retrospective data that show an increased risk of infected pancreatic necrosis with early cholecystectomy in the setting of peripancreatic collections. If patients eventually undergo open or laparoscopic necrosectomy, then cholecystectomy can be performed simultaneously.

Patients presenting with alcoholic pancreatitis should be enrolled in programs to encourage alcohol abstinence. Given the fact that alcoholic pancreatitis generally occurs after prolonged alcohol abuse, long-term behavioral therapy and counseling may be required. Those with hyperlipidemia-induced pancreatitis benefit from fibrate therapy as well as diet modification. Hypercalcemia causing pancreatitis may be from multiple etiologies, though the most common is hyperparathyroidism, and patients should undergo evaluation for a parathyroidectomy.

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Gallstone Pancreatitis

Katherine A. Morgan, MD, and William P. Lancaster, MD

Acute pancreatitis (AP) is the most common gastrointestinal diagnosis for hospital admission and a leading source of healthcare costs in the United States; the most common cause of AP is gallstones. The prevalence of gallstones in the United States is approximately 30%. A much smaller proportion of patients with gallstones will develop symptoms or a complication, but this still represents a substantial proportion of the population.

The treatment for gallstone pancreatitis (GSP) includes managing the acute episode and preventing another event with cholecystectomy. The timing of cholecystectomy is dictated by the severity of pancreatitis. In patients with mild disease, cholecystectomy should be performed promptly, ideally during the same admission, to prevent recurrent disease. Twenty percent of patients, however, will develop severe acute pancreatitis (SAP), which often requires more extensive intervention. In this group of patients with severe disease, marked by local complications (e.g., peripancreatic fluid, parenchymal edema, and necrosis) and systemic inflammatory response including other organ compromise, cholecystectomy should be deferred. In the setting of SAP, delaying cholecystectomy until resolution of the acute inflammatory response and the resultant peripancreatic complications is associated with improved morbidity and mortality.

EPIDEMIOLOGY

The annual incidence of AP is approximately 4.9 to 35 per 100,000 population. AP accounts for more than 330,000 emergency department visits and contributes to 5400 deaths per year in the United States. More than $2.5 billion are spent annually on the treatment of AP. According to the Atlanta classification (Table 1), 80% of patients with pancreatitis have mild AP. GSP is the most common type of AP, accounting for 40% to 70% of cases. Risk factors for GSP include increased age, female gender, multiple small stones, and a large cystic duct diameter.

PATHOPHYSIOLOGY

The pathophysiology of GSP includes intrapancreatic activation of pancreatic enzymes leading to autodigestive destruction of pancreatic and retroperitoneal soft tissue as well as a robust systemic inflammatory response due to the production of circulating inflammatory mediators. Local effects include abdominal pain and gastrointestinal tract dysfunction (obstruction, bleeding, perforation), and systemic

TABLE 1 Atlanta Classification for Acute Pancreatitis

Severity	Characteristics
Mild	No organ failure No local or systemic complications
Moderate	Transient organ failure (<48 hours) Local or systemic complications without persistent organ failure
Severe	Persistent organ failure

effects include fever, hemodynamic instability (tachycardia, hypotension), and multiorgan system dysfunction. Although incompletely understood, the prevailing theory for the pathophysiology of GSP implicates pancreatic duct obstruction leading to pancreatic duct disruption. In theory, passing gallstones through the common pancreatobiliary channel cause transient obstruction of the pancreatic duct, which creates stasis, increased pressure, and potentially bile reflux into the pancreatic duct. As a result, pancreatic duct disruption and inappropriate activation of pancreatic enzymes within the gland occurs, causing local inflammation, glandular destruction, injury to adjacent retroperitoneal structures, and the systemic release of systemic inflammatory factors. In the acute period, the associated systemic inflammatory response is the primary cause of morbidity. In the longer term (greater than 2 weeks), secondary infection of pancreatic and peripancreatic necrosis, likely due to bacterial translocation from the gastrointestinal tract, is the driver of significant complications.

CLINICAL PRESENTATION

AP usually presents with acute onset abdominal pain localized to the epigastrium and often with radiation to the back. Patients will typically have associated tachycardia and, in severe cases, hypotension due to hypovolemia and, in severe cases, capillary leak. Fever may be present but is indicative of inflammation rather than infection. Nausea and vomiting are frequent associated symptoms. Differential considerations are acute cholecystitis, choledocholithiasis, acute cholangitis, and peptic ulcer disease. Physical examination usually demonstrates a patient who is unwell in appearance and in mild distress. Jaundice, if present, may indicate obstructive choledocholithiasis. Abdominal examination is notable for tenderness and distention. Bruising in the flank areas, umbilicus, or inguinal regions is suggestive of hemorrhagic pancreatitis.

DIAGNOSIS

The diagnosis of GSP is made by clinical, biochemical, and radiographic data. Patients present most commonly to the emergency department with abdominal pain. The diagnosis is confirmed by laboratory values indicative of AP and transabdominal ultrasound demonstrating gallstones. Serum laboratory values most useful for the diagnosis of AP are the pancreatic enzymes amylase and lipase. Serum levels of these enzymes greater than three times the upper limit of normal can be diagnostic. Serum lipase is more specific than serum amylase in the diagnosis of AP. A rapid rise and fall in serum amylase and lipase levels may be more indicative of gallstone etiology. Elevated liver enzymes and bilirubin are potential associated laboratory abnormalities, secondary to transient biliary obstruction from choledocholithiasis. Persistent elevation of these hepatic chemistries should raise suspicion for continued biliary obstruction from a retained common bile duct stone and possible cholangitis.

The presence of gallstones on transabdominal ultrasound in the setting of laboratory evidence of AP confirms the diagnosis of GSP. Ultrasound is the initial imaging test of choice as it is a noninvasive and highly sensitive test to detect the presence of gallstones. Ultrasound is limited in that it is operator-dependent, and the examination can be limited by bowel gas or patient body habitus. Furthermore, ultrasound cannot assess the degree of pancreatic inflammation. Contrast-enhanced computed tomography (CT) is the imaging modality of choice to assess the degree of pancreatic inflammation and assess for local complications of acute peripancreatic fluid and necrosis. While not mandatory in cases of mild AP, findings on CT include interstitial and retroperitoneal edema and local fat stranding (Fig. 1).

SEVERITY

The revised Atlanta classification (Table 1) is used to grade the severity of AP and is a function of the degree of pancreatic and systemic inflammation and any resulting organ dysfunction. Systematically determining the severity of AP helps guide management strategy and inform prognosis (Table 1). In general, 20% of patients with AP will have severe disease, 20% of patients with severe AP will develop necrosis, and 20% of patients with pancreatic necrosis will develop secondary infection. Thus, the majority of patients with GSP will have a mild form of disease that requires transient supportive care. In contrast, patients with SAP will require more and longer support, often needing intensive care unit admission and prolonged length of hospital stay. Furthermore, the severity of disease determines, in large part, the timing of cholecystectomy. Other considerations that can influence the severity of illness in GSP, but are not directly attributable to AP, include the presence of coexisting disease such as acute cholecystitis or cholangitis.

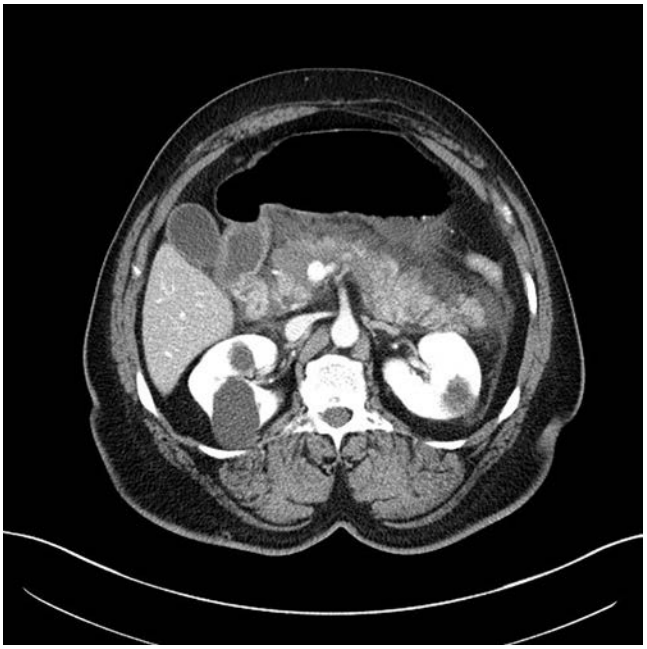


FIG. 1 CT demonstrating interstitial and retroperitoneal edema and local fat stranding.

MANAGEMENT: INITIAL TREATMENT

The initial management of patients with GSP begins with hospital admission for supportive care and monitoring, with severe cases admitted to the intensive care unit. Intravenous fluid resuscitation should be undertaken with balanced electrolyte solution to correct hypovolemia and capillary leak. Careful attention should be paid to managing abdominal pain, as this is usually the most prominent symptom. The pancreas is the most richly innervated abdominal organ, and narcotic analgesia is frequently required. Enteral nutrition should be promptly instituted, with a trial of an oral diet. If the patient is unable to tolerate a diet, then early institution of enteral feeding via nasoenteric feeding tube should be undertaken. Enteral nutrition may prevent translocation of bacteria across the gastrointestinal track, which is a primary etiology of infection in SAP. Parenteral nutrition should be reserved only for the rare case of intolerance of enteral feeding or severe gastrointestinal tract dysfunction.

Care of patients with SAP entails aggressive support of associated organ dysfunction due to the acute systemic inflammatory response. Antibiotic therapy is reserved for documented infection (positive culture or air in necrotic collection). Use of prophylactic antibiotics may increase morbidity and mortality.

In patients with GSP and elevated bilirubin, biliary tract imaging should be undertaken to rule out an obstructing common bile

duct stone. While highly sensitive for cholelithiasis, transabdominal ultrasound is not sensitive for choledocholithiasis. Magnetic resonance cholangiopancreatography (MRCP) is a useful, noninvasive, sensitive modality to evaluate for choledocholithiasis. Routine use of endoscopic retrograde cholangiography (ERC) in patients with GSP is not recommended. However, ERC should be undertaken in cases of suspected obstructive choledocholithiasis and acute cholangitis.

MANAGEMENT: TIMING OF CHOLECYSTECTOMY

In patients with mild AP secondary to gallstones, cholecystectomy should be undertaken during the same hospitalization. When the gallbladder remains in situ, recurrent pancreatitis occurs in approximately 30% of patients within the ensuing 3 months following the initial episode of pancreatitis, and subsequent episodes are often more severe than the initial episode. The recommendation for cholecystectomy during the index hospitalization is not absolute. In patients with a reliable follow-up plan, cholecystectomy can occur on an elective basis, provided it occurs within relative proximity to the index admission. To minimize procedure-related morbidity, cholecystectomy is best undertaken when there is evidence of disease resolution. Generally, disease resolution is indicated by resumption of normal oral intake, cessation of abdominal pain, and normalization of any leukocytosis.

In patients with SAP, cholecystectomy is deferred until disease resolution or until definitive management of peripancreatic complications is undertaken. In these ill patients, the primary consideration in treatment is management of the current episode of pancreatitis rather than prevention of another episode. Early cholecystectomy in patients with SAP may risk secondary infection of pancreatic necrosis.

MANAGEMENT: IDIOPATHIC ACUTE PANCREATITIS

In a subset of patients with AP, the etiology of disease is unclear. With no apparent history of other risk factors (i.e., alcohol or tobacco use, known provocative medications, genetic predisposition) and negative initial abdominal imaging, endoscopic ultrasound (EUS) may be considered to evaluate for microlithiasis.

In patients with idiopathic AP, empiric cholecystectomy may be beneficial and has been shown in a randomized trial by the Dutch Pancreatitis Study Group to decrease the risk of recurrent pancreatitis events.

SYSTEMIC COMPLICATIONS OF GALLSTONE PANCREATITIS

Patients with SAP are best managed by an interdisciplinary team including surgeons, gastroenterologists, interventional radiologists, intensivists, and dieticians. Early morbidity and mortality are due to organ dysfunction from systemic inflammatory response. Later complications occur from secondary infection of pancreatic necrosis. After 2 to 4 weeks of illness, peripancreatic fluid collections mature into walled-off pancreatic necrosis (WOPN). Patients with persistent unwellness secondary to WOPN or those with infected pancreatic necrosis (IPN) are best managed with drainage or debridement. Delaying intervention with debridement to this later phase of disease rather than during the acute phase of illness marked by systemic inflammation results in a lower mortality risk.

Debridement of pancreatic necrosis can be undertaken by a variety of approaches, including open laparotomy, percutaneous drainage alone, percutaneous drainage followed by videoscopic-assisted retroperitoneal debridement ("step-up"; VARD), endoscopic transgastric, and surgical transgastric (laparoscopic or open). The optimal approach for debridement varies by case and is determined by multiple factors including the anatomy of the disease, patient physiology, surgeon and endoscopist experience, and center expertise. When possible, the least invasive approach should be undertaken to minimize the inflammatory insult while effectively controlling infection and removing necrotic tissue.

In the modern era, open debridement, while considered the gold standard, is reserved for patients with diffuse distribution of necrosis not amenable to less-invasive approaches. Percutaneous drainage via interventional radiology guidance as a sole therapy may be enough to resolve up to 50% of cases of pancreatic necrosis, particularly when there is a small burden of solid necrotic tissue. The step-up approach (first described in the Pancreatitis, Necrosectomy versus Step up Approach [PANTER] trial by the Dutch Pancreatitis Study Group in 2010) consists of percutaneous catheter drainage, followed by VARD. The PANTER trial showed that the step-up approach has a significantly lower major complication rate than the open approach, including new-onset multiple organ failure, perforation of a visceral organ, bleeding, and/or the development of an enterocutaneous fistula. Transgastric debridement (endoscopic or surgical) entails approaching the retroperitoneal necrosis cavity through the posterior wall of the stomach. In the 2018 TENSION trial, another randomized trial by the Dutch Pancreatitis Study Group, the endoscopic transgastric approach to debridement was found to have comparable outcomes to the surgical step-up approach.

SUMMARY

AP is an important public healthcare concern and a potentially life-threatening disease. Gallstones are the most common etiology, and the establishment of this diagnosis is important in guiding management. Transabdominal ultrasound is a sensitive modality for determining the presence of cholelithiasis. EUS can be undertaken to evaluate for microlithiasis. MRCP can be utilized to evaluate for obstructive choledocholithiasis in patients with elevated bilirubin. The use of ERCP in GSP is reserved for patients with persistent choledocholithiasis or cholangitis. In mild GSP, cholecystectomy should be performed promptly after resolution to prevent recurrence. In cases of SAP, the acute complications related to the pancreatitis episode (e.g., the systemic inflammatory response and pancreatic necrosis) are the priority in management. Cholecystectomy should be delayed until resolution of the illness or until definitive surgical management is undertaken. Cholecystectomy should be considered in cases of idiopathic AP.

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Pancreas Divisum and Other Variants of Dominant Dorsal Duct Anatomy

David B. Adams, MD, and Gregory A. Coté, MD, MS

Three strategies are used in the surgical management of inflammatory disorders of the pancreas: improve drainage, resect damaged tissue, or combine the first two with a simultaneous resection and drainage procedure. These principles apply to the management of recurrent acute pancreatitis and chronic pancreatitis associated with dominant dorsal duct anatomy, which is more commonly called *pancreas divisum*. The prudent surgeon always remembers that pancreas divisum is as common as left-handedness: 10% of the population has pancreas divisum. The anatomic variant known as pancreas divisum develops in the busy 6-week-old embryo (Fig. 1). Migration, rotation, and vacuolization are happening everywhere in the 6- to 8-week embryonic foregut. During this developmental period, the dorsal and ventral pancreatic buds fuse and realign their ductal systems. In the usual fusion of the ductal systems, the ventral duct or duct of Wirsung becomes the main pancreatic duct (Fig. 2A,B). The dorsal duct, the duct of Santorini, is the minor duct (see Fig. 2A). When dorsal and ventral ductal fusion is incomplete, the duct of Santorini drains the majority of the pancreas through an orifice that is notably smaller than the orifice of a normal sphincter of Oddi (Fig. 2C,D). The duct of Santorini may have a narrow filamentous pathway to the duct of Wirsung or may drain a portion of the head independently (Fig. 2E). Hence the concept was promulgated in the 1970s, that in pancreas divisum there is an anatomic impediment to the normal drainage of pancreatic exocrine secretions, which results in an obstructive pancreatopathy.

In pancreas divisum, which is the main pancreatic duct? Avoiding the descriptor "main" prevents confusion in discussion of pancreas divisum. When divisum anatomy is present, the dorsal duct, formerly known as the duct of Santorini, is called the *dominant duct*. The terms *complete fusion* and *incomplete fusion* have been used to describe variants of pancreatic ductal anatomy associated with dominant dorsal duct anatomy. Complete divisum typically denotes a dominant dorsal duct with no vestigial communication to the ventral system (duct of Wirsung). Incomplete divisum denotes a dominant dorsal duct with a residual, albeit miniscule, communication between the dorsal duct and the ventral duct. Variations of the dominant dorsal duct are many and infrequent enough that radiologic and endoscopic delineation may be confusing. The classic radiographic image has the dominant pancreatic duct crossing the terminal bile duct and entering the descending duodenum (Fig. 3). Usually, a small ductal system drains the ventral head of the pancreas and enters the duodenum through the major papilla with the terminal bile duct. Be aware of the entity called *acquired pancreas divisum*, which is associated with chronic pancreatitis and malignancy. Either process may result in total occlusion of the ventral duct, causing the duct of Santorini to assume responsibility for pancreatic exocrine outflow via the minor papilla. Whenever there is a question of acquired pancreas divisum (also called *pseudodivisum*) without a demonstrated mass on magnetic resonance imaging (MRI) or computed tomographic scan (CT scan), endoscopic ultrasound (EUS) scan should be undertaken to rule out malignancy.

In the nineteenth century, foregut surgeons were commonly talented anatomists. In the twentieth century, physiology was of increasing importance to the innovative surgeon. The twenty-first century has seen the addition of molecular biology to the management of surgical disorders. The history of the understanding and treatment of pancreas divisum has followed a similar pathway. In the past, pancreas divisum was labeled a congenital anomaly that could cause obstructive pain and pancreatitis. With the development of diagnostic endoscopic retrograde cholangiopancreatography (ERCP) in the 1970s, idiopathic recurrent pancreatitis was attributed to pancreas divisum, and became a target for surgical management with duodenotomy and minor duct sphincteroplasty. As therapeutic endoscopy developed, endoscopic minor duct sphincterotomy or papillotomy supplanted the open surgical approach. Although sphincteroplasty was successful in the majority of patients in early studies, long-term failures became evident. Improving patient selection based on physiologic and anatomic parameters with measurement of pancreatic ductal response and exocrine output to hormonal stimulation of the exocrine pancreas was used. However, early optimism of improving patient selection via physiologic assessment did not meaningfully improve long-term outcomes.

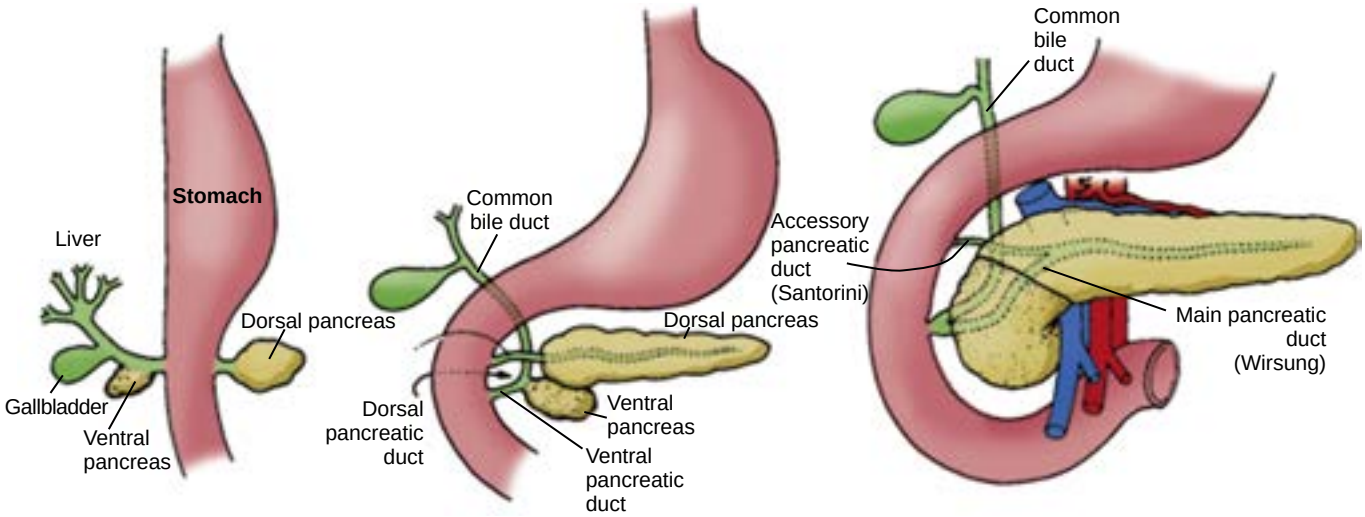


FIG. 1 Embryologic development of the pancreas.

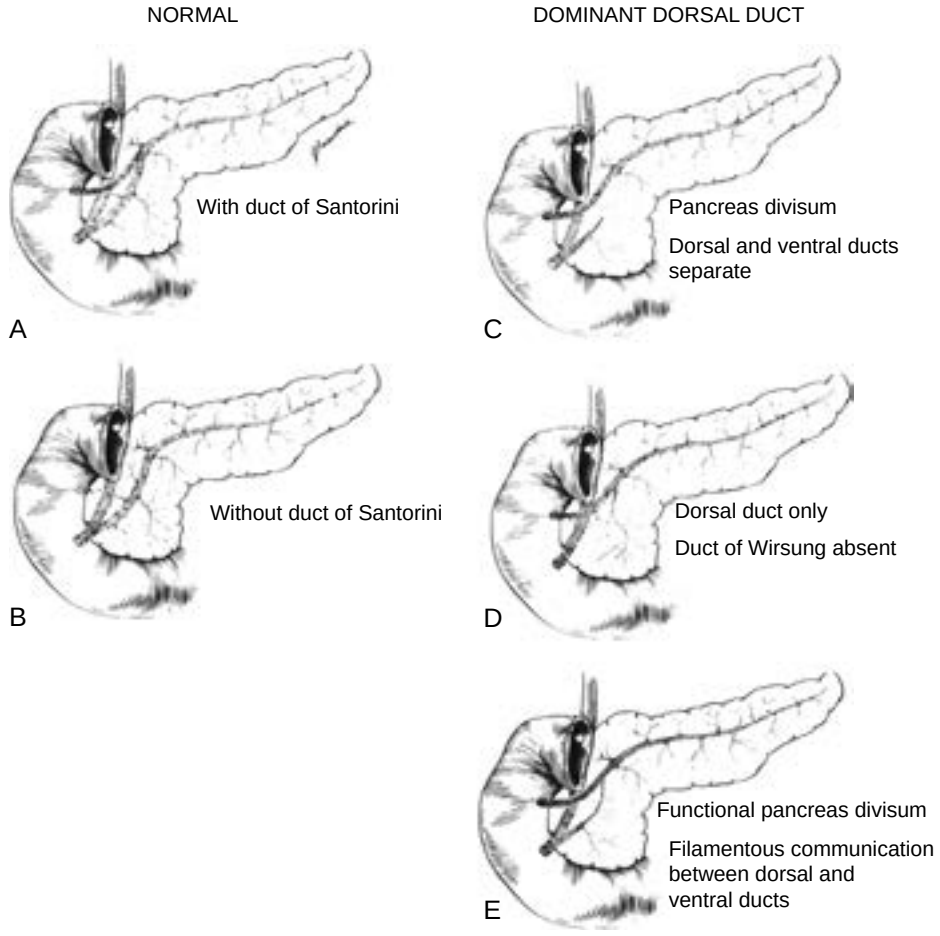


FIG. 2 Most common pancreatic ductal anatomy **(A, B)** and pancreas divisum and its variants **(C–E)**.



FIG. 3 Pancreas divisum magnetic resonance cholangiopancreatography with the dorsal duct (Santorini labeled with *downward arrow*) crossing the terminal bile duct, which unites with the ventral duct remnant (Wirsung labeled with *upward arrow*). Dorsal and ventral ducts terminate respectively at major and minor papilla.

Chronic pancreatitis and acute recurrent pancreatitis are disorders that lack strong evidence on which surgical practice can be based. Many other similar "gray zone" disorders are multifactorial in origin. Scurvy is a disease with a single and simple cause that can be cured with vitamin C. If chronic pancreatitis were like scurvy and had a single cause, it would be easily curable. Chronic pancreatitis has many known risk factors, many of which are overlapping, such as alcohol and smoking. Anatomic, environmental, and genetic factors are likely to interact with the divisum phenotype in causing or contributing to pancreatitis. Pancreas divisum is clearly associated with a higher prevalence of genetic mutations that predispose to pancreatitis; this has led to the current concept that pancreas divisum is not a cause of pancreatitis by itself but acts as a partner with genetic mutations. In patients with idiopathic pancreatitis, pancreas divisum is not an independent risk factor when compared with controls without pancreas divisum. However, pancreas divisum frequency is higher in patients with genetic mutations and pancreatitis, especially those with *CFTR* mutations or polymorphisms, suggesting a cumulative effect of these two cofactors. *SPINK1* and *PRSS1* functional genetic anomalies are also associated with pancreas divisum and acute recurrent and chronic pancreatitis.

DIAGNOSIS

The clinical presentation of pancreatitis associated with dominant dorsal duct anatomy has two phenotypes: acute recurrent pancreatitis and chronic pancreatitis. Current concepts suggest that the former leads to the latter. Rarely does chronic pancreatitis associated with pancreas divisum result in severe fibrosing pancreatitis associated

with biliary, duodenal, or splanchnic venous obstruction. Pain intractable to medical management is the main reason patients with pancreas divisum seek the help of surgeons and gastroenterologists. Patients with acute pancreatitis associated with pancreas divisum present in the same manner as patients with other etiologies for pancreatitis. Pain that triggers nausea and vomiting is the predominant symptom. The pain is notable for its intensity, character, and location. Patients localize the pain to the epigastrium with radiation into the interscapular region. Pain is commonly characterized by the sensation of someone twisting a knife in the upper abdomen. The pain is often rated as 11 on a scale of 1 to 10. Serum lipase is elevated, as may be the leukocyte count and other inflammatory serologic markers. When the acute illness is severe, pancreatic and peripancreatic inflammatory changes will be seen on CT scan and MRI studies. If pancreatic necrosis develops in the presence of pancreas divisum, other pancreatitis risk factors should be considered. It is uncommon for acute pancreatitis associated with pancreas divisum to lead to pancreatic and peripancreatic necrosis. The usual course is that of a self-limited illness that resolves with expectant, nonoperative management and hospitalization of less than 1 week. With resolution of the acute illness, patients return to normal function and activities and pancreas morphology presumably returns to normal. If recurrent bouts of acute pancreatitis continue, changes of chronic pancreatitis may become evident on cross-sectional imaging.

A hopeful hypothesis recommends that endoscopic minor duct sphincterotomy be undertaken before the development of chronic inflammatory and fibrotic changes. The goals of endoscopic therapy are to (1) eliminate future episodes of acute pancreatitis; (2) reduce the frequency or severity of recurrent bouts of acute pancreatitis; and (3) prevent the development of overt chronic pancreatitis and its complications, primarily the development of peripancreatic neural inflammatory pathways that lead to centralization of pain. It is generally assumed that if acute pancreatitis bouts can be eliminated, the third objective would follow suit. However, the chief indication for surgical therapy of pancreas divisum is pain; endocrine and exocrine insufficiency is rare, as are biliary, duodenal, and splanchnic venous occlusion.

The more difficult patient is one who has had one bout of acute pancreatitis or no documented evidence of pancreatitis but who has pancreas divisum and chronic pain that is characteristic of pancreatitis. When patient quality of life is diminished by frequent emergency department visits, work absences, and loss of social contacts, evaluation with MRI and EUS is indicated. If objective evidence of obstructive chronic pancreatitis is noted, then endoscopic or surgical intervention may be indicated. However, the difficulty in waiting for chronic morphologic changes to develop is that once chronic fibrosis has developed in the head of the pancreas, endoscopic and surgical minor duct sphincterotomy have a limited success rate. Division of the sparse smooth muscle fibers of the minor sphincter is unlikely to alter the hardened fibrosis of the surrounding pancreatic parenchyma. The prudent surgeon remembers that when you cut scar tissue, you get more scar tissue. When you operate for pain, you get pain. The splanchnic neural architecture is vast and lacks specificity. Biliary, gastric, esophageal, and intestinal disorders all may appear similar to pain and nausea associated with chronic pancreatitis. Nevertheless, surgeons and gastroenterologists who undertake the care of patients with chronic pancreatitis and pancreas divisum engage in changing what is possible and offer the hope of helping a patient whose quality of life is diminished by unpredictable hospital visits and isolation from work and family. This care requires the collaboration of pancreatic surgeons, endoscopic specialists in pancreatic disease, behavioral psychologists, and pain management specialists. In general, endoscopic therapy for pancreas divisum is typically recommended for pancreatic-type pain in association with obstructive morphology (e.g., a main pancreatic duct stone or stricture) or documented recurrent acute pancreatitis without another clear and reversible cause. Minor sphincterotomy for abdominal pain alone is unproven and a slippery slope; once the orifice is compromised, there is always the possibility of orifice restenosis and bona fide duct obstruction. For patients with idiopathic acute recurrent pancreatitis and pancreas divisum, the impact of minor endoscopic sphincterotomy is currently being investigated in a sham-controlled, multicenter, randomized trial (NCT03609944).

ENDOSCOPIC TREATMENT

Identifying the Minor Papilla and Positioning the Endoscope

Although the pathogenicity of pancreas divisum remains controversial, the endoscopic approach to minor papillotomy is more elegant. The first technical challenge to therapy is successfully identifying the minor papilla. Duodenoscopes are designed for optimal orientation at the level of the major papilla, so positioning the endoscope for minor papilla cannulation usually requires a "semi-long" position. This is illustrated in Figure 4, in which the scope is resting along the greater curvature of the stomach. This position is less stable than the traditional "short" position of the duodenoscope used for the majority of major papilla cases. Nevertheless, the semi-long position typically orients the minor papilla directly in front of the working channel; the minor papilla is usually located 2 to 5 cm superior to the major papilla, along the medial wall but slightly lateral to the major papilla. In some cases, the minor papilla may be located underneath an overlying duodenal fold that requires retraction with a catheter or other device before cannulation ensues. Because this procedure requires a long scope position that is uncomfortable for patients who are prone on a fluoroscopy table, it is almost universally performed with anesthesia-administered sedation with or without endotracheal intubation.

Occasionally, the minor papilla is patulous and the actual orifice unidentifiable even after minutes of careful endoscopic observation. Blindly probing with catheters and guidewires rapidly may cause periampullary edema and transform a straightforward procedure into a complicated one. Probing often leads to false tracks adjacent to the true lumen, rarely causing perforation but often making cannulation impossible. Therefore, if a minor papillary orifice is unidentifiable, the minor papilla can be sprayed with a dilute dye such as methylene blue or India ink. After this maneuver, pancreatic juice outflow should lead to clearing of the dye at the minor orifice (Fig. 5). Alternatively, or in conjunction with this approach, secretin may be administered (0.2 μg/kg) intravenously over 1 minute to stimulate pancreatic juice flow. This often unveils the minor papillary orifice within minutes of administration and continued careful endoscopic observation.

An absolute last resort involves the use of a needle-tipped catheter that is gently pressed into the minor papilla, followed by light injection of radio contrast dye to delineate the configuration of the Santorini duct. If the needle is inserted into the submucosal layer of the minor papilla or duodenum, such an injection may result in a submucosal bleb and obliterate the papillary anatomy for a short period, often making minor papillary cannulation impossible during that procedure.

Cannulation

Once the minor papillary orifice is clearly delineated, most endoscopists prefer to gain access using a tapered cannula or sphincterotome (3Fr or 4Fr tip) with a hydrophilic, straight guidewire. Most experts prefer a smaller caliber (0.018-, 0.021-, or 0.025-inch) guidewire because the orifice is considerably smaller than the major papilla. The leading 3 to 4 mm of guidewire protruding from the catheter tip is used to grip the minor orifice; at this point, the endoscopist or assistant may probe gently with the guidewire under fluoroscopic guidance; if the guidewire advances with minimal resistance, then 2 to 5 cm of guidewire may be advanced into the duct before contrast injection. Guidewires should not be advanced deeply to the body or tail of the pancreas without antecedent injection of a small amount

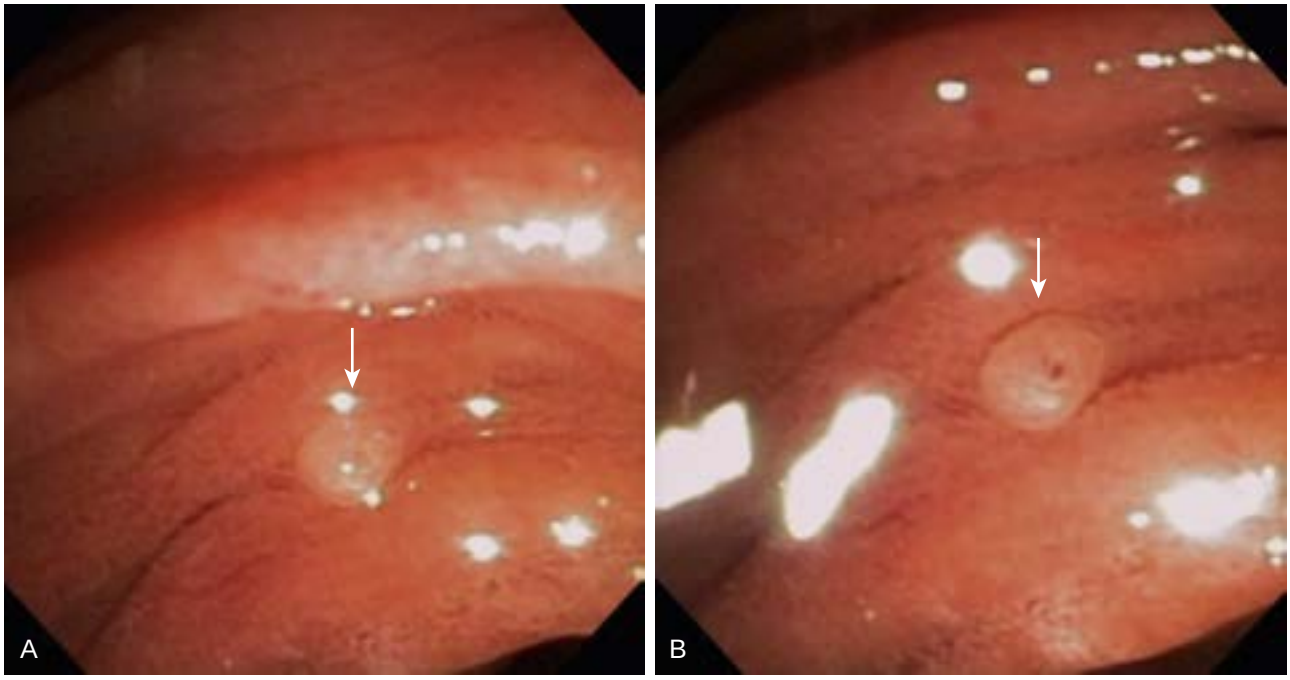


FIG. 4 Endoscopic image of the minor papilla (*arrow*) with a "closed" orifice **(A)** and an "open" orifice **(B)**.



FIG. 5 Endoscopic image of minor papillotomy "in progress," which also shows the major papilla downstream for reference *(arrow)*.

of contrast to delineate the course of the duct and avoid side branch puncture. Alternatively, the cannula or sphincterotome may be inserted gently into the minor orifice first, followed by probing with the guidewire. This is suboptimal in many cases because the orifice is usually less than 1 mm (3Fr) and the smallest cannulating devices are 3Fr at the tip.

Once the guidewire is clearly seated in the main pancreatic duct, it should be advanced carefully along the main duct to the distal body or pancreatic tail. This provides adequate rail support over which the cannula or sphincterotome can be advanced deeply into the duct for further opacification and positioning for sphincterotomy.

Minor Endoscopic Sphincterotomy

There are two approaches to minor endoscopic sphincterotomy, each of which has advantages and disadvantages. There are no data to support one approach over the other. The first approach is a pull-type minor sphincterotomy that mimics the standard technique for biliary and pancreatic sphincterotomy at the major papilla. With a sphincterotome, the device is bowed within the minor orifice, and electrocautery is applied to cut the superior aspect of the "muscle." This word is in quotations because many minor papillae have no or miniscule smooth muscle, leaving the characterization as a "sphincter muscle" very much in doubt. Electrocautery is typically a blend of alternating/mixed cut and coagulation currents, to minimize char while permitting an adequate incision to enlarge the orifice. Some experts advocate using a pure cut current for minor sphincterotomy, to minimize the risk of orifice restenosis; this comes with a slightly higher risk of bleeding and has not been shown to affect long-term outcomes. The advantage of the pull-type technique is that it is most likely to minimize the risk of an incomplete incision; however, if an excessive amount of cut wire is left inside the pancreatic duct during the sphincterotomy, this is likely to induce post-ERCP pancreatitis and delayed high-grade strictures at the orifice.

An alternative and widely accepted approach is to perform a needle-knife sphincterotomy over a pancreatic stent. In this case, a small caliber (3Fr to 5Fr) pancreatic stent is deployed over the guidewire. With a needle-knife sphincterotome, the minor sphincterotomy is performed by cutting on the superior aspect of the stent until the stent is exposed within the duct itself. This technique is believed to have a lower risk of post-sphincterotomy perforation but may be associated with a higher rate of incompletely dividing the minor orifice. In cases of failed minor cannulation, a precut or freehand (without the guidance of a pancreatic stent) needle-knife sphincterotomy may be attempted to expose the minor orifice for deeper access. Given the higher rates of post-ERCP pancreatitis and unproven technical benefits, this maneuver should be used very sparingly. Unlike the biliary sphincter complex, the duct of Santorini rarely has a long intraduodenal segment to guide the depth and orientation of the incision.

Pancreatitis Prevention

For the past two decades, the mainstay for preventing post-ERCP pancreatitis has been the use of small caliber pancreatic stents (3Fr to 5Fr). These have been shown to reduce the risk of post-ERCP pancreatitis in multiple randomized clinical trials, presumably by reducing intraductal pressure in the critical hours or days after ERCP and its associated papillary trauma. The efficacy of prophylactic stents after minor papilla endotherapy mirrors that for patients with standard pancreatic duct anatomy. Importantly, patients with pancreas divisum who undergo ERCP solely for major papilla therapy have a lower baseline risk of post-ERCP pancreatitis; once minor papilla cannulation is attempted, however, the risk approaches that of the highest-risk populations. Therefore, most experts are uncomfortable performing an endoscopic minor sphincterotomy without placement of a small caliber pancreatic duct stent immediately before or after the incision. The stents pass out of the minor orifice spontaneously in more than 90% of cases; the minority require a second endoscopy to pull the stent if it is retained after 10 to 14 days on a follow-up radiograph.

Postprocedure, rectal indomethacin (100 mg) is the first widely accepted pharmacologic intervention to minimize the risk of post-ERCP pancreatitis. The medication is administered anytime immediately before, during, or at the completion of the ERCP, and presumably reduces the risk of post-ERCP pancreatitis by interrupting the earliest inflammatory cascades triggered by papillary trauma and intraductal hypertension. Its efficacy as a freestanding preventive modality—without pancreatic stents—remains unproven for patients with pancreas divisum undergoing minor endoscopic sphincterotomy. However, the medication is inexpensive and low risk, so has become widely popular as an adjunct for high-risk patients.

Postprocedure Management

The majority of patients undergoing ERCP may be discharged within 2 hours after the procedure. Preprocedure and early postprocedure pain or nausea are important predictors of unplanned admission after ERCP. Intravenous fluids, preferably lactated Ringer's solution, should be administered during ERCP and in the recovery room in case pancreatitis ensues. If there are no symptoms concerning for post-ERCP pancreatitis and the procedure was otherwise uneventful, patients may be discharged home after a short period of observation.

Approximately 10% to 15% of patients will require overnight observation after ERCP; admission rates after endoscopic minor sphincterotomy are unknown but the post-ERCP pancreatitis rate is also 10% to 15%. The majority of these patients will improve within 72 hours of the procedure, but a small minority (1%–2% of all patients with post-ERCP pancreatitis) may develop severe acute pancreatitis and local complications such as pseudocysts or necrosis. The possibility of post-ERCP pancreatitis—mild or severe—must be considered when weighing the risks and benefits of endoscopic therapy.

SURGICAL TREATMENT

Minor Duct Sphincteroplasty

Operative sphincteroplasty of the sphincter of Henle was the mainstay of therapy before the development of endoscopic sphincterotomy. It is hard to imagine how an operative sphincteroplasty can be better than an endoscopic sphincterotomy, given the sparseness of smooth muscle fibers that surround the pancreatic duct as it courses into the duodenum. Occasional patients with bypassed foregut anatomy may elect open surgical sphincterotomy and forgo a retrograde endoscopic approach or a hybrid laparoscopic and endoscopic prograde approach. Surgical outcomes with open sphincteroplasty are best when endoscopic sphincterotomy has not been done before. The first cut is the best one. It is tempting to undertake open sphincteroplasty in patients with altered foregut anatomy, such as patients with gastric bypass. These patients may be well served by a hybrid procedure with concomitant laparoscopic gastrostomy of the bypassed stomach and endoscopic prograde sphincterotomy. A gastrostomy tube is left in place to secure access for removal of the anastomotic stent later. Patients who have previously undergone successful endoscopic sphincterotomy with recurrent fibrosis may be candidates for operative sphincteroplasty. The concept is that open minor duct sphincteroplasty with loop magnification and fine absorbable suturing of the duct will have better outcomes than endoscopic sphincterotomy. The difficulty in undertaking this course of action is that patients with chronic fibrosis of the head of the pancreas do poorly with sphincteroplasty, and preoperative identification of pancreatic fibrosis is imperfect.

Technique

The most recent ERCP and magnetic resonance cholangiopancreatography are displayed on the operating theater monitors closest to the surgeon, who has on a headlamp and magnifying loops. The abdomen is entered through an upper midline incision. The falciform ligament is divided when it limits placement of a wound protector or retraction of the liver. A self-retaining retractor is placed to retract the abdominal wall to divide the lateral duodenal attachments and the ligamentous attachments of the transverse colon to the duodenal pancreatic union. After the wide kocherization of the duodenum and mobilization of the hepatic flexure of the colon inferiorly and laterally, the duodenum is mobilized medially to the midline. Exposure is maintained with the self-retaining retractors placed around the wound circumference, retracting liver, stomach, and transverse colon out of sight. A laparotomy pad is placed behind the duodenum to elevate it toward the midline. A longitudinal duodenotomy is made in the descending duodenum, angled slightly from medial to lateral as the electrocautery knife goes from proximal to distal duodenum. Intraluminal exposure is maintained by grasping the medial and superior duodenal wall with a Babcock clamp or with stay sutures of 3-0 silk. The major papilla is identified with palpation and visualization of bile expressed with manual compression of the gallbladder and common bile duct. Centimeters proximal to the major papilla, the minor papilla can be palpated on the medial wall of the duodenum. Care is taken not to distort duodenal mucosa by direct suction and grasping with forceps, as minor mucosal trauma can obscure visualization of the minor papilla. The minor papilla is palpated and cannulated with a lacrimal duct probe (Fig. 6). When the papilla cannot be found, secretin stimulation can be used, but this increases the risk of postoperative pancreatitis, particularly if operative drainage has limited success. Sphincterotomy is accomplished by dividing the sphincter muscle with needle-knife low-energy cautery over the lacrimal duct probe. Care is taken to cut only red muscle fibers. When yellow pancreatic tissue is encountered, the sphincterotomy is complete. Two or three interrupted sutures of 5-0 monofilament absorbable sutures are placed to reapproximate duodenal and ductal mucosa (Fig. 7). Minor duct sphincteroplasty is distinctly different from that of a biliary sphincteroplasty in which the common bile duct lies parallel and juxtaposed to the duodenum, which allows for a lengthy sphincterotomy. The minor duct enters the duodenum at right angles from the pancreas. There is not a lot of room to cut this sphincter. A 3Fr or 5Fr double pigtail stent is placed across the anastomosis. It is removed endoscopically 6 weeks later. The duodenotomy is closed with a running suture of 3-0 absorbable monofilament suture, reinforced as needed with interrupted sutures of 3-0 silk. The fascia is reapproximated with interrupted zero absorbable sutures. The skin is closed with a 4-0 running subcuticular suture. Closed suction drainage of the retroduodenal space is not used routinely. Because stenosis of the major papilla is associated with pancreas divisum, some would advocate performing biliary sphincteroplasty and pancreatic ductal septoplasty whenever minor duct sphincteroplasty is undertaken. This indication is exceptional but not irrational.

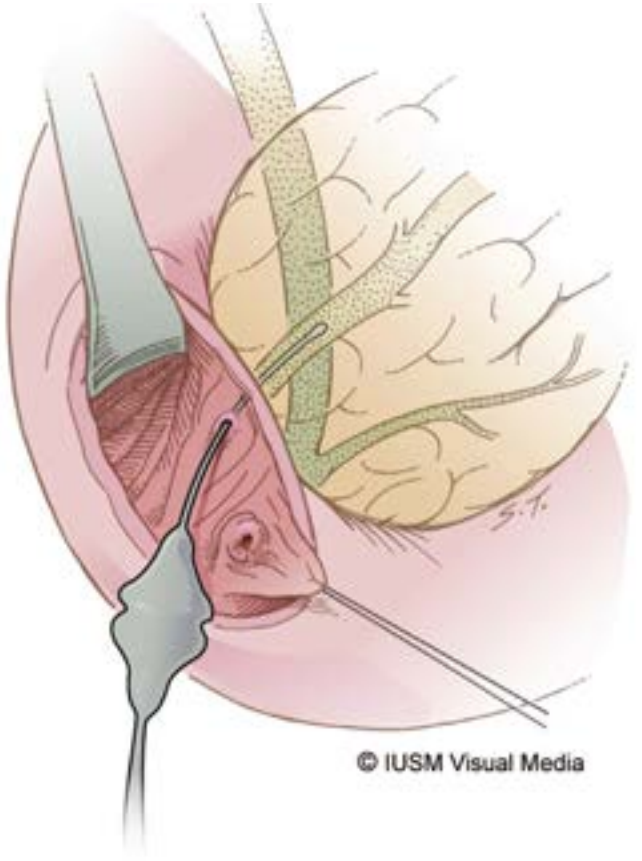


FIG. 6 Through a longitudinal duodenotomy, the minor papilla is identified and cannulated with a lacrimal duct probe.

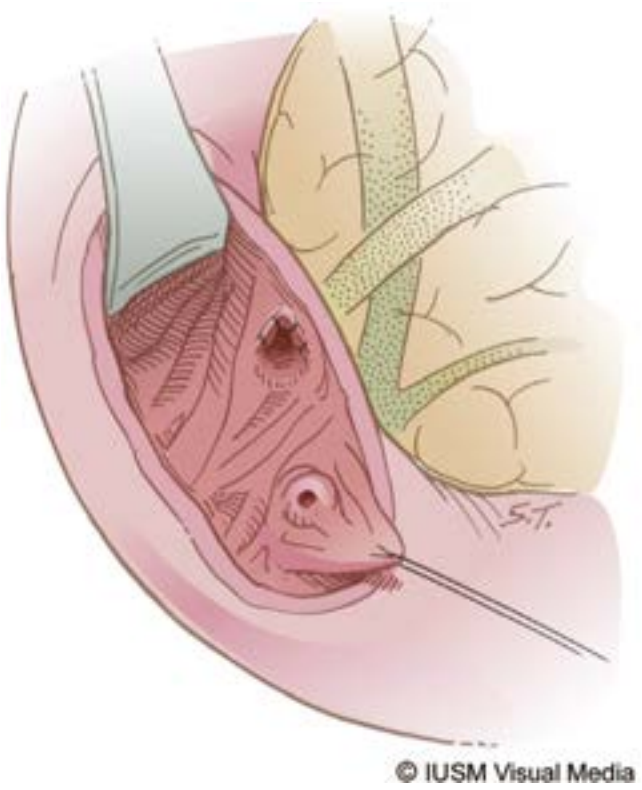


FIG. 7 After division of the muscular fibers of the sphincter of Henle with needle-knife electrocautery, the termination of the dorsal pancreatic duct is anastomosed to the duodenal mucosa with interrupted sutures.

Postoperative Management

Patients are managed on a fast track much as one would manage a patient after an open cholecystectomy. Nasogastric and urinary bladder intubation are avoided. Diet is advanced early as tolerated. Complications particular to this operation are pancreatitis and duodenotomy dehiscence (Table 1). Postoperative pancreatitis is uncommon and presents in typical fashion with pain, tachycardia, and serum lipase and leukocyte elevation. Duodenal dehiscence presents in a subtle fashion, similar to a duodenal stump leak after Billroth II gastrectomy. Vague upper abdominal pain and nausea precede by days the appearance of systemic toxicity with fever, tachycardia, tachypnea, and leukocytosis. Alert vigilance for this complication is needed because it is uncommon, subtle in presentation, and devastating if unrecognized early.

LATERAL PANCREATICOJEJUNOSTOMY

Dominant ductal dilation is an indication for lateral pancreaticojejunostomy (LPJ) in chronic pancreatitis associated with pancreas divisum. Outcomes after LPJ are similar to those reported with chronic pancreatitis not associated with pancreas divisum. In particular, the patient with the borderline dilated pancreatic duct not greater than 7 mm in diameter may benefit from LPJ when diffuse fibrosis of the pancreas is present with a fibrotic encapsulation of the pancreas. LPJ has the theoretic advantage of releasing the pancreas from its so-called pancreatic compartment syndrome. Part of the discussion of LPJ in the management of chronic pancreatitis of all causes is that if LPJ fails and the patient progresses to consideration of total pancreatectomy with islet autotransplantation (TPIAT), islet yields are diminished in patients who have had LPJ, related to either the underlying disease state or technical challenges presented by islet isolation in patients who have a longitudinal disruption of the pancreatic duct. The technique of LPJ in pancreas divisum does not differ from that discussed elsewhere in this book. Because the pancreas ductotomy is extended medially adjacent to the duodenum, the gastroduodenal artery should be ligated before its division.

TABLE 1 Surgical Outcome After Minor Duct Sphincteroplasty in Patients with Pancreas Divisum

Study	N	Morbidity	Mortality	Good Response	Mean Follow-up (mo)
Warshaw et al. (1990)	88	NR	0	71%	53
Bradley (1996)	37	NR	0	54%	60
Madura (2005)	74	25%	0	64%	NR
Morgan et al. (2008)	17	10%	0	54%	43

NR, Not reported.

TABLE 2 Management Strategies for Pancreas Divisum in the Setting of Chronic Pancreatitis Intractable to Medical Management or with Recurrent Acute Pancreatitis

Condition	Strategy
Nonfamilial, dilated duct >7 mm	Lateral pancreaticojejunostomy
Familial	Total pancreatectomy with islet autotransplantation
Nondilated duct with recurrent acute pancreatitis	Endoscopic minor papillotomy
Nondilated duct endotherapy failure	Operative sphincteroplasty
Nondilated duct endotherapy failure with moderate to severe chronic pancreatitis in the head	Pancreatoduodenectomy
Operative sphincteroplasty failure	Pancreatoduodenectomy
Pancreatoduodenectomy failure	Total pancreatectomy with islet autotransplantation

WHIPPLE PROCEDURE

Pancreatoduodenectomy may be indicated in patients with pancreas divisum who have failed minor duct sphincteroplasty when changes of chronic pancreatitis develop in the head of the pancreas. The operative technique is not different from that described elsewhere in this book. When a resection of the head is indicated in pancreas divisum, the divided neck of the pancreas is usually soft with a nondilated pancreatic duct, one at risk for anastomotic leak. Therefore, internal and external anastomotic stenting and postoperative octreotide infusion may diminish the risk of postoperative pancreatic fistulas. If head resection in pancreas divisum fails and patients become candidates for TPIAT, islet yields may be uncompromised. Islet volume is greater in the tail and body than in the head of the pancreas, and islet loss is limited in a head resection for pancreas divisum. When anastomotic obstruction occurs after a Whipple procedure, acinar cells atrophy before destruction of the islets. The resultant islet-rich, acinar-poor atrophied pancreas may be favorable isolation for islet autotransplantation. The issue of whether patients with pancreas divisum with chronic pancreatitis should undergo a speculative Whipple procedure or a TPIAT is unanswered.

HYBRID PROCEDURES

Variations of the Whipple procedure and the Puestow procedure have been used in chronic pancreatitis associated with pancreas divisum in a fashion similar to their use in chronic pancreatitis not associated with pancreas divisum. Although typically the Beger and Frey procedures are selected for patients with an inflammatory mass in the head of the pancreas, they have been used in pancreas divisum not associated with enlargement of the head of the pancreas. The Frey procedure was developed because of the ascribed failure of the LPJ to drain the head and uncinate process of the pancreas. In pancreas divisum, the head should be drained effectively with a longitudinal ductotomy. The use of multiple resection and drainage techniques is an indication of the difficulty in patient selection and management in chronic pancreatitis associated with pancreas divisum.

TOTAL PANCREATECTOMY WITH ISLET AUTOTRANSPLANTATION

TPIAT is indicated in patients with chronic pancreatitis with intractable pain who have failed medical, endoscopic, and surgical management. Pancreas divisum is a risk factor for chronic pancreatitis in about 15% of the cohort in the reports of TPIAT in the management of chronic pancreatitis. Typical patients with pancreas divisum who are selected to TPIAT have undergone endoscopic sphincterotomy, operative sphincteroplasty, and pancreatic head resection in succession over many years. The unanswered question is whether TPIAT should be undertaken sooner rather than later if endoscopic treatment fails. That discussion is beyond the scope of this chapter.

CONCLUSION

Given the paucity of comparative effectiveness studies evaluating the impact of endoscopic or surgical minor papillotomy on nonobstructive recurrent acute and chronic pancreatitis, the management of pancreas divisum is primarily based on experience. Although the divisum anatomic variant is common, its association with chronic pancreatitis is by no means a *sine qua non*. When pancreas divisum is associated with intractable pain associated with chronic pancreatitis or with recurrent pancreatitis, the approach should mimic that for patients with standard duct anatomy: (1) alcohol and tobacco cessation is necessary; (2) a trial of pancreatic enzyme replacement therapy may be considered, especially if exocrine pancreas insufficiency is documented; and (3) genetic mutations and polymorphisms should be investigated, knowing that the odds identifying high-risk mutations are higher in the setting of divisum. A management strategy based on a regional experience extending with the surgical management of pancreas divisum is suggested in Table 2. The pathway outlined in Table 2 differs from much of the experience in the current literature and underscores the influence of regional population differences and their attendant practices. As the pathogenesis of pancreatitis is better understood, treatment strategies will become less intuitive and experience-based and more effective.

To seek and to find evidence on which to base the management of pancreas divisum is to repeat Samuel Johnson's experience described in the preface to his 1755 *A Dictionary of the English Language*: "I saw that one inquiry only gave occasion to another, that book referred to book, that to search was not always to find, and to find was not always to be informed; and that thus to pursue perfection, was, like the first inhabitants of Arcadia, to chase the sun, which, when they had reached the hill where he seemed to rest, was still beheld at the same distance from them."

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Diagnosis and Management of Autoimmune Pancreatitis

Zhi Ven Fong, MD, MPH, and Andrew L. Warshaw, MD

INTRODUCTION

Autoimmune pancreatitis (AIP) is inflammation of the pancreas characterized histologically by lymphoplasmacytic infiltration and fibrosis that may or may not be associated with a pancreatic mass, and therapeutically by its dramatic response to corticosteroid administration. There are two subtypes of AIP with different clinical profiles, two different diseases with similar histology (Table 1). Type I AIP is classified as *lymphoplasmacytic sclerosing pancreatitis.* It is more common in older men and is associated with elevated serum immunoglobulin G4 (IgG4) levels and extrapancreatic autoimmune diseases such as Sjogren syndrome, rheumatoid arthritis, primary sclerosing cholangitis, orbital pseudotumor, retroperitoneal fibrosis, and inflammatory bowel disease. Extrapancreatic involvement can manifest before, during, or after the onset of AIP. Conversely, type II AIP, classified as *idiopathic duct-centric pancreatitis,* has no predilection toward any age group and often has normal serum IgG4 levels. Its clinical profile is distinctively different from the systemic manifestations of type I AIP, resembling more of a localized, pancreas-specific process associated with inflammatory bowel disease as its only extrapancreatic site (see Table 1).

The common presenting symptoms of AIP include weight loss, abdominal pain, and endocrine as well as exocrine insufficiency. It can also present with painless jaundice caused by a distal common bile duct stricture, masquerading as pancreatic ductal adenocarcinoma. Many surgical series report a 2% to 3% AIP resection rate for presumed pancreatic cancer. However, there is no evidence of increased risk of pancreatic cancer in patients with AIP, making it all the more important for providers to be aware of and avoid the pitfalls of operating on AIP. Awareness of AIP and its medical treatment may help differentiate it from other pathologies that require operations and also indicate when an operation is required.

DIAGNOSIS AND EVALUATION

The diagnostic approach to AIP can be based on the following five cardinal findings:

1. Cross-sectional (CT/MRI) and ductal imaging (ERCP) of the pancreas

TABLE 1 Clinical Profiles of Type I and Type II Autoimmune Pancreatitis

Clinical Feature	Type I AIP	Type II AIP
Age at presentation	>50 years of age	30 to 50 years of age
Sex	M > F	M = F
Serum IgG4 elevation	Yes	No
Histopathology	Lymphoplasmacytic infiltration with storiform fibrosis Obliterative phlebitis High levels of IgG4 staining	Lymphoplasmacytic infiltration with storiform fibrosis Granulocytic epithelial lesions
Other organ involvement	Yes	No
Association with inflammatory bowel disease	Low	High
Response to corticosteroids	Good	Good
Relapse after corticosteroid treatment	High	Low

AIP, Autoimmune pancreatitis; *F,* female; *IgG4,* immunoglobulin G4; *M,* male.

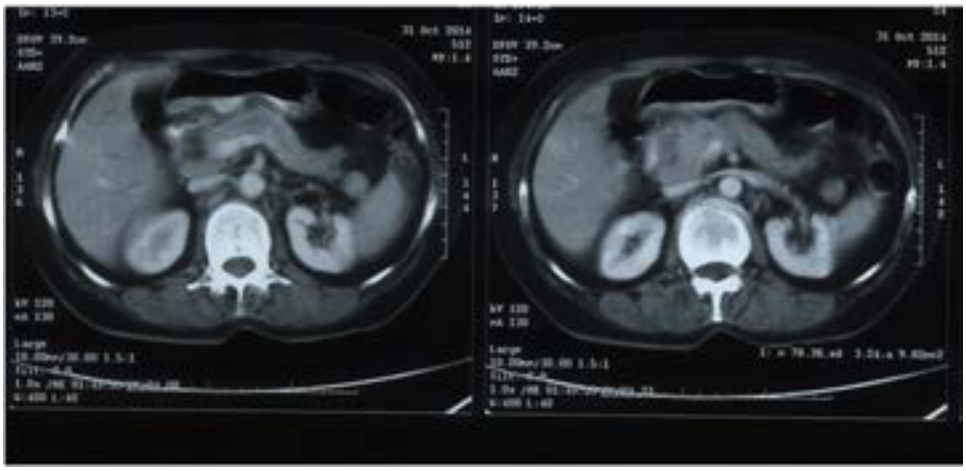


FIG. 1 Radiographic finding of a lobulated, hypodense pancreatic head mass in a patient with autoimmune pancreatitis. *(Modified from Gill M, Brar K, Godara R, et al. Autoimmune pancreatitis masquerading as carcinoma head of pancreas: A case report and review of literature.* Ann Med Surg [Lond]. *2019;45:82–85.)*

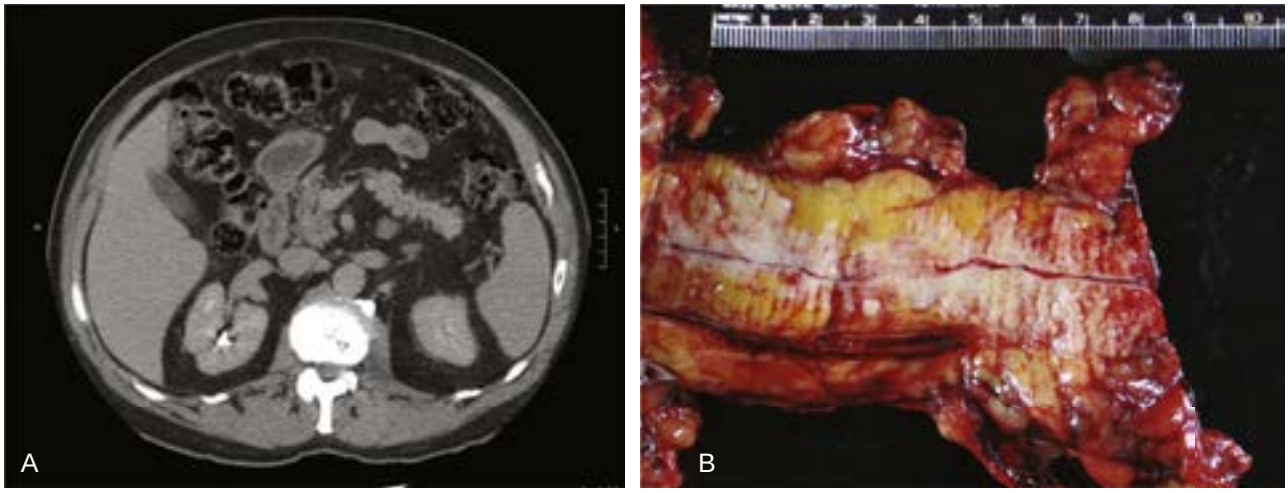


FIG. 2 Radiographic and pathologic features of autoimmune pancreatitis. **(A)** CT scan demonstrating a pancreatic duct stricture that tapers at the body region with no upstream dilation. **(B)** Correlating pathologic specimen demonstrating periductal fibrosis that correlates with the ductal strictures appreciated on CT.

2. Serum IgG4 levels
3. Other organ involvement
4. Histopathology
5. Response to corticosteroid therapy

Cross-Sectional and Ductal Imaging of the Pancreas

The classic radiographic appearance of AIP on cross-sectional imaging (either CT or MRI) is of a diffusely enlarged, sausage-shaped pancreas with homogenous attenuation and little to no visible pancreatic duct. It can sometimes be associated with a rimlike enhancement, termed a *halo*. It can also present as a focal mass in the pancreatic head mimicking pancreatic ductal adenocarcinoma (Fig. 1). In this case, clarification of the diagnosis requires histopathologic examination of a core biopsy of the resected specimen. This is especially common in type II AIP wherein a focal masslike lesion occurs in up to 35% of cases. Cross-sectional imaging and ERCP in AIP also commonly demonstrate long-segment or multiple pancreatic duct strictures but without upstream dilation, which is characteristic of pancreatic ductal adenocarcinoma (Fig. 2).

Serum IgG4 Levels

Serum IgG4 is the single best diagnostic tool for AIP. The sensitivity of an elevated serum IgG4 is as high as 80% to 99% in patients with type I AIP, but only 17% in those with type II AIP. Given the variability in the upper limits of normal IgG4 levels between laboratories and the potential for false positives, only a 2-fold elevation in IgG4 levels should be considered suggestive of the diagnosis of AIP. Although patients with pancreatic cancer can also present with elevated serum IgG4 levels, fewer than 1% have levels twice that of the upper limit of normal. Therefore, elevation in serologic markers should be corroborated with associated clinical, pathologic, or radiographic findings.

Histopathology

The histology of the pancreas can be examined as part of a pancreas-directed core biopsy or as a resected pathologic specimen. The findings differ between type I and type II AIP (Tables 2 and 3). For type 1 AIP, the finding of any of the three following features

TABLE 2 International Consensus Diagnostic Criteria for Type I Autoimmune Pancreatitis

Diagnosis	Primary Basis for Diagnosis	Imaging Evidence	Collateral Evidence
Definitive type I AIP	Histology	Typical/indeterminate	At least three of the following on core biopsy or resection: 1. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2. Obliterative phlebitis 3. Storiform fibrosis 4. Abundant (910 cells/HPF) IgG4-positive cells
	Imaging	Typical	Any one of the following: 1. Elevated IgG4 levels 2. At least two of the classic histopathology findings 3. Other organ involvement proven histologically or classic radiographic appearance 4. Response to corticosteroids
		Indeterminate	At least two of the following: 1. Diffuse enlargement of pancreatic parenchyma with delayed enhancement on imaging 2. Pancreatic duct strictures without marked upstream dilation 3. Elevated IgG4 levels 4. Other organ involvement proven histologically or classic radiographic appearance 5. At least three of the classic histopathology findings 6. Response to corticosteroids
	Response to steroids	Indeterminate	Elevated IgG4 levels/other organ involvement proven histologically or classic radiographic appearance + Response to corticosteroids **OR** Pancreatic duct strictures without marked upstream dilation + Elevated IgG4 levels/other organ involvement proven histologically or classic radiographic appearance/at least two of the classic histopathology findings + Response to corticosteroids.
Probable type I AIP		Indeterminate	Elevated IgG4 levels/other organ involvement proven histologically or classic radiographic appearance/at least two of the classic histopathology findings + Response to corticosteroids

AIP, Autoimmune pancreatitis; *HPF,* high-power field; *IgG4,* immunoglobulin G4.

can be diagnostic: periductal lymphoplasmacytic infiltrate without granulocytic infiltration, obliterative phlebitis, storiform fibrosis, or abundant (>10 cells/high-power field [HPF]) IgG4-positive cells. The diagnosis of type II AIP requires both granulocytic infiltration of the duct wall with or without granulocytic acinar inflammation and absent or scant (0–10 cells/HPF) IgG4-positive cells.

Other Organ Involvement

The involvement of extrapancreatic organs is more characteristic of type I AIP and not type II. As previously mentioned, these include Sjogren syndrome, rheumatoid arthritis, primary sclerosing cholangitis, orbital pseudotumor, retroperitoneal fibrosis, and/or inflammatory bowel disease. The histologic criteria of any three of the following in the extrapancreatic organs are considered diagnostic: marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration, storiform fibrosis, obliterative phlebitis, or abundant (>10 cells/HPF) IgG4-positive cells.

Response to Corticosteroid Therapy

In patients with either form of AIP, corticosteroid administration should result in marked radiographic improvement of pancreatitis and normalization of IgG4 levels within 2 to 4 weeks. However, response to corticosteroid therapy alone is not diagnostic of AIP. Patients with pancreatic ductal adenocarcinoma can also demonstrate subjective symptomatic improvement and a sense of well-being when given corticosteroid therapy. A persistently elevated or rising

TABLE 3 International Consensus Diagnostic Criteria for Type II Autoimmune Pancreatitis

Diagnosis	Imaging Evidence	Collateral Evidence
Definitive type II AIP	Typical/indeterminate	Histologic findings of both granulocytic infiltration of duct wall with or without granulocytic acinar inflammation and absent or scant IgG4-positive cells **OR** Clinical inflammatory bowel disease + Both granulocytic and lymphoplasmacytic acinar infiltrate and absent or scant IgG4-positive cells + Response to corticosteroids
Probable type II AIP	Typical/indeterminate	Both granulocytic and lymphoplasmacytic acinar infiltrate and absent or scant IgG4-positive cells/clinical inflammatory bowel disease + Response to corticosteroids

AIP, Autoimmune pancreatitis; *IgG4,* immunoglobulin G4.

serum carbohydrate antigen 19-9 (CA 19-9) should alert the provider to the likelihood of cancer.

INTERNATIONAL CONSENSUS DIAGNOSTIC CRITERIA

Given the unreliability of any single aforementioned "cardinal" findings by themselves, a combination of the features is required to reliably make a diagnosis of AIP. For type I AIP, a combination of features is often adequate without the need for histology. However, given the absence of a reliable serum biomarker and extrapancreatic involvement, the diagnosis of type II AIP requires a tissue biopsy for histologic diagnosis. In 2011, the International Association of Pancreatology reviewed the literature and offered an international consensus for the diagnosis of AIP. Tables 2 and 3 detail the criteria for type I and type II AIP, respectively. Although complex, these diagnostic criteria have been demonstrated to be highly reliable, with validation studies reporting sensitivity and specificity rates of 95% and 100%, respectively.

FINDINGS NOT TYPICAL OF AIP

Just as important as recognizing AIP's cardinal features, providers should be aware of symptoms that are typically not associated with AIP to avoid misdiagnosis. Although AIP can present as abdominal pain, it typically does not present as painful pancreatitis requiring narcotics. It also does not present as marked cachexia with inability to eat, which is more suggestive of pancreatic cancer. Radiographically, it is also typically not associated with pseudocysts and calculi seen with alcohol-induced pancreatitis or with ductal dilation upstream to the point of stricture, which occur with pancreatic neoplasms.

TREATMENT

Medical Treatment

AIP generally responds very well to corticosteroid administration, with symptoms such as jaundice, endocrine insufficiency, and exocrine insufficiency resolving within 2 to 4 weeks of treatment initiation (Fig. 3). For patients with mild jaundice and no signs of infection, endoscopic biliary stenting is rarely indicated, and they should be treated with corticosteroids alone. Endoscopic stenting should actually be avoided if possible, given the elevated risk of infection in patients with AIP who will typically be treated with long-term corticosteroids. Non-response to corticosteroid administration should cue the provider to consider an alternate diagnosis such as cancer. The International Consensus Diagnostic Criteria for Autoimmune Pancreatitis recommends 0.6 to 1 mg/kg per day of prednisone for 2 weeks, followed by interval imaging and CA 19-9 levels. If the patient is responding to therapy, the prednisone can be tapered by 5 to 10 mg per day every 1 to 2 weeks until a daily dose of 20 mg, then decreased by 5 mg every 2 weeks.

Patients with imaging features of sausage-like swelling and peripancreatic halo have been found to have a favorable response to corticosteroids, likely reflecting an early inflammatory phase. Conversely, patients with ductal strictures or focal swelling are likely to have a poorer response to corticosteroids, perhaps as a result of greater fibrosis. In patients who do not respond to corticosteroids, treatment with immunomodulatory drugs such as rituximab and azathioprine can be considered, although more studies are required before they can be routinely recommended.

AIP recurrence or relapse is common, with a reported occurrence ranging from 31% to 60% during the tapering or after discontinuation of corticosteroids. The Japanese Consensus Guidelines for AIP proposed maintenance therapy with 5 mg per day of prednisone for 3 years to mitigate disease relapse or recurrence. However, it is still unclear if maintenance therapy improves long-term outcomes enough to warrant the side effects of being on long-term steroids. Some studies have demonstrated that patients who have elevated pretreatment IgE levels or proximal bile duct stricture or IgG4-sclerosing cholangitis are at a higher risk of relapse and should be considered for maintenance corticosteroid therapy.

In patients whose diagnosis cannot be confirmed despite undergoing biopsy of the pancreas more than once, surgical resection of the involved segment can be considered in lieu of unresolved concerns for potential malignancy.

Surgical Treatment

The two main indications for surgical resection are as follows:

1. Diagnostic uncertainty and concern for cancer
2. Unresponsiveness to corticosteroid therapy or immunomodulators and continuing symptoms

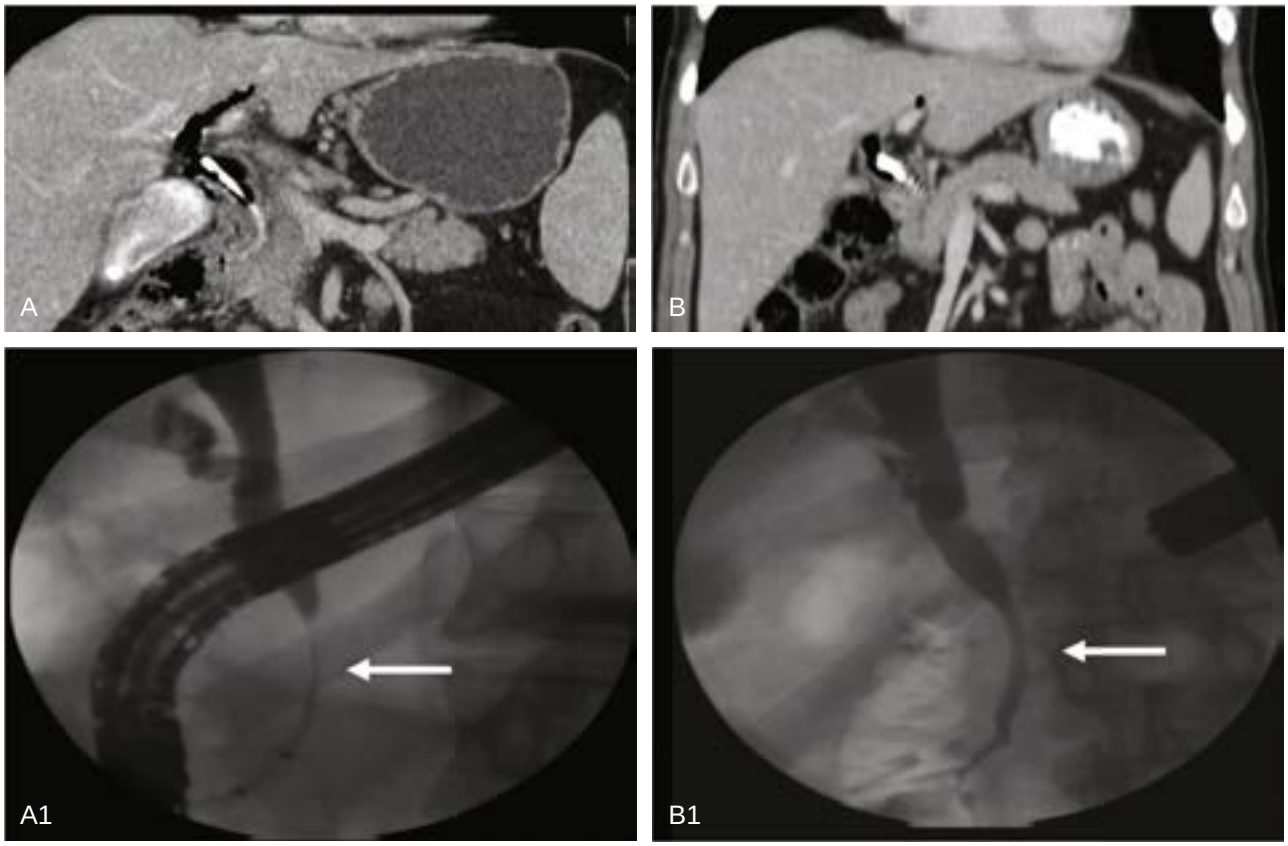


FIG. 3 Treatment effect of corticosteroids on autoimmune pancreatitis. **(A)** CT scan demonstrating enlargement with a patchy hypoenhancement rind surrounding the pancreatic head along with common bile duct wall thickening. **(A1)** Endoscopic retrograde cholangiopancreatography demonstrating a strictured common bile duct *(arrow)*. **(B)** Posttreatment CT demonstrating resolution of pancreatic head hypoenhancement after 3 weeks of 40 mg/day of prednisone. **(B1)** ERCP cholangiogram showing interval improvement of the common bile duct stricture *(arrow)*.

It is important to note that despite all of the aforementioned cardinal features of AIP, diagnostic uncertainty may still remain. Surgical resection should be considered when there is sufficient suspicion for malignancy. Resection should be tailored toward the predominant area of inflammation: pancreatoduodenectomy for a mass in the head of the pancreas and distal pancreatectomy for masses in the body and/or tail of the pancreas.

The peripancreatic inflammation induced by AIP creates a fibrotic reaction that distorts normal anatomic planes and can tether peripancreatic vessels, making the portal vein and superior mesenteric vein dissection more difficult. In one surgical series, the Johns Hopkins group compared pancreatectomy outcomes for 37 patients with AIP versus those with other diagnoses and reported a higher incidence of "difficult superior mesenteric vein dissection" of 71% versus 44% in the non-AIP group ($P < 0.05$). They also reported greater operative blood loss (mean 1290 cc vs. 832 cc in the non-AIP group, $P < 0.05$), albeit with similar transfusion requirements, postoperative length of hospital stay, and overall complication rates. Notably, 68% of patients who underwent resection for AIP reported improved quality of life, while 18% and 14% reported no change or diminished quality of life, respectively. In the largest surgical series to date (n = 74) reported from the Massachusetts General Hospital and the Mayo Clinic, 51% of patients underwent classic pancreatoduodenectomy, 24% underwent pylorus-preserving pancreatoduodenectomy, 14% underwent distal pancreatectomy with splenectomy, 7% underwent distal pancreatectomy without splenectomy, and only 4% required total pancreatectomy. The reported median estimated blood loss was 600 cc, the major morbidity (Clavien Dindo Grade III or greater) was 14%, and the perioperative mortality rate was 1%. Because of difficult dissection or inability to clear the superior mesenteric vein without injury, 20% of patients required vein resection and reconstruction. The incidence of postoperative pancreatic fistula was only 7%, possibly because these patients characteristically had a firm, fibrotic pancreatic gland. Nonetheless, recurrent AIP developed subsequently in the pancreatic remnant in 17% of patients, underscoring the importance of continued follow-up, even after surgical resection. It is also worth mentioning that all 17% of recurrences were treated medically and did not require reoperation.

Total pancreatectomy has been reported only as single cases. It may be reasonably indicated in type I AIP involving the entire pancreas in a patient with persistent pain after failed corticosteroid treatment. Added to the immediate morbidity and mortality of a total pancreatectomy are the lifelong burdens of endocrine and exocrine insufficiency. Because the islets tend to be spared in AIP, concurrent islet cell transplantation can be considered.

FOLLOW-UP AND SURVEILLANCE

As noted, the recurrence and relapse rate of AIP is significant after either medical or surgical treatment. Given the limited long-term data on AIP, there has been no formal recommendation for the follow-up of patients with treated AIP. Perhaps most commonly used is the Mayo Clinic protocol, which is based on organ system involvement. For patients with biliary strictures, serologic testing (liver function test, IgG4, and CA 19-9 levels) every 12 weeks for the first 1 to 2 years is prescribed. In patients without biliary involvement, no surveillance is required unless patients present

with recurring symptoms, which warrant cross-sectional imaging with either CT or magnetic resonance cholangiopancreatography (MRCP).

Even though IgG4 is recommended in the Mayo follow-up protocol, studies have demonstrated that it has little value in predicting or diagnosing clinical recurrence after initial treatment. Patients frequently present with elevated levels without any associated clinical symptoms or manifestations. CA 19-9 levels are similarly nonspecific as elevated levels can be seen in both benign and malignant conditions, but measurement of both in combination may be more discriminating.

SUMMARY

AIP is a rare form of mass-forming pancreatic inflammation that can masquerade as pancreatic cancer and can lead to unnecessary operations. Accurate recognition of the cardinal features of AIP, a medically treated condition, must be balanced against missing the chance to resect a lethal malignancy. A better understanding and heightened awareness of AIP has led to a decreasing number of unnecessary operations performed in AIP.

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Management of Pancreatic Necrosis

Linda Ye, MD, and O. Joe Hines, MD

DEFINITIONS AND DIAGNOSIS

Acute pancreatitis is a common indication for inpatient hospitalization in the United States. Patients may present with epigastric abdominal pain radiating to the back, nausea, vomiting, abdominal distention, or signs of dehydration. Acute pancreatitis is diagnosed based on two of the following three criteria: (1) abdominal pain consistent with acute pancreatitis, (2) serum lipase or amylase activity >3 times greater than the upper limit of normal, and (3) findings of pancreatic inflammation on imaging.

The etiology of acute pancreatitis varies widely, with the more common causes including gallstones, alcohol, idiopathic/autoimmune, metabolic (e.g., hypertriglyceridemia, hypercalcemia), iatrogenic (e.g., postendoscopic retrograde cholangiopancreatography), trauma, medications, or anatomic abnormalities (e.g., pancreas divisum).

Severity Classification of Acute Pancreatitis

The severity of acute pancreatitis is most commonly defined based on the 2012 Atlanta classification (Table 1), which includes three grades: mild, moderately severe, and severe. Mild acute pancreatitis is not associated with local or systemic complications or organ failure, and mortality is very rare (<5%), as the course is self-limited. Moderately severe acute pancreatitis occurs in 15% of patients, in whom there is transient organ failure that resolves within 48 hours, local or systemic complications without persistent organ failure, or both. Severe acute pancreatitis accounts for about 5% of presentations, defined by persistent organ failure >48 hours, and can involve single or multiple organs. Mortality risk significantly increases with severe acute pancreatitis up to 36% to 50%, with extremely high risk of mortality with infected pancreatic necrosis. A limitation of the Atlanta classification is that it does not account for real-time measurements of disease activity in a dynamic disease, such as acute pancreatitis. Final severity grades evolve over the disease course and require continued clinical and radiologic follow-up.

Other grading systems have been validated to predict severity of acute pancreatitis, including Pancreatitis Activity Scoring System (PASS), which uses an additive, continuous monitoring system to provide dynamic measures of disease activity during the entire course of illness. Clinically important parameters include organ failure, systemic inflammatory response, pain, pain medication, and intolerance to solid diet. Other scoring systems include Ranson's criteria, the Acute Physiology and Chronic Health Examination (APACHE) II score, bedside index of severity in acute pancreatitis (BISAP) score, and CT severity index. The CT severity score is based on the degree of necrosis, inflammation, and presence of fluid collections on imaging.

Local Complications of Acute Pancreatitis

By definition, local complications are associated with moderately severe and severe acute pancreatitis and should be suspected in patients with a protracted clinical course. Symptomatically, patients may experience persistent or worsening abdominal pain, poor appetite or tolerance of diet, fever, organ failure, and sepsis. Table 2 defines the local complications of acute pancreatitis, CT findings, and typical timing of diagnosis.

Local complications of acute pancreatitis can be classified in two broad categories. Interstitial edematous pancreatitis is an acute inflammation and diffuse enlargement of the pancreas without necrosis. Two types of local collections may develop in these severe cases of pancreatitis not associated with necrosis: acute peripancreatic fluid collection (APFC) and pancreatic pseudocyst. APFCs are homogenous, nonencapsulated fluid collections adjacent to the pancreas without necrosis, typically diagnosed within 4 weeks of symptom onset. Pancreatic pseudocysts are encapsulated fluid collections with a well-defined inflammatory wall without significant necrosis seen after 4 weeks of disease onset. Most APFCs and pseudocysts resolve spontaneously.

TABLE 1 Grades of Severity of Acute Pancreatitis (2012 Revised Atlanta Classification)

Grade	Organ Failure	Local or Systemic Complications	Risk of Mortality
Mild	Absent	Absent	Very rare (<5%)
Moderately severe	Transient (<48 hours)	Present, without persistent organ failure	Low
Severe	Persistent (>48 hours)	Present	High (36%–50%); extremely high with infected necrosis

Final severity grade may continue to evolve throughout the course of disease. Convenient time points to reevaluate are 24 hours, 48 hours, 7 days after hospital admission, and weekly thereafter.
Adapted from Banks PA et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.

TABLE 2 Local Complications of Acute Pancreatitis (2012 Revised Atlanta Classification)

Term	Definition	CT Findings	Timing of Diagnosis
Interstitial edematous pancreatitis	Acute inflammation and diffuse enlargement of the pancreas due to edema without evidence of necrosis	Homogenous enhancement of the pancreas Inflammatory changes of the peripancreatic fat with some peripancreatic fluid No definable encapsulating fluid collection	<4 weeks after onset of acute pancreatitis
Acute peripancreatic fluid collection (APFC)	Homogenous, nonencapsulated fluid collection adjacent to the pancreas associated with pancreatitis without evidence of necrosis	Homogenous fluid-dense collection No definable wall encapsulating the collection Adjacent to the pancreas (no intrapancreatic extension)	<4 weeks after onset of interstitial edematous pancreatitis
Pancreatic pseudocyst	Encapsulated fluid collections with a well-defined inflammatory wall with minimal or no necrosis	Well-circumscribed homogeneous fluid density No nonliquid component Well-defined wall (completely encapsulated)	>4 weeks after onset of interstitial edematous pancreatitis
Necrotizing pancreatitis	Inflammation associated with necrosis of the pancreatic parenchyma and/or peripancreatic tissue	Nonenhancing pancreatic parenchyma Findings of peripancreatic necrosis (e.g., ANC and WON)	<4 weeks after onset of acute pancreatitis
Acute necrotic collection (ANC)	Collection containing both fluid and necrosis associated with acute necrotizing pancreatitis, which may involve the pancreatic parenchyma, peripancreatic tissues, or both	Heterogeneous and non-liquid density of varying degrees No definable wall encapsulating the collection Can be intra- and/or extrapancreatic	<4 weeks after onset of acute pancreatitis
Walled-off necrosis (WON)	Mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with a well-defined inflammatory wall	Heterogeneous with liquid and nonliquid densities with possible loculations Well-defined, completely encapsulating wall	>4 weeks after onset of necrotizing pancreatitis

Adapted from Banks PA et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.

Necrotizing pancreatitis is inflammation associated with necrosis of the pancreatic parenchyma, peripancreatic tissue, or both. Two different types of necrotic collections may develop in the setting of pancreatic necrosis: acute necrotic collection (ANC) and walled-off necrosis (WON). ANCs are collections containing both fluid and necrosis associated with acute necrotizing pancreatitis, diagnosed

within the first 4 weeks of symptom onset. In contrast, WON is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with a well-defined inflammatory wall seen at least 4 weeks after disease onset. These fluid collections are initially sterile but may become superinfected. Patients with pancreatic necrosis may have a variety of clinical presentations, from asymptomatic to abdominal pain, nausea, vomiting, early satiety, or weight loss.

Other local complications of acute pancreatitis include hemorrhagic pancreatitis, gastric outlet obstruction, splenic or portal vein thrombosis, pseudoaneurysms, and colonic infarction. Systemic complications may include acute kidney injury, adynamic ileus, respiratory failure, sepsis or septic shock, and abdominal compartment syndrome.

Imaging Modalities

Due to the deep-seated anatomy of the pancreas, serial cross-sectional imaging is critical for determining the severity and evolution of pancreatitis. Contrast-enhanced CT is the standard imaging modality for diagnosis of pancreatitis and is particularly useful in establishing the presence and extent of necrosis (Fig. 1), fluid collections, and other local complications (e.g., venous thrombosis or pseudoaneurysms). Intravenous contrast is preferred, as it allows demarcation between the enhancing, healthy pancreatic parenchyma and the nonperfusing necrotizing pancreatitis, as well as evaluation of the surrounding vasculature. Initial imaging may not adequately capture the extent of disease, as the severity of the pancreatitis continues to evolve over several days after initial presentation. Repeat imaging is often necessary at least 48 to 72 hours after initial imaging and, if complications exist, may be done weekly during hospitalization or when the clinical status changes. The presence of rim-enhancement and gas within a necrotic collection typically indicates secondary infection (Fig. 2). The disadvantages of CT are that contrast administration may worsen an already compromised renal function associated with severe pancreatitis, lifetime radiation exposure may quickly accumulate with serial scans, and the difficulty in discriminating the degree of solid debris within necrotic collections, for which magnetic resonance imaging (MRI) or transabdominal ultrasound (US) may be beneficial.

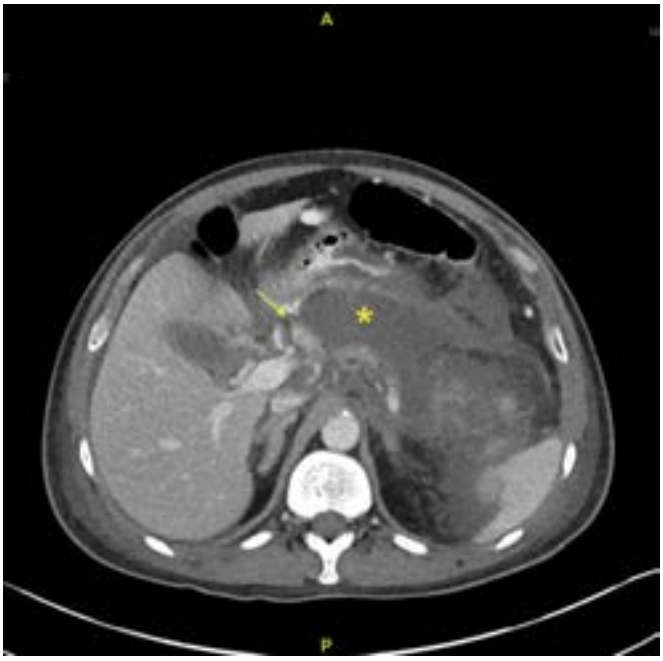


FIG. 1 Necrotizing pancreatitis. Contrast-enhanced CT image of acute pancreatitis with extensive hypoenhancing necrosis *(asterisk)* of the pancreatic body and tail with surrounding edema and small amount of enhancing parenchyma at the pancreatic head *(arrow)*.



FIG. 2 Infected pancreatic necrosis with percutaneous drainage. Contrast-enhanced CT image of infected necrotizing pancreatitis with a rim-enhancing complex fluid collection containing multiple foci of gas and an image-guided percutaneous drain placed into the lateral aspect of the collection through the left flank.

T1- and T2-weighted MRI sequences with magnetic resonance cholangiopancreatography (MRCP) can be useful in determining the extent of necrosis, degree of solid debris, presence of stones in the biliary tree, and presence of a disconnected pancreatic duct. In addition, MRI and MRCP can detect pancreatic necrosis and defects in the biliary tree without gadolinium contrast, which is useful in those with renal impairment.

US is less effective at visualizing the pancreas due to overlying bowel but can determine whether gallstones are present in the gallbladder or common bile duct.

INITIAL MANAGEMENT

Patients with moderately severe or severe acute pancreatitis may develop hypovolemia due to a systemic inflammatory response, which can result in hypotension, tachycardia, oliguria, and other systemic complications requiring close, intensive resuscitation and monitoring. Generally, referral to a specialist center is highly recommended for patients with severe pancreatitis or those who may require procedural intervention.

Monitored Care

Initial assessment of acute pancreatitis should include noninvasive monitoring targeting heart rate, mean arterial pressure, and urine output. Continuous monitoring may be necessary in patients with persistent tachycardia, hypotension, and oliguria, which may indicate inadequate fluid resuscitation or developing shock.

Patients with severe acute pancreatitis benefit from invasive monitoring targeting a central venous pressure of 8 to 12 mm Hg and mixed venous oxygen saturation of at least 70%, which has been

shown to result in fewer days of hospitalization and ventilation, less organ failure, and a lower mortality rate. There should be a low threshold to transfer these patients with severe acute pancreatitis to an intensive care unit for close monitoring due to these hemodynamic alterations and fluctuating disease course.

Fluid Resuscitation

Early and intensive fluid resuscitation is necessary in acute pancreatitis due to fluid shifts resulting from a systemic inflammatory response. As discussed earlier, resuscitation should target heart rate, mean arterial pressure, urine output, and, in severe cases, central venous pressure and mixed venous oxygen saturation. Ringer's lactate is recommended for initial fluid resuscitation due to association with antiinflammatory effects and less metabolic acidosis. Initial goal-directed fluid therapy should be 5 to 10 mL/kg/h and titrated to resuscitation goals.

Patients receiving large volume fluid resuscitation should also be monitored for volume overload. Clinical signs of volume overload may present as tachypnea, hypoxia, lower extremity edema, and pleural effusions on chest radiograph. Patients may benefit from diuresis once the initial state of hypovolemia resolves.

Prevention of Infection

While the systemic inflammatory response of acute pancreatitis can mimic sepsis, empiric intravenous antibiotics are not indicated. In addition, prophylactic antibiotics are not recommended for prevention of infectious complications in acute pancreatitis, as necrosis associated with severe acute pancreatitis is thought to be sterile initially, and selection of resistant bacteria may become problematic if the necrosis becomes superinfected. However, if infected pancreatic necrosis is documented radiographically or by positive fluid culture, antibiotics should be initiated and continued to stabilize the patient and attempt to defer intervention until at least 4 weeks. Antibiotics in the carbapenem family have been shown to be more effective at penetrating the pancreatic necrosis than cephalosporins or fluoroquinolones.

Probiotic prophylaxis is not recommended for prevention of infectious complications. A multicenter randomized trial demonstrated no difference in rates of infectious complications with probiotics; however, the risk of death more than doubled in the group that received probiotics, possibly due to intestinal ischemia.

Currently, there are insufficient data for or against selective gut decontamination; however, a multicenter trial demonstrated decreased mortality and incidence of gram-negative infection in patients treated with an oral paste containing colistin, amphotericin, and norfloxacin.

Nutrition

Previously, it was commonly believed that enteral feeding worsened pancreatic inflammation; thus, the practice was for patients to be kept nil per os (NPO) until the pancreatitis completely resolved before initiating feeding. Recent evidence suggests that, when possible, early oral feeding (<24 hours) is recommended as tolerated rather than keeping the patient NPO. Enteral feeds can alternatively be safely delivered via nasogastric or nasojejunal routes if the patient is unable to tolerate orally due to nausea or gastric outlet obstruction. Early enteral nutrition decreases infectious complications, severity of organ failure, need for surgical interventions, and mortality compared with parenteral nutrition.

INDICATIONS AND TIMING OF INTERVENTIONS

Historically, severe acute necrotizing pancreatitis was an absolute indication for surgical intervention. However, retrospective studies have since revealed that surgical intervention has a mortality rate of 75% when performed in the first 2 weeks of symptom onset, 45% when delayed to 2 to 4 weeks after symptom onset, and 8% when intervention is delayed beyond 30 days. Invasive interventions are generally not indicated for asymptomatic patients with sterile collections, as these may eventually resorb and resolve over time without intervention.

Drainage should be performed for infected pancreatic fluid collections in patients who fail to improve with conservative management alone or for patients with symptomatic sterile necrosis (e.g., gastric outlet obstruction, pain, PO intolerance, disconnected duct) >8 weeks after onset of pancreatitis. However, there is strong evidence that the optimal timing for surgical or procedural interventions should be at least 4 weeks after symptom onset to allow for the fluid collection to mature and "wall-off." The process of maturation includes parenchymal demarcation, development of an inflammatory rind, and liquefaction of the contents of the collection. Attempts to debride the friable, inflamed tissue before maturation risks hemorrhage, overwhelming inflammatory response, and fistula development. Demarcation and liquefaction of the collection allow for preservation of healthy pancreatic parenchyma during debridement, which may prevent development of endocrine and exocrine pancreatic insufficiency.

With the advancement of less invasive endoscopic and percutaneous drainage procedures, surgery can be deferred until at least 4 weeks when the fluid collection matures or avoided entirely. However, if the patient has evidence of infected necrosis with clinical deterioration, urgent percutaneous drainage may be required for immediate source control regardless of the maturity of the collection. Note that endoscopic drainage requires the necrotic collection to be walled-off and typically cannot be performed for collections less than 4 weeks after symptom onset.

Emergent surgical or procedural intervention may otherwise be indicated in other complications of severe acute pancreatitis, including intestinal ischemia, perforated viscous, acute and uncontrolled bleeding, or abdominal compartment syndrome. In these cases, the complications should be addressed, and surgical debridement of sterile necrosis should still be avoided.

THE STEP-UP APPROACH

Previously, infected pancreatic necrosis was an absolute indication for urgent open necrosectomy, which carried a 50% mortality rate. The advancement of endoscopic and percutaneous drainage procedures and minimally invasive surgeries has changed the management algorithm of necrotizing pancreatitis and improved outcomes by temporizing, delaying, or altogether avoiding operative intervention. Now, the standard for treatment of necrotizing pancreatitis is based on the "step-up approach," an algorithm that first utilizes endoscopic or percutaneous drainage of the necrotic collection before "stepping up" to endoscopic or surgical necrosectomy (Fig. 3).

A multidisciplinary team of surgeons, interventional gastroenterologists, and interventional radiologists is essential to the success of the step-up approach, as certain interventions may not be as anatomically feasible. The optimal method of drainage has not yet been defined, and either percutaneous or endoscopic drainage may be initially pursued or in combination, although recent studies suggest a higher success rate with endoscopic drainage. Combination drainage using both percutaneous and endoscopic modalities may be beneficial for decreasing pancreatic fistula and decreasing the need for surgical necrosectomy.

Percutaneous Drainage

Percutaneous drainage is performed under image guidance by an interventional radiologist while the patient is awake or under moderate sedation. Collections most amenable to drainage are liquefied; however, serial upsizing to a larger bore drainage catheter is often required for adequate drainage of mixed liquid and solid necrotic debris. This also allows for intracatheter irrigation with saline or

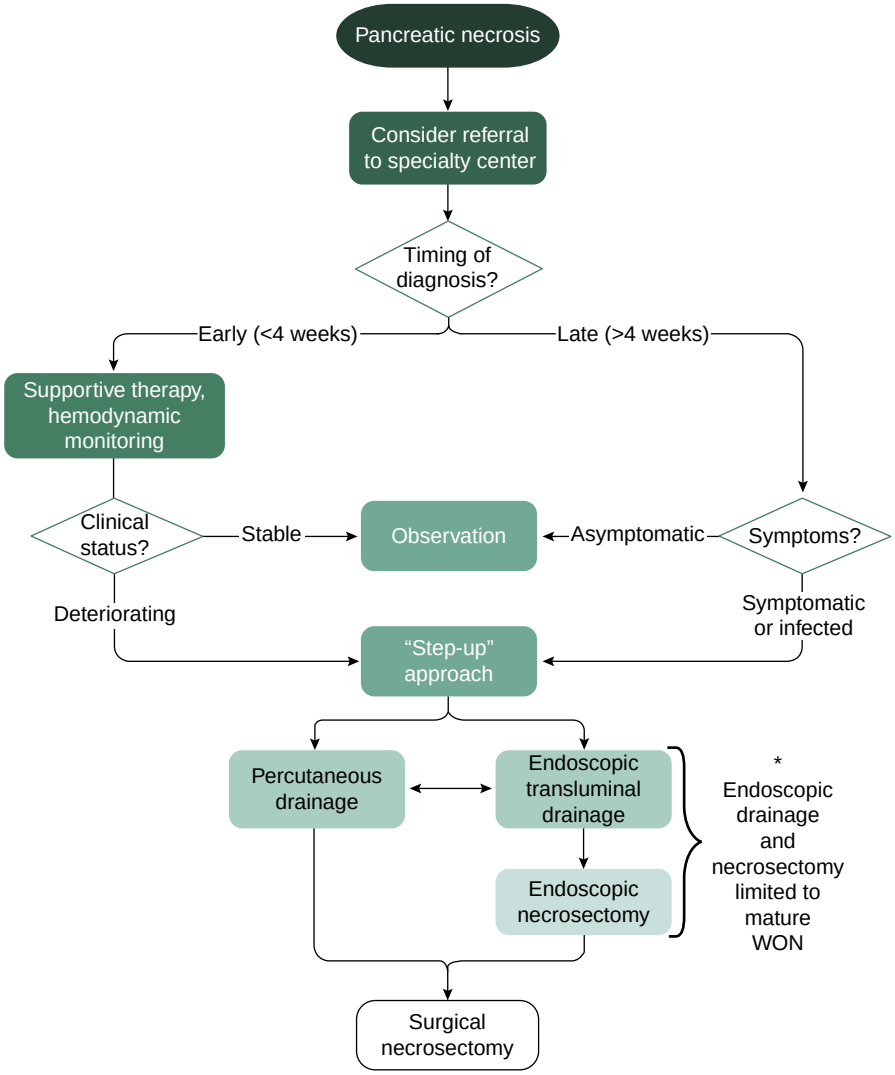


FIG. 3 Treatment algorithm for pancreatic necrosis.

hydrogen peroxide. The necrotic collection should preferably be accessed retroperitoneally to allow for guided access for potential retroperitoneoscopic debridement, if needed. Collections with significant extension to the retroperitoneum or paracolic gutters may benefit most from percutaneous rather than endoscopic drainage. A disadvantage of percutaneous drainage is the risk of persistent pancreaticocutaneous fistula, especially in patients where the necrotic collection is suspected to be communicating with the pancreatic duct.

A step-up approach of percutaneous drainage followed by video-assisted retroperitoneal debridement (VARD), if needed, has been found to be superior to primary surgical necrosectomy. The PANTER trial by the Dutch Acute Pancreatitis Study Group demonstrated that the step-up approach had significantly fewer complications and less new onset organ failure compared with open surgical debridement. Multiple studies since have shown that up to half of patients were successfully managed with percutaneous drainage alone, obviating the need for surgical necrosectomy. In addition, if percutaneous drainage fails, endoscopic drainage can be considered, or vice versa.

Endoscopic Drainage and Necrosectomy

Endoscopic drainage and necrosectomy are best applied to mature WONs located within 2 cm of the stomach or duodenum. During endoscopic drainage, esophagogastroduodenoscopy (EGD) and endoscopic ultrasound (EUS) are performed under conscious sedation or anesthesia to identify and confirm the location of the necrotic pancreatic collection (Fig. 4). The stomach wall is punctured with a needle, the cystgastrotomy tract is balloon-dilated, and pigtail stents and/or a lumen-apposing metal stent are placed for continued transgastric drainage into the stomach. A nasogastric tube can be placed within the necrotic collection for intra- or postprocedure irrigation. During necrosectomy, the cystgastrotomy is further dilated, the endoscope is inserted into the collection, and mechanical debridement is performed. These procedures can be technically challenging, typically require multiple repeat procedures for complete drainage, and should be performed by an advanced interventional gastroenterologist at a specialty center. After at least 4 to 6 weeks of maturation of the cystgastrotomy tract, the stents can then be removed.

Endoscopic necrosectomy has improved patient outcomes compared with primary open or laparoscopic surgical necrosectomy. In the PENGUIN trial, the Dutch Acute Pancreatitis Study Group found that endoscopic necrosectomy had a reduced composite rate of major complications or death, fewer pancreatic fistulas, and less new onset organ failure. Studies have since shown that operative debridement can be avoided in up to two-thirds of patients who undergo endoscopic necrosectomy.

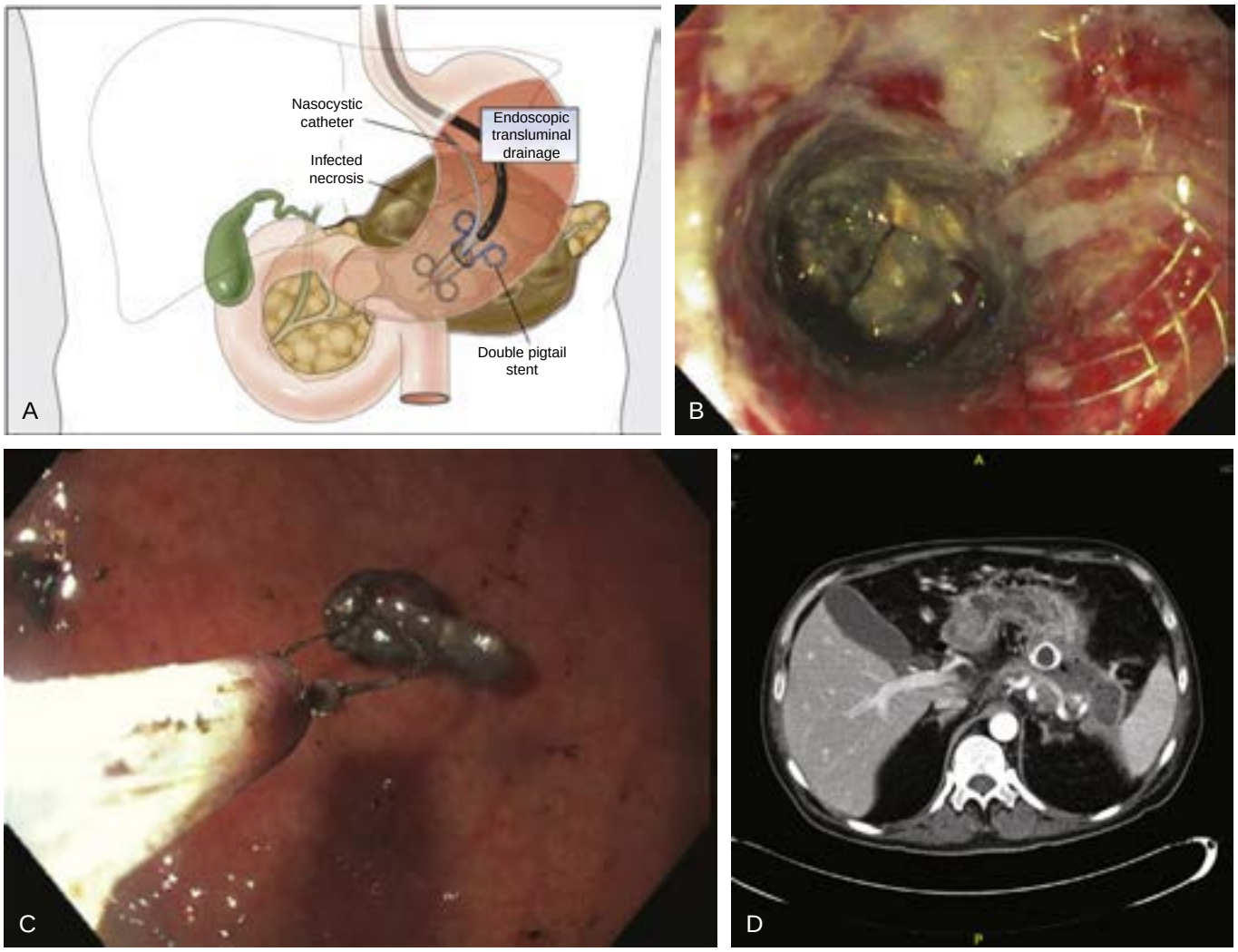


FIG. 4 Endoscopic transluminal drainage of infected necrotizing pancreatitis. **(A)** The necrotic collection is accessed endoscopically at the posterior stomach using EGD and EUS, a cystgastrotomy is made, and the collection can be irrigated using a nasogastric tube and drained transluminally using double pigtail stents or lumen-apposing metal stent (LAMS). **(B)** Endoscopic image of a LAMS placed in the cystgastrotomy between the stomach and the necrotic collection. **(C)** Endoscopic necrosectomy is performed by mechanical debridement through the cystgastrotomy. **(D)** CT image of a LAMS in place between the stomach and necrotic collection that allows for patency of the cystgastrotomy during healing and continued transgastric drainage. *(***A** *adapted from van Brunschot S et al. Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotizing pancreatitis (TENSION trial): design and rationale of a randomized controlled multicenter trial [ISRCTN09186711].* BMC Gastroenterol. *2013;13:161.)*

Percutaneous and endoscopic drainage have similar success rates, and either or both interventions can be pursued. In the TENSION trial, there was no difference in rates of complications or death between patients who underwent endoscopic drainage followed by necrosectomy compared with those who underwent percutaneous catheter drainage followed by VARD. However, the rates of pancreatic fistula and hospital length of stay were lower in the endoscopic group.

One of the trials showed percutaneous drainage alone was adequate to clear the necrosis in up to a third of patients.

Surgical Management

When patients fail percutaneous or endoscopic drainage, surgical debridement of the necrotic collection can be performed. The patient should be counseled on the risk of morbidity and mortality associated with surgical intervention, which varies among the multiple approaches and techniques.

Minimally Invasive Necrosectomy

Despite open necrosectomy being the previous gold standard for management of infected pancreatic necrosis, minimally invasive necrosectomy is currently favored over open necrosectomy due to reduction of systemic complications and organ failure. The pancreas can be accessed transperitoneally or retroperitoneally.

Benefits of the transperitoneal approach include improved visualization due to use of insufflation, the ability to assess the entire abdominal cavity for other complications, consideration of simultaneous cholecystectomy if biliary origin is suspected, the possibility of using the robotic platform for increased stability and improved fine dissection, and the option to create a cystgastrostomy or cystjejunostomy anastomosis for continued internal drainage of mature collections. However, the main risks are contamination of otherwise sterile spaces in the peritoneal cavity and limited ability to reoperate due to scar tissue formation. Through this transperitoneal approach, the pancreatic necrosis can be accessed through the gastrocolic ligament and preferably the transverse mesocolon.

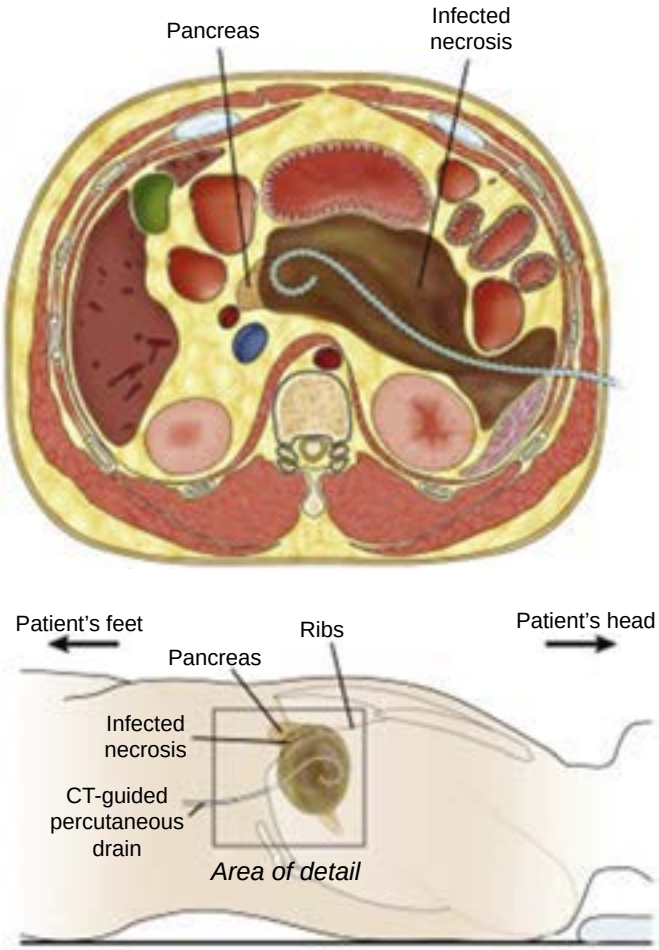


FIG. 5 Retroperitoneoscopic pancreatic debridement. Schematic of the approach of a video-assisted retroperitoneoscopic debridement (VARD). Access to the collection can be guided by a previously placed image-guided percutaneous drain through the left flank. *(Adapted from van Brunschot S et al. Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotizing pancreatitis (TENSION trial): design and rationale of a randomized controlled multicenter trial [ISRCTN09186711]. BMC Gastroenterol. 2013;13:161.)*

VARD is an alternate approach for surgical necrosectomy, which minimizes the risk of contamination of the peritoneal cavity (Fig. 5). If a percutaneous drain has been placed through the retroperitoneal space, the drain tract can be used to guide access to the fluid collection, typically via a left flank entry point. The incision is extended down to the necrotic cavity, where a laparoscope is inserted, and mechanical debridement occurs under direct visualization. Surgical drains should then be placed through this tract to allow for continued external drainage or continuous postoperative lavage. The disadvantage to VARD is the limited visualization due to lack of gas insufflation and distensible space.

Open Necrosectomy

Previously the gold standard, open debridement is now infrequently performed in the setting of minimally invasive techniques due to significant risks of incisional hernia, pancreatic fistula, organ failure, and death. The abdomen is incised through a midline laparotomy or bilateral subcostal incision, and the retroperitoneum is accessed through the lesser sac. Once the necrotic collection is entered, the fluid is evacuated and necrotic pancreatic tissue is manually debrided. Care should be taken to minimize debridement of viable tissue. Occasionally, a temporary abdominal closure may be used if the necrosis is too poorly demarcated to complete debridement with plan for reoperation in 48 to 72 hours. At the time of closure, the abdomen can be closed over drains for external drainage or continuous postoperative lavage.

Postoperative Management and Complications

Typically, these patients are kept intubated immediately postoperatively and transferred to the intensive care unit for close monitoring and resuscitation due to expected massive third spacing and fluid shifts in the first 48 to 72 hours. A nasojejunal tube placed intraoperatively may be used to start early enteral feeds if there are no concerns for immediate surgical complications.

The short-term postoperative course may be complicated by intraabdominal fluid collections requiring percutaneous drainage, bleeding, and pancreatic fistula requiring prolonged external drainage. Significant early postoperative bleeding is likely due to avulsion of small peripancreatic vessels, which may require reexploration for control of hemorrhage.

Long-term postoperative complications include incisional hernia (~40% following open debridement), pancreatic endocrine and exocrine insufficiency, and bleeding. Late postoperative bleeding may be due to rupture of pseudoaneurysm, which can be managed by visceral angiography or reoperation.

CONCLUSION

Necrotizing pancreatitis is a feared complication of severe acute pancreatitis, with a high rate of morbidity and mortality, especially when infected. The disease process is complex and requires careful consideration in all aspects of management: from early resuscitation, enteral nutrition, thoughtful antibiosis, timing, and selection of interventions, to continued close monitoring postoperatively. Due to

improved understanding of the disease process and recent advancements in interventional radiologic and gastroenterologic techniques, surgical intervention can be delayed or even avoided using the "step-up approach," in which percutaneous or endoscopic drainage are performed, followed by endoscopic or surgical necrosectomy, if needed. In addition, minimally invasive surgeries, including VARD, are now well-described and allow for necrosectomy in patients who have failed nonoperative intervention, overall decreasing the morbidity once associated with primary surgical intervention.

Suggested Readings

Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA*. 2012;307(10):1053–1061.

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Management of Pancreatic Pseudocyst

Ammar A. Javed, MD, and Kelly J. Lafaro, MD, MPH

INTRODUCTION

Acute pancreatitis is often self-limited with minimal long-term implications. However, a small subset of patients with acute pancreatitis will develop either necrosis or persistent fluid collections. Pancreatic pseudocysts are localized peripancreatic fluid collections with a well-defined wall composed of fibrotic tissue that contain amylase-rich fluid and other pancreatic enzymes with minimal or no solid material. They have been reported in approximately 5% to 15% of patients following acute pancreatitis. Patients often present with vague nonspecific symptoms, including abdominal pain, nausea, and vomiting, and therefore can go undiagnosed. A majority are a sequalae of acute or chronic pancreatitis but can also occur after blunt abdominal trauma or iatrogenic pancreatic injury. With increased utilization of diagnostic imaging, the incidence of pancreatic pseudocysts is on the rise, and it is now the most common type of pancreatic cystic lesion. As clinicians, it is important to distinguish pancreatic pseudocysts from other pancreatic cystic lesions including intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and serous cyst adenomas (SCAs), given that management differs significantly. This often involves obtaining a detailed history; radiologic examination including contrast-enhanced CT, ERCP, MRI), and evaluation of cyst fluid for enzymes and tumor markers obtained via fine-needle aspiration (FNA). The clinical course and severity of disease is broadly variable; therefore, a thorough knowledge of the disease is required to deliver appropriate care in a timely manner. Up to 90% of peripancreatic fluid collections in patients with interstitial edematous pancreatitis resolve spontaneously and only require supportive care. However, there remains a cohort in whom they persist and require intervention. Treatment algorithms to guide clinical care of these patients have undergone considerable modifications, and their clinical application has demonstrated improvement in patients' outcomes.

This chapter provides an up-to-date summary of the literature and guidelines available for the diagnosis, evaluation, and management of pancreatic pseudocyst.

DEFINITION AND CLASSIFICATION

The term *pseudocyst* is often used to describe any well-defined fluid collection following pancreatitis. It is very important to accurately diagnose pancreatic pseudocysts and distinguish them from other entities as the evaluation and management is different.

The 2012 revised Atlanta classification system has tried to standardize the definitions of acute pancreatitis. The Atlanta classification divides acute pancreatitis into two types: necrotizing and interstitial edematous (no necrosis). Any peripancreatic fluid collection is then further classified based on the timing, using a 4-week cutoff. A fluid collection forming after interstitial edematous acute pancreatitis within 4 weeks is known as an *acute pancreatic fluid collection,* while those persisting after 4 weeks are known as *pancreatic pseudocysts.* Importantly, it distinguishes between pseudocysts and fluid collections forming after necrotizing pancreatitis, which are classified as *acute necrotic collection* at less than 4 weeks and *walled-off necrosis* (WON) for collections that persist after 4 weeks.

Once a diagnosis of pancreatic pseudocyst is made, it is important to identify the pancreatic duct anatomy, the relationship of the pseudocyst to the pancreatic duct, and any anomalies present. Multiple classification systems have been proposed based on the underlying cause, location, and extent of communication with the pancreatic duct. These can be used to guide patient management. Traditionally, this was evaluated using ERCP; however, with significant advances, MRCP is now more commonly used.

In the system proposed by D'Egidio and Schein, pancreatic pseudocysts occurring after an episode of acute pancreatitis are classified as type I, often presenting with normal ductal anatomy and no communication. Type II can occur after acute or chronic pancreatitis and demonstrate an abnormal duct with ductal communication. Lastly, type III pseudocysts are those that are a sequalae of chronic pancreatitis in which ductal obstruction is present with a retention cyst. Subsequently, Nealon and Walser in 2002 proposed a system based on ductal anatomy to guide management. Those associated with acute pancreatitis were classified as types I to V: type I with a normal duct and no ductal communication, type II with a normal duct and ductal communication, type III with an otherwise normal duct with stricture and no communication, type IV with an otherwise normal duct with a stricture and communication, and type V with an otherwise normal duct with a complete cutoff. Those related to chronic pancreatitis include type VI in which there is no communication and type VII with ductal communication (Fig. 1).

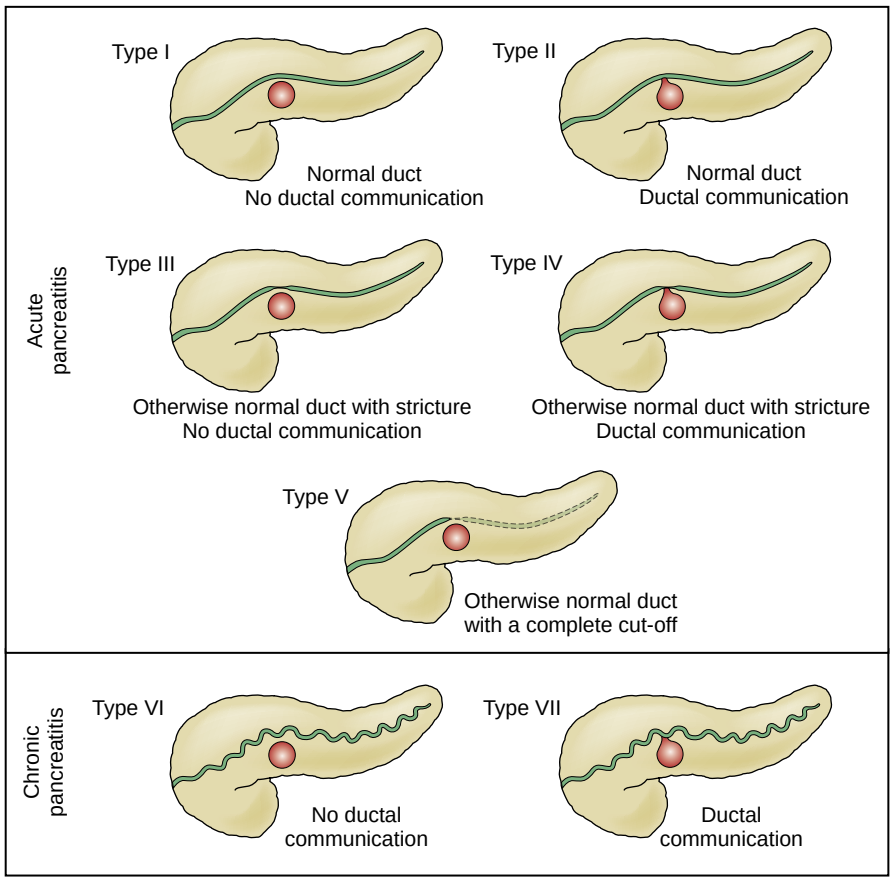


FIG. 1 D'Egidio and Schein classification of pancreatic pseudocysts.

In 2015, Pan et al. proposed another system based on the clinical manifestation and cyst features (Fig. 2).

PATHOPHYSIOLOGY

The underlying mechanism behind the formation of pancreatic pseudocyst involves disruption of the main pancreatic duct or its branches as a result of injury or inflammation of the gland. This disruption leads to extravasation of pancreatic fluid into the parenchyma, which subsequently leads to formation of a peripancreatic collection. This is based on the observation that pseudocysts are filled with amylase-rich fluid with pancreatic enzymes. The fluid has been shown to contain cytokines and inflammatory mediators but it lacks macroscopic debris. The fluid collects, and over time a capsule forms around it, perhaps caused by the inflammatory components such as fibroblasts and platelets. This capsule lacks an epithelial lining, which can help distinguish it from true pancreatic cysts.

The most frequent etiology is pancreatitis. Acute pancreatitis remains the leading cause of all hospital admissions related to gastrointestinal diseases in the United States, accounting for approximately 300,000 visits annually. The preceding factors include alcohol consumption, biliary stones, blunt abdominal trauma, or iatrogenic injury to the pancreas. Of these patients, approximately 5% to 20% will go on to develop a pancreatic pseudocyst. The collections mature around 4 to 6 weeks after the acute insult and are predominantly located around the body or the tail of the pancreas. In comparison, the rate of pancreatic pseudocyst is higher in patients with chronic pancreatitis (20%–40%); however, the underlying mechanism is poorly understood. It has been proposed that it could be caused by calcification of the ducts leading to a blockage and disruption as a majority of patients with chronic pancreatitis do not have a significant history of acute pancreatitis episodes. Abdominal trauma can also lead to pseudocysts. The most frequent mechanism of posttraumatic pseudocyst is a motor vehicle accident in which the force is generated from the seatbelt. This occurs most frequently in the midbody of the pancreas, where it crosses over the spine. The force can lead to pancreatic duct disruption and pseudocyst formation.

Unlike in WON seen in necrotizing pancreatitis, pseudocysts rarely become infected. In cases of infected pseudocysts, these have often been manipulated with percutaneous or endoscopic instrumentation. Infected pseudocysts, unlike noninfected pseudocysts, are almost always symptomatic. Infected pseudocysts can present clinically with sepsis and radiographically with inflammation and rapid growth.

PRESENTATION AND EVALUATION

There are no symptoms that are specific for pancreatic pseudocysts as most are asymptomatic. However, patients may present with nonspecific symptoms including vague abdominal or back pain, bloating and fullness with meals, early satiety, nausea, vomiting, or rarely jaundice following an episode of pancreatitis. Uncommonly, patients may present with fever, signs of peritonitis, or shock, which may occur with an infected pseudocyst (now termed *pancreatic abscess*) or with pseudocyst-related hemorrhage. Peripancreatic fluid collections are often identified on radiologic imaging performed for an episode of acute pancreatitis or pancreatic trauma. Diagnosis of a pancreatic pseudocyst is often made based on persistent symptoms following an episode of acute pancreatitis or surveillance imaging following diagnosis of a peripancreatic fluid collection; however,

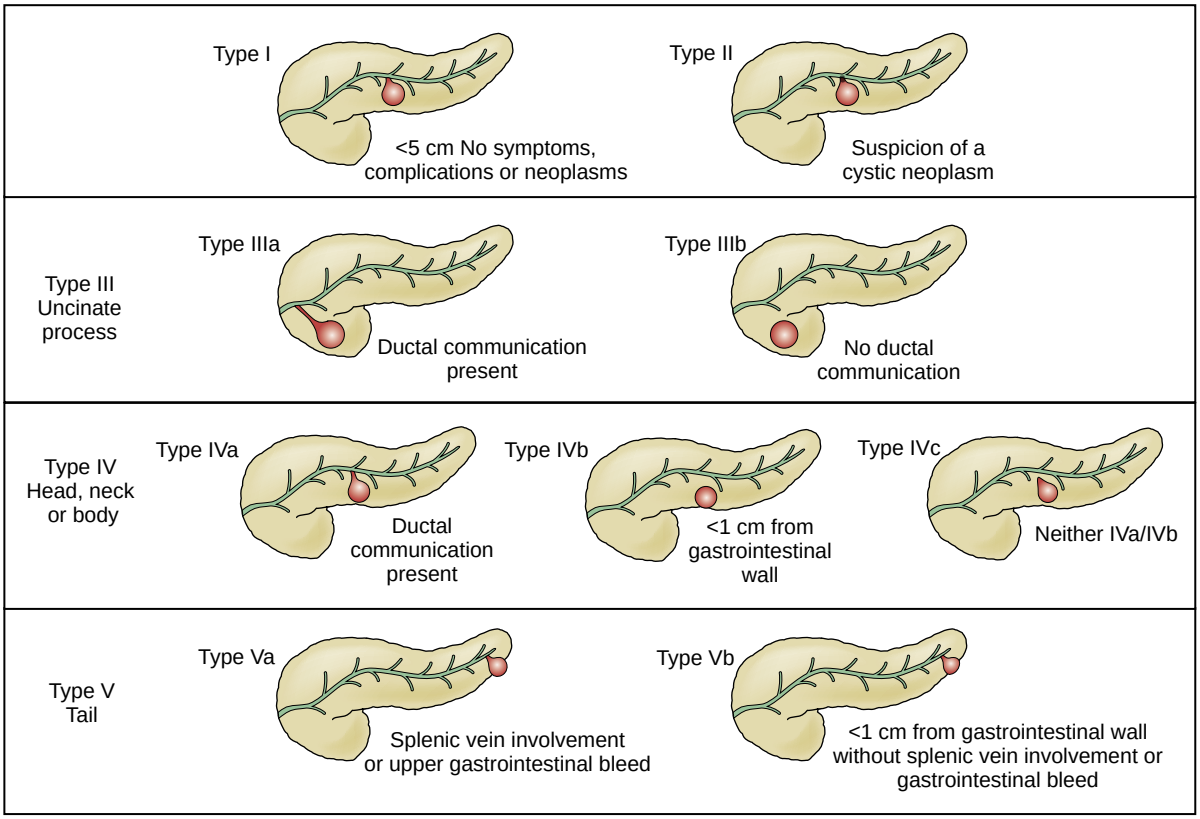


FIG. 2 Classification of pancreatic pseudocysts. *(From Pan G, Wan MH, Xie KL, et al. Classification and management of pancreatic pseudocysts.* Medicine. *2015;94[24]:e960.)*

it can occur in rare cases after no identifiable recent episode of pancreatitis.

Patient history is important to narrow down the differential diagnosis as well as identify the etiology of the pseudocyst. The history should focus on previous episodes of acute pancreatitis, abdominal pain or trauma, and its timing. If the patient has in fact had a recent episode of pancreatitis or chronic pancreatitis, questions should focus on the triggering factors including gallstones, alcohol use, medications, hypertriglyceridemia, and autoimmune or familial pancreatitis. Up to 15% of patients who present with a pseudocyst will have no identifiable episode of pancreatitis or trauma. In cases with no precipitating events, it is critical to consider alternative cystic lesions of the pancreas including IPMNs, MCNs, or serous cystadenomas given the differences in management. In select cases in which this is not able to be elucidated via history and imaging, endoscopic ultrasound (EUS) and FNA for evaluation of fluid and biopsy of the cyst wall may be necessary. Physical examination may add value if the patient has a large palpable mass in the upper abdomen. However, depending on body habitus and size and location of the pseudocyst, an examination may be unrevealing.

It is important to note that serum amylase is elevated in approximately 50% of patients with a pseudocyst. This does not indicate recurrent pancreatitis or a failure of resolution of their index episode of pancreatitis but is often mislabeled, leading to prolonged NPO status and inadequate nutrition.

Abdominal cross-sectional imaging with contrast-enhanced CT or MRI is standard for diagnosing, evaluating and surveilling pseudocysts. Contrast-enhanced abdominal CT has a high sensitivity of 82% to 100% and a specificity of 98% in the diagnosis of pancreatic pseudocysts. They allow for evaluation of size and location as well as delineate the anatomy to allow for any surgical planning. CT is the study of choice for surveillance of peripancreatic fluid collections to assess resolution versus pseudocyst formation. CT is highly accurate in distinguishing between pseudocysts and WON. Another diagnostic challenge lies in differentiating between pseudocysts and other pancreatic cystic neoplasms (IPMNs, MCNs, and SCAs).

MRI/MRCP can also be a useful imaging modality in the setting of pseudocysts and often may provide complementary information to the contrast-enhanced CT scan. MRCP can identify ductal communication with the pseudocyst, pancreatic duct anomalies (such as disconnected duct), and pancreatic duct strictures, all of which may alter the treatment strategy. Historically, ERCPs were performed in patients with pseudocysts to delineate ductal anatomy; however, advances in MRI/MRCP have made this obsolete. If MRI/MRCP is not available and the ductal anatomy is in question, ERCP should be performed for definitive delineation of ductal anatomy. ERCP also adds the ability to simultaneously diagnose and provide therapeutic intervention such as dilation of pancreatic duct strictures or placement of a pancreatic duct stent across a defect in the duct.

If there is no inciting episode of acute pancreatitis or trauma and it cannot be clearly determined on CT or MRI, EUS and FNA can help in this regard. Findings that are more suggestive of a cystic neoplasm include dilation of the pancreatic ducts, thick cyst walls, septations, or presence of a mural nodule. Its role in patients with pseudocysts lies primarily in differentiating them from other pancreatic cystic lesions based on cyst fluid cytology (carcinoembryonic antigen [CEA], amylase, cancer antigen [CA]125) and in guiding endoscopic drainage on the pseudocysts.

Recently, a new imaging modality called *cinematic rendering* has been introduced and has been deemed to be helpful in differentiating pseudocysts from other pancreatic cystic neoplasms (Fig. 3). This may become increasingly used in the future as the technology continues to improve, especially when the diagnosis is not solidified by contrast-enhanced CT or MRI. A preceding episode of acute or



FIG. 3 Cinematic rendering of pancreatic protocol CT demonstrating a pancreatic pseudocyst.



FIG. 4 Pancreatic protocol CT demonstrating a peripancreatic, well-circumscribed, thick-walled fluid-filled mass.

chronic pancreatitis coupled with radiologic evidence of a peripancreatic, well-circumscribed, thick-walled fluid-filled mass is pathognomic for a pancreatic pseudocyst (Fig. 4).

MANAGEMENT

A variety of treatment modalities are available for the management of pancreatic pseudocysts. Clinical and radiologic features that should be considered when determining the optimal approach include the symptoms, size and location of the cyst, its relationship to the main pancreatic duct, and the underlying pathology. As noted previously, a majority of these lesions resolve spontaneously with supportive care, especially those seen in acute pancreatitis versus chronic pancreatitis. In 2013, the American College of Gastroenterology published guidelines suggesting that asymptomatic pseudocysts should not be treated regardless of size, location, and extension. This principle still holds true today; however, as with every rule, there are exceptions. Patients in whom the diagnosis is not certain or with rapidly enlarging pseudocysts should undergo further workup and potentially surgical intervention. In addition, patients who travel frequently or whose occupation takes them to regions without readily accessible medical care should be considered for intervention, even in the setting of asymptomatic pseudocysts. In addition, pseudocysts >10 cm have a higher incidence of life-threatening complications including rupture, hemorrhage, and secondary infection. For these reasons, the decision for each patient must be individually assessed.

Resolution typically occurs within 6 weeks, and if asymptomatic, conservative management and close monitoring is the appropriate treatment; pain is controlled with analgesics, and nausea and vomiting are controlled with an antiemetic. Additionally, further insult to the pancreas is decreased by recommending a low-fat diet and limiting alcohol intake. These patients should then be followed. If an increase in size is observed, an intervention may be required given that larger lesions are more likely to be symptomatic and cause complications. These patients should be educated on the signs and symptoms related to potential complications so they can seek immediate care. Features that are indicative of a low chance of resolution include increasing size or no regression within the first 6 weeks, worsening symptoms, presence of calcifications in the pancreatic ducts, strictures, multiple cysts, location in the tail of the pancreas, or complex cysts involving surrounding structures.

Contrastingly, pseudocysts that develop complications (necrosis, hemorrhage, rupture, infection) require immediate attention. As discussed earlier, patients typically present with fever, chills, worsening abdominal pain, nausea, vomiting, anorexia, and hypotension. Unless the patient is unstable, data suggest that any intervention should be avoided for the first 6 weeks, which allows the pseudocyst to mature and is associated with lower morbidity and mortality. The treatment of choice is dependent on patient presentation and the extent and location of disease. This could entail percutaneous, endoscopic, or surgical drainage or excision of the collection as discussed subsequently. A clinician treating these patients must remember that the overarching goal of the evaluation and management of these patients is to identify complications early on and minimize patient morbidity and mortality.

Percutaneous Drainage

Percutaneous drainage can be performed with ultrasound or CT guidance. This can be performed as a simple percutaneous aspiration drainage or a continuous percutaneous drainage, the latter having a higher success rate. A pigtail catheter is introduced into the lesion via a needle-inserted guidewire and left in place until the fluid output is minimal. This is by far the least invasive approach for pseudocyst treatment; however, there are several disadvantages of using this approach, including significant patient discomfort as the catheter tends to clog and may need frequent repositioning, higher rates of complications including secondary infections, and lower rates of success compared with endoscopic or surgical drainage. In addition,

patients may develop a chronic pancreatic fistula if there is communication between the pancreatic duct and the pseudocyst. It does not address any pancreatic duct pathology.

Percutaneous drainage is contraindicated in patients with strictures of the pancreatic duct and those who cannot manage catheter care at home. Therefore, this modality is generally reserved for patients who are critically ill, have infected or complicated pseudocysts, and are not ideal candidates for endoscopic or surgical management.

Endoscopic Procedures

Over the past decade, advancements in the field have made endoscopic drainage of pseudocysts safe and feasible. They can achieve comparable success to surgical approaches and offer the advantage of being less invasive. Endoscopic cyst gastrostomy has become the mainstay of treatment of pseudocysts. The goal is to drain the lesion into the gastrointestinal tract, thus avoiding the need for an external drain, which can lead to secondary infection. This can be achieved via the transpapillary drainage (TPD) approach or the transmural drainage (TMD) approach across the stomach or duodenal wall using EUS.

Transpapillary drainage of the cyst is a feasible option when communication between the pseudocysts and the main pancreatic duct can be identified. It is also particularly useful when the collection is further away from the bowel. Balloon dilation is performed under ERCP guidance, and stenting is performed across the tract between the pseudocyst and the main pancreatic duct, resulting in decompression and drainage. Any strictures that are encountered in the main pancreatic duct should be dilated to achieve the most favorable outcome. This approach is less successful in patients who have distally located pseudocysts, have multiple strictures in the MPD, or have a type IIIb duct anatomy (disconnected duct).

The transmural approach has become increasingly used and is now the most common first management option, especially in patients who are high risk for surgical intervention. It is dependent on the proximity of the pseudocyst to the gastrointestinal tract. Lesions that are <1 cm away with radiologic and endoscopic evidence of compression of the intestinal wall are amenable to this approach. In the transmural approach, a channel is created between the lumen of the stomach or duodenum with the pseudocyst depending on where the site of compression is. This is accomplished with needle aspiration of the site followed by creation of a small gastrotomy or duodenostomy. Balloon dilation of the tract is performed and a self-expanding metal stent and/or pigtail catheter is placed across this tract to form a cystgastrostomy or cystduodenostomy. More recently the use of EUS has helped overcome the need for identification of a compression site (Fig. 5). Furthermore it can help avoid

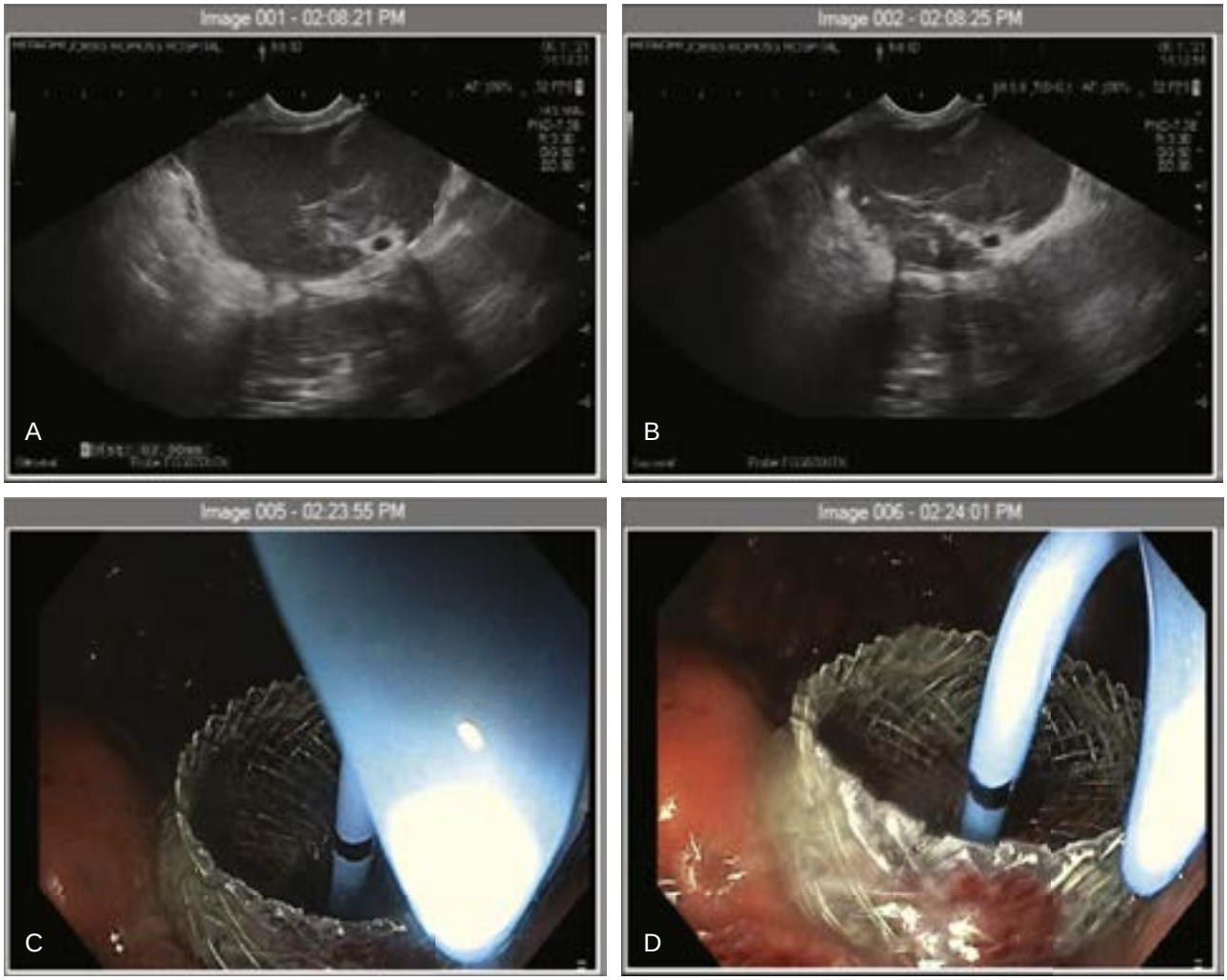


FIG. 5 **(A** and **B)** Endoscopic ultrasound of a pseudocyst. **(C** and **D)** Cyst gastrostomy with a 20-mm self-expanding lumen opposing a metal stent in place to maintain the tract and a 7Fr double-pigtail catheter thread through to facilitate drainage.

injury to adjacent blood vessels. With incorporation of EUS the rate of complications associated with TSM has decreased. Importantly, before endoscopic transmural drainage, presence of varices, pseudoaneurysms, or malignancy must be ruled out.

The transmural approach can be done simultaneously with an ERCP and pancreatic duct balloon dilation or stent in the setting of proximal pancreatic duct strictures to allow improved internal drainage and decrease the chance of failure. Patients who undergo TMD should be monitored with the catheters in place with repeat imaging to document successful drainage before stent removal. Some data suggest that removal of the stents before 6 weeks leads to higher recurrence rates; therefore, stents should remain for this period if feasible.

Limited data are available on comparison between TPD and TMD with mixed findings. The size and site of the lesion, pancreatic ductal anatomy, and the expertise of the gastroenterologist should be considered when selecting the appropriate approach.

Surgical Management

With improvements in endoscopic techniques, the role of surgical management has decreased; however, surgical drainage still remains an important part of the treatment paradigm. The goal is to internally drain the collation into the stomach, duodenum, or jejunum. Multiple small studies have suggested improved outcomes with endoscopic management; however, fewer additional interventions were necessary in the surgically drained patients. Surgical drainage can therefore be considered in patients in whom the pseudocysts are not amenable to treatment using percutaneous or endoscopic drainage modalities. These include larger pseudocysts, those located in the tail (away from the bowel), complex ductal strictures, multiple lesions, uncontrolled hemorrhage, or concerns for malignancy. Surgical drainage leads to resolution in over 90% of patients; however, reoperation may be required in patients with a history of chronic pancreatitis or persistent alcohol abuse.

Surgical drainage may be done as an open or minimally invasive procedure and involves creation of an anastomosis between the cyst wall and either the gastric, duodenal, or jejunal wall to facilitate drainage. The most common drainage procedures are the cystgastrostomy and cystjejunostomy, and selection should be based on review of the imaging before surgery. Often, pseudocysts develop in the lesser sac along the posterior aspect of the stomach, which often makes cystgastrostomy the easiest technical operation and is the one most commonly employed. This allows for little manipulation of the gastrointestinal tract, however, and it requires an anterior gastrostomy to access the stomach. Some studies have noted higher rates of bleeding complications compared with cystjejunostomy. Factors including gastric varices or prior gastric surgeries should also be considered and may make cystjejunostomy a safer option in these patients.

As noted earlier, cystogastrostomy requires an anterior wall longitudinal gastrotomy over the area of the pseudocyst. Two stay sutures may be placed, one on each edge of the gastrostomy to allow for better visualization. A bulge is often noted in the posterior wall of the stomach; however, intraoperative ultrasound may be used if this is not evident. The pseudocyst is then entered through the posterior gastric wall using electrocautery and contents suctioned out. At this point, either a handsewn anastomosis using a running monofilament suture or a stapler is performed. Some advocate using an EEA circular stapler. A biopsy of the pseudocyst wall should always be taken. The anterior gastrotomy should then be closed with a running suture.

Minimally invasive surgery has also gained popularity in recent times. Laparoscopic- or robot-assisted cystogastrostomy or cystjejunostomy can be performed using the same options as their open counterparts. For a minimally invasive cystogastrostomy, an anterior, posterior, or transgastric approach can be used. In the former approach, an anterior gastrostomy is performed using a harmonic device to access the gastric mucosa. An ultrasound probe is then used to identify the pseudocyst, and an opening is created to drain the lesion. Biopsies are obtained for histopathologic analysis, an anastomosis is created between the posterior wall of the stomach and the cyst using either running suture or stapler, and the anterior gastrostomy is closed. For the posterior approach, the gastrocolic ligament is divided, and the lesser sac is entered. The pseudocyst is identified, and a cystogastrostomy is performed using a stapler between the lesion and the posterior gastric wall. Although technically challenging, the posterior approach offers better visualization of the cysts. For the transgastric approach, the balloon-tipped trocars are inserted directly into the stomach, and the stomach is insufflated. Recently, the use of the robotic approach for surgical drainage of pancreatic pseudocysts has also been reported, demonstrating the feasibility and safety of using this approach. The robotic approach allows for better visualization and easier intracorporal suturing. Whether one type of surgical drainage approach (open, laparoscopic, or robotic) has any advantage over an other remains to be elucidated.

POSTOPERATIVE CONCERNS

Many possible complications can occur in patients with pancreatic pseudocysts, namely, infection of the pseudocyst or pancreatic abscess, hemorrhage, splenic vein thrombosis, gastric outlet obstruction, or rupture. Pancreatic abscess generally occurs in the setting of an instrumented pseudocyst. Immediate source control with drainage must be employed in this scenario. Hemorrhage or bleeding from the pseudocyst can occur as a result of a drainage procedure or spontaneously. The most common vessel implicated is the splenic artery, followed by the gastroduodenal artery and the pancreaticoduodenal arteries. Patients who are suspected of bleeding should have an emergent angiogram and embolization of any bleeding vessels. Surgical interventions have high morbidity and low success in the setting of hemorrhage. In the case of rupture, patients may present with free fluid on CT scan. This fluid is not distinguishable from ascites on imaging; therefore, fluid sampling may be necessary. High amylase levels would confirm pancreatic pseudocyst rupture in this setting. Management in the case of free rupture should focus on the treatment of the underlying cause of the pseudocyst and any pancreatic duct anomalies. It is important in patients with pseudocysts, especially those who have undergone intervention, to have a high index of suspicion for complications, as they can be devastating if not treated in a timely manner.

CONCLUSION

Acute pancreatitis is a complex disease with variable severity and an unpredictable course, making it a clinical challenge for surgeons. Sequelae including pseudocysts may complicate and prolong the recovery process. A majority resolve spontaneously and require only supportive therapy. For those that do not resolve, complications can be life-threatening, and timely diagnosis and assessment are warranted. As management options continue to evolve with improved imaging and endoscopic interventions, the location and size of the pseudocysts, relationship to the main pancreatic duct, and severity of disease should be considered for accurate patient stratification and selection of appropriate treatment modality by a multidisciplinary team. Despite the decreased role of surgery over time in the treatment paradigm of pseudocysts, there is still a defined role in patients with complicated pseudocysts and those who fail endoscopic management.

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Pancreatic Ductal Disruptions Leading to Pancreatic Fistula, Pancreatic Ascites, or Pancreatic Pleural Effusion

David Sanders, MD, Shivanand Bomman, MD, and Richard Kozarek, MD

DEFINITIONS

The following is a list of terms that are commonly associated with pancreatic ductal disruption:

- **Pancreatic ductal disruption:** A loss of ductal integrity anywhere in the pancreatic ductal system (i.e., a main pancreatic duct or tertiary ductules) demonstrated by computed tomography (CT), sinogram through a percutaneous drain that reveals a pancreatic duct, endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP). Disruption also is suggested by a persistent finding of amylase-rich drain fluid.
- **Pancreatic fistula:** Passage of pancreatic juice through a pancreatic ductal disruption that exits the pancreatic parenchyma. This fistula can reside totally within the capsule of the pancreas and therefore can be minimal and self-healing. Alternatively, the fistula can breach the capsule of the pancreas, resulting in pancreatic juice entering the retroperitoneal or peritoneal cavities. A controlled pancreatocutaneous fistula is a condition in which an ongoing pancreatic fistula is well drained by a percutaneous catheter, preventing pancreatic juice from extending elsewhere.
- **Acute peripancreatic fluid collection:** This term was defined by the revised Atlanta classification of acute pancreatitis. It is an accumulation of pancreatic juice (enzyme-rich fluid) in the peripancreatic area to include the adjacent retroperitoneal (Fig. 1A) or peritoneal cavity, and it appears within 4 weeks after onset of acute interstitial pancreatitis.
- **Pancreatic pseudocyst:** An intrapancreatic or peripancreatic fluid collection that develops a well-circumscribed wall. It is usually determined by imaging studies (Fig. 1B) and generally appears more than 4 weeks after the onset of acute interstitial pancreatitis.
- **Pancreatic necrosis:** Implies a permanent condition that occurs when a portion of the pancreas loses its blood supply because of severe inflammation. Contrast-enhanced computed tomography (CT) shows lack of enhancement of the pancreatic parenchyma (Fig. 1C). Pancreatic parenchymal necrosis can be associated with a distinct nonparenchymal necrosis called *peripancreatic necrosis.* Multiple serial CTs during the entire clinical course should be interpreted carefully so as not to misread necrosis when the lack of enhancement may be caused by inflammation or overlying fluid collections.
- **Acute necrotic collection:** By definition, this is a pancreatic or peripancreatic collection containing variable amounts of fluid and necrosis associated with necrotizing pancreatitis.
- **Walled-off pancreatic necrosis (WOPN):** In contrast with an acute necrotizing collection, WOPN is a pancreatic or peripancreatic collection that has matured into an encapsulated collection with a well-defined inflammatory wall (Fig. 1D). WOPN usually occurs more than 4 to 8 weeks after onset of necrotizing pancreatitis.
- **Pancreatic ascites**: A collection of pancreatic juice from a pancreatic ductal disruption that communicates into the peritoneal cavity (Fig. 2), usually from the lesser sac. Pancreatic ascites is usually well tolerated by the patient unless the proenzymes in the ascites become activated. This process can occur with infected ascites. Approximately one-half of patients with pancreatic ascites also have a concomitant pseudocyst present, suggesting that the cause of the ascites may have been leakage from the pseudocyst. Diagnosis is made with a paracentesis in which there is a serum-albumin ascites gradient (SAAG) below 1.1 g/dL, a total protein level >3 g/dL, and an elevated ascitic amylase.
- **Pancreatic pleural effusion:** A collection of enzyme-rich pancreatic juice in the pleural cavity on either side of the chest (Fig. 3). This collection originates from a pancreatic ductal disruption "fistulizing" into the retroperitoneum. The collection is not walled off in the extracapsular peripancreatic space but rather communicates through pleuroperitoneal foramina into the right or left pleural cavity. The location of the ductal disruption in the pancreatic ductal system determines whether the right or left pleural cavity is the site of collection (i.e., a ductal disruption dorsally over the portal vein may accumulate in the right chest, whereas a disruption dorsally from the pancreatic tail may accumulate in the left chest). The presence of a right or left pleural effusion is a clue to the site of the ductal disruption within the pancreas. Diagnosis is made based on an exudative effusion (Light's criteria) with an elevated pleural amylase.
- **Disconnected pancreatic duct syndrome:** A condition in which proximal and distal sides of the pancreas are separated permanently by pancreatic ductal disruption. Flow from the upstream disconnected side of the pancreas can no longer drain through the downstream native pancreatic duct. Persistent secretion of the disconnected segment cannot enter the enteral stream, resulting in formation of peripancreatic fluid collection, peripancreatic necrosis, or a pseudocyst. The disconnection in the majority of patients occurs after pancreatic necrosis of the head or neck/body of the gland (Fig. 4). A common site of disruption is at the pancreatic neck, probably because of the watershed blood supply to the neck being from the pancreaticoduodenal artery and splenic artery arcades. When the gland can be seen to be disconnected on CT, this represents the most extreme finding of the disconnected pancreatic duct syndrome and is a consequence of complete necrosis of a central portion of the pancreas (Fig. 5).

CLINICAL PRESENTATION AND DIAGNOSIS

Identification of Pancreatic Ductal Disruption

Approximately 90% of patients developing acute pancreatitis experience a self-limiting course of abdominal pain and an elevated lipase that resolves within 7 days. However, when clinical symptoms persist longer than 1 week, a pancreatic ductal disruption is likely developing. The availability of CT scans has now defined the stepwise progression of potential complications. Indications of ductal disruption include the development of an acute peripancreatic fluid collection, pancreatic pseudocyst, or pancreatic necrosis. In studies by Nealon and colleagues, pancreatic ductal anatomy has been categorized successfully in association with pseudocysts, regardless of the presence of pancreatic necrosis (Fig. 6). According to the types of pancreatic ductal injury after acute pancreatitis, consequences were predicted and therapies were directed. A type III injury results in disconnected pancreatic duct syndrome and was associated with a more refractory clinical course: no spontaneous resolution, higher incidences of pancreatic fistula and recurrent pancreatitis, longer drainage time, and necessity for more aggressive treatment to include debridement.

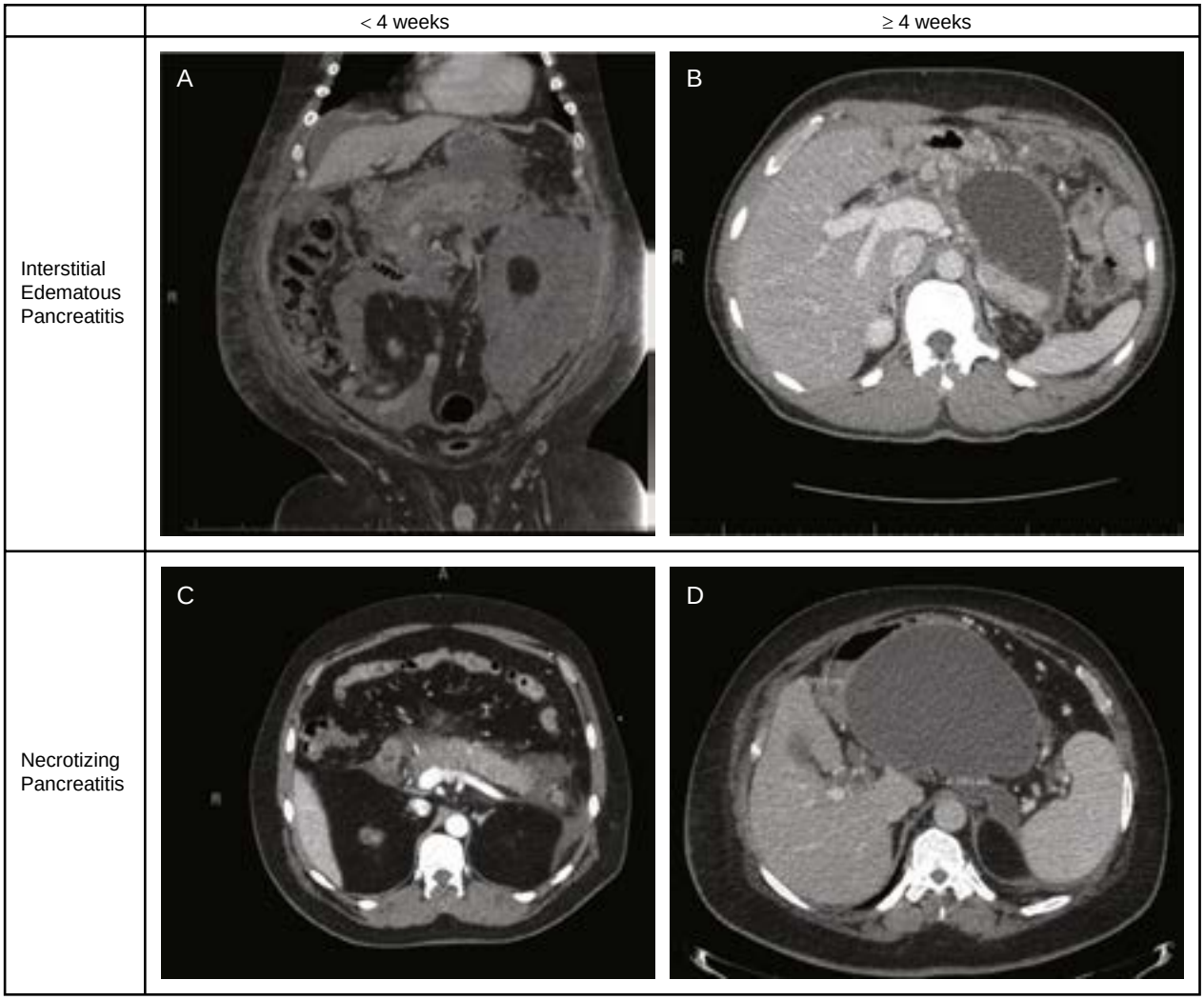


FIG. 1 This image provides case examples of the revised Atlanta classification. **(A)** Acute pancreatitis with multiple acute peripancreatic fluid collections. **(B)** A pseudocyst in a patient with chronic pancreatitis from chronic alcohol use. **(C)** Necrosis of the tail of the pancreas without enhancement of the pancreatic parenchyma. **(D)** Walled-off pancreatic necrosis with compression of the stomach. *(From Banks PA, Bollen TL, Dervenis C, et al. Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus.* Gut. *2013;62:102–111.)*

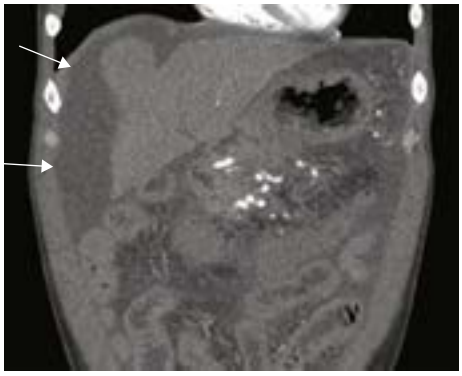


FIG. 2 Demonstration of ascites in the abdomen, best appreciated around the liver and under the diaphragm *(arrows)*.

Diagnostic Approach

Goal-directed therapy in the acute phase of acute pancreatitis includes volume resuscitation, electrolyte replacement, pain control,

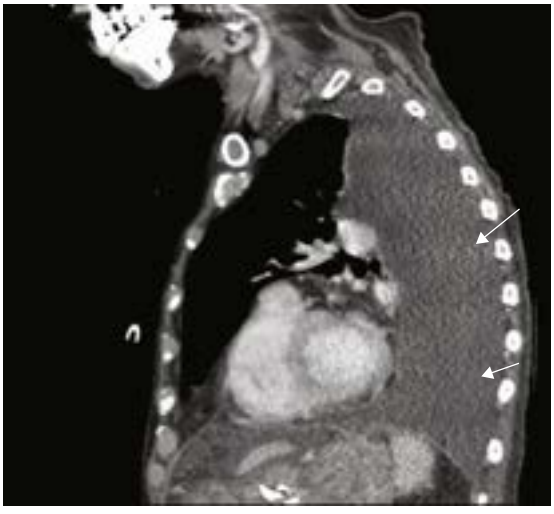


FIG. 3 Pleural effusion with layering posteriorly in the supine position *(arrows)*. The patient required thoracentesis for drainage.

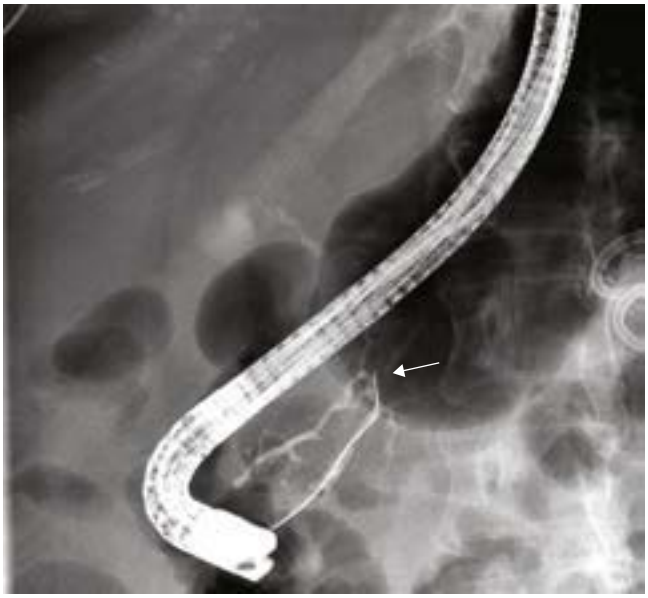


FIG. 4 A patient with acute pancreatitis from alcohol complicated by a ductal disruption and pancreatic ascites. A pancreatogram demonstrates ductal obstruction *(arrow)* that could not be bridged with a pancreatic stent.

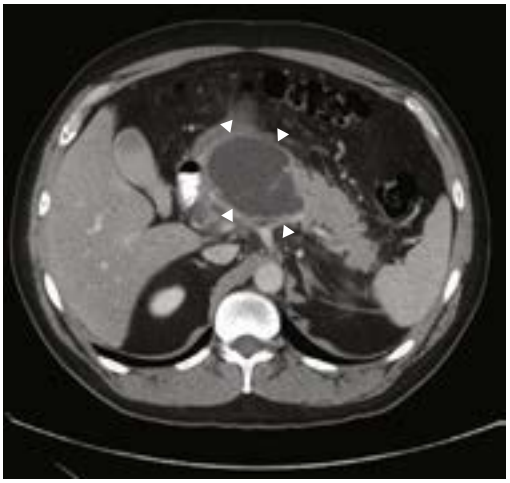


FIG. 5 Image demonstrating pancreatic disruption. The distal pancreas is separated from the head of the pancreas by a collection *(arrowheads)*.

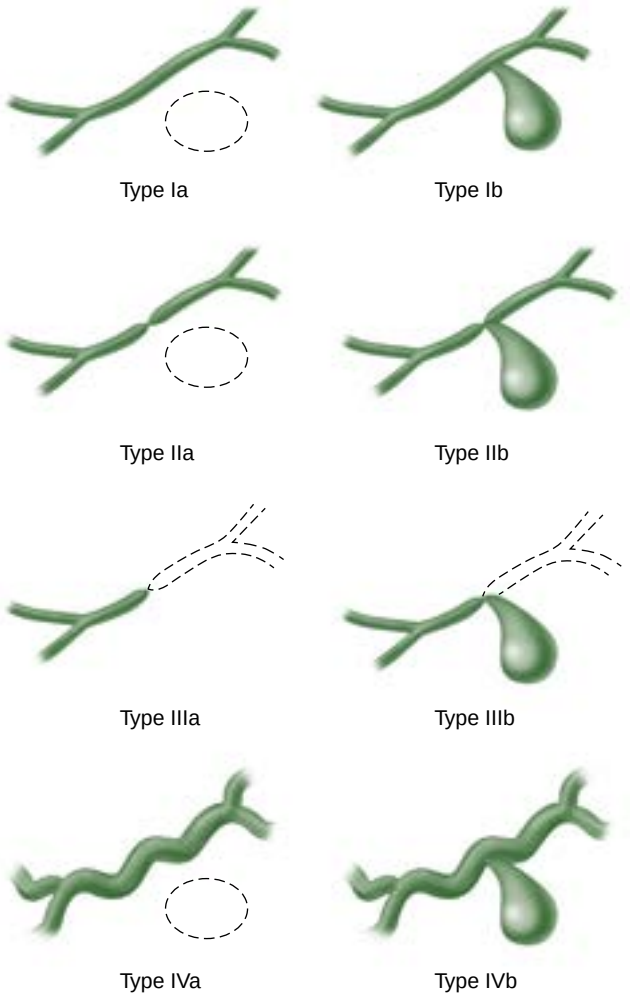


FIG. 6 System to characterize pancreatic ductal anatomy after acute pancreatitis. Type I: normal duct. Type II: pancreatic duct stricture. Type III: pancreatic duct occlusion (disconnected pancreatic duct syndrome). Type IV: chronic pancreatitis. Type Ia represents no communication between the pancreatic duct and the pseudocyst. Type Ib represents communication between the pancreatic duct and the pseudocyst, and so on. *(From Nealon WH, Bhutani M, Riall TS, et al. A unifying concept: pancreatic ductal anatomy both predicts and determines the major complications resulting from pancreatitis.* J Am Coll Surg. *2009;208:793.)*

antiemetics, and nutritional support. If the patient is not improving with conservative treatment, then an assessment to define possible ductal disruption is recommended. Early recognition assists in prognostication and management. Contrast-enhanced CT is primarily used to identify pancreatic necrosis and the consequences of a leak including the presence, location, and size of peripancreatic fluid collection. To accurately define the presence and location of the disruption, an ERCP or MRCP is essential. If the leak is ventral in the pancreas, then the pancreatic juice will accumulate inside the lesser sac. Peripancreatic fluid collections can also accumulate in the retroperitoneum by dorsal rupture through the pancreatic capsule, from the tail to collect over the left renal space or from the dorsal head in the pancreaticoduodenal groove to collect over the right pararenal space. Pancreatic juice collections in this location commonly form a classic pseudocyst. The inflammatory process ultimately results in a thickened wall. More commonly, lesser sac fluid collections will form a pseudocyst rather than leak out into the peritoneal cavity to result in pancreatic ascites. Pleural effusions are also readily detected by CT. Pleural effusions are secondary to pancreatic juice leaking from a ductal disruption and then penetrating the pancreatic capsule into the retroperitoneal space. When undrained, the dissecting fluid can enter the left pleural cavity from a disruption in the pancreatic tail or body and communicate into the left chest through pleuroperitoneal foramina. The juice can enter the right pleural cavity from a ductal disruption of the pancreatic neck, dorsally over the pancreatic head but ventral to the portal vein. This space is a channel to the thorax because pancreatic juice can pass behind the hepatoduodenal ligament, through the pleuroperitoneal foramina, and into the right chest. On its way to either pleural cavity, a fluid collection made up of pancreatic juice can approach the esophageal hiatus, resulting in a periesophageal fluid collection that can dissect into the mediastinum.

INDICATIONS AND RATIONALE FOR TREATMENT

If a patient has CT findings of persistent pancreatic juice leakage, such as persistent or enlarging peripancreatic collections, and demonstrates clinical deterioration (Box 1), then pancreatic collections should be drained. If pancreatic juice leakage is uncontrolled, the following patterns have been observed: (1) peripancreatic necrosis with or without infection, (2) formation of pseudoaneurysm (Fig. 7A, B), erosion into a blood vessel without pseudoaneurysm, or erosion into a hollow viscus, or (3) communication with the free peritoneal cavity, mediastinum, or pleural cavities. We have found that the likelihood of infection increases the longer the pancreatic juice is uncontrolled, which results in progressive peripancreatic damage. Undrained peripancreatic infection causes organ failure in the late phase and can result in significantly higher mortality rates.

BOX 1 Indications for Percutaneous Catheter Drainage

Presence of Peripancreatic Collections by Computed Tomography Plus

Clinical Signs

Persistent or enlarging fluid collection by CT
Persistent abdominal distension/ileus
Systemic inflammatory response syndrome and/or organ failure
Persistent or increasing inflammatory data (C-reactive protein, white blood cell count, or interleukin 6)
Persistent increase in serum amylase or lipase activity suggesting persistent pancreatic juice leakage

Symptoms

Refractory abdominal pain despite use of opioids
Inability to begin oral intake

A mature pseudocyst is more common in referred patients with a prolonged course but is uncommon in our own primary cases because of the step-up approach to fluid collections. This observation results from our bias: all fluid collections that are symptomatic should be drained proactively with minimally invasive methods.

Percutaneous Catheter Drainage

Percutaneous catheter drainage (PCD) is a minimally invasive drainage method, allowing interventional radiologists to place a catheter with the shortest and safest route into the collections under CT guidance. Safe access routes are those that avoid the intestines, large vessels, and pleural space. Historically, CT-guided PCD involved placement of a 12Fr pigtail drainage catheter (Cook Inc., Bloomington, IN) that is attached to a low-pressure, closed-suction drainage system (TRU-CLOSE, UreSil, Skokie, IL). The catheters are flushed with 10 to 20 mL of sterile saline three times daily. Subsequent CT scan timing is directed by clinical status and drain patency. Each CT is followed by a fluoroscopic drain study, allowing cavity lavage and drain reposition, exchange, or upsize. Frequent imaging allows detection and treatment of new peripancreatic collections that can be drained using additional PCD sites.

Drainage fluid can be monitored for appearance and volume throughout the clinical course. Samples of the fluid are assessed for amylase, Gram stain, and microbiologic culture at the time of PCD and if required based on the patient's clinical course. Drainage catheters are removed when the cavities are determined to be collapsed by CT and output is minimal. The goal of PCD is to achieve "effective drainage." Drainage remains effective if there is maintenance of correct drain positioning and patency. Even though the drain may have been placed in the center of a fluid collection, subsequent CTs and serial fluoroscopic drain studies provide information regarding adequate positioning. The drain should be maneuvered to the site of leakage from the pancreas (not necessarily the center of the original collection) to avoid long sinus tracts and extension of the fluid collection (Fig. 8).

Drain patency can be maintained by frequent fluoroscopic drain studies, such as exchanging, upsizing, and lavage. Once again, our PCD protocol provides continuous control of extravasated pancreatic

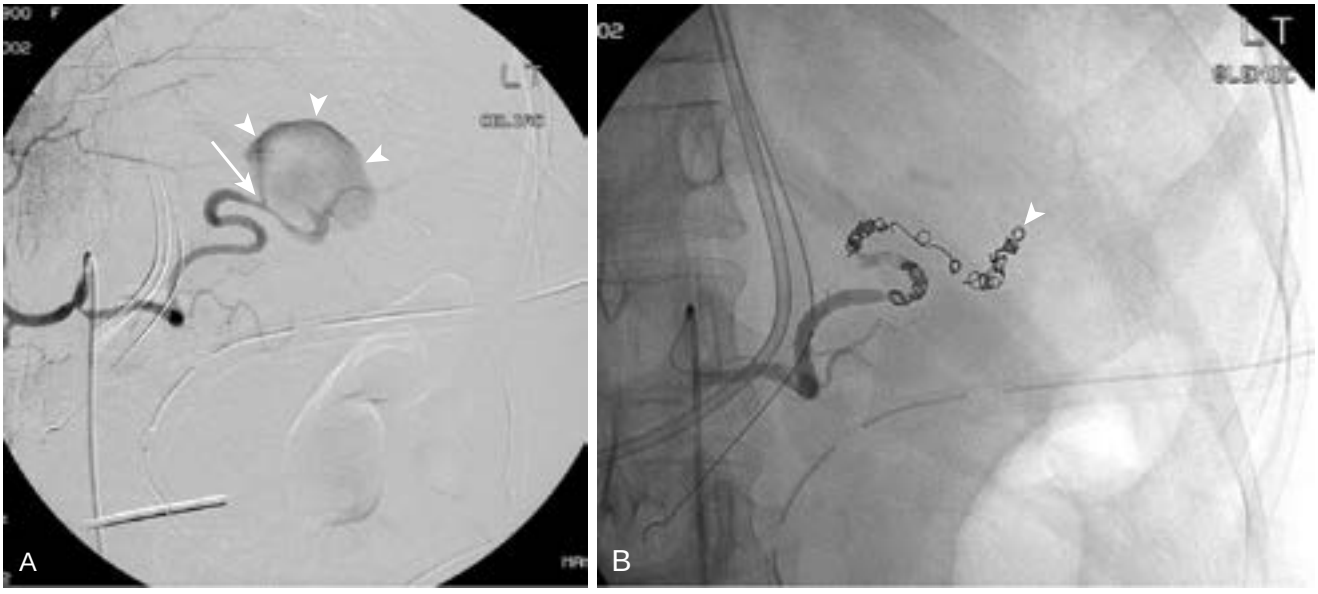


FIG. 7 Digital subtraction arteriogram in a 46-year-old female patient with necrotizing pancreatitis and multiple drainage catheters with severe bleeding through drainage catheters with cardiopulmonary arrest. **(A)** Emergent celiac arteriogram reveals extravasation of contrast from the midportion of the splenic artery into one of the drained cavities *(arrowheads)* through a pseudoaneurysm *(arrow)*. **(B)** Selective splenic arteriogram after successful occlusion of the artery with Gelfoam (Pfizer, New York, NY) and multiple coils (one is marked with an *arrowhead*) shows no flow within the artery and no extravasation.



FIG. 8 A 66-year-old male patient with severe acute necrotizing pancreatitis. **(A)** Abdominal computed tomography shows peripancreatic fluid collection localized inferiorly to the pancreatic head *(arrowheads)*. **(B)** A fistulogram drain study shows communication of contrast from peripancreatic fluid collection through the main pancreatic duct *(arrow)*. **(C)** The tip of the drain was placed at the site of pancreatic duct disruption.

juice by maintaining patent drains that are placed or ultimately maneuvered to the site of leakage. Once achieved, further progression of peripancreatic necrosis should be halted. Once imaging shows no progression of necrosis, the necrosum can become liquefied with frequent irrigation. Necrosis cavities will collapse over time if associated with effective drainage, appropriate antibiotics, and adequate nutrition. There may be symptomatic ascites or pleural effusion during the clinical course, which can be managed by ultrasound-guided aspiration or PCD. The goal of intervention is not to focus on the peripheral collections, but to control pancreatic juice leakage at the site of leakage. PCD is an attractive approach because it is less invasive and can be used in a proactive manner early in the disease course. PCD and post-PCD fluoroscopic procedures should be diligently pursued to achieve "effective drainage" using repetitive procedures. Surgical debridement always is reserved as the last resort if conservative treatment including minimally invasive necrosectomy fails.

Percutaneous Transgastric Catheter Drainage

Percutaneous transgastric catheter drainage provides another option of drainage route when a better drainage window on CT other than the transgastric route is not available (Fig. 9A, B). This option enhances minimally invasive drainage techniques and avoids the default to surgical necrosectomy. Moreover, especially in the later clinical course, percutaneous transgastric catheter drainage facilitates internalization of external drains for cases developing disconnected pancreatic duct syndrome and prevents development of a pancreatocutaneous fistula. Although we must acknowledge the possibility of introducing gastroenteric organisms into the peripancreatic space via the percutaneous transgastric catheter into the retroperitoneum, the drainage fluid can still be used to monitor appearance and volume and sample for amylase activity and microbiologic culture through the externalized catheter. Serial drain studies via this catheter provide important information regarding the site and presence of a pancreatic ductal disruption. In the later clinical course, a percutaneous transgastric drainage catheter can be internalized by two 10Fr × 10-cm pigtail catheters (Cook Inc., Bloomington, IN) under fluoroscopy, providing internal transgastric drainage to treat a persistent pancreatic fistula (see Fig. 9C). The percutaneous site does not have to be abandoned but can be used as a gastrostomy site for decompressing the stomach or placing a gastrojejunostomy tube for jejunal feedings.

Endoscopic Treatment

After recognition of a pancreatic leak, a pancreatic sphincterotomy and transpapillary stent placed by ERCP can relieve downstream obstruction and decompress the pancreatic ductal system. This returns the flow of pancreatic fluid back to the duodenum. In patients with a disconnected pancreatic duct syndrome, it is desirable to place a transpapillary stent bridging from the proximal (downstream) side of the pancreas to the distal (upstream) side beyond the site of disruption. However, if not feasible, pancreatic juice leakage from the upstream side of the pancreatic ductal disruption requires percutaneous or transluminal drainage. Endoscopic ultrasound (EUS)-guided transmural stenting ("cyst" gastrostomy or "cyst" duodenostomy) for treatment of WOPN can be performed as an alternative to or in combination with PCD. Endoscopic drainage procedures allow patients to avoid external catheter placement and to establish internal drainage of leaked pancreatic juice to the gastrointestinal tract, especially for patients with disconnected pancreatic duct syndrome. For an endoscopic approach, the WOPN must be located adjacent to the gastric wall or duodenum to be eligible for the endoscopic drainage procedure (Fig. 10A). The collection must also be adherent to the gastrointestinal tract to be safely intervened on with transluminal drainage.

Our center has advocated for a combined percutaneous and endoscopic approach (dual-modality drainage) for symptomatic WOPN. After PCD, the patient is taken immediately to the endoscopy suite, and general anesthesia is administered. The necrosum is accessed endoscopically under EUS control by using a 19-gauge needle. After

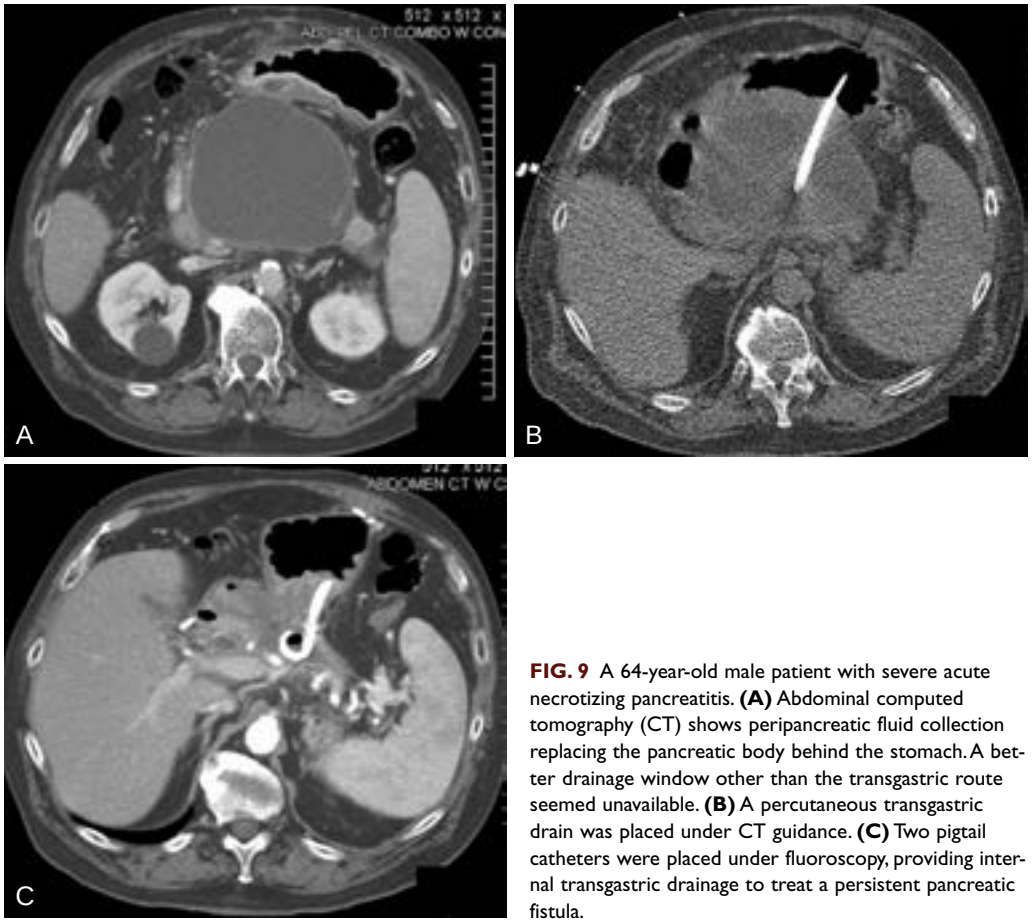


FIG. 9 A 64-year-old male patient with severe acute necrotizing pancreatitis. **(A)** Abdominal computed tomography (CT) shows peripancreatic fluid collection replacing the pancreatic body behind the stomach. A better drainage window other than the transgastric route seemed unavailable. **(B)** A percutaneous transgastric drain was placed under CT guidance. **(C)** Two pigtail catheters were placed under fluoroscopy, providing internal transgastric drainage to treat a persistent pancreatic fistula.

wire-guide access is achieved, the tract is dilated by using either a 4Fr or 6Fr dilating catheter (Cook) or a CRE balloon dilator (Boston Scientific, Natick, MA). Two 7Fr 3-cm double-pigtail stents (Cook) are placed across the gastric or duodenal wall to maintain the tract. More recently, an EUS-directed transenteric drainage system with a Lumen Apposing Metal Stent (LAMS; Boston Scientific) has been developed (Fig. 10B). This has a cautery-enhanced deployment catheter with immediate deployment of a LAMS. A single 7Fr 3-cm double-pigtail stent is placed across the metal stent (Fig. 10C). In the case of multiple areas of WOPN, multiple percutaneous drainage catheters are placed; however, transenteric stents are placed into the necrosum, which is closest in proximity to the gastrointestinal tract. Once placed, transenteric plastic stents are not manipulated intentionally throughout the course of treatment. For patients with disconnected glands, the transenteric stents can be left in place long term (Fig. 11). In our series of 117 patients who received dual-modality drainage for symptomatic WOPN, no patients required surgical necrosectomy, and there was no procedure-related mortality. No patients developed a pancreaticocutaneous fistula.

The major advances in transluminal drainage have allowed for endoscopic necrosectomy with comparable efficacy to surgery. The LAMS can be left in place for multiple attempts at necrosectomy. A plastic stent is often left across the LAMS to reduce the risk of bleeding. Necrosectomy can be performed with snares, forceps, and irrigation (Fig. 12). Despite the improvements in technique, adverse events that include bleeding, perforation, and air embolism can occur.

Surgical Management

Traditionally, the treatment approach for infected pancreatic necrosis was surgical necrosectomy with a high mortality of 20% to 40%. The standard of care later transitioned toward a minimally invasive step-up approach that recommends starting treatment with PCD followed by a minimally invasive surgical procedure such as video-assisted retroperitoneal debridement (VARD) and performing open necrosectomy only as a last resort when other treatment modalities fail. This approach showed that 35% of the patients treated with a minimally invasive step-up drainage procedure avoided any surgical procedure with similar mortality to that primary open necrosectomy. Nonetheless, VARD has been shown to be safe and effective and can be used to avert more invasive procedures or as a bridging therapy between PCD and open necrosectomy. In 2018, a Dutch multicenter randomized superiority trial (TENSION trial) compared the endoscopic step-up approach (EUS-guided transluminal drainage, followed by endoscopic necrosectomy if necessary) with the traditional surgical step-up approach. The primary endpoint was a composite of major complications or death within 6 months of randomization and occurred in 43% of patients in the endoscopy group versus 45% in the surgical group. This study showed that the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death; however, it decreased the rate of pancreatic fistula and length of hospital stay. With this study, the preferred treatment choice has shifted toward an endoscopic step-up approach.

In symptomatic patients with a disconnected pancreatic duct syndrome, especially in an upstream leak that is not efficiently drained, distal pancreatectomy is indicated. Pancreatic head resection may be required for downstream obstruction in the pancreatic head and upstream duct disruption that is also in the head of the gland (Fig. 13). Fortunately, the application of transmural internalized drainage by percutaneous or endoscopic technique has reduced the necessity of these more invasive and complex procedures. Exploring

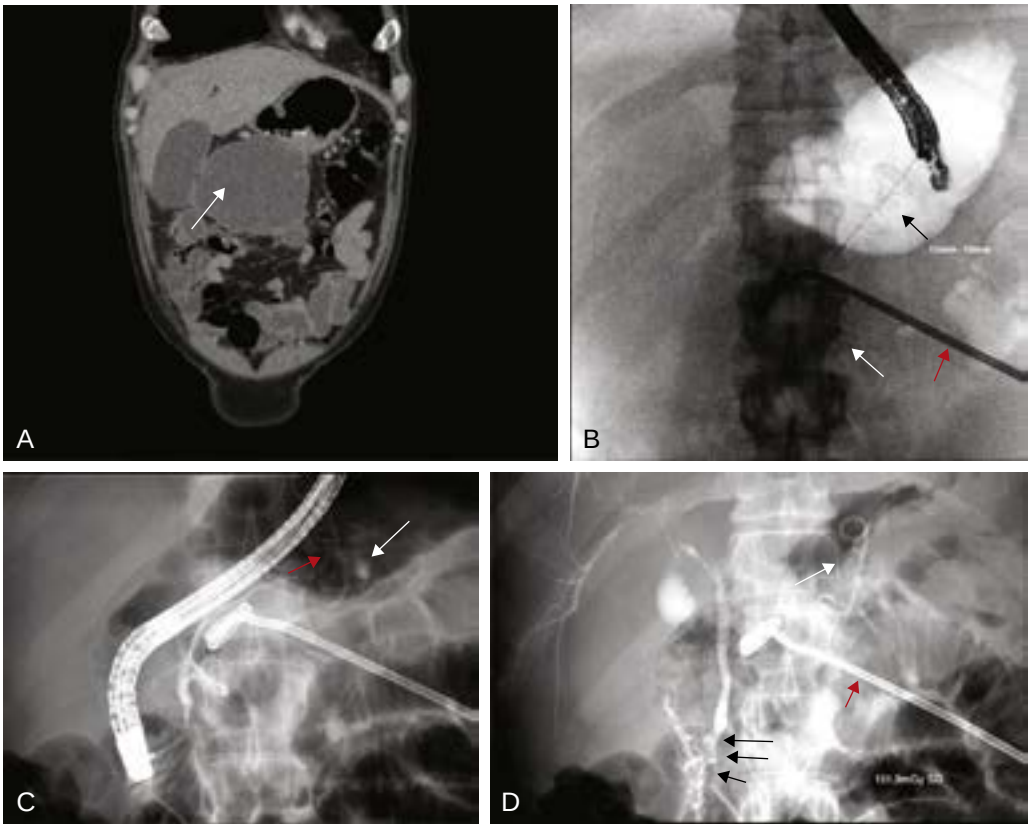


FIG. 10 An example of dual-modality drainage after severe acute pancreatitis with walled-off pancreatic necrosis (WOPN). Computed tomography (CT) showing WOPN in close proximity to the stomach *(arrow)*. **(B)** Endoscopic ultrasound guidance with placement of a wire into the WOPN *(white arrow)*. Placement of a 15-mm by 10-mm lumen apposing metal stent *(LAMS, black arrow)*. Previously placed CT-guided external drain placed percutaneously into the collection *(red arrow)*. **(C)** Pancreatogram showed a leak near the tail without a disconnected gland *(white arrow)*. A 7Fr 3-cm pigtail stent is placed across the LAMS *(red arrow)*. **(D)** Final image showing a 5Fr 3-cm plastic pancreatic duct stent *(black arrows)*, LAMS *(white arrow)*, and external drain *(red arrow)*.

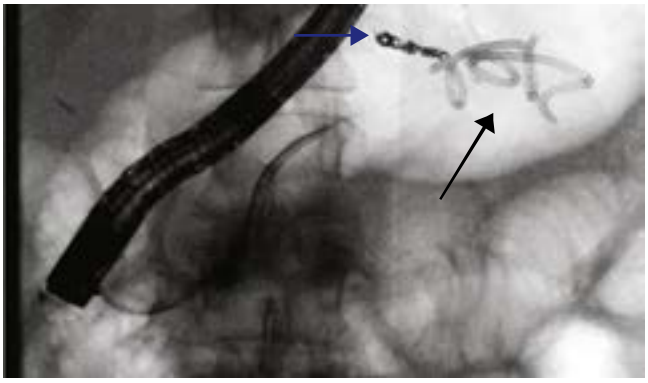


FIG. 11 A patient with gallstone pancreatitis and severe acute pancreatitis with eventual walled-off pancreatic necrosis (WOPN). The pancreatogram is shown after dual-modality drainage with disconnected duct syndrome after the WOPN resolved. The transgastric stents (two 7Fr 3-cm pigtails) drain the tail of the pancreas *(black arrow)*. The proximal pancreas is drained by the major papilla. Note that the coils placed for a pseudoaneurysm bleed from the splenic artery *(blue arrow)*.

the peripancreatic space is a morbid procedure because of the dense scarring and left-sided portal hypertension resulting from splenic vein occlusion and severe inflammation. Prolonged internalized drainage can help avoid open surgical procedures as the upstream pancreas usually gets progressively atrophic and reduces its secretion over time with internal drainage alone. This can preserve pancreatic endocrine function in the atrophic disconnected tail of the pancreas.

Multidisciplinary Team Approach

Patients with pancreatic ductal disruption should be managed during their entire clinical course in a multidisciplinary fashion involving a team of interventional radiologists, hospitalists, nurses, dieticians, pharmacists, infectious disease specialists, intensive care specialists, gastroenterologists, and pancreatobiliary surgeons. The selection of the treatment option should be tailored to the patient's presentation. Two important prerequisites are necessary for this approach. First is the assembly of a team, which requires years of recruitment using influence and leadership at centers of expertise in the treatment of these patients. Second, and possibly just as difficult as team assembly, is the design and use of a common algorithm that allows the reporting of data supported with the "power of *n*."

SUMMARY

Pancreatic ductal disruptions are refractory complications after acute pancreatitis. Patients with suggestive findings of uncontrolled pancreatic juice leakage should be drained to avoid complications. PCD is more feasible and a less invasive technique than surgical necrosectomy. Effective drainage is achieved by patent drain(s) located at the site of pancreatic juice leakage. Dual-modality drainage with combined PCD and endoscopic transenteric drainage is useful for patients with symptomatic WOPN. A multidisciplinary team approach is mandatory to successfully manage these complex patients.

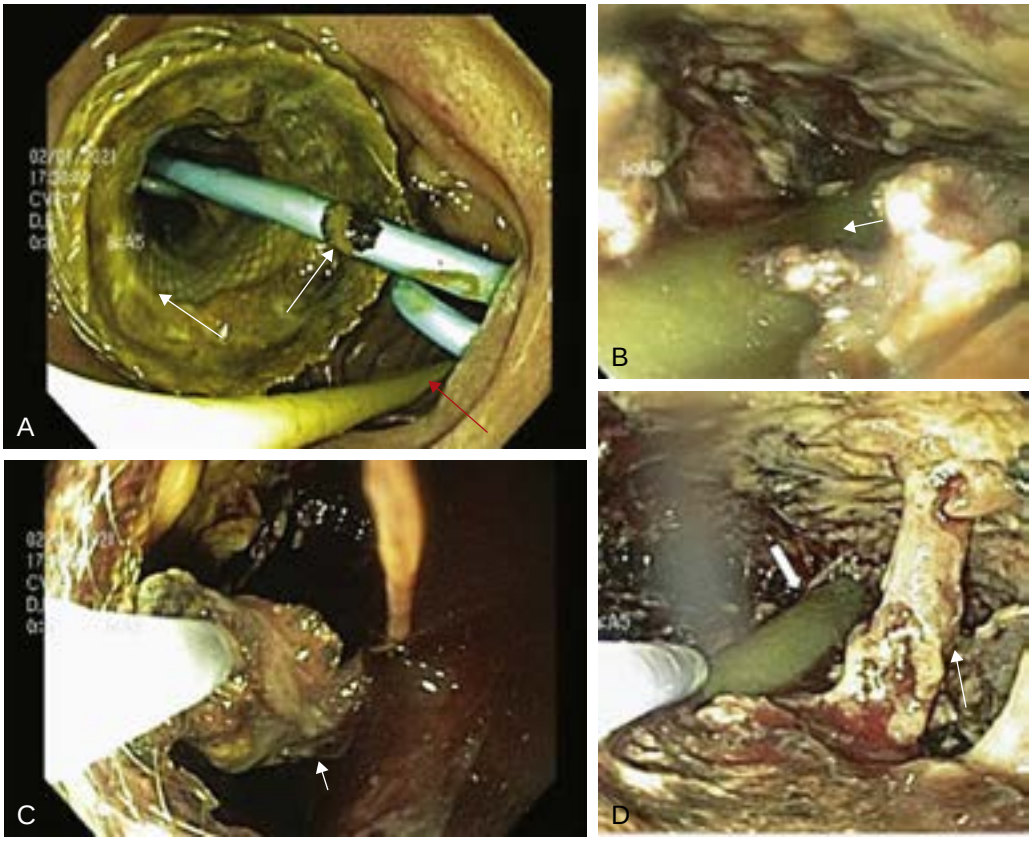


FIG. 12 **(A)** Lumen-apposing metal stent with a plastic stent across the duodenum *(white arrows)*. The nasojejunal feeding tube remains in position *(red arrow)*. **(B)** Endoscopic images of the walled-off pancreatic necrosis. An external drain is seen in the cavity *(arrow)*. **(C)** Necrosectomy with a snare *(arrow)*. **(D)** Final image showing the snare, external drain *(thick arrow)*, and a penetrating vessel *(thin arrow)* within the necrotic cavity.

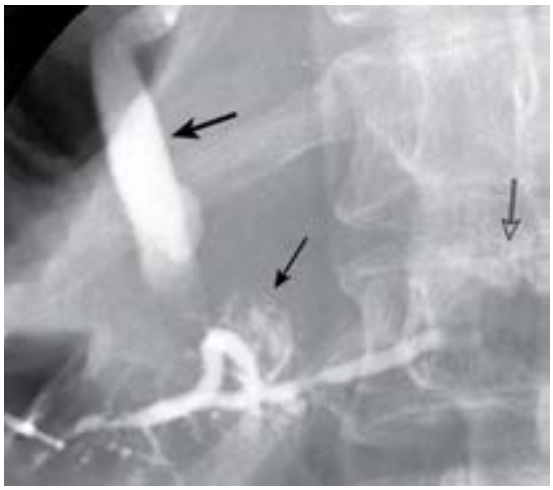


FIG. 13 In a patient with pancreatic ascites and pancreas divisum, the dorsal pancreatic duct in the pancreatic head is leaking in two locations. The first is shown as contrast leaked through a disruption into the lesser sac *(thin closed arrow)*. The second is from the upstream pancreatic duct that is obstructed over the vertebral bodies. A faint collection of contrast in the lesser sac is marked with an *open arrow*. These disruptions accounted for the pancreatic ascites. Just before the pancreatic duct injection through the minor ampulla, the common bile duct *(large closed arrow)* had been filled from the major ampulla. After trans-minor-papilla stenting, the ascites resolved, but pain continued, and the downstream disruption did not seal. An uncomplicated pancreatoduodenectomy resolved these problems when the inflammation was at a minimum.

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Management of Chronic Pancreatitis

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DEFINITION

Chronic pancreatitis (CP) is a progressive disease characterized by chronic inflammation leading to irreversible damage to the endocrine and/or exocrine functions of the pancreas. Recurrent episodes of pancreatic inflammation lead to extensive tissue remodeling and fibrotic changes in the pancreatic parenchyma resulting in loss of native acinar cells (exocrine) and islet cells (endocrine). In contrast, acute pancreatitis is differentiated from CP by full recovery of the organ; however, recurrent acute pancreatitis can result in CP over time.

Chronic pancreatitis can be common, with a prevalence rate of up to 125 per 100,000 individuals. There has been a 41.5% decrease in hospital admissions for CP since 1997, and the average hospital length of stay has decreased from 6.2 days to 4.9 days; however, it has been estimated that the disease results in direct costs of $2.7 billion plus indirect costs related to loss of work and chronic opioid dependence.

The most common presenting symptom of pancreatitis is abdominal pain, epigastric in nature and often radiating to the back. This pain can be mild or severely debilitating in nature, resulting in a significant decrease in quality of life. Other complications of CP include malabsorption, diabetes mellitus, and pancreatic cancer.

It is important to note that new-onset pancreatitis in people older than 50 years of age without a gallstone or a history of alcohol abuse or trauma to the pancreas should be presumed to have a new pancreas neoplasm until proven otherwise. We have seen many patients older than 50 years of age who were assigned a new diagnosis of recurrent acute pancreatitis when in fact a subtle obstructing neoplasm in the pancreas head was the cause of the recurrent pancreatitis. For patients older than 50 years of age who have a new episode of acute pancreatitis and no current or recent gallstone disease, alcohol abuse, or history of trauma to the pancreas, we conduct a full evaluation to look for a neoplasm. If one is not found, we follow patients closely every 3 to 6 months with a pancreas protocol CT to look for changes.

ETIOLOGY

There is a common misperception that most cases of chronic pancreatitis are caused by alcohol abuse. This misperception stems from the past, when there was a lack of science to support the role of genetic mutations as a cause of pancreatitis.

We often observe that patients referred to us for chronic pancreatitis are sensitive about questions related to alcohol use because they have been labeled as having alcoholic pancreatitis when they do not. It is exceedingly rare for mild or occasional alcohol use to be the cause of chronic pancreatitis. Alcohol abuse is a well-known cause of acute pancreatitis, and although repeated episodes of acute pancreatitis do result in chronic pancreatitis, like liver cirrhosis, it takes several years to cause chronic changes. The only exception is when a single episode of severe acute pancreatitis or trauma can cause a mechanical disruption of the pancreatic duct leading to chronic changes. This could be a partial or complete disconnect of the pancreatic duct, resulting in back pressure of the pancreatic fluid.

In general, isolated disruptions of the pancreatic duct should be treated as mechanical problems and not as an intrinsic problem with the pancreatic tissue. In short, isolated mechanical causes of chronic pancreatitis hinder pancreatic duct drainage and are best treated with drainage procedures. However, these are far less common than intrinsic problems with the pancreatic tissue with or without drainage problems, and these findings are best managed with resection or hybrid resection drainage procedures. It is always important to factor in how debilitated a patient is and his or her life expectancy.

Alcohol is a well-known cause of direct acinar cell injury to the pancreas because of its metabolites from oxidative metabolism. However, we are increasingly recognizing that cases previously attributed to *idiopathic CP*, which was the label for 28% to 80% of those with CP, are actually caused by a genetic mutation (Table 1).

We often refer to genetic causes of pancreatitis as opposed to hereditary pancreatitis (HP). However, HP accounts for 2% to 3% of cases of chronic pancreatitis in the United States. HP is an autosomal dominant condition with wide variation in clinical phenotype. This variability is attributed to the influence of both environmental and inherited factors. Most genetic mutations are associated with disruption or alteration of the exocrine pancreas trypsin system. Version 2 of the TIGAR-O classification (an acronym standing for Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent, and severe acute pancreatitis and obstructive) lists *PRSS1, SPINK1, CFTR, CTRC, CASR,* and *CEL* as pathogenic mutations and other contributing modifier genes such as *CLDN2*. Inappropriate activation of trypsinogen leads to irreversible pancreatic cell injury and occurs with mutations in trypsin-1 *(PRSS1),* pancreatic secretory trypsin inhibitor *(SPINK1),* and chymotrypsin C *(CTRC).* Mutations in cystic fibrosis transmembrane conductance regulator (CFTR) result in pancreatic cell injury caused by a change in bicarbonate secretion by pancreatic ductal cells.

HP increases the risk of developing recurrent acute pancreatitis and results in chronic pancreatitis in at least 50% of cases. The risks of pancreatic fibrosis, chronic pain, malabsorption, diabetes mellitus, and pancreatic cancer are also increased.

Both genetic and environmental factors are thought to contribute to the development of CP. The TIGAR-O classification has long been used as a tool to capture the risk and/or to determine the etiology of pancreatitis. In 2019, an updated TIGAR-O version 2 was published with a long and short form aimed to assist clinicians in identifying common etiologies (Box 1).

Smoking is also known to be an independent risk factor for chronic pancreatitis. Smoking has a dose-dependent association with the development of CP and causes acinar cell injury via nicotine-derived metabolites.

Other risk factors for CP include hypertriglyceridemia, autoimmune disorders, hypercalcemia, scorpion bites (which may be the etiology for some military personnel who served in scorpion areas such as the Middle East), and conditions that result in chronic or recurrent pancreatic duct obstruction.

The etiology of chronic pain itself in CP is thought to be a result of chronic inflammation. Recurrent pancreatic inflammation results in hypersensitivity of pain responses to pancreatic stimulation, which in turn creates sensitization of primary nociceptive neurons.

DIAGNOSIS

The evaluation of a patient with suspected chronic pancreatitis begins with a thorough history and physical examination, but the history taking is often the critical part of making the correct diagnosis. It often requires understanding patterns in their pain and if they experienced any abdominal trauma before the initial onset of their pain. Tracking patterns of the pain also require understanding the character of the pain. Most adults have some form of back pain, so simply attributing that to chronic pancreatitis or a small pancreatic cyst is a common pitfall. Most importantly, it is important to determine if the pain is debilitating. And as a reminder, in patients older than 50 years of age with new-onset acute pancreatitis, either a single episode or multiple episodes over a few years, without chronic changes, it is important to consider a possible early malignancy.

TABLE 1 Partial List of Genetic Mutations That Are Sometimes Associated with Pancreatitis

Gene	Name	Inheritance	Mechanism of Action
SPINK1	Serine protease inhibitor, Kazel-type 1	Autosomal Dominant/ Autosomal Recessive	An increase of trypsinogen activation leads to autodigestion of the pancreatic tissue.
PRSS1	Serine Protease	Autosomal Dominant	An increase of trypsin activity results in autodigestion of the pancreatic tissue.
CFTR	Cystic fibrosis transmembrane conduction protein	Autosomal Dominant/ Autosomal Recessive	Abnormal sodium and chloride transport alters pancreatic secretions.
CTRC	Chymotrypsin C	Autosomal Dominant	A decrease of CTRC secretion alters regulation of trypsin, resulting in autodigestion of pancreatic tissue. Homozygous mutation classically presents as cystic fibrosis and often chronic pancreatitis.
CASR	Calcium sensing receptor	Autosomal Dominant	An increase of calcium ion level results in the increase of trypsin activation and dysregulation.
CEL	Carboxyl-ester lipase	Autosomal Dominant	Impaired pancreas secretion increases the risk for exocrine pancreas dysfunction.

BOX 1 TIGAR-O Version 2 Classification of Etiology of Chronic Pancreatitis (Short Form)

Toxic-Metabolic

Alcohol-related
Smoking
Hypercalcemia
Hypertriglyceridemia
Medications
Toxins—other
Metabolic—other

Idiopathic

Early onset (<35 years of age)
Late onset (>35 years of age)

Genetic

Suspected; with no or limited genotyping available
Autosomal dominant (*PRSS1* mutations)
Autosomal recessive *(CFTR, SPINK1, 2)*
Complex genetics (non-mendelian, complex genotypes)
Modifier genes (*PRSS1-PRSS1* locus, *CLDN2* locus)
Hypertriglyceridemia syndromes

Autoimmune/Steroid Responsive Pancreatitis (AIP)

AIP type 1—IgG4-related disease
AIP type 2

Recurrent/Severe Acute Pancreatitis (RAP/SAP)

Acute pancreatitis
Extrapancreatic pancreatitis (e.g., biliary, post-ERCP, traumatic)
Recurrent acute pancreatitis

Obstructive

Pancreas divisum
Ampullary stenosis
Main duct pancreatic stones
Widespread pancreatic calcifications
Main duct strictures
Localized mass causing obstruction

ERCP, Endoscopic retrograde cholangiopancreatography.

BOX 2 Diagnostic Criteria for Chronic Pancreatitis

Recurrent bouts of pain with or without ≥ threefold the normal upper limit of amylase or lipase levels *and* one or more of the following criteria:

- Radiologic evidence comprising strictures and dilation in side branches and/or the main pancreatic duct and/or intraductal and/or parenchymal pancreatic calcifications by contrast-enhanced CT and MRCP
- Histologic proof of chronic pancreatitis from biopsy samples undertaken by endoscopic ultrasonography or from a surgically resected specimen

Abdominal pain is the most common presenting symptom, with pain frequently described as epigastric in nature and radiating to the back. Weight loss is present in approximately 80% of patients at presentation. Steatorrhea and later malnutrition as well as glucose intolerance can develop.

CP is distinguished from recurrent acute pancreatitis by the finding of irreversible pancreatic injury. Radiologic evidence is needed for a formal official diagnosis.

In the past, a plain film abdominal x-ray was the initial imaging modality used in the diagnosis of CP looking for upper abdominal calcifications, but these findings were only present in those with severe advanced disease. Today contrast-enhanced CT and/or magnetic resonance cholangiopancreatography (MRCP) (sensitivity 75% in settings of advanced disease) have become the imaging modalities of choice. Our study of choice is a pancreas protocol CT; however, it is important not to perform unnecessary CT scans in younger patients because many of these individuals are scanned when they present to the emergency department and thus have a high cumulative radiation exposure; this is less of an issue for patients older than 50 years of age. Side or main pancreatic duct strictures and/or ductal or parenchymal pancreatic calcifications on CT or MRCP are indicative of the irreversible injury seen with CP (Box 2).

Some younger patients with recurrent debilitating episodes of acute pancreatitis may have normal-appearing glands. Many of these people have genetic mutations causing their episodes. Over many years, these episodes can result in chronic changes and pain between episodes.

Although not essential in the diagnosis of CP, endoscopic ultrasound (EUS) can use Cambridge classification and Rosemont criteria

to assess chronic injury to the pancreas. The criteria accounts for the imaging characteristics of calcifications, filling defects, dilation, irregularity, and so on. The Cambridge classification has also translationally been applied to CT imaging in the workup of CP.

Though CT, MRCP, and EUS are useful tools in the diagnosis of CP, a significant amount of irreversible injury must occur before imaging findings are evident. With this in mind, an international collaboration including The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group, and the European Pancreatic Club was held with the goal of identifying criteria for the diagnosis of early CP, before onset of irreversible injury, but no consensus statement could be developed for diagnostic criteria. In short, CP is largely a clinical diagnosis that uses imaging to explain why patients may be experiencing debilitating pain.

MANAGEMENT

Pharmacologic

CP indicates irreversible pancreatic injury; therefore a medical cure is not possible. Instead, medical management for CP includes addressing modifiable causes to prevent further disease progression and managing symptoms and complications. Patients should be encouraged to quit smoking and/or abstain from alcohol if they are contributing factors.

Pain is the biggest driver of decreased quality of life and disability in patients with CP. Both non-narcotic and narcotic analgesics can be used in managing pain, preferably in a stepwise fashion titrated to symptom improvement. Antidepressants, anticonvulsants, and anxiolytics are adjuvant analgesics that have had a moderate effect in managing CP-induced pain.

Exocrine insufficiency, manifested by steatorrhea, weight loss, or malnutrition, can be treated with pancreatic enzyme replacement. Endocrine insufficiency patients with CP should be screened annually for diabetes with fasting plasma glucose and hemoglobin A1c levels. Hyperglycemic control can be managed either with oral anti-hyperglycemic agents or insulin therapy when indicated.

Nonpharmacologic

Endoscopic

Endoscopic therapy for CP can be pursued as a first-line treatment when the insult is obstructive in nature, usually indicated by a dilated main pancreatic duct. Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (with or without stent placement) can sometimes relieve pancreatic duct pressure and allow drainage of pancreatic secretions, but it is rarely a lasting solution. In fact, some patients are stented for too long before presenting for surgical options. If the obstruction is caused by an impacted stone and is not relieved by ERCP, extracorporeal shock wave lithotripsy (ESWL) or intraductal lithotripsy can be employed.

Endoscopic ductal dilators can be used to treat pancreatic duct strictures not relieved by ERCP sphincterotomy. Additionally, serial stent placement and exchanges can help prevent re-stenosis of structures. New strictures should be evaluated for malignancy including sending brushings for cytology. As the degree of ductal dilation does not correlate with symptoms, symptom improvement rather than ductal decompression following intervention would indicate treatment success.

EUS-guided neurolysis or nerve block with bupivacaine and corticosteroids near the celiac plexus can be used for relief of medical refractory pain from CP. This results in pain relief in about 50% of patients, though this relief may only be short term.

Surgical

Surgical intervention for CP is reserved for patients who have failed medical and endoscopic therapy or in response to adjacent organ anatomic complications such as biliary or duodenal obstruction and splenic vein occlusion resulting in gastric variceal bleeding. The goal of surgical intervention is improvement of abdominal pain and improved quality of life, with preservation of pancreatic tissue whenever possible. Around 80% of patients report pain relief following surgery, though surgery itself comes with significant morbidity risk and should be used sparingly in patients with a reduced life expectancy.

The surgical approach is dependent on the pattern of disease determined preoperatively with cross-sectional imaging. Surgical approaches include drainage procedures to relieve ductal obstruction, resection procedures to remove significantly affected portions of the pancreas, or a combination of the two (resection and drainage).

Any patient suspected of having a neoplasm should have a resection procedure instead of a drainage-only procedure.

Drainage Procedures

Drainage procedures (e.g., the Puestow procedure) are best applied when there is a traumatic disruption of the pancreatic duct. Outside of this infrequent indication, we favor a hybrid procedure such as the Frey procedure—our procedure of choice. Drainage procedures also allow for preservation of remaining functional pancreatic cells as no pancreas tissue is removed.

Following drainage techniques, up to 82% of patients have reported improvement in their CP–related pain, although 50% of these patients report pain recurrence in long-term follow-up, particularly those with continued alcohol use.

Longitudinal Pancreatojejunostomy. Longitudinal (or lateral) pancreatojejunostomy, also known as the *modified Puestow procedure* or *Partington Rochelle procedure,* involves longitudinally opening the anterior aspect of the pancreatic duct and creating a side-to-side pancreatojejunostomy (PJ) with distal Roux-en-Y reconstruction. The longitudinal anastomosis is thought to counter the challenge of multiple pancreatic ductal strictures.

Once the anterior aspect of the pancreas is exposed, the main pancreatic duct can be identified either by palpation or with intraoperative ultrasound. This is then confirmed by aspirating with a 20-gauge angiocatheter and then threading the catheter into the PD to help guide incision of the duct. Duct incision should start 1 to 2 cm from the duodenal wall and extend to 1 cm from the pancreatic tail. All ductal stones should be removed. A jejunal limb can then be mobilized and passed through a transverse mesocolon defect and laid along the pancreatic body with the transected end lying over the pancreatic tail. Once a mirror enterotomy to the opened PD is made, the PJ anastomosis is created usually with permanent suture in one or two layers. Most often, this has been done via an open approach, though we have performed most of these procedures in this chapter using a laparoscopic and robotic approach. We observe that the Puestow procedure is often overused and is often applied to patients who can benefit more from a Frey procedure that clears the pancreas head disease better and ensures more complete drainage (Fig. 1).

Combined Resection and Drainage Procedures

The combined resection and drainage approach is indicated in patients with pancreatic ductal dilation secondary to obstruction who also have an enlarged/inflamed pancreatic head. Drainage procedures include the Frey and Beger procedures (both of which are considered duodenal preserving) and the Berne procedure, which is a modified Beger procedure. Studies comparing Frey and Beger procedures have shown comparable pain relief in up to 94% of patients with rates of endocrine and exocrine dysfunction varying from 10% to 30%. Combined resection procedures tend to have a higher reoperation rates for biliary stenosis.

Frey Procedure. The Frey procedure includes opening the pancreatic duct along its length into the head and uncinate process of the pancreas followed by coring out the fibrotic diseased pancreatic head. In essence, the Frey procedure is a longitudinal pancreatojejunostomy with the added benefit of removing the majority of the

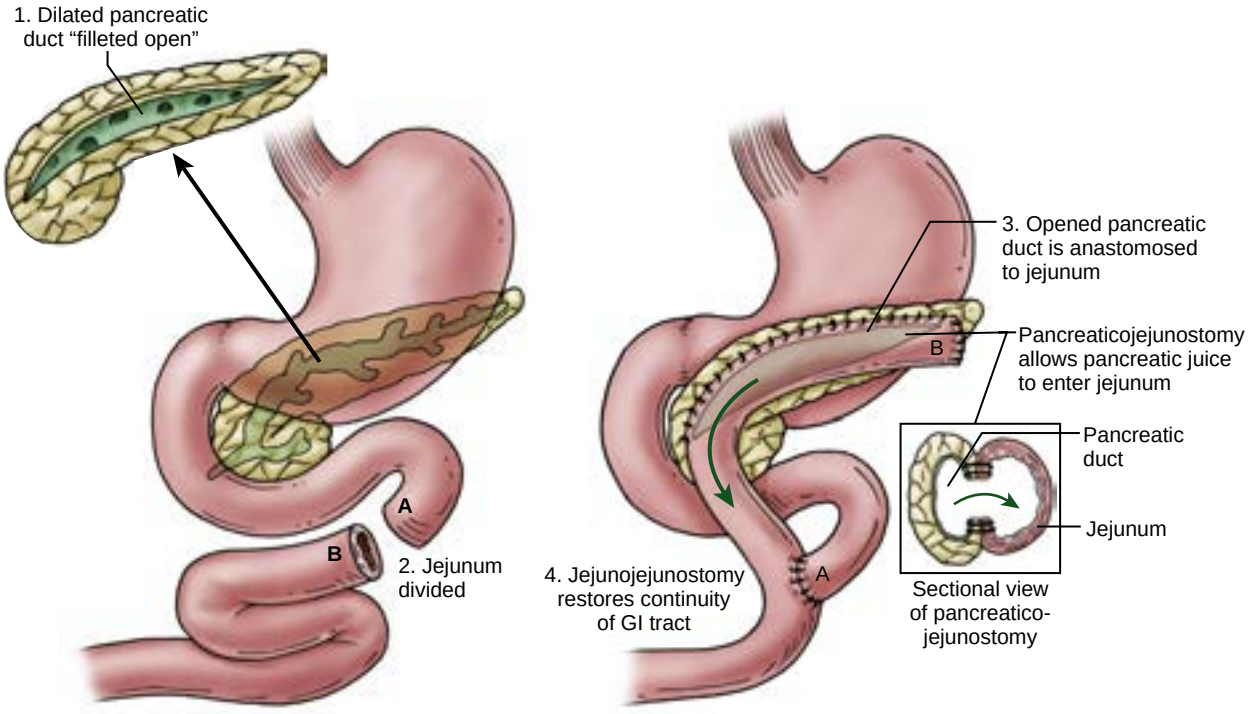


FIG. 1 Longitudinal pancreaticojejunostomy. *(Redrawn from Oyefule O, Roy M, Simpfendorfer CH. Open Longitudinal Pancreaticojejunostomy. In: Rosenthal R, Rosales A, Lo Menzo E, Dip F, eds.* Mental Conditioning to Perform Common Operations in General Surgery Training. *Cham: Springer; 2020.)*

diseased pancreatic head. Another advantage of this procedure is it is not necessary to divide the pancreatic neck. Pancreatic head resection is limited to the portion of the pancreas that is superficial to the intrapancreatic portion of the common bile duct.

Beger Procedure. The Beger procedure is indicated when there is an enlarged pancreatic head without significant distal pancreatic duct obstruction. Surgery involves a subtotal resection of the pancreatic head. Following anterior pancreatic exposure and kocherization of the duodenum, the common bile duct is identified along with the common hepatic artery and superior mesenteric artery just inferior to the uncinated process. A tunnel is created between the pancreatic neck and portal vein followed by pancreatic neck transection, leaving a small cuff of tissue along the duodenal wall, preserving the intrapancreatic common bile duct. A Roux limb is then mobilized retrocolic. An end-to-side pancreaticojejunostomy is created between the jejunal limb and pancreatic tail. A second anastomosis between the pancreatic head remnant and the jejunal limb is also created, around 8 cm distal to the first anastomosis. A modification of this technique is the Berne procedure, which preserves more of the pancreatic parenchyma overlying the superior mesenteric artery and portal vein (Fig. 2).

Resection Procedures

Resection procedures, such as the Whipple procedure, are indicated in CP patients when there is a suspicion of a pancreas head neoplasm. The head of the pancreas is often considered to be the primary driver of pancreatic inflammation in CP, resulting in damage to surrounding sensory nerves that contribute to the chronic pain experienced.

Pancreatoduodenectomy. Pancreatoduodenectomy (Whipple procedure) involves resection of the pancreatic head, duodenum, and distal bile duct, leaving the pancreatic tail intact. This surgical approach can be applied in patients with head-dominant disease with or without pancreatic ductal dilation. Classically the Whipple procedure involves resection of the duodenum with antrectomy. Equivalent pain improvement scores have been shown between the classic Whipple and pylorus-preserving approaches. The pylorus-preserving approach has been associated with higher rates of delayed gastric emptying and has the increased risk of portal vein dissection, which can be dangerous in this population given the scarring from CP.

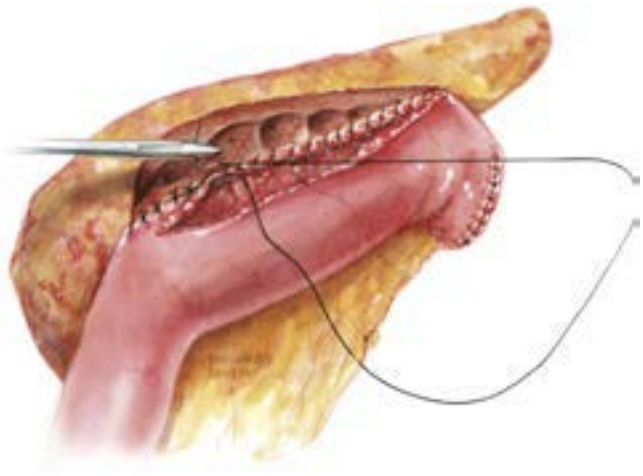


FIG. 2 Lateral pancreaticojejunostomy (Puestow procedure). The original operation described by Puestow and Gillesby in 1958 included resection of the pancreatic tail and splenectomy. Currently, the Partington-Rochelle modification of the original Puestow procedure often is used; this consists of a spleen-preserving longitudinal side-to-side Roux-en-Y pancreaticojejunostomy, without pancreatic tail resection. *(From Cameron JL, Sandone C.* Atlas of Gastrointestinal Surgery. *vol 2. 2nd ed. 2014; Shelton, CT:PMPH-USA.)*

Distal Pancreatectomy. Distal pancreatectomy involves removal of the distal portion of the pancreas (distal to the superior mesenteric vein) and the spleen. Indications for this approach include patients with CP who develop clinically evident splenic vein thrombosis with left-sided portal hypertension or those with

proximal pancreatic duct obstruction not amenable to endoscopic management. This approach is rarely used in the management of CP as the disease is rarely isolated to the pancreatic tail and generally results in short-term pain relief.

Total Pancreatectomy with Islet Cell Autotransplantation. Total pancreatectomy (TPIAT) is a definitive cure for CP and is reserved as a last resort for patients in whom CP has been refractory to all other interventions and who have a significantly impaired quality of life. Tragically, many patients nationwide who undergo a TPIAT do not appreciate the challenges of the future insulin and pancreatic enzyme dependence that may result. The islet autotransplant rarely works long term; therefore we only offer this procedure when patients are prepared to become an insulin-dependent diabetic. Of note, this form of post-pancreatectomy diabetes, when it occurs, is more difficult to manage than type 1 or 2 diabetes because the person lacks glucagon and other pancreatic hormones involved in glucose regulation.

To be clear, we tell every patient undergoing a TPIAT that one of the downsides of the procedure is that they will develop diabetes and that it is just a matter of time. For some, diabetes has already begun, but TPIAT may accelerate its progression. Though there have been improvements in islet cell processing and transplantation, islet cells rarely have long-term adequate insulin-producing function (10 years) where insulin injections are not required. Patient selection is critical when pursuing TPIAT. Patients who have a genetic cause of pancreatitis, do not smoke, are not addicted to opioids, and have not had prior pancreatic surgery have the best postoperative outcomes. In addition to meeting clinical criteria, we often say that these patients must "beg for the procedure" for us to offer it. This means we have multiple office consultations with a patient before offering the procedure.

TPIAT involves the removal of the entire pancreas, either open or laparoscopically. We use laparoscopy as the preferred approach because it is associated with less perioperative pain. The pancreas is then enzymatically digested, and the islet cells are isolated and infused via the portal vein into the liver. Postoperatively, patients are generally kept on insulin regimens in an attempt to rest the newly transplanted islets, and insulin requirements are assessed at each postoperative visit. Relief or reduction of pancreatic pain has been reported in up to 93% of patients at 1 year following TPIAT.

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Genetic Testing and High-Risk Pancreatic Cancer Screening

Daniel J. Delitto, MD, PhD, and Kevin E. Behrns, MD

CASE PRESENTATION

Our discussion of genetic testing and high-risk pancreatic cancer will be placed in clinical context by considering an illustrative patient presentation. The patient is a 48-year-old male who presents with a history of painless jaundice of 10 days' duration. He has lost 7-10 pounds unintentionally over the past 3 months, but otherwise has been well. His family history is significant for a 51-year-old sister who had a breast cancer several years ago and was noted to have a *BRCA* mutation associated with the cancer. He has no other siblings, and his mother died at a young age from an unspecified cancer. A CT scan confirmed a typical pancreatic head carcinoma with a double duct sign. The patient underwent an uncomplicated pancreatoduodenectomy with an uneventful recovery. Pathologic analysis revealed a 3.2-cm adenocarcinoma of the pancreas with negative margins and 2 of 17 lymph nodes positive for cancer. Aside from adjuvant chemotherapy, how should the patient be managed?

CLINICAL QUESTIONS TO BE ADDRESSED

In the context of this patient's presentation and family history, several pertinent clinical questions should be addressed. First, should this patient be considered a high-risk individual (HRI), and should he undergo genetic testing for a germline mutation? If a germline mutation is present, should the adjuvant therapy regimen to be administered be adjusted? How should his three children be counseled? In the following text, we will consider these questions and others with the goal of providing a succinct overview and approach to genetic testing in individuals with high-risk pancreatic cancer.

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is projected to be the second leading cause of cancer deaths by 2030. Despite incremental advances in multidisciplinary treatment strategies, 5-year survival remains less than 10%. This poor prognosis is caused, in part, by challenges in timely diagnosis. The majority of PDACs are diagnosed in the locally advanced or metastatic setting. In contrast with many of the more prevalent solid tumors, no screening paradigm designed to detect PDAC has proven effective for the general population. In addition to general considerations regarding sensitivity and cost, pancreatic surgery remains the only curative intervention and carries a high morbidity rate. To address the relatively low incidence of PDAC in the general population, recent advances in genetic screening have led to the identification of HRIs. Combined with improvements in diagnostic imaging, several programs have demonstrated feasibility in screening these populations for PDAC.

HIGH-RISK INDIVIDUALS

The definition of an HRI continues to evolve as estimates of lifetime PDAC risk improve. To address appropriate screening guidelines in HRIs, the International Cancer of the Pancreas Screening (CAPS) Consortium convened in 2010. More recent CAPS guidelines define high-risk groups, albeit with considerable controversy in risk estimates for PDAC. The first group represents patients with a family history in the absence of known germline syndromes. To be considered an HRI, family history should consist of three or more blood relatives with at least one first-degree relative or two or more first-degree relatives with PDAC.

Patients are also considered HRIs if deleterious germline mutations are present in *BRCA1, BRCA2, PALB2, ATM, TP53, CDKN2A, STK11, PRSS1, CPA1, CTRC,* or mismatch repair genes associated with Lynch syndrome. Associated malignancies and lifetime PDAC risk estimates are displayed in Table 1 for each high-risk cohort. It is important to recognize that HRIs are a heterogeneous group with respect to PDAC risk. The detection rate from early screening must therefore be interpreted carefully from prospectively evaluated cohorts.

EFFECTIVENESS OF SCREENING

The CAPS consortium has published the largest screening series to date for PDAC in HRIs. Of the 354 patients included, 97% were members of familial PDAC cohorts, and 16% carried known deleterious germline mutations. All patients underwent baseline endoscopic ultrasound (EUS), and the majority underwent CT as well. Subsequent imaging included a combination of EUS, CT, and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), with at least one modality performed annually. At a median follow-up of 5 years, 68 (19%) patients demonstrated imaging findings with worrisome features for a pancreatic neoplasm. Surgical resection was performed in 44 patients, of whom 14 had PDAC and 10 had an intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia or PanIN-3. Thus, the detection rate of clinically significant dysplasia or invasive cancer for the entire cohort was 7%. Notably, nearly half of these patients (3% of the total cohort) were caught before the development of PDAC.

For patients with screening-detected PDAC, the 5-year survival rate was 60%. This figure is favorable compared with SEER data demonstrating 5-year survival rates of 10% in all patients and 20% to 30% in localized PDAC. Regarding risks associated with surgery, an updated analysis of postoperative outcomes in the CAPS cohort demonstrated 35% morbidity and 0% mortality. Taken together, these data suggest that PDAC screening programs for HRIs may be of considerable benefit.

PDAC screening for HRIs has also been evaluated in smaller cohorts with mixed results. Data from Toronto followed 262 HRIs over a median of 4 years. During this time, three patients were diagnosed with PDAC, two of whom had metastatic disease at diagnosis. A group of 109 HRIs were followed at Memorial Sloan Kettering Cancer Center, leading to 6 pancreatectomies for high-risk imaging features. Of the 6 patients undergoing resection, 1 patient had PDAC, and 3 patients had either PanIN3 or IPMN with at least moderate dysplasia. Columbia University reported results from a single EUS or MRI in 51 HRIs, revealing five patients (10%) with either PDAC or IPMN with moderate to high-grade dysplasia. A German series followed 76 HRIs, ultimately resulting in 7 pancreatectomies for benign lesions. In contrast, a Dutch study followed 44 HRIs with a single screening EUS, discovering 3 patients (7%) with asymptomatic PDAC. Results from published series are summarized in Table 2.

Given the heterogeneity in lifetime PDAC risk among different HRI cohorts, it is not surprising to see a range of estimated detection rates from screening protocols. In general, cohorts with a higher percentage of known germline mutation carriers and stronger family histories were associated with higher detection rates from screening. However, given the variability in results among these studies, the efficacy of early screening in HRIs continues to be debated. The cumulative data suggest that certain populations may benefit from early screening programs, but defining these populations remains challenging.

TABLE 1 Estimated Lifetime Risk of Pancreatic Ductal Adenocarcinoma in High-Risk Individuals

HRI Cohort	Estimated Lifetime Risk (%)	Associated Malignancies
Two first-degree relatives with PDAC	8-12	N/A
Three first-degree relatives with PDAC	40	N/A
BRCA1	2-5	Breast, ovary, prostate
BRCA2	5-10	Breast, ovary, prostate
PALB2	2-5	Breast, ovary
ATM (ataxia telangiectasia)	2-5	Breast, prostate
TP53 (Li-Fraumeni syndrome)	>3	Breast, sarcoma, brain, adrenal, leukemia
CDKN2A (familial atypical multiple mole melanoma syndrome)	15-20	Melanoma
MLH1, MSH2, MSH6, PMS2 (Lynch syndrome)	3-4	Colon/rectum, stomach, small intestine, ovary, uterus, urinary tract, prostate
STK11 (Peutz-Jeghers syndrome)	11-36	Breast, lung, colon/rectum, stomach, small intestine, ovary, uterus, cervix, testicle
PRSS1, CPA1, CTRC (hereditary pancreatitis)	40	N/A

N/A, Not applicable; *PDAC,* pancreatic ductal adenocarcinoma.

TABLE 2 Outcomes from High-Risk Individual Screening Cohorts

Series	*N*	Rate of Major Pancreatic Resection (%)	PDAC Detection Rate (%)	Moderate- to High-Grade Dysplasia Detection Rate (%)
Canto et al.	354	12.4	4.0	2.8
Al-Sukhni et al.	262	1.5	1.1	0
Ludwig et al.	109	5.5	0.9	2.8
Langer et al.	76	7.8	0	0
Verna et al.	51	9.8	3.1	7.8
Poley et al.	44	6.8	6.8	0

PDAC, Pancreatic ductal adenocarcinoma.

SCREENING GUIDELINES

The guidelines for screening patients at high risk for pancreatic adenocarcinoma are well delineated by the International Cancer of the Pancreas Screening Consortium and the National Comprehensive Cancer Network (NCCN). In brief, the age of initiation of screening for HRIs without a defined germline mutation is 50 years. For patients who have a germline mutation, the age to begin screening is 40 to 45 years of age, especially for individuals who harbor a mutation of *CDKN2A*. The age to initiate screening for high-risk patients is debated by the experts, but most HRIs who develop pancreatic cancer are diagnosed after 55 years of age. Limited evidence suggests that other risk factors such as smoking influence the age of screening initiation.

The diagnostic studies that are most helpful screening high-risk patients are MRI, MRCP, and EUS. These modalities are preferred because they do not emit ionizing radiation like CT and thus eliminate the risk of development of ionizing radiation-induced cancers. EUS may have the added advantage of being able to detect small cystic lesions, which may be precursors of cancer, albeit at a low rate. There is limited evidence that CA 19-9 is of diagnostic benefit in HRIs, but it should be studied to determine its utility. Conversely, glucose concentrations should be measured on a regular basis because early onset of hyperglycemia may be a harbinger of new-onset diabetes mellitus associated with pancreatic adenocarcinoma. Circulating tumor DNA measurements hold promise as innovative tests that may help identify patients with pancreatic adenocarcinoma. Regardless of the screening tools implemented, annual screening is recommended for most patients, but individuals with a *CDKN2A* are at higher risk and may be surveilled at 6-month intervals.

Patients who exhibit abnormalities on screening tests should undergo either EUS-guided biopsy of a defined lesion or surgical resection that removes a well-defined mass or dominant cyst. In general, resection of the pancreas in patients with high-risk disease should mimic the practice of patients with sporadic tumors in that partial resection is favored over total pancreatectomy. Only those patients that meet high-risk criteria, have known mutations, and have imaging that demonstrates several lesions occupying the entirety of the gland should be subject to total pancreatectomy. Patients with a diffuse IPMN may meet these criteria because they can present with synchronous and metachronous lesions distributed throughout the pancreas.

MANAGEMENT OF CYSTIC LESIONS IN HIGH-RISK INDIVIDUALS

Cystic lesions of the pancreas are not infrequently identified in high-risk patients enrolled in surveillance programs screening for pancreatic cancer. It is unknown if the behavior of pancreatic cysts in HRIs differs from that of cysts in non–high-risk persons. Furthermore, the utility of 2017 Fukuoka guidelines and the consortium statements of CAPS is not well described in the management of high-risk patients. Pancreatic cysts occur in 2% to 14% of individuals who undergo cross-sectional imaging without a history of pancreatic disease or the presence of a germline mutation, but up to 40% of HRIs will have pancreatic cysts identified on imaging or EUS. In a study by Dbouk et al., 356 of 732 (48%) HRIs had cysts detected during surveillance. Only 24 (6.7%) patients, however, underwent surgical resection for worrisome features, and one quarter of them had germline mutations. Of the 332 remaining patients, 12 (3.6%) developed solid

pancreatic lesions concerning for malignancy. The solid lesions that developed in the 12 patients were in areas that had cystic disease. Of note, neither the 2017 Fukuoka guidelines nor the CAPS consortium criteria were helpful in the diagnosis and management of cystic lesions, thus new tools are necessary to guide clinicians in the management of pancreatic cysts in HRIs.

PARADIGM SHIFT OF CRITICAL ASSESSMENT

Traditionally, we have taught trainees to think about patient management from the standpoint of symptoms, signs, and diagnostic tests. Although this approach has allowed us to collect vast amounts of data, it is based on the presence of symptoms and signs, which often arise too late to permit effectual care. This is especially true in patients with pancreatic cancer and even more so in HRIs. Today, we should use the information and tools at hand to make an earlier diagnosis and not think about symptoms and signs first, but about the true underlying genetic alterations that lead to the development of pancreatic cancer. We need to use individuals' genomic data to guide our critical assessment and investigation so we can address health issues earlier. This will require a shift in how we think about not just patients, but populations and cohorts that are at risk for developing pancreatic cancer. This shift in thinking is well-outlined by Whitcomb et al., and further reading is suggested for interested readers.

CASE PRESENTATION REVISITED

The case presented at the beginning of this chapter and the information provided subsequently should provide a clear picture of how to manage HRIs with pancreatic cancer. A patient like the one presented should definitively have germline testing because he has a sibling with a genetic mutation known to be present in hereditary pancreatic cancer, and the family meets the criteria for HRIs that require screening. If the patient had a mutation, then consideration of use of a platinum-based agent may be advisable. Furthermore, his children should have germline testing, genetic counseling, and screening with MRI or EUS at the appropriate age depending on the mutation, but not later than 50 years of age.

CONCLUSION

In conclusion, accumulating information aids in the identification of patients at high-risk for pancreatic cancer. Patients at high-risk should undergo genetic testing, pancreatic tumor surveillance by MRI or EUS, and appropriate management based on the germline mutations. In addition, their family members should be screened and undergo surveillance if a mutation is present. Finally, careful documentation of germline mutations and other mutations that may be present is paramount to developing a novel approach to the diagnosis of pancreatic cancer in high-risk patients.

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Management of Periampullary Cancers

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INTRODUCTION

Periampullary cancers include a diverse group of neoplasms that arise within 2 cm of the ampulla of Vater. Pancreatic ductal adenocarcinomas (PDACs) are the most common cancer arising in this location, but other cancers, including ampullary adenocarcinoma, extrahepatic cholangiocarcinoma, and duodenal adenocarcinoma occur less commonly. The convergence of several critical anatomic structures gives rise to a shared clinical presentation of these cancers, despite having different tissues of origin. Multidisciplinary review of the diagnostic workup is often helpful as endoscopic, radiologic, and pathologic expertise may be needed to secure a diagnosis. Not uncommonly, the final diagnosis may only be established after a surgical resection when the entire specimen is available for analysis. Because PDACs are the most common cancers of this region, this chapter will focus on the diagnostic approach, staging, and treatment of PDAC and highlight the similarities and differences in the management of ampullary adenocarcinomas, extrahepatic cholangiocarcinomas, and duodenal adenocarcinomas as well.

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

Clinical Presentation

The most common symptoms experienced by patients with periampullary cancers are jaundice, upper abdominal or back pain, and weight loss. A history of significant unintentional weight loss is not

uncommon and can be caused by exocrine insufficiency, which manifests as steatorrhea, or subclinical gastric outlet obstruction. The presence of intractable nausea or vomiting may be symptoms of a concomitant gastric outlet obstruction and can be corroborated by radiographic findings of extreme gastric distention. In addition, new-onset (within 2 years) diabetes in the setting of weight loss is concerning for pancreatogenic (type 3c) diabetes mellitus related to PDAC. Approximately 40% of patients with PDAC present with new-onset diabetes. Although the physical examination is often unrevealing, the presence of palpable periumbilical or left supraclavicular lymph nodes may be indicative of metastatic disease and may warrant further workup with positron emission tomography (PET) or biopsy.

Careful questioning regarding family history of cancer may reveal a history of PDAC; breast, ovarian, or colon cancer; or melanoma. Approximately 10% of PDACs are thought to be related to a heritable pathogenic variant, and the most common alterations occur in the *BRCA2* gene. Additional hereditary syndromes associated with periampullary tumors include Lynch syndrome (ampullary cancer and PDAC), familial adenomatous polyposis syndrome (duodenal cancer and PDAC), and Peutz-Jeghers syndrome (duodenal cancer and PDAC). National Comprehensive Cancer Network guidelines now recommend routine genetic counseling and genetic testing for *all* patients diagnosed with PDAC. If an alteration is identified, genetic testing (and high-risk cancer screening) may be offered to additional family members. In addition, identification of germline pathogenic variants may also have therapeutic implications for the patient, as some genetic variants may be predictive of specific chemotherapeutic sensitivities (e.g., patients with *BRCA* pathogenic variants may have increased sensitivity to platinum agents and poly-ADP ribose polymerase inhibitors).

Imaging Studies

Because most patients with periampullary tumors present with jaundice, there is an impulse to perform a endoscopic retrograde cholangiopancreatography (ERCP) as the first diagnostic study as it may be both diagnostic and therapeutic. In contrast with biliary obstruction secondary to choledocholithiasis, which can occur acutely and is often associated with significant pain and cholangitis, periampullary cancers usually present with gradual painless jaundice that is uncommonly associated with cholangitis. For this reason, although patients may present with jaundice, emergent therapeutic endoscopic intervention is rarely needed. Emphasis should be placed on obtaining a computed tomography (CT) scan on patients suspected of having pancreatic cancer before any invasive intervention, such as an ERCP. Rarely does a patient present with a clinical picture that would mandate an invasive procedure before obtaining a diagnostic CT scan. The incidence of ERCP-associated pancreatitis is approximately 4%, and procedure-related complications can result in significant peripancreatic inflammation, which can obscure the relationship between the primary tumor and adjacent vasculature, resulting in inaccurate assessment of the initial clinical stage (Fig. 1). Prioritizing a high-quality CT scan before any invasive intervention ensures accurate initial staging of the disease.

For periampullary tumors, CT is the preferred diagnostic study to assess the location of the primary tumor in relation to adjacent vascular structures and to assess for distant metastases. The CT scan should include the chest as well as a pancreatic protocol CT scan. The latter includes thin (1-mm slice thickness) image acquisition of the pancreas through both late arterial and venous phases. The late-arterial phase is usually the best phase to identify PDAC as the timing provides the maximum contrast difference between normally enhancing pancreatic parenchyma and the PDACs, which are generally hypoenhancing. In addition, this is the best phase for analyzing the tumor-artery relationships and to note the presence of any aberrant arterial anatomy. The portal venous phase is valuable for assessing variant venous anatomy and tumor-vessel abutment or encasement. In addition, metastatic lesions in the liver are often best appreciated in the venous phase. Additional diagnostic studies, such as a magnetic resonance imaging (MRI) or PET may be helpful if indeterminate liver lesions or suspicious nodal involvement are detected on CT imaging.

In addition to delineating tumor-vessel anatomy, cross-sectional imaging provides additional valuable information as to the origin of the periampullary tumor. In general, PDAC of the periampullary region is associated with: (1) a mass in the head of the pancreas, (2) a double duct sign involving dilation of both the common bile duct and main pancreatic duct, and (3) distal pancreatic atrophy. The absence of any or all of these findings may suggest that the tumor may be a non-PDAC periampullary cancer. For example, ampullary adenocarcinomas, duodenal adenocarcinomas, or distal cholangiocarcinomas can cause biliary obstruction without concomitant pancreatic ductal obstruction or atrophy. Ampullary and duodenal adenocarcinomas

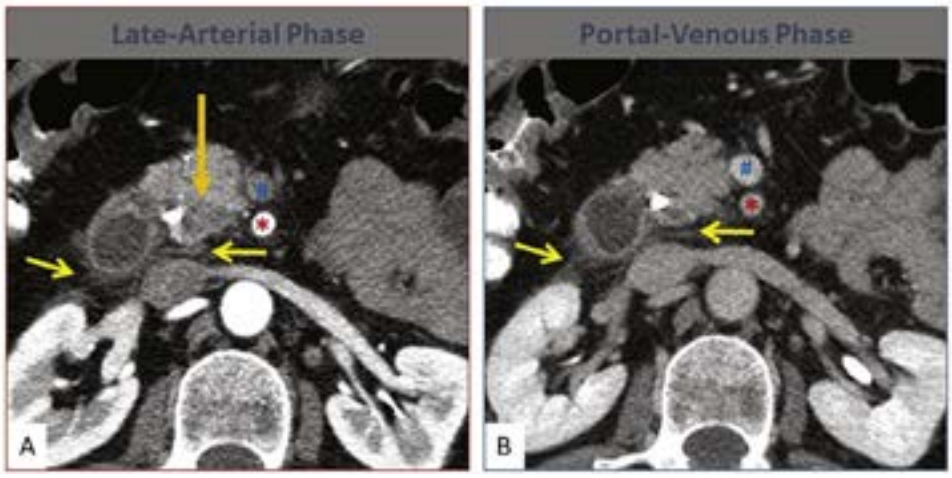


FIG. 1 Resectable pancreatic adenocarcinoma. CT scans in the late-arterial **(A)** and portal-venous **(B)** phases demonstrate a low-attenuation mass completely confined to the pancreas with no tumor contact of the superior mesenteric artery *(red asterisk)* and vein *(blue hashtag)* with primary tumor best viewed on the arterial phase. Note that a plastic endobiliary stent was placed before this staging CT with subtle peripancreatic and periduodenal fat stranding, likely representing postplacement pancreatitis/inflammation *(yellow arrows)*. Sometimes inflammation can be confused with extrapancreatic tumor extension and confound interpretation for accurate staging. Typically, the staging CT should be performed before stent placement to avoid this pitfall.

may be associated with a luminal mass involving the duodenum and may be best appreciated on coronal CT reformats or by direct endoscopic evaluation. Distal cholangiocarcinoma often results in biliary obstruction with subtle enhancement of the bile duct in the absence of anatomic mass (duodenal, ampullary, or pancreatic).

Clinical Staging

Accurate clinical staging provides the framework for multidisciplinary management and shared decision making with patients. Although consensus among clinicians may not exist (Table 1), all published guidelines generally agree on two overarching clinical stages of PDAC: potentially operable (resectable and borderline resectable disease) and likely inoperable (locally advanced and metastatic disease). Resectable disease (Fig. 2) is defined by an absence of tumor extension to the superior mesenteric artery (SMA), celiac axis, or hepatic artery with a patent superior mesenteric vein (SMV)/portal vein (PV) confluence. Lack of arterial abutment is characterized by the presence of normal soft tissue planes between the tumor and the arteries. Associated SMV/PV abutment/encasement may be acceptable, provided that adequate inflow and outflow targets are identified for potential reconstruction. The distinction between borderline resectable (Fig. 3) and locally advanced disease (Fig. 4) is determined by the degree of tumor-artery interface (abutment is defined as ≤180 degrees and encasement is >180 degrees). Borderline resectable disease is defined as tumor abutment ≤180 degrees of the SMA or celiac axis because of the clinical observation that induction therapy may sterilize at least the periphery of the tumor, thereby facilitating a complete resection. As the tumor-artery interface increases from abutment to encasement, a complete gross resection of all disease is likely not possible without arterial resection. The borderline resectable category also includes tumor abutment/encasement of a short segment of the hepatic artery, usually at the origin of the gastroduodenal artery, or an occluded SMV/PV, amenable to reconstruction. In contrast, locally advanced tumors are characterized by arterial encasement ≥180 degrees of the celiac artery or SMA. The locally advanced category also includes patients with SMV/PV occlusion with no technical option for reconstruction. Finally, metastatic disease is defined by the presence of extrapancreatic metastases.

TABLE 1 Comparison of Radiographic Differences in Definitions for Resectable, Borderline Resectable, and Locally Advanced Pancreatic Cancer

	Commonality	NCCN	AHPBA/SSO/SSAT	MDA/MCW
RESECTABLE				
SMA, celiac artery, CHA	No abutment	No abutment	No abutment, with clear fat planes	No abutment
SMV/PV	No abutment	No abutment, or ≤180-degree contact without contour irregularity	No abutment, distortion, thrombus, or encasement	No abutment, or <50% narrowing
BORDERLINE RESECTABLE				
SMV/PV	Abutment	Abutment, ≤180-degree contact with contour irregularity, or thrombosis	Abutment, impingement, encasement, or short-segment occlusion	Abutment, short-segment occlusion, or >50% narrowing with reconstruction
SMA	Abutment	Abutment	Abutment	Abutment
Celiac artery	Abutment	Abutment	Abutment	Abutment
CHA	Abutment* or short-segment encasement†	Abutment or short-segment encasement	Abutment or short-segment encasement	Abutment or short-segment encasement
LOCALLY ADVANCED				
SMV/PV	Involvement or occlusion without reconstruction options	Unreconstructable SMV/PV	Major extensive thrombosis	Occlusion without reconstruction options
SMA	Encasement	Encasement	Circumferential encasement	Encasement
Celiac artery	Encasement	Encasement	Circumferential encasement	Encasement without reconstruction options
CHA	Encasement	Encasement	Circumferential encasement	Encasement without reconstruction options

*Abutment indicates that the tumor involves <180-degree vessel circumference.
†Encasement indicates >180-degree vessel circumference.
AHPBA/SSO/SSAT, Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; *CHA,* common hepatic artery; *MDA/MCW,* MD Anderson/Medical College of Wisconsin; *NCCN,* National Comprehensive Cancer Network; *SMA,* superior mesenteric artery; *SMV/PV,* superior mesenteric vein/portal vein.

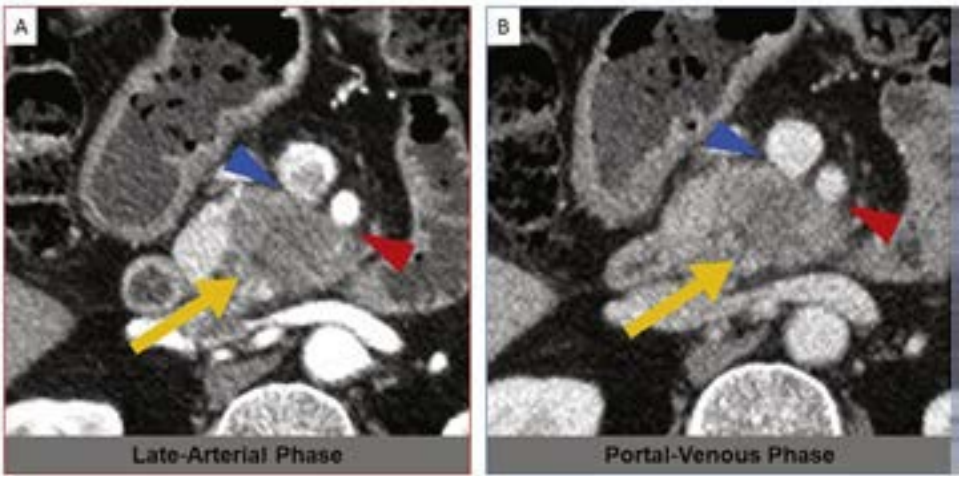


FIG. 2 Borderline resectable pancreatic adenocarcinoma. Late-arterial **(A)** and portal-venous **(B)** phases demonstrate a large low-attenuation mass compatible with pancreatic adenocarcinoma *(arrow)*. The anterior margin of the tumor abuts (less than 180 degrees) the posterior walls of the superior mesenteric artery *(red arrowhead)* and vein *(blue arrowhead)*.

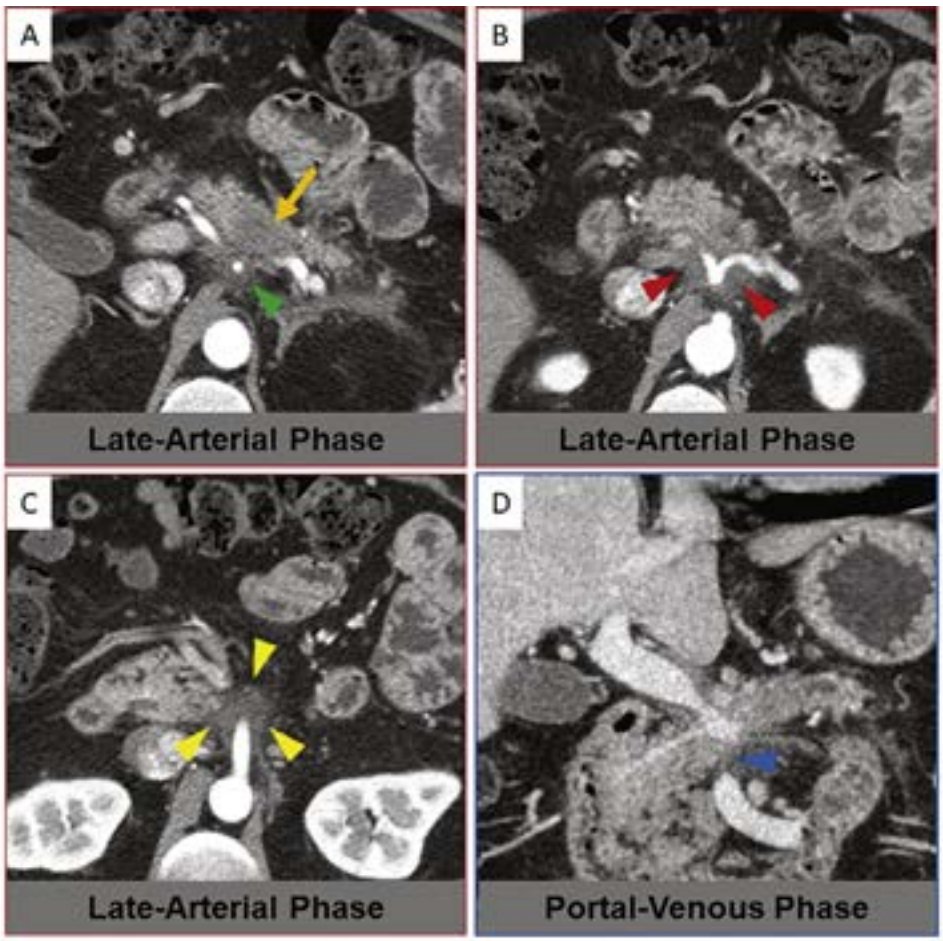


FIG. 3 Locally advanced pancreatic adenocarcinoma. Late-arterial phases **(A–C)** at several levels demonstrate a low-attenuation mass in the pancreatic body *(arrow)* with advanced locoregional extrapancreatic tumor extension and soft tissue encasing (greater than 180 degrees) the left-gastric artery *(green arrowhead)*, celiac bifurcation *(red arrowheads)*, and superior mesenteric artery *(yellow arrowheads)*. **(D)** Portal-venous phase coronal image demonstrates the mass causing severe narrowing of the cephalad superior mesenteric vein with a "gap" below the portal-splenic superior mesenteric vein venous confluence *(blue arrowhead)*.

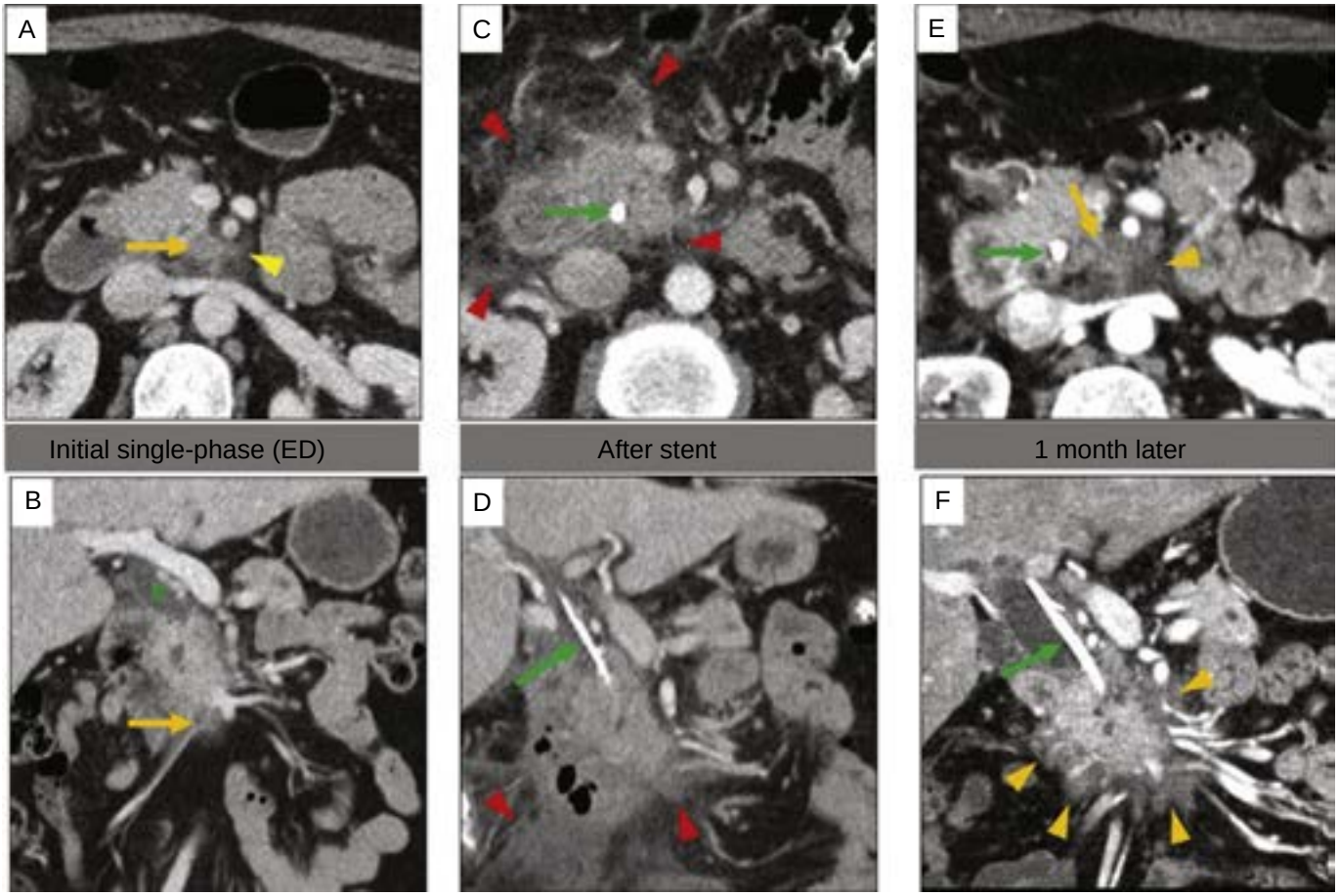


FIG. 4 Postintervention pancreatitis. Initial single-phase CT scans in the axial **(A)** and coronal **(B)** planes demonstrate a subtle uncinate process low-attenuation mass *(arrow)* with subtle extrapancreatic fat stranding (inflammation and/or tumor) possibly abutting the superior mesenteric artery *(arrowhead)*. Note the obstruction with dilation of the extrahepatic bile duct *(green B)*. Before obtaining a dual-phase CT, the patient was emergently taken to endoscopy to relieve biliary obstruction with a plastic stent *(green arrows)*. CT after biliary stenting in the axial **(C)** and coronal **(D)** planes demonstrated a subtle tumor in the uncinate process that is not well seen, and there is extensive peripancreatic, periduodenal, and transverse mesocolonic inflammation *(red arrowheads)* compatible with postprocedure pancreatitis. One month later, dual-phase CT was acquired to complete staging. Axial **(E)** and coronal **(F)** images demonstrate that the subtle uncinate process mass can be visible again, and there is now extensive peripancreatic soft-tissue entrapping/encasing several superior mesenteric artery and vein branches *(yellow arrowheads)*. The soft tissue is likely postpancreatitis inflammation; however, these findings are indeterminate by CT and confound accurate staging.

Endoscopic Procedures

Following CT imaging, the next procedure should be an endoscopic ultrasound (EUS) examination with fine-needle aspiration (FNA) or fine-needle biopsy for tissue diagnosis. EUS is preferred over percutaneous CT-guided biopsy, which has been associated with up to a 16% rate of peritoneal carcinomatosis, presumably related to dissemination of malignant cells along the biopsy tract. For tissue diagnosis, rapid on-site cytopathologic evaluation increases the diagnostic success of EUS/FNA biopsies. Rapid on-site evaluation allows for repeated endoscopic sampling until an adequate cytologic specimen can be obtained and facilitates the simultaneous placement of a decompressive metal stent in patients with obstructive jaundice. Thus, rapid on-site cytopathologic evaluation allows for a "one-stop shop" approach, such that a diagnosis can be made and durable biliary drainage can be achieved during one anesthetic procedure. In general, uncovered metal endobiliary stents are preferred over plastic stents for higher patency rates (104 days vs. 83 days) and lower rates of complications (12% vs. 35%). Covered metal stents have higher rates of stent migration and higher rates of stent-related cholecystitis because they can cover and occlude the cystic duct orifice.

Laboratory Studies

Standard laboratory testing for a periampullary tumor should include complete blood count, comprehensive metabolic panel, albumin, glycosylated hemoglobin, and tumor markers carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA). Patients with PDAC or cholangiocarcinoma may have elevations in CA 19-9 levels, while CEA may be preferentially elevated in duodenal and ampullary cancers. Approximately 75% of patients with PDAC will have an elevated CA 19-9 at the time of diagnosis. CA 19-9 is a sialylated Lewis blood antigen and a quantitative biomarker for patients with PDAC. It can be falsely elevated in the setting of hyperbilirubinemia and should be considered evaluable only when the total bilirubin is less than 2 mg/dL. Trends in CA 19-9 levels have been correlated with treatment response and are considered an important clinical adjunct to radiographic response. Among patients who are CA 19-9 nonproducers, 25% may have an elevated CEA, and changes in CEA have been similarly observed to correlate with treatment response and prognosis. It is important to remember that CEA levels are significantly higher in smokers compared with nonsmokers, and appropriate thresholds should be used accordingly.

MULTIDISCIPLINARY MANAGEMENT

Rationale for Neoadjuvant Therapy

The rationale for neoadjuvant therapy is based on the observation that the vast majority of patients with localized PDAC who undergo surgical resection, even with the addition of (postoperative) adjuvant therapy, have a limited median survival benefit of only 20 to 24 months. Despite optimization of surgical technique and perioperative management, most patients succumb to metastatic disease after curative-intent surgery. Therefore, there is a universal agreement that all patients with PDAC should receive chemotherapy, independent of stage of disease. Adjuvant therapy has been the standard of care for many decades based on the results of several large randomized controlled trials. Although a recent randomized controlled trial comparing adjuvant gemcitabine versus 5-fluorouracil/irinotecan/oxaliplatin (PRODIGE-24) demonstrated historic improvements in median overall survival (54 months) with the triple therapy arm, it is important to consider that adjuvant clinical trials have an inherent selection bias in their design, as patients who are enrolled in adjuvant trials must have recovered from a pancreatectomy with minimal complication, have preserved performance status, and have no evidence of disease progression. Unfortunately, retrospective data from large cancer registries have demonstrated that the delivery of adjuvant therapy is unpredictable, with up to 50% of patients never receiving adjuvant therapy. This finding was recapitulated in the results of another recent randomized controlled trial that compared perioperative (neoadjuvant and adjuvant) therapy to surgery followed by adjuvant therapy (PREOPANC trial) in patients with localized PDAC. Only 65 of the 128 patients (51%) in the surgery- first arm received any adjuvant therapy. Even within this subset of patients, not all patients were able to complete the full course of adjuvant chemotherapy. In addition, in the adjuvant setting, the primary tumor has been removed, so the ability to assess treatment response to the chemotherapy is limited. Because response to chemotherapeutic regimens is not uniform across all patients, some patients may be subjected to ineffective systemic therapy and incur unnecessary toxicity.

In contrast with a surgery-first approach, neoadjuvant therapy has several advantages: (1) early delivery of systemic therapy for presumed micrometastases, (2) ability to identify aggressive tumor biology that may be resistant to available systemic therapies, (3) assessment of treatment response in the primary tumor, and (4) improved patient selection for surgery by stage of disease and response to therapy. For patients with an elevated CA 19-9 level at the time of diagnosis, changes in CA 19-9 levels have been demonstrated to correspond to treatment response and be prognostic of overall survival. Among patients who receive neoadjuvant therapy, approximately one-third of patients will normalize their CA 19-9 levels before surgery, one-third of patients will normalize their CA 19-9 levels after surgery, and one-third of patients will never normalize their CA 19-9 levels, even after neoadjuvant therapy and surgery. Among patients with operable PDACs, approximately 70% of patients who initiate neoadjuvant therapy will be able to complete neoadjuvant therapy and surgical resection. Of the 30% of patients who do not undergo resection, approximately 92% of those patients have metastatic disease progression during neoadjuvant therapy, 3% may have local disease progression that precludes surgical resection, and 5% have a poor performance status that may prohibit surgical resection. The first randomized trial to compare a neoadjuvant therapy (given as preoperative and postoperative therapy) to up-front surgical resection and adjuvant therapy was the PREOPANC trial. The long-term results of the PREOPANC trial were recently published and demonstrated improved overall survival for patients with resectable and borderline resectable PDAC who received perioperative therapy compared with a surgery-first approach (HR: 0.73; $P = 0.025$). Several institutions have also reported their outcomes with neoadjuvant therapy. Among patients who are able to complete neoadjuvant therapy and surgery, the median overall survival exceeds 40 months at most centers. An ongoing clinical trial (Alliance A021806) will further evaluate neoadjuvant versus surgery-first treatment approaches using contemporary chemotherapeutic regimens. Many centers are already adopting neoadjuvant therapy for patients with localized PDAC. Currently, all consensus guidelines recommend neoadjuvant therapy for borderline resectable disease, and an increasing number of centers advocate neoadjuvant therapy for resectable disease as well. Likely, future investigations will move away from comparing neoadjuvant versus adjuvant approaches and focus on defining the optimal neoadjuvant therapy for patients, including the best chemotherapeutic regimen, duration of treatment, and whether to include chemoradiation. At the Medical College of Wisconsin, patients with PDAC are currently being treated with a total neoadjuvant therapy approach. This consists of 4 months of neoadjuvant chemotherapy (with interval restaging at 2 months to assess for treatment response and change in chemotherapy in the absence of response) followed by chemoradiation and surgery.

The data to support neoadjuvant therapy for distal cholangiocarcinoma, ampullary adenocarcinoma, and duodenal adenocarcinoma are more limited than in PDAC. Nevertheless, the challenges of delivering adjuvant therapy following a pancreaticoduodenectomy are independent of histology; therefore, some centers favor neoadjuvant therapy for large tumors or in the presence of nodal metastases. Non-PDAC periampullary tumors often have a normal pancreas with soft parenchyma and nondilated main pancreatic duct. In this setting, the use of neoadjuvant chemoradiation may be advantageous and has been associated with decreased rates of postoperative pancreatic fistulas, likely as a result of radiation-induced gland fibrosis. There have been limited randomized controlled trials examining the benefit of adjuvant therapy among patients with resected periampullary tumors. In cholangiocarcinoma, two trials that included patients with resected periampullary tumors (ESPAC-3) or cholangiocarcinomas (PRODIGE-12) did not demonstrate an improvement in overall survival with adjuvant therapy. The BILCAP trial was a randomized controlled trial that compared adjuvant chemotherapy versus placebo in patients with resected cholangiocarcinoma (including intrahepatic, hilar, extrahepatic) and gallbladder cancers. The trial demonstrated an improvement in median overall survival with adjuvant capecitabine (HR 0.75, 95% CI: 0.58–0.97). For ampullary adenocarcinomas, a subgroup analysis from the ESPAC-3 trial suggests that adjuvant chemotherapy (either gemcitabine or 5-fluoruracil) was associated with improved survival. For duodenal adenocarcinomas, the ongoing BALLAD trial is currently enrolling and comparing the benefit of adjuvant chemotherapy (5-fluorouracil and oxaliplatin) to observation. Despite the limited data, patients with non-PDAC periampullary tumors with stage T2+ primary tumor or node-positive disease are at high risk of recurrence, and multimodality therapy is often considered for these patients.

SURGICAL MANAGEMENT

Preoperative Preparation

Preoperative evaluation should include a detailed history and physical examination. A pancreatic-protocol CT examination should be repeated within 1 month of the planned surgery. Reassessment of the tumor-vessel relationship is essential and should include a careful evaluation of the tumor's relationship to the SMA, SMV-PV, celiac axis, and hepatic artery. It is important to evaluate for the presence of aberrant arterial anatomy (replaced right or left hepatic artery) or the presence of a median arcuate ligament. Assessment of the venous anatomy should also note the insertion of the inferior mesenteric vein (into the splenic vein or SMV) and the location of the first jejunal branch (either anterior or posterior to the SMA). Depending on the extent of the tumor-vessel involvement, the need for autologous

conduits, such as the saphenous vein or internal jugular vein, can been anticipated based on preoperative imaging. Often it is helpful to reference the CT at the time of diagnosis to evaluate for the presence of venous narrowing or contour irregularity (bird's beak or teardrop deformity). If present, even after a robust radiographic response to neoadjuvant therapy, vascular resection and reconstruction may be necessary.

Pancreaticoduodenectomy

Pancreaticoduodenectomy is the most common operation for tumors of the periampullary region. The procedure involves removal of the pancreatic head, duodenum, gallbladder, and bile duct with or without removal of the gastric antrum. Before an extended abdominal incision, we recommend that a diagnostic laparoscopy be performed as 10% of patients will have small-volume metastatic disease that is not detected on preoperative imaging. After careful inspection of the liver and all visceral and parietal surfaces, we generally utilize an upper midline incision. The round ligament is carefully taken down from the abdominal wall and preserved as a pedicled flap on entering the abdomen and as a physical barrier to cover the gastroduodenal artery (GDA) stump at the end of the case. The subsequent surgical resection of the head of the pancreas can be broken down into the following six steps.

1. The purpose of step 1 is to define the infrapancreatic SMV. The greater omentum is elevated from the transverse colon, and the hepatic flexure of the colon is mobilized to the level of the duodenum. The lesser sac is entered and the visceral peritoneum along the inferior border of the pancreas is incised medially to laterally to expose the infrapancreatic SMV and junction of the middle colic vein and the SMV. The middle colic vein may enter directly into the anterior surface of the infrapancreatic SMV or arise as a common trunk with the gastroepiploic vein (gastrocolic trunk). If the middle colic vein and gastroepiploic vein share a common trunk, the common trunk can be preserved (and the gastroepiploic vein divided) or the entire trunk divided. When there is extensive inflammatory change or scarring at the root of mesentery, it may not be possible to identify the infrapancreatic SMV early in the surgery. In such cases, the SMV will be exposed during step 6 after the pancreatic neck is divided in a caudal direction from the level of the portal vein. Occasionally, when there is a large tumor in the uncinate process, it may be necessary to divide the middle colic vein and resect a portion of transverse colon mesentery en bloc with the pancreatic head. For tumors that additionally extend inferiorly and posteriorly to involve the third or fourth portions of the duodenum, a Cattall-Braasch maneuver may be necessary to allow adequate visualization of the root of mesentery. When completed, this maneuver allows cephalad retraction of the right colon and small bowel to expose the third and fourth portions of the duodenum.
2. The purpose of step 2 is to mobilize the duodenum and head of the pancreas. A Kocher maneuver is begun at the transverse portion (third portion) of the duodenum by identifying the inferior vena cava. The duodenum and pancreatic head are mobilized medially to the level of the left renal vein. It is particularly helpful to divide the leaf of peritoneum that is posterior to the mesenteric vessels. With the head of pancreas rotated medially, this peritoneum is located at the most posterior aspect (medial to the head of the pancreas). Releasing the tissue at this level from the third portion of the duodenum to the level of the foramen of Winslow greatly facilitates the subsequent dissection of the SMA.
3. Step 3 involves the portal dissection and defining the superior border of the pancreatic head. To begin, the common hepatic artery is identified, and the hepatic artery lymph node is removed. This will facilitate visualization of the common hepatic artery as it gives off the GDA and proper hepatic artery, and it often exposes the medial border of the portal vein. A diminutive right gastric artery may be encountered and should be ligated. The origin of the GDA can be dissected, but before ligation it is often helpful to first expose the lateral aspect of the porta hepatis, especially if variant arterial anatomy is suspected. If the foramen of Winslow was initially obliterated as a result of adhesions, it should be reestablished to palpate the porta hepatis and appreciate the pulsation of an anomalous hepatic artery. If a cholecystectomy has not previously been performed, the gallbladder is taken down in a retrograde fashion, and the common hepatic duct is transected at the level of the cystic duct (Fig. 5). In cases in which an anomalous location of the right hepatic artery has been identified on preoperative CT, it is important to isolate the aberrant arterial anatomy before dividing the common hepatic duct as the artery is often in close proximity of the duct and can be injured. A replaced or an accessory right hepatic artery arising from the proximal SMA usually courses posterolateral to the PV. Following transection of the bile duct, biliary fluid cultures may be sent, and any indwelling endobiliary stents are removed. Intraoperative bile cultures may be used to guide therapeutic antibiotic treatment postoperatively, and a bulldog clamp can be placed on the transected hepatic duct to limit spillage of contaminated bile. The bile duct margin can be sent for frozen section at this time. Division of the common hepatic duct allows for exposure of the anterior surface of the portal vein and facilitates the dissection and mobilization of the lateral aspect of the GDA and proper hepatic artery. Overly aggressive dissection at the GDA origin can result in intimal dissection of the hepatic artery. Careful sharp dissection is preferred in this area. Division of the GDA allows mobilization of the proper hepatic artery off the underlying PV and exposes the superior border of the pancreas (Fig. 6). The superior pancreaticoduodenal vein (Vein of



FIG. 5 Step 3: Top down cholecystectomy to identify the junction of the cystic duct to the common hepatic duct. Division of the common hepatic duct above the level of the cystic duct. *(Illustration by Corinne Sandone. From Cameron J, Sandone C. Atlas of Gastrointestinal Surgery, vol 1, ed 2. Shelton, CT: People's Medical Publishing; 2007.)*

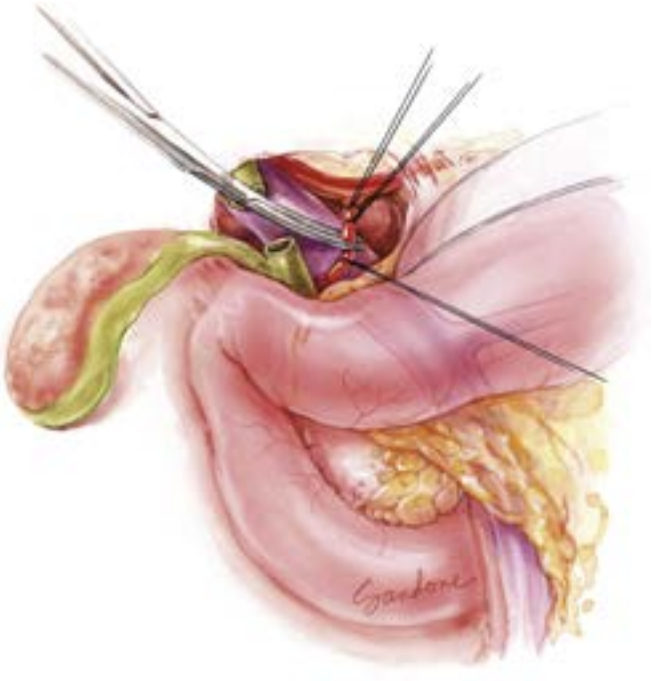


FIG. 6 Step 4: Portal dissection involves identification of the common hepatic artery (CHA) and the origin of the gastroduodenal artery (GDA). Division of the common hepatic duct (CHD) facilitates the exposure of the origin of the GDA for ligation. *(Illustration by Corinne Sandone. From Cameron J, Sandone C. Atlas of Gastrointestinal Surgery, vol 1, ed 2. Shelton, CT: People's Medical Publishing; 2007.)*

Belcher) is a constant venous tributary of the PV, which drains the cephalad aspect of the pancreatic head and is located at the superolateral aspect of the PV. Bleeding caused by traction injury to this venous tributary may be difficult to control at this time in the surgery.

4. Step 4 involves transection of either the duodenum or stomach. Pylorus preservation may be considered in patients with small periampullary neoplasms, but it should not be performed in patients with bulky pancreatic head tumors or those with duodenal tumors involving the first or second portions of the duodenum. To ensure adequate blood supply to the duodenojejunostomy, the duodenum is generally divided approximately 2 cm distal to the pylorus. In the setting of preoperative radiation, removal of the antrum is recommended as this area is usually within the radiation field. The stomach is transected with a gastrointestinal stapler at the level of the third or fourth transverse vein on the lesser curvature and at the confluence of the gastroepiploic veins on the greater curvature, completing a standard antrectomy. When opening pars flacida, one should specifically look for and preserve an accessory or replaced left hepatic artery arising from the left gastric artery.
5. Step 5 involves dividing the jejunum and mobilizing the ligament of Treitz. The loose attachments of the ligament of Treitz are taken down carefully to avoid injury to the inferior mesenteric vein. The jejunum is then transected with a gastrointestinal stapler approximately 10 cm distal to the ligament of Treitz, and the mesentery is divided to the level of the fourth and third portions of the duodenum (Fig. 7). The devascularized segment of duodenum and jejunum is then reflected under the mesenteric vessels to the right side of the abdomen.
6. Step 6 is the final step of the resection and involves removal of the head of the pancreas from the SMV/PV and SMA. Hemostatic sutures can be placed along the superior and inferior borders of

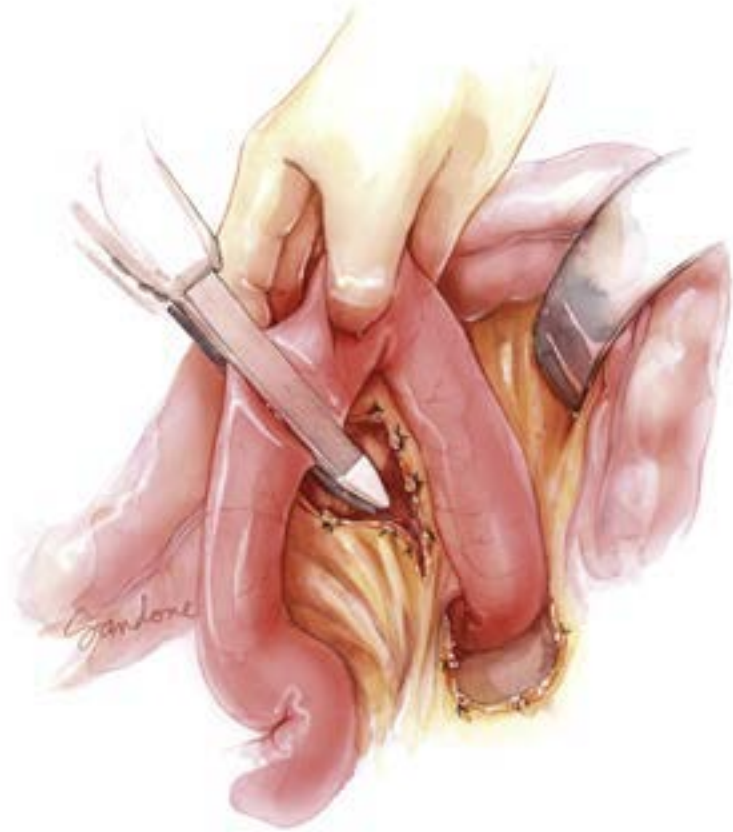


FIG. 7 Step 5: Transection of the jejunum followed by division of the mesentery. The duodenum and jejunum are then reflected under the mesenteric vessels to the right abdomen. *(Illustration by Corinne Sandone. From Cameron J, Sandone C. Atlas of Gastrointestinal Surgery, vol 1, ed 2. Shelton, CT: People's Medical Publishing; 2007.)*



FIG. 8 Step 6: Division of the neck of the pancreas and separation of the head of the pancreas from the superior mesenteric vein (SMV) and superior mesenteric artery (SMA). *(Illustration by Corinne Sandone. From Cameron J, Sandone C. Atlas of Gastrointestinal Surgery, vol 1, ed 2. Shelton, CT: People's Medical Publishing; 2007.)*

the pancreas. The pancreas is transected with electrocautery at the level of the PV (Fig. 8). The pancreatic margin can be sent at this time. Vessel loops can now be passed around the distal SMV, PV, and splenic vein for vascular control. With mobilization of the SMV-PV confluence, retraction of the vein medially facilitates the identification of the SMA posteriorly. Direct exposure of the SMA avoids iatrogenic injury and ensures direct ligation of the inferior pancreaticoduodenal arteries. Failure to fully mobilize the SMV-PV confluence risks injury to the SMA and often will result in a positive SMA resection margin. The specimen is separated from the SMV by ligation and division of the small venous tributaries to the uncinate process and pancreatic head. The first jejunal branch is usually encountered at the caudal aspect of the pancreatic head. The jejunal branch can usually be preserved by ligating small tributaries to the uncinate process. Injury to the distal SMV at this level or a tangential laceration in its jejunal branch (as it courses posterior to the SMA) is difficult to control and probably represents the most frequent cause of iatrogenic SMA injury as one attempts to suture a venous injury before full exposure of the SMA. Once the uncinate process is separated from the distal SMV, medial retraction of the SMV-PV confluence allows one to expose the SMA. Once the first jejunal branch is released, the inferior pancreaticoduodenal artery is usually encountered immediately cranially. The specimen is then separated from the right lateral wall of the SMA and sent to pathology.

Vascular Resection

Resection of the SMV and/or PV may need to be performed if tumor extension precludes safe dissection of the SMV and PV off the pancreatic head and uncinate process. In general, this can be predicted based on preoperative imaging as deformity of the SMV/PV caused by tumor involvement usually portends the need for vascular resection. Importantly, preoperative anticipation for the need for vascular resection facilitates the intraoperative management as a planned event rather than an emergent response to a vascular injury. When vascular resection is anticipated, it is helpful to have included the upper thigh or neck into the sterile field to facilitate access to the saphenous vein or internal jugular vein. Historically, division of the splenic vein was considered standard practice as this facilitates exposure of the SMA medial to the SMV and allows for greater mobility of the SMV and PV for reconstruction. When possible, the splenic vein–PV confluence should be preserved as ligation of the splenic vein can result in future sinistral hypertension, especially if the left coronary vein is not preserved. A generous 2- to 3-cm segment of SMV-PV confluence can be resected without the need for interposition grafting if the splenic vein is divided. When performing a venous resection, inflow occlusion of the SMA with systemic heparinization is helpful to minimize small bowel ischemia and edema. Marking the anterior surface of the SMV and PV before venous resection assists in maintaining the orientation of the anastomosis. The proximal and distal targets are circumferentially dissected, and vascular clamps are placed 2 to 3 cm proximal (on the PV) and distal (on the SMV) to the involved venous segment; the vein is then transected, allowing tumor removal. If the resection involves more than 2 to 3 cm of vein and cannot be reconstructed with a tension-free anastomosis, an autologous vein graft (such as internal jugular vein) can be used as an interposition graft. Autologous conduits are preferred over synthetic grafts because of the potential for infection and superior long-term patency rates. Currently, the role of major arterial resection for PDAC remains controversial and should be performed only in highly selected patients who have completed an extensive course of neoadjuvant therapy. Given the surgical morbidity and mortality with such procedures, arterial resections should be limited to highly selected cases and be performed at centers with the institutional volume and experience to support these patients.

Reconstruction

Reconstruction usually starts with the pancreaticojejunostomy followed by the hepaticojejunostomy and gastrojejunostomy or duodenojejunostomy. For the pancreaticojejunostomy, mobilization of approximately 2 cm of the pancreatic remnant facilitates exposure and placement of sutures. We prefer to pass the jejunal limb through the transverse mesocolon to the left of the middle colic vessels. If the pancreatic gland is soft, a two-layer, end-to-side, duct-to-mucosa pancreaticojejunostomy is performed. If the gland is firm and the pancreatic duct is dilated, a single layer duct-to-mucosa anastomosis can be performed. The anastomosis between the pancreatic duct and the small bowel mucosa is completed with interrupted 4-0 or 5-0 monofilament sutures. When the pancreatic parenchyma is soft, pledgets may be used to buttress the gland and prevent the sutures from tearing through the pancreatic tissue.

A single-layer hepaticojejunostomy is created approximately 10 cm distal the pancreaticojejunostomy using interrupted 4-0 or 5-0 absorbable monofilament sutures. An interrupted technique is utilized to avoid purse-stringing of the anastomosis. It is important to align the jejunum with the bile duct to avoid tension on the pancreatic and biliary anastomoses. Finally, an antecolic, end-to-side gastrojejunostomy is constructed in two layers at least 50 cm from the hepaticojejunostomy to minimize bile reflux cholangitis. Starting from the greater curvature, a portion of the gastric staple line is removed. The jejunal limb should be aligned so the efferent limb is adjacent to the greater curvature of the stomach, and the gastrojejunostomy is usually constructed with an interrupted outer layer of sutures and a running inner layer. The use of drains remains an active area of controversy in the field of pancreatic surgery, and many surgeons still drain both the hepaticojejunostomy and the pancreaticojejunostomy. Finally, the previously mobilized round ligament is placed over the GDA stump to minimize the risk for pseudoaneurysm formation at the site of the stump in the event of a pancreatic anastomotic leak.

Minimally Invasive Approaches

Pancreaticoduodenectomy is increasingly being performed with laparoscopic or more commonly robotic approaches. A minimally invasive approach has been associated with decreased pain, fewer wound complications, and shorter length of stay. There is a significant learning curve for minimally invasive pancreaticoduodenectomy requiring approximately 80 cases for proficiency, although in the setting of a formal training program with mentorship and formal skills curriculum, this learning curve can be greatly reduced. At this time, execution of a minimally invasive pancreaticoduodenectomy should be performed in carefully selected patients with favorable anatomy at an institution with surgeons experienced in this technique.

POSTOPERATIVE CARE

Following surgery, a standardized approach to postoperative care can improve surgical outcomes and reduce hospital stay. A variety of programs have implemented enhanced recovery after surgery protocols that emphasize avoidance of hyperglycemia, maintaining a near-zero fluid balance, early drain removal, early oral intake, minimization of narcotics, and mobilization. In general, in the absence of significant gastroparesis or preoperative gastric outlet obstruction, nasogastric tubes can be removed on postoperative day 1 with introduction of limited clear liquids. The diet can be advanced over the next 1 to 2 days in the absence of nausea or vomiting. Optimal perioperative pain management may vary from center to center depending on the expertise and availability of the anesthesia pain team. Although epidurals can provide excellent pain control, associated hypotension may require additional fluid resuscitation. Alternatively, many centers utilize patient-controlled analgesia pumps in combination with transversus abdominis plane blocks. Early mobilization is encouraged in preventing deep venous thrombosis and reducing postoperative ileus. Early postoperative drain removal has been advocated in patients with a low or intermediate risk of pancreatic fistula at postoperative days 1, 3, or 5 based on drain amylase cut points of 300 IU/L, 150 IU/L, and 50 IU/L, respectively. If a drain is in place after diet advancement, the character of drain fluid should be monitored for changes suggestive of either a pancreatic fistula or a chyle leak. For most patients, surgical drains can be removed before discharge.

Postoperative Complications

In general, the most common complications following pancreaticoduodenectomy are pancreatic fistula (10%–30%) and delayed gastric emptying (10%–15%). Postpancreatectomy hemorrhage occurs less commonly (5%) but is the most dreaded complication after pancreatectomy given its associated high mortality. Scoring systems have been developed by the International Study Group of Pancreatic Surgery (ISGPS) to define the severity of each of these complications (Table 2).

Pancreatic Fistula

Pancreatic fistula rates are related to the gland texture, main pancreatic duct diameter, intraoperative blood loss, and the types of periampullary cancers, with patients with non-PDAC histologies being at the highest risk for the development of a fistula. Based on the aforementioned features, a Fistula Risk Score Calculator was

TABLE 2 International Study Group of Pancreatic Surgery Consensus Definitions on Postoperative Complications

	GRADE		
Complication	**A**	**B**	**C**
DELAYED GASTRIC EMPTYING*			
Nasogastric tube requirement, reinsertion on postoperative day (POD)	4–7 days, >POD 3	8–14 days, >POD 7	>14 days, >POD 14
Days of oral intolerance	7	14	21
Vomiting and gastric distention	+/–	+	+
Use of prokinetics	+/–	+	+
POSTOPERATIVE PANCREATIC FISTULA†	Biochemical leak	Persistent drainage >3 weeks, clinically relevant change in management, percutaneous/endoscopic drainage, angiographic procedures, infection without organ failure	Reoperation, organ failure, death
POSTOPERATIVE PANCREATIC HEMORRHAGE‡			
Onset (early (24 hours, late >24 hours)/severity	Early/mild	Early/severe or late/mild	Late/severe
Location	Intraluminal/extraluminal	Intraluminal/extraluminal	Intraluminal/extraluminal
Clinical condition	Good	Good to moderately impaired	Severely impaired, life-threatening

*Functional gastroparesis after surgery without mechanical obstruction as determined by upper gastrointestinal contrast series or endoscopic evaluation.
†Amylase >3 times upper limit institutional normal serum amylase value.
‡All postoperative episodes of hemorrhage after pancreatic resection including gastrointestinal or intraabdominal hemorrhage, and early or delayed postoperative bleeding.

developed to predict postoperative risk of pancreatic fistula and to guide the management of perianastomotic drains. Pancreatic fistulas are generally detected by the presence of amylase-rich fluid from the surgical drains or the presence of a peripancreatic fluid collection on CT imaging. Pancreatic fistula can be associated with signs of infection (leukocytosis, fever) and can cause delayed gastric emptying or postpancreatectomy hemorrhage. If a deep space infection is present, it is important to obtain adequate drainage not only for source control, but also to prevent the fluid from necessitating out the surgical site, leading to fascial dehiscence. ISGPS grade B fistulas can usually be managed with drainage, antibiotics, and the use of somatostatin analogues. On rare occasions, patients with severe disruption of the pancreaticojejunostomy may require surgical reexploration for definitive management.

Delayed Gastric Emptying

Delayed gastric emptying remains a troublesome complication after pancreaticoduodenectomy, the pathophysiology of which is not fully understood and is likely multifactorial. Differences in surgical technique have been analyzed. The incidence of delayed gastric emptying appears to be lower with antecolic as compared with retrocolic gastrojejunostomy. Rates of delayed gastric emptying do not appear to be different when comparing standard pancreaticoduodenectomy to pylorus-preserving pancreaticoduodenectomy. However, it is possible that surgical technique may affect delayed gastric emptying. A recent review of robotic pancreaticoduodenectomies identified an acute angle (<30 degrees) between the stomach and the efferent jejunal limb as a risk factor for delayed gastric emptying. A CT examination is often helpful to rule out a subclinical pancreatic fistula or intraabdominal abscess as a cause of delayed gastric emptying. An upper gastrointestinal series may be helpful to assess gastric emptying. With significant stasis, nasogastric tube decompression and initiation of prokinetics (erythromycin or metoclopramide) are the mainstays of therapy. Upper endoscopy can be considered to rule out an associated marginal ulcer. In rare cases, refractory delayed gastric emptying may require a percutaneous gastrostomy tube and parental nutrition, but most cases are self-limiting and will resolve with time and supportive care.

Postpancreatectomy Hemorrhage

Postpancreatectomy hemorrhage can be either early (within 24 hours of surgery) or late (usually postoperative days 7–14). Early postpancreatectomy hemorrhage is caused by technical failures related to inadequate hemostasis and generally requires reoperation. Late postpancreatectomy hemorrhage is most commonly related to either bleeding from a pseudoaneurysm (frequently associated with a pancreatic fistula) or ulceration at the site of the gastrojejunostomy. Patients who suffer from postpancreatectomy hemorrhage may present with a herald bleed with blood in the surgical drains or as a gastrointestinal bleed. Often the hemorrhage is acute and catastrophic, requiring rapid recognition, controlled resuscitation, and mobilization of the interventional radiology team. Bleeding can be controlled with endovascular embolization of the pseudoaneurysm or stenting across the involved artery. When possible, if the bleeding is related to a GDA pseudoaneurysm and coil embolization of the aneurysm sac is not possible, stenting of the common hepatic artery is preferred over embolization. Mortality rates can be as high as 10% to 16% as postembolization patients may have additional complications such as intraabdominal abscess, hepatic abscess, and or hepatic insufficiency.

SUMMARY

Although periampullary tumors represent a heterogenous collection of unique cancers, they share common challenges in terms of diagnosis and staging. Increasingly, neoadjuvant therapy is recommended for patients with PDAC and may play an important role in the management of non-PDAC tumors as well. Increasingly, the complexity of delivering multidisciplinary care will require close coordination of care among surgeons, medical oncologists, and radiation oncologists, with the goal of optimizing systemic and local therapies. In the setting of neoadjuvant therapy, treatment response may help to further guide surgical selection. Pancreaticoduodenectomy remains the surgical treatment for these cancers, and careful preoperative planning is needed to minimize intraoperative and postoperative complications.

Suggested Readings

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Management of Complications after the Whipple Procedure

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Pancreatic surgery is widely considered one of the toughest, riskiest, and most discouraging surgical subspecialties for both trainees and experienced surgeons, a notion that is condensed within the classical tenet, "Eat when you can, sleep when you can, and don't mess with the pancreas." In fact, not only is advanced technical proficiency required but consummate skills and knowledge are also necessary to prevent, mitigate, diagnose, and treat postoperative complications. Over the decades, postoperative mortality has significantly declined to 2% to 5% for pancreatoduodenectomy (PD). This achievement is largely attributable to the regionalization of patients to specialized, high-volume institutions, where dedicated, highly trained, and experienced surgeons are present, along with multidisciplinary teams being constantly available—sustaining a phenomenon known as the *volume-outcome relationship*. Moreover, a shift toward nonoperative, "step-up" approaches has become the standard of care for contemporary postpancreatectomy complication management, realizing favorable effects in terms of performance outcomes and resource utilization.

However, despite the reduction in mortality, complication rates following pancreatoduodenectomy remain high (up to 40%–60%), posing safety improvement as a primary goal for the contemporary pancreatic surgeon. Additional parameters beyond crude complication rates must be considered to define the real burden of the Whipple procedure. Starting with semiquantitative measures such as the Modified Accordion Severity Weight classification (introduced to standardize the definition of complication *severity* according to the interventions employed to treat them), novel metrics have been derived to provide useful parameters for both procedure- and institution-outcome comparisons (Table 1). For instance, after attributing each complication a "severity weight" from 0 (no treatment required) to 1.0 (death attributable to that complication), the Postoperative Morbidity Index expresses the total complication *burden* that is quantitative in nature. It is calculated by dividing the sum of the highest-grade complication weights for patients who experienced at least one complication by the total number of patients. With a spectrum of possible values ranging from 0 (no patient had any complication) to 1.0 (all patients died because of complications), the average PMI for PD performed at high-volume institutions is established as 0.18, thus indicating an overall low complication burden across the total population subjected to the procedure. However, the average burden in complication-bearing patients is established at 0.346, indicating that, on average, patients who suffer complications following PD have a *severe* complication as defined by the Accordion scale (i.e. Accordion ≥3). Similarly, the Average Complication Burden (ACB) is another performance metric calculated by dividing the sum of severity weights attributed to a particular complication (e.g., pancreatic fistula) by the number of patients who sustain it as the highest-grade complication, thus providing an index of severity for distinct complications. A similar approach uses the Comprehensive Complication Index (CCI). Given the high incidence of complications overall, these metrics provide precise information regarding the *impact* of a given procedure by weighing the severity (i.e. invasiveness) of the approaches employed to eventually treat the complication. Therefore they should now be part of the pancreatic surgeon's vernacular (moving beyond simple description of overall complication frequency) and be employed by physicians and institutions for quantitative outcome comparisons and benchmarking.

Given the complexity and uniqueness of the Whipple procedure, which requires the creation of three unique anastomoses in addition to possible vascular or multivisceral resections, postoperative complications can be classified as either general or procedure-specific. Surgical site infections, pneumonia, urinary tract infections, thromboembolic events, and acute renal, cardiopulmonary, liver, and/or multisystem failure are considered among the former. Conversely, the International Study Group of Pancreatic Surgery (ISGPS) has established standardized definitions and grading systems for some events specifically associated with pancreatic resections, such as pancreatic fistula (CR-POPF), delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), chyle leak, and postpancreatectomy acute pancreatitis.

CLINICALLY RELEVANT POSTOPERATIVE PANCREATIC FISTULA

With an incidence around 15% according to contemporary standards, CR-POPF is responsible for substantial morbidity and resource utilization following pancreatoduodenectomy (mean ACB: 0.432). As it represents the single major contributor to mortality following such a procedure (36%), it is usually defined as its *Achilles heel.* Pancreatic fistula is defined as an abnormal communication between the pancreatic ductal system and another epithelial surface containing pancreas-derived, enzyme-rich fluid. In the case of PD, it derives from a complete or partial dehiscence of the pancreatico-enteric anastomosis, resulting in pancreatic and intestinal juice spilling into the abdominal cavity. Both patient-specific and operative factors have been identified to increase the likelihood of pancreatic fistula development. Among them, soft gland texture, diminutive duct diameter, disease pathology other than pancreatic cancer and pancreatitis, and elevated intraoperative blood loss are well-recognized risk factors, and the additive contribution of these four elements equates the calculation of the Fistula Risk Score (FRS; Table 2). This tool enables the surgeon to objectively quantify the risk of CR-POPF development at the time of anastomosis creation on a 0 to 10 scale, thus segregating into unique fistula risk zones and providing the opportunity to employ unique fistula mitigation approaches tailored to the patient risk. Significantly, the FRS has been employed to compare the effectiveness of several intraoperative approaches in reducing the incidence and burden of CR-POPF and surgeon/institution outcomes in a properly risk-adjusted fashion. Visceral obesity and not receiving preoperative chemoradiation, which are in turn associated with fatty, nonfibrotic pancreatic parenchyma, have also been proposed as independent risk factors, whereas the contributions of the gut microbiome and early postoperative pancreatitis to anastomotic healing impairment need further scrutiny.

According to the ISGPS nomenclature, a pancreatic fistula is ascertained whenever any measurable output of drain fluid

TABLE 1 Modified Accordion Classification System with Severity Weights

Grade	Definition	Description	Severity Weight
1	Mild	Treatment of complication requires only minor invasive bedside procedures (e.g., drainage of wound infections; insertion of intravenous lines, urinary catheters, and nasogastric tubes). Physiotherapy, antiemetics, antipyretics, diuretics, and electrolytes are also permitted.	0.11
2	Moderate	Pharmacologic treatment with drugs other than those allowed for minor complications are required, such as antibiotics. Blood transfusions and total parenteral nutrition are also included.	0.26
3	Severe A	No general anesthesia is required to treat the complication (e.g., endoscopic or interventional procedures, or reoperation without general anesthesia).	0.37
4	Severe B	General anesthesia is required to treat the complication, or single organ failure has developed.	0.60
5	Severe C	General anesthesia is required to treat the complication, and single organ failure has developed, or multisystemic organ failure has developed.	0.79
6	Death	Postoperative death.	1.00

TABLE 2 Fistula Risk Score for Prediction of Clinically Relevant Pancreatic Fistula After Pancreatoduodenectomy

Risk Factor	Parameter	Points
Gland Texture	Firm	0
	Soft	2
Disease Pathology	Pancreatic carcinoma/ pancreatitis	0
	Other	1
Pancreatic Duct Diameter (mm)	≥5	0
	4	1
	3	2
	2	3
	≤1	4
Estimated Blood Loss (mL)	≤400	0
	401–700	1
	701–1000	2
	≥1001	3

BOX 1 2016 International Study Group of Pancreatic Surgery Updated Criteria for Postoperative Pancreatic Fistula

Amylase >3 times upper limit institutional normal serum amylase value
↓
Biochemical leak
↓
Persistent drainage >3 weeks*
Clinically relevant change in management of postoperative pancreatic fistula
Percutaneous or endoscopic drainage*
Angiographic procedures for bleeding*
Signs of infection without organ failure*
↓
Grade B pancreatic fistula
↓
Reoperation*
Organ failure*
Death*
↓
Grade C pancreatic fistula

*Treatment/event postoperative pancreatic fistula related.
Modified from Bassi, C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery*. 2017;161:584–591.

containing an amylase level three times higher than the upper limit of normal serum amylase is detected on or after postoperative day 3. Therefore because the definition of POPF relies on drain fluid amylase measurement, a percutaneous drain (placed either intraoperatively or postoperatively) is required to collect fluid. Conversely, neither fluid appearance nor volume thresholds should be considered as diagnostic criteria. Notably, to be considered a pancreatic fistula, this must be *clinically relevant,* meaning that there is true, untoward impact on the patient for which specific interventions are employed by the surgeon to treat such a condition. To cement this notion, the 2016 updated ISGPS grading system renamed grade A POPFs (namely, cases in which an amylase-rich drain fluid is present with no meaningful deviation in the normal clinical course of the patient) as *biochemical leaks,* whereas only B and C grades constitute CR-POPFs, and should be therefore reported in outcome analyses (Box 1). Notably, CR-POPF is graded only retrospectively on the basis of the specific intervention enacted by the surgeon: such a revised classification enables the surgeon to express qualitatively the clinical severity of pancreatic fistulas, while also providing a standardized, common language for comparative studies.

Notably, there are no practical guidelines indicating the optimal diagnostic approach and treatment of pancreatic fistula, and consensus regarding implementation of the numerous management options available is often lacking—even among experts. Concurrent with high drain fluid amylase levels, the suspicion of POPF begins whenever a deviation in the normal clinical course of a patient appears, both early and later in the postoperative period. Pancreatic juice leaks typically feed intraabdominal collections, which can easily become infected, impinge upon surrounding organs, fistulize through the skin, and ultimately erode peripancreatic vessels. If an intraabdominal drain is in place, a "sinister" fluid effluent (defined as creamy, Coke-like, or pea soup–like) is usually detected. Contrast-enhanced CT can reveal a pancreaticoenteric anastomosis disruption with surrounding free fluid (with or without gas) as well as peripancreatic collections. Notably, peripancreatic vessels should be carefully examined for wall irregularities, thrombosis, active bleeding, or pseudo-aneurysm development.

In such circumstances, conservative, noninvasive management is always advocated as the first approach. Adequate nutritional support has been considered a key element of fistula management because patients are in a hypercatabolic state with electrolyte depletion being accentuated by high-output fistulae. Notably, as suggested by an ISGPS consensus statement, there appears to be no benefit from avoiding oral intake for those who can tolerate it. In fact, recent randomized controlled trials indicate equivalent fistula closure rates with oral feeding when compared with artificial nutrition, with no significant increase in fluid output. A standard diet, rather than low-fat meals, is now allowed by most experts in such circumstances. However, when oral intake is not feasible, enteral nutrition through either a nasojejunal tube or a feeding jejunostomy should be preferred over parenteral nutrition to prevent enteric bacterial overgrowth and infectious complications associated with long-term fasting. Conversely, there is no concrete evidence supporting the efficacy of somatostatin-analogue administration in reducing fistula output and promoting fistula closure. Therefore such drugs should not be employed as standard treatment. Finally, there is no standardization of drain management in CR-POPF patients. With the purpose of intraabdominal drainage being to evacuate infected or amylase-rich fluids, drains can be safely removed as soon as fluid volume falls below 50 mL per day. The characteristics are serosanguinous with no purulent, biliary, or enteric components, and the amylase value has relatively normalized. However, even in such cases, late fistulas presenting after drain removal or hospital discharge are possible and should not be dismissed.

Fever, abdominal tenderness and pain, impaired bowel function, leukocytosis, and elevated C-reactive protein are usually present in the case of infected collections associated with POPF. CT scans often show gas bubbles within peripancreatic collections, which indicate internal bacterial growth or communication with the GI tract. In such circumstances, rapid deterioration toward sepsis and severe hemorrhage should be foreseen. Therefore most experienced

pancreatic surgeons prefer to transfer the patient to an intermediate or intensive care unit. A step-up approach comprising noninvasive treatment as the first tactic is now unanimously recommended, leaving surgical exploration as a final option in the case of failure of nonoperative interventions. Fluids should be adequately administered to prevent hypotension, dehydration, and electrolyte imbalances. If no preoperative or intraoperative cultures are available, broad-spectrum antibiotics should be chosen empirically considering institution-specific epidemiologic data. Gram-positive, enteric gram-negative, and anaerobe bacteria must be routinely covered, along with fungi when parenteral nutrition has been initiated. Subsequently, antibiotic treatment may be targeted according to drain effluent cultures, if necessary.

The goal of interventional procedures is to obtain source control by removing intraabdominal infection to minimize the septic insult to the patient and favor tissue healing. Percutaneous drain placement represents the intervention of choice when peripancreatic fluid collections are present, and its superiority compared with relaparotomy as initial treatment has been repeatedly demonstrated. Although ultrasound-guided catheter placement may be possible in the case of large, superficial collections, CT-guided procedures performed by dedicated interventional radiologists are preferred to prevent vascular and intestinal injuries. Endoscopic ultrasound-guided drainage procedures are also gaining consensus in such circumstances, in line with consolidated results obtained with the treatment of pancreatic pseudocysts. In this respect, it is noteworthy to emphasize the need for dedicated support systems with unrestricted availability of interventional radiology, endoscopy, infectious disease, and critical care services at institutions where pancreatic surgery is performed. Most patients are successfully managed with such a nonoperative approach. It should also be noted that in certain circumstances, fluid collections may not be either mature enough or safely accessible for drainage techniques. In such circumstances, antibiotic administration alone may suffice, but this is predicated on the degree of the patient's illness being relatively low in concert with active surveillance/anticipation for progressive clinical downturn paired with swift clinical reaction.

The major retrospective study conducted thus far comparing primary nonoperative and surgical management for CR-POPF indicates that up to 77% of patients treated with primary catheter drainage display CR-POPF resolution without the need for surgery, with a significant advantage compared with those undergoing primary surgery in terms of mortality (14% vs. 36%), multiorgan failure (16% vs. 39%), new-onset diabetes (12% vs. 44%), need for additional relaparotomies (22% vs. 45%), intensive care unit admission (37% vs. 87%), and length of stay (median: 29 vs. 55 days). However, relaparotomy must be considered in the case of no clinical improvement with maximal supporting care, collections inaccessible to percutaneous/endoscopic drainage, evidence of bowel perforation or necrosis, as well as suspicion of peripancreatic bleeding not suitable for endovascular treatment. No consensus regarding appropriate timing and optimal operative conduct is available because these constitute rare and daunting circumstances, even for seasoned pancreatic surgeons. Given the presence of inflammatory necrotic tissue and adhesions, the more time passes from index surgery, the more challenging and riskier the reintervention becomes. Among the multiple surgical options proposed, extensive debridement of peripancreatic necrotic tissue with wide drainage is a baseline mandate. Wide drainage only (a so-called *less is more approach*) and salvage completion pancreatectomy (albeit with a mortality rate as high as 50%) are both endorsed by expert surgeons in the case of evident anastomotic disruption, while any attempt to reconstruct the pancreatic anastomosis or convert to a different anastomosis (e.g., from pancreatico-jejunostomy to gastro-jejunostomy) is commonly discouraged. Other salvage approaches to consider are directly intubating and externalizing the duct, or a "bridge-stenting" to the disconnected jejunal loop, with the aim of diverting most of the pancreatic juice either externally or internally. However, it should be said that such procedures are almost anecdotal, even for long-time, experienced pancreatic surgeons, and this scenario is among the most challenging they may ever face in their career. Decision making is largely dependent on intraoperative findings and anatomy, the patient's hemodynamic stability, and the surgeon's skills. In fact, massive pancreatic necrosis consequent to pancreatic fistula is frequently accompanied by the failure of hepaticojejunostomy or gastrojejunostomy and diffuse peritonitis. Therefore whichever approach is employed, laparotomy with subsequent second-look operations are sometimes necessary, and mortality surpasses 50%.

POST-PANCREATECTOMY ACUTE PANCREATITIS (PPAP)

In 2021, the ISGPS consortium proposed definition criteria of post-pancreatectomy acute pancreatitis (PPAP) as a distinct complication from pancreatic fistula. From the biologic standpoint, PPAP describes an acute pancreatic inflammatory process occurring in the (early) postoperative period — probably as a consequence of manipulation, trauma, ischemia/hypoperfusion of the pancreatic parenchyma, or stasis of pancreatic juice associated to the surgical procedure. If on the one side such a notion is not novel (in fact, debate on its existence, definition, and impact has ignited a years'-long scientific *querelle*), qualifying PPAP as an independent, noteworthy event to be reported and addressed represents a cultural step forward in the pancreatic surgery community.

As per the ISGPS criteria, sustained hyperamylasemia (namely, an increase of serum amylase activity greater than institutional upper limit persisting in the first 48 hours postoperatively) is the backbone of PPAP diagnosis, along with cross-sectional imaging confirmation of intra- and peri-pancreatic edema, fluid collections, or necrosis. Notably, the threshold in serum amylase measurement chosen for PPAP diagnosis is lower than the one traditionally employed for diagnosis of acute pancreatitis (namely, 3 the upper normal limit), since even a moderate, but persistent, amylase increase has been correlated with overall and severe morbidity after surgery.

Furthermore, keeping with the logic employed for the grading of POPF, clinically relevant PPAP is defined by the need of either noninvasive (e.g., pharmacologic, endoscopic, or interventional radiologic treatment — grade B PPAP) or invasive approaches (e.g., reintervention, treatment of single or multiorgan failure for at least 48 hours — grade C POPF). As of this writing (summer 2022), the only study utilizing the ISGPS nomenclature reported a 21% rate of PPAP following pancreatoduodenectomy. Interestingly, in such series CR-POPF incidence was 4× as high among patients with PPAP (41 vs.12%), and half the patients who developed CR-POPF were also diagnosed with PPAP.

At first, as one of the strongest independent predictors of POPF, it might seem that PPAP simply precedes or accompanies fistula development by impairing the healing of the pancreatic anastomosis. However, debate is still ongoing on whether PPAP constitutes a precursor (namely, a proper causal event) or a phenomenon (namely, a biochemical marker) of ongoing pancreatic fistula. More likely, POPF and PPAP constitute elements of the same biologic process involving the dehiscence of pancreatico-enteric anastomosis. Interestingly, recent studies have also demonstrated the association between PPAP and abdominal and systemic complications in patients *without* CR-POPF, such as organ space infections, collections, hemorrhage, and sepsis, thus justifying the introduction of PPAP as an independent clinical entity.

Given its recent appearance in the surgical vocabulary, no study has yet defined any specific treatment/mitigation approach for PPAP after the Whipple procedure nor, in general, pancreatectomies. Hopefully, a consensus definition and grading system for PPAP will serve as a foundation to identify diagnostic and

TABLE 3 International Study Group of Pancreatic Surgery Consensus Definitions of Postpancreatectomy Hemorrhage

DEFINITIONS
Time of Onset
Early hemorrhage (≤24 hours after the end of the index operation)
Late hemorrhage (>24 hours after the end of the index operation)
Location
Intraluminal (anastomotic suture lines, cut surface of the pancreas, stress ulceration, pseudoaneurysm)
Extraluminal (arterial or venous vessels, diffuse bleeding from resection area, anastomotic suture lines, pseudoaneurysm)
Severity of Hemorrhage
Mild
Decrease in hemoglobin concentration <3 g/dL
No significant clinical impairment
Transfusion of no more than 2 to 3 units packed cells within 24 hours of surgery or 1 to 3 units beyond 24 hours
No requirement for reoperation or interventional angiographic embolization
Severe
Decrease in hemoglobin concentration ≥3 g/dL
Clinically significant impairment (tachycardia, hypotension, oliguria, hypovolemic shock)
Transfusion requirement >3 units packed cells
Need for invasive treatment (interventional angiographic embolization or relaparotomy)

GRADING SCALE		
Grade	**Onset, Severity, and Location**	**Clinical Condition**
A	Early, mild intraluminal or extraluminal bleeding	Good
B	Early, severe intraluminal or extraluminal bleeding	Good to moderately impaired
C	Late, mild intraluminal or extraluminal bleeding	Severely impaired, life-threatening
	Late, severe intraluminal or extraluminal bleeding	

Modified from Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*. 2007;142:20–25.

prognostic criteria in order to recognize risk factors of PPAP, as well as prevent, mitigate, and, eventually, treat its sequelae.

POSTPANCREATECTOMY HEMORRHAGE

With a reported incidence around 10%, PPH can represent a life-threatening complication and often requires emergent invasive procedures. This broad-ranging concept is classified according to its time of onset (early vs. late), site of bleeding (intraluminal vs. extraluminal) and severity (mild vs. severe) per the ISGPS terminology (Table 3). Although a decrease in hemoglobin levels is commonly observed because of the equilibrium of intraoperative blood loss combined with fluid administration in the early postoperative period, early bleeding (≤24 hours) is usually attributable to technical failure in obtaining hemostasis or, alternatively, underlying coagulopathy. Common sites of bleeding are the hepatic and superior mesenteric arteries, the gastroduodenal artery stump, the pancreatic stump, and the pancreatico-duodenal vessels in the retroperitoneum. In this particular circumstance of major bleeding with hemodynamic instability, immediate surgical reexploration is recommended because the source of bleeding is often easily identified and controlled, with the subsequent postoperative course being likely uneventful.

Conversely, delayed PPH can occur up to several days or weeks after index surgery, and it is usually associated with, and often caused by, coexistent complications such as POPF, bile leaks, intraabdominal collections, or bowel perforation. In fact, vessel erosion by enzyme-rich or infected fluid derived from anastomotic leaks, in association with vascular wall lesions caused inadvertently during skeletonization or reconstruction, can lead to pseudoaneurysm formation and bleeding. Therefore PPH always should be considered when other intraabdominal complications occur, and postoperative contrast-enhanced imaging evaluation must also include a thorough assessment of major peripancreatic vessel integrity to identify wall irregularities, pseudoaneurysms, and subtle bleeding. Notably, a self-limiting small amount of blood emanating from drains, often referred to as a *sentinel bleed*, precedes a major hemorrhage in up to one-third of cases, thus imposing rapid assessment of hemodynamic and laboratory parameters to prevent a fatality. As soon as a late hemorrhage is suspected, contrast-enhanced CT is requisite (Fig. 1A) Proper fluid resuscitation should be implemented immediately, with red blood cell and fresh plasma transfusions being considered to facilitate the patient's coagulative capacity and maintain adequate peripheral oxygenation. In the case of hematemesis, a nasogastric tube must be rapidly inserted: notably, this can result not only from intraluminal upper GI bleeding, but also from intraperitoneal hemorrhage with the blood entering the GI tract through a dehiscent anastomosis. Even for the hemodynamically stable patient, intensive care unit transfer is advisable for adequate monitoring and support because initially mild hemorrhage can rapidly evolve into overwhelming bleeding and shock. Subsequently, once the patient is hemodynamically stable, either interventional angiography or endoscopy should be considered depending on the suspected site of bleeding. Multiple approaches are available to achieve hemostasis depending on the site and the

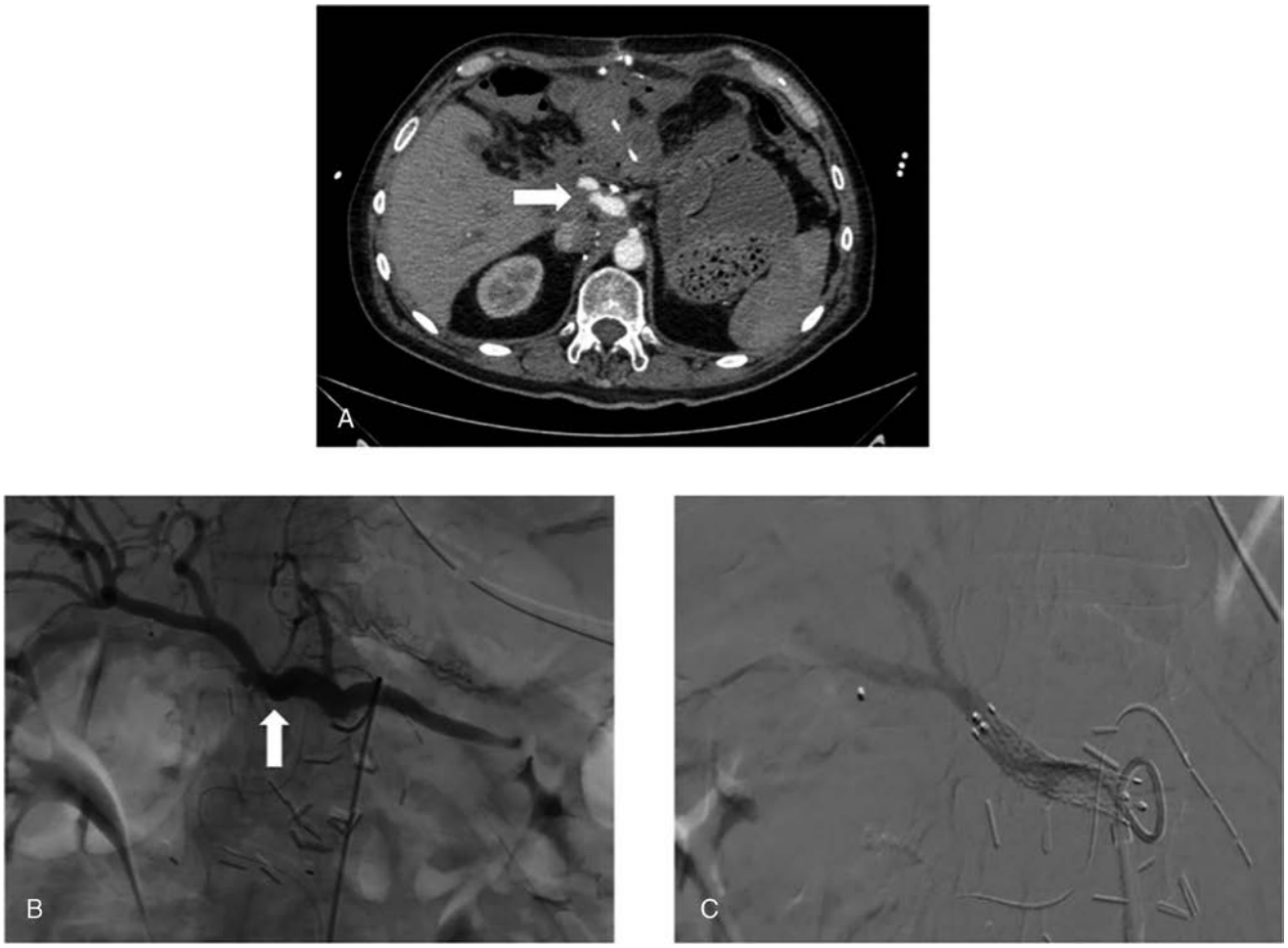


FIG. 1 **(A)** Contrast-enhanced CT scan of a patient with CR-POPF developing hypotension, tachycardia, and oliguria. The common hepatic artery *(arrow)* is surrounded by fluid with internal air bubbles. Vessel profile irregularity is evident, with high suspicion for pseudoaneurysm development. **(B)** A selective celiac trunk arteriography confirms common hepatic artery irregularity with a 6-mm pseudoaneurysm *(arrow)* proximal to the gastroduodenal artery stump. The proper hepatic artery, left hepatic artery, and splenic artery appear normal. **(C)** A cover metal stent is placed from the common to the proper hepatic artery to exclude both the pseudoaneurysm and the gastroduodenal artery stump from blood flow. Control angiogram shows no active bleeding.

caliber of the damaged vessel. Vessel embolization with coils or glue or covered stenting is employed in the case of endovascular procedures (Fig. 1B, C), whereas argon-plasma coagulation or clipping are available during endoscopic approaches. Interventional procedures are now considered as the first approach for late PPH, with relaparotomy being reserved for deteriorating, hemodynamically instable patients or those not responsive to noninvasive approaches. In fact, especially when POPF and peritonitis are present, surgical access to the bleeding vessel is made harder because of hematomas, peripancreatic abscesses, dehiscent anastomoses, and adhesions, and once at the epicenter, vascular integrity is fragile, making control and definitive resolution dubious. As is the case with CR-POPF (see earlier), re-laparotomies are associated with high mortality rates and the need for second looks to obtain definitive hemostasis and abdominal wall closure.

DELAYED GASTRIC EMPTYING

Frequently associated with CR-POPF, intraabdominal collections, and tissue inflammation, delayed gastric emptying is described as another common complication following the Whipple procedure, with historically reported occurrence varying from 30% to 40%. Fortunately, despite such considerable incidence, DGE management is mostly supportive and rarely requires interventional procedures. Improvements in POPF prevention/management as well as the common adoption of an antecolic placement of the gastroenteric anastomosis have likely hastened progress over time, to the point where the incidence of this should now be considered in the 10% range. As with its presumed pathophysiology (pyloric spasm and/or gastroparesis caused by enteric neuropeptide dysregulation, stomach denervation, devascularization, peripancreatic inflammation, and possibly fluid overload), the definitions of DGE employed in the literature over the years were nebulous, thus hampering their applicability. According to the 2007 ISGPS consensus definition (Table 4), maintenance of a nasogastric tube for more than 3 days (or need for reinsertion following postoperative day 3) and the inability to tolerate solid food by postoperative day 7 should be considered DGE. Notably, unlike CR-POPF, there are neither quantitative nor biochemical diagnostic criteria, thus leading to imprecise estimation of the real incidence DGE according to various practice habits employed at different institutions. DGE should be suspected whenever a patient has trouble resuming oral feeding after surgery,

TABLE 4 International Study Group of Pancreatic Surgery Consensus Definition of Delayed Gastric Emptying

Grade	Nasogastric Tube Requirement	Days of Oral Intolerance (POD)	Vomiting and Gastric Distension	Use of Prokinetics
A	4 to 7 days or reinsertion >POD 3	7	±	±
B	8 to 14 days or reinsertion >POD 7	14	+	+
C	>14 days or reinsertion >POD 14	21	+	+

Definition: Functional gastroparesis after surgery without mechanical obstruction as determined by upper gastrointestinal contrast series or endoscopic evaluation.
POD, Postoperative day.
Modified from Wente MN, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2007;142:761–768.

with early typical complaints presenting as abdominal distension, discomfort, bloating, and nausea. Most manifest with vomiting after initial tolerance of oral intake, thus requiring discontinuation and resumed nasogastric decompression. Notably, these attributes are also common with generalized ileus, so teasing the two entities apart is challenging. Accordingly, three severity grades are established by the ISGPS consensus based on the delay of oral intake resumption and the therapeutic approaches employed by the surgeon to treat such a condition (see Table 4).

By definition, DGE is a functional condition, therefore the diagnosis of such implies that causes of upper gastrointestinal mechanical obstruction (such as gastrojejunal anastomosis stricture, perianastomotic ulcer, or abscess) are excluded. CT scans and upper GI endoscopy are usually necessary to rule out the presence of such mechanical factors, while a Gastrografin swallow usually confirms gastric distension and a slower passage of contrast into the jejunal loop. Prolonged nasogastric tube decompression and antiemetic/prokinetic drug administration are almost always necessary, resulting in prolonged fasting and delayed discharge. Subsequently, resumption of oral intake should be undertaken gradually. In the authors' experiences, chewing gum, carbonated drinks, and cold food (such as ice cream) may be helpful in stimulating peristalsis and promoting feeding resumption. For those unable to tolerate food for several days, artificial nutrition must be considered, but this is necessary in only a fraction of all DGE circumstances. Despite not being demonstrated as superior in terms of DGE resolution, enteral nutrition should be preferred over total parenteral nutrition. The vast majority of DGE cases are self-limiting and generally have minor effects on postoperative recovery. In fact, prolonged enteral feeding (weeks) through jejunostomy or percutaneous endoscopic gastrostomy is exceedingly rare. However, the psychological burden of DGE on patients (as well as costs associated with longer hospital stays, medication employed, and delays to adjuvant therapies) should not be underestimated.

CHYLE LEAK

Among the pancreatectomy-specific complications coded by the ISGPS, chyle leak has been recently described, perhaps because of its relatively rare occurrence. It results from the accidental damage or disruption of the cisterna chyli or its major tributaries during the operation because they are located behind the pancreatic head and body, lateral to the aorta, or adjacent to the superior mesenteric artery and vein within the mesenteric pedicle. Diagnosis can be suspected whenever milky drain fluid appearance is evident after resumption of oral feeding, especially if an extended peripancreatic lymphadenectomy or periadventitial aortic/proximal superior mesenteric artery dissection had been performed. Per the ISGPS consensus, chyle leak is defined when the drain fluid triglyceride content is ≥110 mg/dL/1.2 mmol/L on or after postoperative day 3. Often though, this is rather self-evident by its white, opaque characteristic alone. Similar to the CR-POPF definition, no fluid volume threshold is required for the diagnosis. As chyle leak is confirmed, surgeons usually employ a prudent step-up approach encompassing dietary restrictions, such as a no/low-fat diet, enteral nutrition with middle-chain triglyceride (MCT) implementation, or even total parenteral nutrition. Specifically, because MCTs are directly emitted into the venous blood rather than gut lymphatic after absorption, MCT-enriched preparation should be preferred in chile leak patients without reducing the caloric intake. At the authors' institutions, a 72 hour nil-per-os challenge is started as soon as chyle leak is suspected, with most patients recovering without the need for further intervention. Percutaneous drainage of intraabdominal chyle ascites may be necessary for patients with related symptoms, whereas additional procedures such as lymphatic duct embolization or relaparotomy for direct suture are thankfully anecdotal.

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Vascular Reconstruction During the Whipple Operation

Benedict Kinny-Köster, MD, and Jin He, MD, PhD

Vascular resection and reconstruction are often encountered during pancreatoduodenectomy (Whipple operation) for pancreatic malignancies. Venous and arterial reconstructions allow for margin-free resection of tumors that demonstrate vascular involvement. Because tumors that are attached to the mesoportal venous, hepatic arterial, or superior mesenteric arterial system are usually located in the pancreatic head or uncinate process, strategies of reconstruction are particularly (but not exclusively) relevant during pancreatoduodenectomy.

A radical tumor resection in combination with chemotherapy is considered the only curative-intent treatment approach in pancreatic ductal adenocarcinoma (PDAC) without evidence for distant spread. This treatment paradigm became increasingly promising with the improved efficacy of the FOLFIRINOX combination chemotherapy (folinic acid/leucovorin, fluorouracil/5FU, irinotecan, oxaliplatin). In addition to elective oncologic indications, the principles of vascular reconstruction apply for situations when surgeons are confronted with the intraoperative injury of essential vessels. Here, knowledge about the individual patient's anatomy, such as aberrant hepatic arteries, may influence surgical strategies.

Besides primary tangential or end-to-end repair, patches and conduits can be utilized to bridge long tangential or segmental vascular defects. Furthermore, the postoperative management of complications is critical for the clinical success as vascular reconstructions are associated with increased perioperative morbidity. Potential complications include postpancreatectomy hemorrhage, postoperative thrombosis, liver or bowel ischemia, portal hypertension, ascites, infection, and diarrhea.

Herein, we summarize technical considerations including options of conduit materials and implications on postoperative management based on the current literature and cumulative experiences from a high-volume center.

PATIENT SELECTION FOR ELECTIVE VASCULAR PANCREATIC SURGERY

Currently, a pancreatic mass without distant metastases that is attached to surrounding vasculature is being categorized into *resectable, borderline resectable,* or *locally advanced* according to the extent of circumferential vessel involvement on radiographic imaging (National Comprehensive Cancer Network guidelines for PDAC, last update 2021). Preoperative chemotherapy is often considered if the serum tumor marker CA19-9 is high, indicating an increased risk of systemic (micrometastatic) spread. Because imaging scans have limited specificity to differentiate vital tumor from scar tissue after FOLRININOX chemotherapy, we recommend that every patient without distant metastatic spread after preoperative chemotherapy undergoes surgical exploration. We also reported that discriminating different depths of invasion for major arteries with regard to their distinct histologic layers (tunica adventitia with overlying nerval plexus vs. tunica media) has direct surgical implications.

Overall, surgical exploration with possible pancreatoduodenectomy and vascular resection/reconstruction is associated with improved survival in patients with favorable clinical predictors (e.g., normalized CA 19-9 during chemotherapy or long progression-free interval) and especially relevant for young patients with great performance status.

VENOUS RECONSTRUCTION

When performing pancreatoduodenectomy for patients with venous involvement, venous resection should be performed en bloc with the tumor specimen to achieve a negative margin. The surrounding mesoportal venous drainage of the intestines can be involved by tumor between the distal superior mesenteric vein (SMV) in the area of the jejunal and ileal tributaries and the proximal portal vein (PV) toward the liver hilum. If the primary tumor can be resected with tangential venous resection, primary tangential repair should be attempted either transversely or longitudinally if subsequent narrowing of the vein diameter is not exceeding 50%. Otherwise, a vascular patch may be utilized (bovine pericardium, autologous peritoneum, or falciform ligament). For segmental resections, a primary end-to-end reconstruction should be carried out if a tension-free anastomosis can be performed. This is often feasible for vascular defects less than 3 cm in length. Mobilization of the liver through dissection of the surrounding ligaments may support this approach.

For a long segmental resection, conduits with a sufficient size match are important tools for reconstruction (Fig. 1). For this purpose, we preferably utilize the left renal vein, greater saphenous vein, or occasionally left internal jugular vein as autologous interposition grafts. Although robust evidence about patency and postoperative outcomes is lacking, we have experienced favorable results over synthetic PTFE (polytetrafluoroethylene) conduits or cryopreserved allogenous vein grafts that constitute alternatives if autologous veins are not accessible. Nevertheless, synthetic PTFE conduits with ring enforcement are a quickly accessible option, especially when facing unexpected intraoperative venous injuries. When using cryopreserved vein grafts, we match them with the patient's blood group.

When the tumor causes occlusion of the SMV through external compression, cavernous collateralization around the pancreatic head is often evident and can provoke massive intraoperative blood loss during the resection phase. For improved control, the distal SMV or even a prominent jejunal/ileal tributary can be bypassed to the PV with a synthetic PTFE conduit ("venous bypass graft first") or to the inferior vena cava (mesocaval shunt) before resection of the Whipple specimen to temporarily divert the intestinal drainage. After resection, the bypassed venous flow should be reevaluated and optimized (e.g., primary reconstruction or autologous vein graft). A permanent mesocaval shunt with a primary anastomosis (end-to-side) or a conduit (distal end-to-end, proximal end-to-side anastomoses) may be an option in patients with particularly caudal tumor involvement after mesoportal reconstruction of the main intestinal drainage, if an additional jejunal or ileal tributary remains with considerable backflow. Preservation of venous collaterals, if feasible, may also facilitate decreased postoperative intestinal congestion and mitigate risks associated with potential postoperative thrombosis of the reconstructed segment.

When performing a venous resection of the confluence, the splenic drainage must be considered to prevent varices of the short gastric veins. If the splenic vein cannot be reinserted, a spleno-renal shunt with a primary anastomosis or a conduit (splenic vein to left renal vein), or a spleno-caval shunt (e.g., if the left renal vein was resected for an interposition graft) prevents sinistral portal hypertension. Importantly, similar considerations apply for the venous drainage of the stomach. Particularly after splenectomy with subsequently interrupted venous flow through the short gastric veins, the coronary vein plays a critical role to prevent upstream congestion and ischemia. If not preserved (e.g., during a total pancreatectomy), insertion into the mesoportal venous axis or inferior vena cava should be attempted.

When performing a venous resection, tangential venous control or distal and proximal venous control is achieved with vascular clamps. For segmental reconstructions, we communicate with the anesthesiologist to administer an intravenous injection of heparin

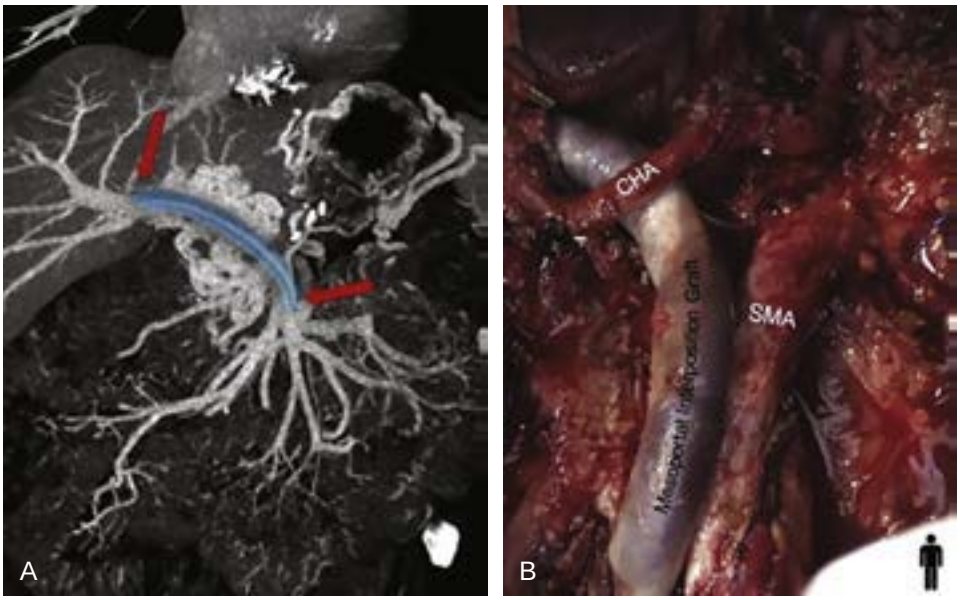


FIG. 1 Reconstruction of the mesoportal venous flow with an interposition graft. **(A)** Cavernous transformation of the PV/SMV illustrated at a three-dimensionally rendered CT scan. Preoperatively planned, feasible locations of distal and proximal anastomoses (red arrows) of a potential conduit (in blue) are shown. **(B)** Mesoportal conduit (cryopreserved saphenous vein) tunneled below the CHA. *CHA,* Common hepatic artery; *PV,* portal vein; *SMA,* superior mesenteric artery; *SMV,* superior mesenteric vein. *(From Kinny-Köster B, van Oosten F, Habib JR, et al. Mesoportal bypass, interposition graft, and mesocaval shunt: Surgical strategies to overcome superior mesenteric vein involvement in pancreatic cancer.* Surgery. *2020;168[6]:1048–1055.)*

(5000 units or 70 units per kg body weight) immediately before clamping. Tangential or segmental reconstruction can be performed with both interrupted or running Prolene sutures (5-0 or 6-0 USP). Just before finishing segmental reconstruction, the distal clamp is reopened before the proximal clamp to release air and potential minor clots. We do not compromise inflow of the SMA during mesoportal venous reconstruction. After reestablished perfusion, flow can be evaluated by intraoperative Duplex ultrasound or transit time flow measurement (TTFM) distally and proximally. Sufficient drainage should be confirmed by resolving intestinal and splenic congestion before performing the pancreatico-jejunostomy.

ARTERIAL RECONSTRUCTION

Arterial reconstructions during the Whipple procedure affect the hepatic arteries and SMA. Reconstruction of the hepatic arterial inflow may involve the common hepatic artery, the proper hepatic artery, or the right and left hepatic arteries individually, especially in patients with an aberrant anatomy (e.g., Michels type 3 anatomy, replaced right hepatic artery originating from the SMA). To understand the implications for reconstruction of a specific artery, it is crucial to review the preoperative arterial phase CT imaging. In addition to the identification of an aberrant liver arterial blood supply, the origin of the celiac trunk (ruling out a median arcuate ligament) and SMA should carefully be evaluated as potential collaterals between the two major branches surrounding the pancreatic head (gastroduodenal artery and its arcades) will be divided and limit compensatory flow in case of occlusion. To clarify on the extent of SMA involvement early intraoperatively, we recommend an "artery-first" approach that aims to confirm feasibility of reconstruction before committing to a point-of-no-return during resection. Tangential resections of the full vessel wall should not be performed because of the high risk for tears of the tunica intima, which may provoke intimal dissection and intraluminal blockage. For short segmental resections, an end-to-end anastomosis can be attempted. However, we have experienced that the extent to mobilize arterial cuffs toward each other is often limited. Thereby, reconstruction with conduits may be necessary. To perform a precise and controlled anastomosis, it is paramount to consider different sites for the proximal anastomosis. Although in most cases the site of transection represents a feasible option for an end-to-end anastomosis, the side wall of the supraceliac aorta, suprarenal aorta, infrarenal aorta, right renal artery, and right iliac artery can be valuable alternatives for a side-to-end anastomosis to a conduit that connects the liver or superior mesenteric territory.

As for venous reconstructions, we prefer autologous venous grafts that must be reversed when implanted to overcome venous valves. In particular situations when long conduits are necessary or when facing unexpected intraoperative arterial injuries, synthetic PTFE grafts are again a valuable choice. In rare instances, the transposition of an artery in close proximity to the resected segment with a matching diameter may be an alternative (e.g., transposition of the splenic artery with splenectomy or left gastric artery). However, although these reconstructions only require one vascular anastomosis, we have experienced a tendency for increased turbulent flow that compromised perfusion. If the middle colic or right colic arteries are involved by the tumor in the mesentery, transection may necessitate a partial colectomy of ischemic segments (multivisceral resection). If the intestines appear edematous after resection of the specimen because of an extensive procedure with prolonged clamping of the superior mesenteric artery (SMA), the bile duct and pancreatic duct may temporarily be drained externally. Reconstruction of intestinal continuity can be performed secondarily within 24 to 48 hours. In patients with arterial reconstruction and a high-risk for fistula from pancreatico-jejunostomy (soft gland texture or duct ≤3 mm), we tend to perform a total pancreatectomy.

When performing an arterial anastomosis, the technical steps are identical to venous reconstruction. Before proceeding with the pancreatico-jejunostomy, sufficient perfusion should be confirmed by Duplex ultrasound or TTFE.

PERIADVENTITIAL DISSECTION OF ARTERIES

Recently, a novel concept coined periadventitial dissection (also referred to as *arterial divestment*) was developed. It is indicated and a valuable option, especially for patients with borderline resectable or locally advanced PDAC after preoperative chemotherapy.

Intraoperative exploration revealed that, although abutting or encasing the SMA on CT, the arterial tunica media often is not invaded (Fig. 2). This allows for resection of the tumor with the tunica adventitia and the attached neural plexus on top of the SMA (PLsma) through dissection within the arterial periadventitial plane. We recommend performing periadventitial dissection hemicircumferentially (to the right side of the SMA, if tumor involvement was less than 180 degrees) to decrease the risk of prolonged postoperative diarrhea. Periadventitial dissection should be performed en bloc through entering of the plane at an area without tumor contact to avoid transection through tumor tissue (no-touch principle). The same principle is applicable to the celiac trunk and common hepatic artery. With this technique, arterial resection and reconstruction can be prevented while still achieving a macroscopically margin-free resection (commonly R0, sometimes R1 with tumor cells apparent within a 1-mm margin). Although oncologic outcome data are still limited, clinical trials are underway to study its efficiency in reducing local recurrences, even in patients without arterial involvement.

ROBOTIC VASCULAR PANCREATIC SURGERY

Robotic pancreatoduodenectomy with short tangential venous reconstructions can be safely performed by experienced robotic pancreatic surgeons after passing a learning curve. However, we typically perform an open procedure whenever a segmental resection of veins or arteries may be required from the assessment of preoperative CT imaging.

The concept of periadventitial dissection together with retropancreatic nerve plexus resection (level 1, 2, or 3 according to Inoue, 2016) should be considered and implemented during robotic pancreatoduodenectomy. Here, the TRIANGLE area (retropancreatic triangular-shaped space enclosed by the common hepatic artery, SMA, and superior mesenteric vein/portal vein) describes the anatomic correlate to achieve a radical dorsal and medial margin during both open and robotic pancreatoduodenectomy. If surgeons face uncontrolled venous or arterial bleeding during robotic resection, careful and blunt compression should be attempted to reach temporary control. Through a hand-assisted port, control may be facilitated with closure of the lumen by a finger. Care should be taken to not enlarge injuries, a scenario that veins are particularly prone to. However, conversion to laparotomy with the opportunity of an improved overview is a critical bailout option (e.g., to access and cross-clamp the supraceliac aorta for arterial bleeding).

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

Evidence to promote postoperative patency of vascular reconstructions and to balance risks of thrombosis versus postoperative hemorrhage are lacking. In our practice, we administer lifelong aspirin for segmental reconstructions (primary end-to-end or with conduits) in the venous or arterial system, and for tangential reconstructions with patches in the venous system. For tangential reconstructions with primary repair, we do not regularly prescribe an antiplatelet regimen (only considered for long reconstructions with considerable narrowing). Therapeutic anticoagulation with low-molecular-weight heparin is rarely administered. Although this describes our standard protocol, adjustments are considered on an individualized basis in certain high-risk situations. It is important to monitor hepatic ischemia postoperatively (AST, ALT, lactate) and to rule out intestinal ischemia (lactate). We perform duplex ultrasound to evaluate vascular patency routinely on postoperative day 1 and continue with serial examinations in patients with ascites or abnormal liver function.

If acute arterial occlusion is suspected with clinical and laboratory signs of ischemia, a dual-phase CT scan is performed. After identification of the exact localization, the extent of occlusion, and potential collaterals, the patient is taken back to the operating room to revise the arterial reconstruction. Although removal of emboli with a Fogarty catheter should be attempted, the reconstruction often must be taken down and recreated. Of note, in patients in whom the CT scan demonstrates partial occlusion or a pseudoaneurysm of the hepatic

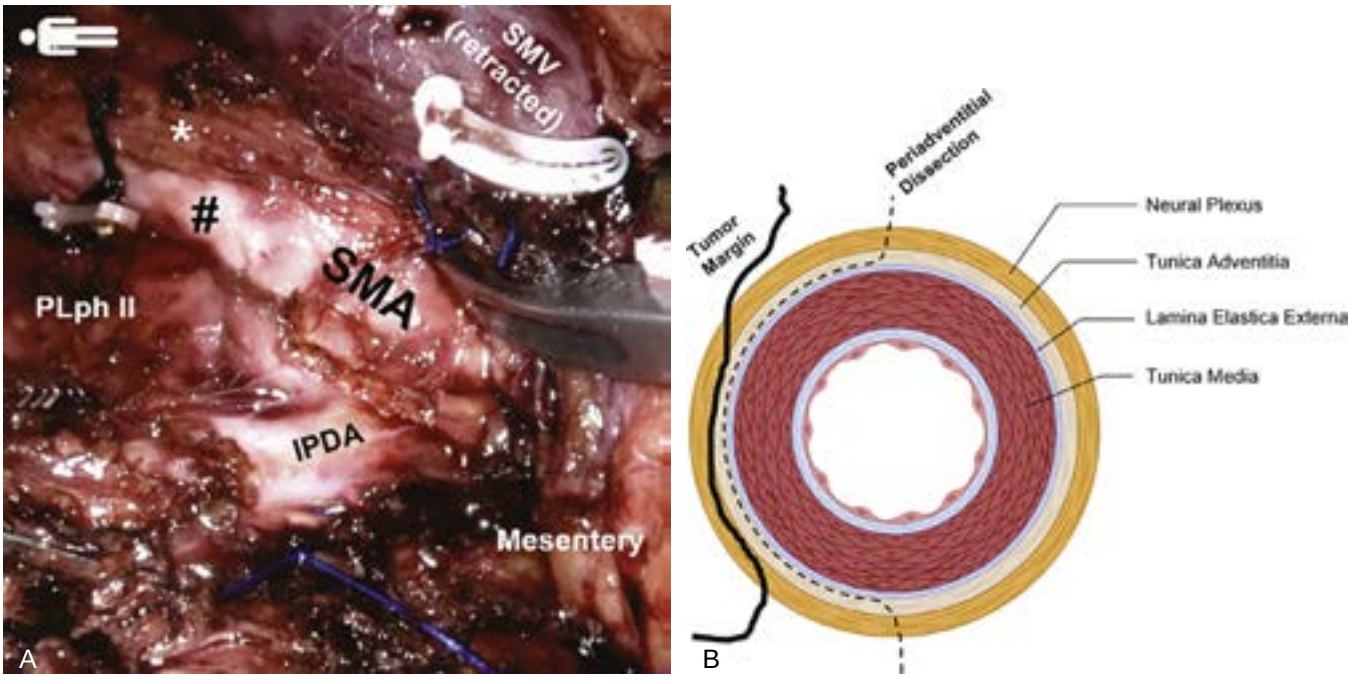


FIG. 2 Illustration of periadventitial dissection and its underlying principle. **(A)** Hemicircumferential periadventitial dissection of the SMA during a robotic pancreatoduodenectomy with a retropancreatic level 3 dissection. # depicts the arterial tunica media with the overlying lamina elastica externa; * marks the neural plexus SMA. **(B)** Schematic cross-section of the performed periadventitial dissection with the anatomic layers of the arterial wall and the applied transection line. *IPDA,* Inferior pancreaticoduodenal artery; *PLph II,* plexus pancreatic head II; *SMA,* superior mesenteric artery; *SMV,* superior mesenteric vein. *(Figure 2B made in ©BioRender, biorender.com.)*

artery, interventional angioplasty with stent placement or coil embolization, respectively, is primarily indicated as opposed to relaparotomy.

If acute (early postoperatively), complete venous occlusion occurs in the portal vein (i.e., distally to the confluens) after venous reconstruction, surgical exploration and removal of thrombotic material should be performed in both proximal and distal directions with a Fogarty maneuver, especially if the liver serum transaminases are rapidly increasing.. If optimization seems feasible from a surgical-technical perspective, the venous reconstruction should be revised to decrease the risk of recurrent thrombosis. For acute occlusion in the superior mesenteric vein, therapeutic anticoagulation should be administered. However, therapy must be balanced with risk of bleeding on an individualized basis. Medical management of ascites with furosemide and spironolactone may be helpful under monitoring of serum electrolytes. For increased losses of fluid through the intraoperatively placed drainages, careful resuscitation with crystalloids should be considered.

Chronic thrombosis in the venous system often does not provoke initial clinical symptoms and does not indicate anticoagulation therapy. However, because of portal hypertension and subsequent collateralization, the development of varices, especially in the esophagus and gastric fundus, require surveillance. In addition to the medical team, the patient should be aware that an event of hematemesis represents an emergency that would demand rapid diagnosis and treatment (esophagogastroscopy).

Postpancreatectomy hemorrhage (PPH) is a major complication after vessel reconstruction. The International Study Group of Pancreatic Surgery differentiates between early versus late (cutoff 24 hours), extraluminal versus intraluminal, and mild versus severe appearance. Early-extraluminal-severe PPH as diagnosed by increased sanguineous drainage output should be attacked primarily with surgical reexploration without prior imaging, especially in unstable patients. If late PPH is suspected (mild/severe and extraluminal/intraluminal), a CT angiogram and subsequent interventional angioplasty are indicated to locate and treat the hemorrhage, which is often caused by an arterial pseudoaneurysm. If unsuccessful, immediate laparotomy is critical to prevent hemorrhagic shock.

After resection or periadventitial dissection of the SMA, (neurogenic) diarrhea, sometimes persisting for 4 to 12 weeks postoperatively, is a complication that burdens patients. When bacterial enteritis is ruled out, oral antidiarrheal drugs may be utilized to mitigate the impaired bowel motility. It is important that fluid and nutrient supply are monitored and replaced appropriately to avoid severe weight loss and a decrease in performance status. In addition, oral supplementation of pancreatic enzymes should be considered to support exocrine pancreatic dysfunction. Sometimes, parenteral nutrition is necessary to bridge limited intestinal absorption. We have experienced that, although prolonged diarrhea is challenging for patients to manage, affected patients will regain bowel function eventually.

SUMMARY

Herein, we describe the technical considerations to perform venous and arterial reconstructions during pancreatoduodenectomy for pancreatic malignancies. These considerations can also be applied to other pancreatic diseases such as advanced neuroendocrine tumors or chronic pancreatitis. Furthermore, we recommend periadventitial dissection, which is an evolving technique that often allows for macroscopically margin-free tumor resections while avoiding arterial resection. These tools allow for oncologic resections with acceptable safety. In addition, these techniques can be utilized for accidental vascular injuries that may appear during pancreatoduodenectomy. Because of the postoperative morbidity and mortality after vascular reconstructions, timely management of complications is of the essence to minimize events of failure to rescue. Elective vascular reconstructions should be performed in high-volume centers where interdisciplinary expertise and resources are readily available (surgeons, interventional radiologists, anesthesiologists). Patients with an indication for vascular reconstruction and periadventitial dissection must be carefully selected based on performance status and indicators of tumor biology to balance the potential harm with promising benefits.

Acknowledgment

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Palliative Interventions for Patients with Operable and Advanced Pancreatic and Periampullary Cancer

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The treatment of patients with pancreatic cancer (PC) is complicated by disease-associated symptoms that can often prevent the successful delivery of systemic therapy. Now that systemic therapy is associated with improved response rates, it is even more important that we have effective strategies for biliary and gastric outlet/duodenal decompression as well as reliable techniques for tumor biopsy given the emerging field of molecular oncology, which relies on somatic mutation testing of tumor samples. Importantly, the definition of palliative care, palliative surgery, or any palliative intervention is the relief of disease-associated symptoms. The treatment of patients with incurable cancer, where the treatment is being applied to maximize length and quality of life, is often (inappropriately) referred to as palliative therapy. If the treatment is not being applied to relieve a symptom, it is not palliative therapy.

For patients with PC, systemic therapy is not possible in the absence of durable biliary decompression and a mechanism to deliver reliable nutrition—usually via an enteral route. Furthermore, systemic therapy will rarely be associated with a response in the

absence of a reasonably good performance status. As physicians have become increasingly specialized, the patient with PC can often be an orphan without a home—the medical oncologist cannot treat the patient with, for example, an elevated bilirubin; the gastroenterologist has placed a stent that may or may not be associated with a decline in liver function tests; the surgeon feels as though there is little role for their involvement as the patient has locally advanced or metastatic disease; and the patient is caught in the middle. Perhaps it would help to provide some guiding principles that we have adopted at the LaBahn Pancreatic Cancer Program:

- The patient with PC needs a home; a team or service responsible for the infrastructure needed to maximize performance status and optimize the patient's chances for receiving active anticancer therapy. Within our program, this is the surgery service, but it can be any subspecialty service. In the absence of a defined team of physicians/physician extenders who will own the challenges that accompany this diagnosis, patients will fail to receive potentially life-extending therapy and often die of biliary sepsis, nutritional depletion, or hypoglycemia. Many phase III trials (of all stages of PC) have demonstrated huge numbers of patients who fail to receive all intended therapy due to the inability to optimally manage bile duct and duodenal obstruction, pain, and other disease-associated symptoms—there is no other solid tumor where such challenges exist.
- The interventional gastroenterologist should never come first. Any patient with bile duct obstruction should receive a good quality CT/MRI before an endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA). The most unfortunate (and preventable) situation involves the patient with a complication of an endoscopic procedure in whom the stage of disease cannot be determined due to the absence of high-quality imaging before procedure-associated pancreatitis or intestinal perforation.
- The management of biliary decompression needs to be tailored to the overall goals of care. For the patient with operable PC for whom neoadjuvant therapy is planned, high-risk procedures should be avoided. If endoscopic stent placement is unsuccessful, the "plan B" options include either a transhepatic catheter or a surgery-first approach. Higher risk endoscopic procedures should be reserved for patients with locally advanced and metastatic disease where a complication of the procedure will not risk a potentially curative treatment approach.
- Duodenal stents should, in general, be avoided in patients with operable disease in the absence of multidisciplinary review. In our experience, an uncovered metal stent in the duodenum does make the operation of pancreaticoduodenectomy more difficult. In such patients, we prefer a minimally invasive (laparoscopic/robotic) gastrojejunostomy.
- Not every patient is treatable, but every patient should receive a thoughtful review of the individual factors that affect this decision: medical comorbidities and whether they can be optimized, success in biliary and gastric outlet decompression if present, and the social determinants of health. By addressing these critically important variables individually, one can make an accurate determination of what is and is not possible. This will also prevent the inappropriate application of surgery in patients where there is too small a chance for complete recovery.

INITIAL EVALUATION OF THE PATIENT WITH PANCREATIC/PERIAMPULLARY CANCER

We have a simple approach—high-quality, triple-phase CT and a careful physical examination followed by EUS-guided FNA/core biopsy (or US-guided core biopsy of extrapancreatic sites if metastatic) and ERCP with metal stent placement when biliary obstruction is present. The EUS and ERCP are typically performed at the same anesthesia induction (monitored anesthesia care). If the diagnosis is established on endoscopic biopsy, a metal stent is placed in the bile duct; if the diagnosis is unclear at the time of endoscopy, a plastic stent is preferred. The patient can then be accurately staged and evaluated for treatment to include assessment of eligibility for a clinical trial. At the time of initial evaluation, the patient and their support system are also seen by genetic counseling, nutritional support, diabetes management, and our psychology services. The programmatic infrastructure needed for such patients is significant and one reason why some feel that all newly diagnosed patients should be managed at a larger referral center for diagnosis, staging, and an opinion regarding treatment sequencing.

Patients with advanced PC face difficult treatment decisions, and open communication about goals of care will help patients to make sound, informed decisions. Understanding personal goals and preferences will help shape conversations concerning treatment recommendations and engage patients in shared decision making. It is also important to elicit patient preferences for how information is communicated and what level of detail is suitable. Along with a foundational understanding, treatment goals should be revisited as necessary at future encounters. Patients with advanced PC are frequently monitored with imaging and basic laboratory tests to assess treatment response; they should also be closely examined for impending complications. These may manifest as signs of current or impending biliary obstruction, bowel obstruction, ascites, tumor infiltration into the abdominal neural plexus (celiac axis), or significant portal venous narrowing/obstruction. In addition, routine assessment of pain, nausea, vomiting, abdominal distension, and cachexia can be helpful. Involvement of palliative care services can often facilitate addressing multiple challenging symptoms.

BILE DUCT OBSTRUCTION

Over 70% of patients with PC will present with biliary obstruction leading to jaundice and malabsorption. The response of the patient to hyperbilirubinemia can be quite variable. Some patients have profound pruritus, fatigue, anorexia, and occasionally nausea and vomiting; others are less affected. We do not have an explanation for the variable patient response to biliary obstruction. Durable relief of biliary obstruction is necessary to allow for the delivery of optimal anticancer therapy, and in those with symptomatic pruritis, to relieve this often-disabling symptom. Multiagent system therapy cannot be delivered in the presence of hyperbilirubinemia. In the setting of normal underlying liver function, it normally takes 1 to 3 weeks for the bilirubin to normalize following stent placement. This assumes a bilirubin in the 10 to 20 mg/dL range; higher bilirubin levels may take longer to normalize.

Rarely, patients may have profound cholestasis in the absence of a history of liver disease. We see this once or twice per year, and it is manifested by an elevated bilirubin that does not decline despite perfect stent placement. Such patients may take 6 to 10 weeks for the bilirubin to normalize. Waiting this long to begin systemic therapy is rather unappealing, and proceeding to surgery incurs unnecessary risk. If the patient has an operable tumor, we would typically proceed with 5-fluorouracil (5FU)-based chemoradiation directed at the primary tumor and regional lymph nodes; infusional 5FU can be safely delivered in the setting of hyperbilirubinemia. We would then plan to use postoperative adjuvant systemic therapy based on the molecular profiling of the primary tumor. An immediate surgical approach to the patient who fails to experience a decline in bilirubin following stent placement is usually ill-advised and reflects a combination of surgeon inexperience and impatience of the multidisciplinary team.

With regard to biliary stents, several series have demonstrated that ERCP can be safely and effectively performed in the vast majority of patients with malignant obstructive jaundice. Early

complications after ERCP occur in 5% of patients when performed by experienced subspecialty gastroenterologists and most commonly include ERCP-induced pancreatitis, bleeding or, rarely, duodenal perforation; hence the importance of high-quality cross-sectional imaging before ERCP. Self-expanding metal stents (SEMS) are clearly superior to plastic stents with respect to stent patency and stent-related complications. Because of the smaller lumen, plastic biliary stents are more likely to occlude from biliary sludge or bacterial overgrowth and often require more frequent stent exchange, whereas SEMS are susceptible to tumor in-growth within the interstices of the stent in some patients. Covered SEMS avoid the complication of tumor in-growth but are prone to stent migration and can cause cystic duct obstruction. In the patient who still has a gallbladder in place, we favor an uncovered metal stent as a covered stent is more likely to be associated with stent-associated cholecystitis due to obstruction of the cystic duct.

Our Guiding Principles for the Management of Bile Duct Obstruction

1. High-quality cross-sectional imaging should always be performed before ERCP or EUS.
2. On-site cytopathology should be performed at the time of EUS-FNA; if the diagnosis of adenocarcinoma is established on immediate slide review, a SEMS (usually uncovered) can be placed while the patient remains sedated. If the diagnosis is unclear (pending review of the cell block made from the sample placed in formalin), then a plastic stent or occasionally a covered SEMS (if the gallbladder is no longer present) is placed.
3. If the ERCP is unsuccessful, there are three options: a surgery-first approach, a rendezvous procedure (placement of a transhepatic wire through the ampulla to guide endoscopic stent placement by the gastroenterologist), or placement of a percutaneous transhepatic catheter (PTC) by Interventional Radiology. We consider a surgery-first approach in patients with localized periampullary (duodenal or ampullary in origin) and a bilirubin level less than 15 to 16 mg/dL. We prefer a rendezvous procedure in all patients with operable PC where neoadjuvant therapy is favored. Transhepatic catheters are reasonable in patients with locally advanced or metastatic disease where cure is not possible. This is because the bile is contaminated with tumor cells in at least one-third of patients with malignant bile duct obstruction, and tumor recurrence can occur at the skin/dermis where the PTC enters the patient to traverse the liver.
4. If a SEMS is placed and the bilirubin fails to decline, we usually repeat the CT scan and the ERCP once to ensure optimal stent placement. If the patient has an operable tumor, we transition to 5FU-based chemoradiation by week 3 or 4 if the bilirubin has not made a significant downward trend. As a general rule, we make our decision with regard to treatment sequencing once staging is complete, and we assume the bilirubin (if elevated) will decline over 2 weeks following stent placement. We typically have initiated systemic therapy within 3 weeks of initial presentation in most all patients with newly diagnosed PC. If by week 3, after stent placement, there is no significant downward trend in bilirubin, and we are sure that the stent is in optimal position and fully expanded, then we will proceed (by week 4) with 5FU-based chemoradiation in those patients with operable tumors. If the patient has advanced disease and the bilirubin is slow to decline, options are limited; 5FU alone may have little benefit over best supportive care. Ursodiol and other supportive measures are initiated as soon as it is apparent that we are dealing with a cholestatic liver.
5. If the patient develops stent-associated cholecystitis, optimal treatment is a percutaneous transhepatic cholecystostomy tube (see selected reference); this will not delay ongoing systemic therapy or chemoradiation—or at least cause a minimal delay—and is favored over laparoscopic or open cholecystectomy.

Operative biliary bypass is an alternative strategy to allow for drainage of an obstructed biliary tree. In patients with locally advanced and metastatic pancreatic or periampullary cancer, they are now, in some cases, outliving the patency of even SEMS—due to the improved response rates seen with available systemic therapies. In such patients, there are two options when metal stents become occluded: an operative bypass or placement of a PTC. For patients of reasonable performance status where ongoing systemic therapy is planned, we would normally proceed with an operative biliary bypass if technically feasible. For those in whom a strategy of best supportive care is planned, a PTC may be the best option. It is usually a mistake to persist with endoscopic attempts at clearing a SEMS once repetitive occlusions have begun to occur. There are several techniques that may be utilized for a biliary bypass. The most common, and durable, technique is a retrocolic choledocho/hepatico-jejunostomy with a Roux-en-Y reconstruction. If a patient has not had a prior cholecystectomy, a cholecystectomy should be performed in addition to the biliary drainage procedure, even in the absence of cholelithiasis or symptoms. Rarely, tumors of the uncinate process may grow into the root of the small bowel mesentery and result in mesenteric foreshortening, making creation of a Roux limb impossible. Importantly, the increased durability of a hepaticojejunostomy must be weighed against the potential for perioperative morbidity, especially in patients with advanced cancer. Operative palliative procedures in patients with advanced cancer must be done with limited morbidity and zero mortality; this is not the time to take unnecessary risk.

GASTRIC OUTLET (DUODENAL) OBSTRUCTION

Nausea and vomiting in patients with advanced PC can be due to mechanical and/or nonmechanical problems. An initial evaluation should include a thorough history and physical followed by radiographic studies to identify obstruction related either to the primary tumor (duodenal obstruction) or a metastatic deposit (malignant small or large bowel obstruction). In the absence of a mechanical etiology, the symptoms may be related to malignant gastroparesis or chemotherapy-associated nausea and are best treated with pharmacologic agents. Suspicion for a mechanical obstruction can be supported by the presence of a dilated stomach on CT scan, and may be confirmed by an upper gastrointestinal fluoroscopy or endoscopy when necessary.

Obstruction of the duodenum due to a malignant tumor of pancreatic, periampullary, or duodenal origin can be treated with either an endoscopic stent or an operative bypass. Duodenal stenting has become a well-established technique to treat malignant gastric outlet obstruction. A SEMS can be endoscopically placed across a malignant stricture or area of narrowing. When successfully placed, approximately 90% of patients can tolerate a soft or somewhat regular diet and adequately hydrate and aliment themselves. Reintervention for tumor infiltration into the uncovered stent can often be managed with the placement of an additional covered SEMS within the existing uncovered stent. If there is associated jaundice, biliary stenting should be performed before duodenal stent placement, as placement of a biliary stent after placement of a duodenal stent is technically difficult.

The decision to perform duodenal stenting or surgical gastrojejunostomy depends on the expected survival of the patients as well as the plans for eventual surgery as the presence of a duodenal stent makes the operation of pancreaticoduodenectomy more difficult. Gastrojejunostomy can be performed via an open or laparoscopic approach. Classically, a retrocolic gastrojejunostomy was performed by sewing the posterior wall of the distal stomach to a loop of proximal jejunum in a stapled or hand-sewn, side-to-side fashion. Studies comparing the efficacy of laparoscopic compared with open gastrojejunostomy are limited; however, a laparoscopic approach allows for the more rapid administration of anticancer therapy.

Our Guiding Principles for the Management of Duodenal Obstruction with and without Bile Duct Obstruction

1. If the patient has an operable pancreatic, periampullary, or duodenal tumor and neoadjuvant therapy is planned, we favor a laparoscopic/robotic gastrojejunostomy.
2. If the patient has advanced disease, a duodenal SEMS can be placed as an outpatient procedure or with a brief hospital admission and may be the preferred approach.
3. In the setting of combined duodenal and distal bile duct obstruction, we would, in general, favor placement of a PTC for relief of biliary obstruction followed by a laparoscopic gastrojejunostomy. We accept the risk for tumor implantation, at the site of the PTC, in this complicated situation. Placement of a duodenal stent or simply a venting gastrostomy tube may be most appropriate in patients with advanced disease. In rare patients with an isolated duodenal or periampullary cancer strategically located in D2, and associated with biliary and duodenal obstruction, there may be a role for a surgery-first approach.
4. In patients with operable disease where neoadjuvant therapy is preferred, the goal of palliative biliary and gastric decompression is to normalize the bilirubin to allow for systemic therapy and provide a durable means of enteral nutrition—so that systemic therapy or chemoradiation can be initiated as soon as possible. As mentioned, placement of a duodenal stent will make a subsequent operation more difficult; therefore, we prefer a PTC and a laparoscopic gastrojejunostomy. As neoadjuvant therapy has become more common for patients with pancreatic and periampullary cancer, accurate staging has taken a back seat to the initiation of systemic therapy, as virtually all stages of disease are now receiving systemic therapy first. This is both good news and bad: good, in that patients with PC are receiving systemic therapy without delay; and bad, in that accurate staging is often not performed other than differentiating localized from metastatic disease. Patients who have either a bile duct or duodenal obstruction often are endoscopically stented—usually a routine procedure for those with bile duct obstruction, but sometimes a mistake in patients with isolated duodenal obstruction who may be candidates for a pancreaticoduodenectomy in the future. For patients with combined bile duct and duodenal obstruction, they are often managed with an attempt at both biliary and duodenal SEMS. In our opinion, this is a mistake for those with potentially operable disease. The involvement of the surgical oncologist in the initial care of the patient with newly diagnosed pancreatic, periampullary, or duodenal cancer cannot be overemphasized. Patients with duodenal obstruction and those with combined bile duct and duodenal obstruction are among the most complicated patients who require multidisciplinary review to select the best form of palliation, which will greatly affect the ability of the patient to receive optimal treatment sequencing (chemotherapy, radiation, and surgery).

OPEN PROPHYLACTIC BILIARY AND GASTRIC BYPASS

As previously mentioned, palliative therapy implies that the patient is suffering from active symptoms. However, at times, palliative care decisions are made to prevent future complications in asymptomatic patients. The classic example of this is when patients, thought to have operable periampullary cancer, are discovered at the time of laparotomy to have unresectable or metastatic disease. This should be a very uncommon event as diagnostic laparoscopy is performed at the time of planned pancreaticoduodenectomy in virtually all patients taken to surgery in an effort to find radiographically occult extrapancreatic metastatic disease and thereby avoid laparotomy. Similarly, in 2022, the preoperative radiographic assessment of local tumor resectability is highly accurate; therefore, unresectability for local tumor-vessel reasons should be a very rare event. That said, if one is found with an open abdomen at the time of laparotomy for planned pancreaticoduodenectomy, and the patient has either very low volume metastatic or locally unresectable disease, we would proceed with an operative biliary bypass for those patients with a bile duct stent in place. There is nothing worse than having to deal with recurrent biliary stent occlusion in a patient who has had a laparotomy for PC but did not receive a biliary bypass; this is an avoidable situation.

The decision to also perform a gastrojejunostomy is made based on the extent of duodenal involvement and the presence or absence of liver or peritoneal disease. Peritoneal carcinomatosis is a particularly challenging pattern of failure and often the least responsive to systemic therapy. We, therefore, would consider a gastrojejunostomy in this setting only if the patient was symptomatic or there was clear anatomic evidence of impending duodenal obstruction. Before the advent of accurate preoperative cross-sectional imaging and routine diagnostic laparoscopy, the finding of advanced local or distant disease was a somewhat common event in patients with PC resulting in a significant body of literature on this topic. In frequently quoted randomized trials, patients with PC who underwent laparotomy for intended resection and were found to be unresectable at the time of operation were randomized to receive prophylactic hepaticojejunostomy or prophylactic hepaticojejunostomy with gastrojejunostomy. In those who received both a hepaticojejunostomy and a prophylactic gastrojejunostomy, no patient developed subsequent symptoms of gastric outlet obstruction before death. In contrast, of the patients who did not receive a gastrojejunostomy, symptoms of gastric outlet obstruction requiring intervention developed in 19% to 41%. Neither study identified increased morbidity, mortality, or differences in overall survival between the two surgical intervention arms. This early experience supported the routine use of double bypass at the time of a nontherapeutic laparotomy for patients with PC.

Although concomitant prophylactic gastric and biliary bypass at the time of nontherapeutic laparotomy has been the standard practice for many years, unresectability at the time of laparotomy is now a rare event. Therefore, many residents and even surgical oncology/HPB fellows have little experience with open operative double bypass. Our preferred approach is a retrocolic hepaticojejunostomy created with a Roux-en-Y limb. We usually create a defect in the transverse mesocolon to the patient's right of the middle colic artery; if this space cannot be easily developed, we make the defect to the left of the middle colic vessels. We remove the gallbladder if it is in place and divide the hepatic duct at the superior border of the indwelling metal stent. Usually, the metal stent cannot be removed. We close the distal bile duct, always culture the bile (as the bacteria contained herein are usually the same ones responsible for any subsequent infections), and create an end-to-side hepaticojejunostomy with interrupted monofilament absorbable suture. We typically have the knots on the inside for the back row and the knots on the outside for the anterior row. Intestinal continuity is restored approximately 40 to 50 cm downstream (caudal to the transverse mesocolon) with creation of a jejunojejunostomy.

If a gastrojejunostomy is also performed, we use the proximal jejunum, just distal to the ligament of Treitz, and proximal to the jejunojejunostomy. We typically create the Roux limb for the biliary anastomosis a generous distance (60–70 cm) from the ligament of Treitz. This form of double bypass has the advantage of diverting the bile from the stomach, thereby avoiding the complication of alkaline reflux gastritis. For the gastrojejunostomy, we create a separate defect in the transverse colon mesentery to the left of the middle colic artery. If there was inadequate room for the Roux limb to the right of the middle colic vessels, both the biliary limb and the proximal jejunum for the gastrojejunostomy can go through the same large defect in the transverse mesocolon to the left of the middle colic vessels. We favor a hand-sewn two-layer gastrojejunostomy fashioned to the posterior aspect of the distal stomach. The only risk of a gastrojejunostomy performed in this fashion is what we refer to as "cycling"; namely, the gastric contents can exit the stomach into the

duodenum (in the absence of tumor-associated obstruction at that time), then reenter the stomach at the site of the gastrojejunostomy, and continue in this circle, not exiting the gastrojejunostomy. This is a very rare complication and more common in patients where there is no significant narrowing of the duodenum.

Our Guiding Principles for the Management of Biliary and Duodenal Obstruction at the Time of Open Laparotomy

1. We virtually always perform a Roux-en-Y hepaticojejunostomy if we have an open abdomen and an unresectable situation due to locally advanced or distant metastatic disease.
2. We have a very low threshold to also perform a prophylactic gastrojejunostomy at the time of biliary bypass. We favor a retrocolic gastrojejunostomy performed proximal to the jejunojejunostomy.

PALLIATIVE PANCREATICODUODENECTOMY

A small volume of literature exists describing the benefits of palliative resection for patients with PC and much of this is confusing due to the incorrect use of the term "palliative". As previously mentioned, "palliative" refers to the relief of symptoms. It is incorrect to refer to an intervention (surgery or any other interventional procedure) as palliative simply because the entire tumor was *not* resected. For example, an incomplete resection at the time of pancreaticoduodenectomy (R1 or R2 resection) is often referred to as a palliative resection—this is an incorrect use of the term. We have performed just a handful of what we would consider to be a palliative pancreaticoduodenectomy. In such situations, we have typically had a patient with locally advanced or low volume metastatic disease who either experiences an endoscopic complication (perforation) or experiences uncontrolled hemorrhage due to tumor-induced ingrowth into the duodenum. These are often sudden, unexpected events and occur at the most inopportune times. Options may be very limited, and in the absence of best supportive care and pain control (end of life support), surgery may be the only option. We have encountered such situations approximately once every 5 years or so. In such situations, we have removed the duodenum and simply closed the pancreas, combined with a biliary and gastric anastomosis; an unattractive operation but one that allows time to discuss treatment and end of life goals with the patient and family.

MALIGNANT BOWEL OBSTRUCTION

Malignant bowel obstruction due to peritoneal carcinomatosis is an ominous complication in patients with PC and one without a good solution. These patients often suffer from severe, debilitating malnutrition and cancer cachexia that can be further exacerbated by malignant ascites. Malignant ascites essentially eliminates surgery as an option for almost any reason, as postoperative ascites usually becomes much worse than before the operation, and wound dehiscence is of significant risk. Relief of nausea and vomiting may require gastric decompression with a nasogastric tube in the acute setting and a venting gastrostomy tube for home management. In very select patients who have no ascites and very low volume disease, an operative exploration and surgical bypass may be considered. We have performed fewer than five or six such operations over the past decade, and they are rarely successful when the underlying cause is carcinomatosis due to PC. Adequate pain control with opioids is critically important, either by the intravenous or subcutaneous route, and can be transitioned to equivalent transdermal doses when the patient has a stable opioid requirement. Antisecretory agents may reduce splanchnic blood flow, intestinal secretions, and cramping abdominal pain; the somatostatin analogue octreotide has been effective for palliation in prospective trials. In addition, haloperidol is effective in relieving nausea and vomiting in patients with malignant bowel obstruction. In the authors' opinion, it is imperative to engage a palliative care specialist for these patients to aid in the transition to comfort care.

MALIGNANT ASCITES

Malignant ascites can lead to debilitating abdominal distension and early satiety. Ascites in the patient with PC is usually due to carcinomatosis; cytology may or may not be positive. In patients who have undergone a prior pancreaticoduodenectomy, occlusion of the superior mesenteric or portal vein may result in venous hypertension in the midgut and also cause intractable ascites. This cause of ascites is very rare in the absence of a prior operation. When occlusion of the superior mesenteric vein (SMV) or portal vein occurs over a long period of time, as is the case with locally advanced tumors of the pancreatic head or uncinate process, collaterals develop around the pancreatic head, thereby preventing mesenteric venous hypertension in almost all patients. When the pancreatic head has been removed (pancreaticoduodenectomy), such collaterals cannot develop; therefore, an occasional patient has developed either ascites or gastrointestinal hemorrhage due to mesenteric venous hypertension in the mid-gut. Extrahepatic portal hypertension of this etiology can be treated with a mesocaval bypass, and we have performed this operation in selected situations (see Suggested Readings).

For patients with malignant ascites, therapeutic paracentesis relieves symptoms, but continued fluid loss will, in general, hasten the demise of the patient. Plasma expanders, such as albumin, have been effective in preventing circulatory collapse and should be used with high volume paracenteses. In patients with an anticipated survival of less than 3 or 4 months, the placement of an indwelling pigtail or tunneled catheter to control ascites, with drainage at home, can be useful. In selected patients, we have also used a peritoneal-venous (Denver) shunt that diverts the ascites into the right internal jugular vein and the systemic venous system. This can be quite effective in some patients; however, catheter occlusion due to build-up of proteinaceous debris is somewhat common.

VASCULAR THROMBOSIS

The incidence of thromboembolic disease in patients with PC is higher than other metastatic cancers and ranges from 10% to 20% in clinical trials and as high as 50% in autopsy series. Thrombosis can occur in the mesenteric veins due to tumor compression or in the peripheral veins due to the overall hypercoagulable state. Narrowing or thrombus within the SMV or portal vein should be treated with anticoagulation therapy whenever possible to prevent propagation of the thrombus to complete occlusion; this is especially important in patients who are receiving neoadjuvant therapy and have an option for surgical resection with vascular reconstruction. An acute thrombus in the mesenteric venous system, splenic vein, or other extraabdominal sites is typically treated with enoxaparin at therapeutic doses. In patients with tumors in the pancreatic head or uncinate process where there is any degree of narrowing of the SMV or portal vein, we prefer at least half-dose therapy, usually with a direct oral anticoagulant (rivoraxaban if there is a biliary stent in place and apixaban if there is no risk for hyperbilirubinemia and liver dysfunction). If mesenteric venous thrombosis occurs during neoadjuvant therapy, it can convert an operable situation into an inoperable one. This is a rare complication, but when it occurs, it is devastating for the patient and their family. Overall, we feel that anticoagulation of some kind is underutilized in patients with PC who are receiving active anticancer therapies.

TUMOR-ASSOCIATED PAIN MANAGEMENT

Patients with unresectable PC often suffer from tumor-associated abdominal and back pain due to direct tumor infiltration of the celiac ganglion. Effective pain management often requires opioid analgesia,

which can have debilitating side effects, including dizziness and sedation. More recently, the trend in pain management has been to optimize pain control with the lowest dose of opioids in combination with other adjunct analgesics to provide effective and consistent pain control.

Celiac plexus block has become increasingly utilized in the treatment of PC-related pain symptoms. A celiac plexus block involves injecting a 50% alcohol solution or other neurolytic agent into the celiac ganglion or splanchnic nerves under CT, EUS, or fluoroscopic guidance. In the event a patient undergoes a nontherapeutic laparotomy, a celiac plexus block may also be performed at that time. Over 80% of patients experience improvement in pain control after a celiac plexus block in blinded or sham studies, as measured by reduction of opioid requirements. Studies have demonstrated improved pain scores at 4 and 8 weeks with a celiac plexus block compared with narcotic therapy alone; a meta-analysis of patients who received a celiac plexus block demonstrated pain relief in 90% at 3 months, and relief persisted long-term in 70% to 90% of patients. Short-term effects related to celiac plexus block include diarrhea, hypotension, and pain related to the procedure, which typically resolve with time. In fact, the presence of diarrhea associated with the performance of the block is one way to be sure that the block was placed in the correct location. For patients with potentially operable PC, we avoid celiac blocks for two reasons: first, the improvement/resolution of a patient's pain is a useful clinical parameter for assessment of response to chemotherapy; and second, dissection of the celiac and SMA origins can be more difficult after a celiac block. For patients with more advanced disease, celiac plexus block should be considered in the initial pain management plan and may be repeated in patients who demonstrated a prior benefit from neurolysis.

DEPRESSION

The rates of depression and suicide among patients with PC are the highest in any cancer population. Elevated levels of circulating cytokines such as interleukin-6 and tumor necrosis factor-α are thought to alter neurohormonal pathways in the brain causing depressive symptoms even before the diagnosis of cancer. Studies report that depression occurs in one- to two-thirds of patients and has a significant impact on quality of life. Many symptoms of depression mimic symptoms associated with PC itself (fatigue, anorexia, weight loss), complicating the diagnosis of depression. However, asking a patient whether they have "felt depressed most of the time" is a validated tool with good sensitivity and specificity for identifying depression even among patients who are terminally ill. Antidepressants are effective in patients with advanced cancers, and supportive counseling may help patients to strengthen coping strategies. An early referral to a psychologist or palliative care specialist can be beneficial to all patients regardless of stage of disease; we have incorporated a full-time psychologist within our multidisciplinary PC program.

CONCLUSION

The initial management of bile duct and duodenal obstruction can often facilitate or completely unravel the initial management of the patient with PC. In this chapter, we have tried to clarify our approach to the palliation of biliary and gastric outlet obstruction based on the stage of disease and goals of therapy. The patient with PC presents a series of complex clinical challenges, which often result in frustration and disappointment on the part of the patient and their family; it is critically important that the same emotions are not present in the treatment team. The multidisciplinary team of physicians, advanced practice providers, and all members of the program need to embrace the complexity of patient management and develop consistent strategies for optimizing patient performance status, liver function, and nutritional support as only then can potentially effective anticancer therapy be considered. As neoadjuvant therapy for operable disease has become more commonly applied to patients with localized PC, especially in the clinical trial setting, the importance of managing bile duct and duodenal obstruction has been brought forward with a clarity not previously appreciated. Healthcare delivery in the United States continues to move in the direction of large integrated systems, involving many hospitals and points of care, providing an opportunity to streamline the initial diagnosis and management of the patient with PC.

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Neoadjuvant and Adjuvant Therapy for Pancreatic Cancer

Lawrence W. Wu, MD, and Daniel A. Laheru, MD

Pancreatic ductal adenocarcinoma is an aggressive malignancy with high mortality. The only possibility of long-term cure involves a complete, microscopically negative (R0) resection. However, there is still high mortality after R0 resection due to recurrence from the presence of radiographically occult micrometastatic disease. As such, chemotherapy is used for all stages of disease, including resectable, borderline resectable, and locally advanced disease. In this chapter, we delineate the most updated stage-specific recommendations.

DEFINING THE CLINICAL STAGE OF DISEASE

The American Joint Commission on Cancer staging of pancreatic adenocarcinoma follows the Tumor, Node, Metastasis framework. This staging system can provide valuable prognostic information. However, it is limited in the preoperative setting because it does not indicate whether a tumor is resectable. The National Comprehensive Cancer Network (NCCN) defines resectability as resectable, borderline resectable, locally advanced, and metastatic (Table 1). These criteria are based on the tumor relationship to vascular anatomy and presence of extrapancreatic disease. Pancreatic protocol computed tomography (CT) scan of the abdomen/pelvis is used to assess the tumor, its relationships to critical vasculature, and presence of intraabdominal metastases.

Resectable pancreatic cancer (Fig. 1A) is defined by a primary tumor that does not contact any arterial vessel (celiac artery [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]) and does not contact the superior mesenteric vein (SMV) or portal vein (PV), or contacts the SMV/PV less than 180 degrees without vein contour irregularity. Borderline resectable disease (Fig. 1B) is defined by limited tumor contact less than 180 degrees with the SMA or CA and without involvement of aorta or uninvolved gastroduodenal artery, contact with CHA without extension to CA or hepatic artery bifurcation or contact with the SMV/PV more than 180 degrees, contact less than 180 degrees with contour irregularity of vein, tumor contact with inferior vena cava, or short segment SMV/PV thrombosis amenable to resection and vein reconstruction. Locally advanced disease (Fig. 1C) includes more than 180-degree involvement of the SMA or CA, or extensive involvement of the SMV/PV without proximal and distal targets for vascular reconstruction. Extensive SMA involvement is considered unresectable because of the poor survival and higher morbidity and mortality expected following SMA resection. Unfortunately, the potential presence of radiographically undetectable micrometastases limits this framework. Nonetheless, this staging system is key for determining the next steps of clinical management.

RESECTABLE PANCREATIC CANCER

For resectable pancreatic cancer, surgery followed by adjuvant therapy has traditionally been the preferred modality of treatment. A complete surgical excision of the pancreatic cancer is the only opportunity for cure, and an upfront surgery captures the disease at a timepoint when it is in a resectable state. Adjuvant chemotherapy should occur within 8 weeks of surgical resection, assuming adequate recovery from the procedure. Before adjuvant therapy, a formal restaging CT scan and serum CA 19-9 should be performed.

Per NCCN, the preferred adjuvant therapies are modified FOLFIRINOX (oxaliplatin, irinotecan, leucovorin and short-term fluorouracil) or gemcitabine plus capecitabine. Modified FOLFIRINOX should be limited to those with ECOG 0-1, and thus gemcitabine plus capecitabine may be more suitable for patients with lower performance status. In the PRODIGE-24/CCTG PA-6 trial, patients who underwent R0 or R1 resection and with ECOG performance status 0 or 1 had improved survival with adjuvant modified FOLFIRINOX over adjuvant gemcitabine alone (21.6 months vs. 12.8 months, hazard ratio 0.58, 95% CI 0.46–0.73). In the ESPAC-4 trial, patients who underwent R0 or R1 resection had improved survival with adjuvant gemcitabine plus capecitabine over adjuvant gemcitabine alone (28.0 months vs. 25.5 months, hazard ratio 0.82, 95% CI 0.68–0.98). There

TABLE 1 Definition of Resectability Status Used by the National Comprehensive Cancer Network (NCCN)

RESECTABLE	
Tumor-artery relationship	No radiographic evidence of arterial contact [celiac artery (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA)].
Tumor-vein relationship	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180 degrees contact without vein contour irregularity
BORDERLINE RESECTABLE	
Tumor-artery relationship	Tumor contact ≤180 degrees of SMA or CA. Tumor contact >180 degrees of the CA without involvement of aorta and uninvolved gastroduodenal artery. Tumor contact with CHA without extension to CA or hepatic artery bifurcation. Tumor contact with variant arterial anatomy (e.g., accessory right hepatic artery).
Tumor-vein relationship	Tumor contact of SMV or PV >180 degrees, tumor contact ≤180 degrees with contour irregularity of vein, tumor contact with inferior vena cava, or short segment SMV/PV thrombosis amenable to resection and vein reconstruction.
LOCALLY ADVANCED	
Tumor-artery relationship	Tumor contact (>180 degrees) of SMA or celiac artery, or contact with CA and aortic involvement.
Tumor-vein relationship	Occlusion of SMV, PV, or SMV-PV without suitable vessels above and below the tumor to allow for reconstruction (no distal or proximal target for vascular reconstruction).

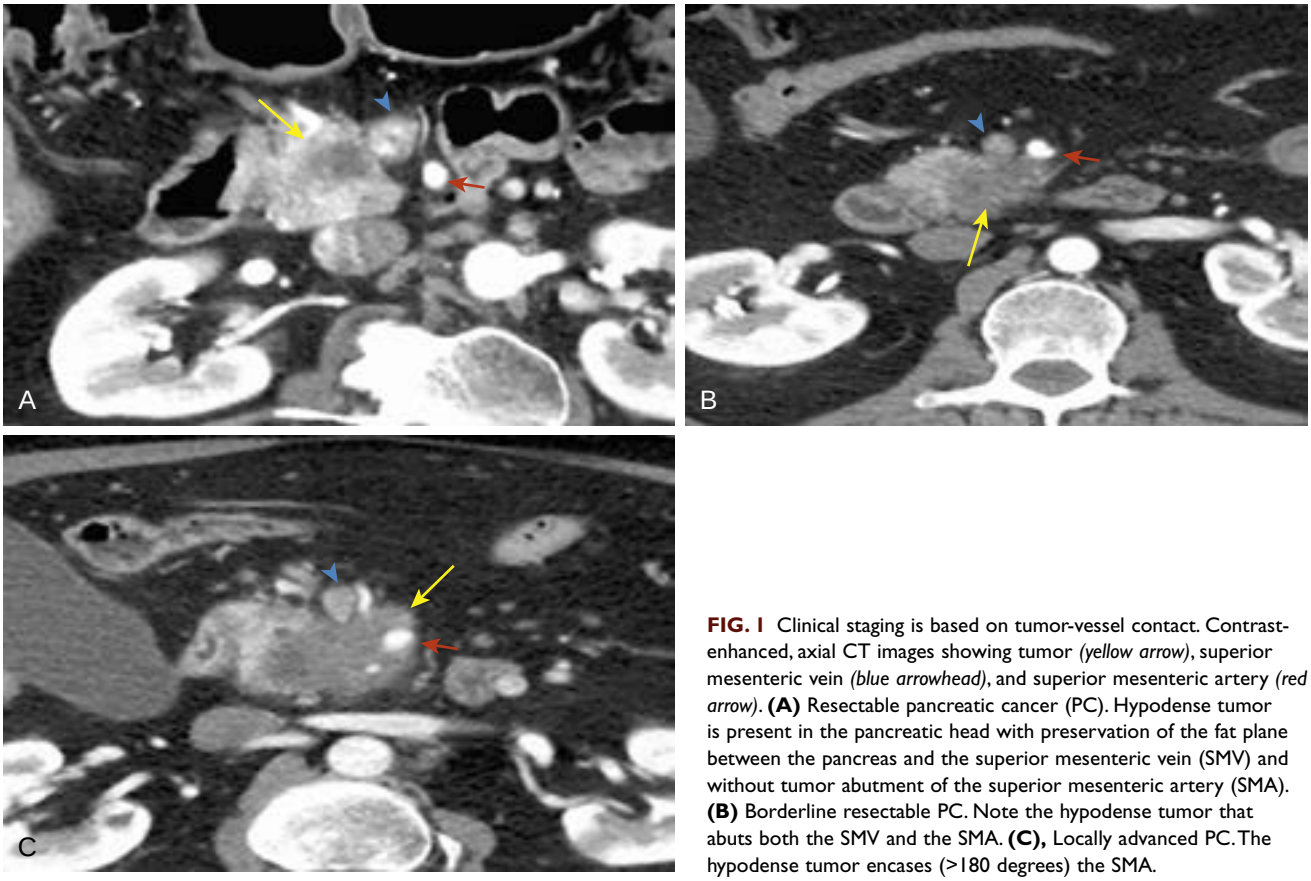


FIG. 1 Clinical staging is based on tumor-vessel contact. Contrast-enhanced, axial CT images showing tumor *(yellow arrow)*, superior mesenteric vein *(blue arrowhead)*, and superior mesenteric artery *(red arrow)*. **(A)** Resectable pancreatic cancer (PC). Hypodense tumor is present in the pancreatic head with preservation of the fat plane between the pancreas and the superior mesenteric vein (SMV) and without tumor abutment of the superior mesenteric artery (SMA). **(B)** Borderline resectable PC. Note the hypodense tumor that abuts both the SMV and the SMA. **(C),** Locally advanced PC. The hypodense tumor encases (>180 degrees) the SMA.

are no trials directly comparing modified FOLFIRINOX or FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) versus gemcitabine plus capecitabine. In the 5-year update for the APACT trial, patients who underwent R0 or R1 resection with ECOG performance status 0 or 1 had improved survival with adjuvant gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel over adjuvant gemcitabine alone (41.8 months vs. 37.7 months, hazard ratio 0.80, 95% CI 0.68–0.95). The full trial results have not been published yet and are not reflected in any of the major treatment guidelines. Gemcitabine alone may be considered for patients with poorer performance status who may not tolerate multiagent therapy, but this comes at increased risk for recurrence.

The role for adjuvant radiation is controversial. In the ESPAC-1 trial, patients who underwent R0 resection were randomized to observation, chemotherapy with fluorouracil and leucovorin, chemoradiotherapy with 20-Gy in 10 daily fractions and fluorouracil, or chemoradiotherapy followed by chemotherapy. There was worse survival in patients treated with any chemoradiotherapy compared with those not treated with any chemoradiotherapy (15.9 months vs. 17.9 months, hazard ratio 1.28, 95% CI 0.99–1.66). The EORTC 40013-22012/FFCD-9203/ GERCOR Phase II study found chemoradiation (gemcitabine + 50.4 Gy in 28 fractions for 5–6 weeks) decreased local recurrence (11% vs. 24%) compared with chemotherapy with gemcitabine alone. However, disease-free survival and overall survival were not statistically different.

The role of neoadjuvant chemotherapy as an alternative to immediate surgery followed by adjuvant chemotherapy is controversial. Delaying immediate surgery during a resectable phase of the disease creates a risk of progression where the tumor becomes inoperable. The neoadjuvant chemotherapy treatment route requires tissue biopsy, which is another procedure that may result in morbidity. Biliary stenting is another procedure that may occur in the interim period between neoadjuvant therapy and surgery that results in additional morbidity.

The benefits of neoadjuvant chemotherapy are likely highest in high-risk, potentially resectable tumors (i.e., highly elevated CA 19-9 >200, large primary tumors, large regional lymph nodes). The benefits of neoadjuvant therapy include (1) the early treatment of micrometastatic disease, which is common and can lead to early postoperative recurrences; (2) enhanced patient selection (patients who do not tolerate neoadjuvant therapy would not benefit from a major resection; disease progression on neoadjuvant therapy indicates more aggressive disease characteristics); (3) improved delivery and completion rates; (4) decreased rate of pancreatic fistula formation; and (5) enhanced efficacy of chemoradiotherapy (given the well-oxygenated environment), with corresponding higher negative margin resection and lymph node-negative rates (Box 1).

The PREOPANC trial randomized patients with borderline resectable or potentially resectable pancreatic cancer (approximately 50% each) to neoadjuvant chemoradiotherapy with gemcitabine or to immediate surgery followed by adjuvant gemcitabine. R0 resection rate was significantly higher with neoadjuvant therapy (71% vs. 40%). There was increased but not statistically significant improvement in median survival with neoadjuvant therapy versus immediate surgery (16 months vs. 14.3 months, hazard ratio 0.78, 95% CI 0.58–1.05). Neoadjuvant therapy was associated with higher rates of serious (grade 3 or higher) adverse events compared with immediate surgery (52% vs. 41%). The phase II PACT-15 trial randomized patients with resectable pancreatic cancer to immediate surgery followed by 6 months of adjuvant gemcitabine; immediate surgery followed by 6 months of adjuvant cisplatin, epirubicin, gemcitabine, and capecitabine (PEGX); or three cycles of neoadjuvant PEGX before surgery and three cycles of adjuvant PEGX. The median overall survival was 38.2 months for the neoadjuvant PEGX group compared with 20.4

BOX 1 Potential Advantages and Disadvantages of Neoadjuvant Therapy

Advantages

- Ability to deliver systemic therapy to all patients
- Identification of patients with aggressive tumor biology (manifested as disease progression) at the time of posttreatment and preoperative restaging who thereby avoid the toxicity of surgery
- Increased efficacy of radiation therapy; free radical production in a well-oxygenated environment
- Decreased radiation-induced toxicity to adjacent normal tissue because the radiated field is resected at the time of pancreatectomy
- Decreased rate of positive resection margins; superior mesenteric artery margin in particular
- Decreased rate of pancreatic fistula formation
- Potential for the tumor size to decrease, especially in borderline resectable tumors, which may facilitate surgical resection

Disadvantages

- Potential for complications from pretreatment endoscopic procedures (endoscopic ultrasound scan and fine-needle aspiration, and endoscopic retrograde cholangiopancreatography)
- Biliary stent–related morbidity; stent occlusion during neoadjuvant therapy
- Disease progression obviating resectability; loss of a window of resectability may occur (rarely) in the borderline resectable patient
- Coordination of multiple physicians during the preoperative phase; discrete handoff from surgeon to medical oncologist to radiation oncologist (as occurs with adjuvant therapy) is not possible in the neoadjuvant setting

months with adjuvant gemcitabine or 26.4 months with adjuvant PEGX. A phase III trial was not pursued, because the standard of care for adjuvant therapy had changed. The preferred neoadjuvant chemotherapy is modified FOLFIRINOX followed by chemoradiotherapy, which is based on evidence primarily from the borderline resectable pancreatic cancer patient population.

All patients with resectable pancreatic cancer should receive chemotherapy. The current evidence supports immediate surgery followed by adjuvant chemotherapy for a total of 6 months. However, if there are high-risk tumor features, it is reasonable to consider neoadjuvant therapy as the patient may have borderline resectable pancreatic cancer.

BORDERLINE RESECTABLE PANCREATIC CANCER

The goal of surgery in pancreatic cancer is to have a R0 resection, which is the only outcome that has a possibility of long-term cure. Patients with borderline resectable disease are at higher risk for incomplete resection, which portends a similar survival rate to those who did not undergo any surgery. Neoadjuvant chemotherapy should be utilized in most cases to improve the chance of an R0 resection.

The preferred regimens are FOLFIRINOX, modified FOLFIRINOX followed by chemoradiation if ECOG 0-1, or gemcitabine plus nab-paclitaxel followed by chemoradiation. For patients with known germline or tumor *BRCA1/2* or *PALB2* mutations, then the preferred regimens are FOLFIRINOX, modified FOLFIRINOX followed by chemoradiation if ECOG 0-1, or gemcitabine and cisplatin followed by chemoradiation. The rationale behind the different chemotherapy is due to increased evidence of increased sensitivity to platinum agents as these mutations are in genes necessary for homologous recombination repair (HRR), which repairs DNA damage. Other related HRR genes include *ATM*, *BAP1*, *BARD1*, *BLM*, *BRIP1*, *CHEK2*, *FAM175A*, *FANCA*, *FANCC*, *NBN*, *RAD50*, *RAD51*, *RAD51C*, and *RTEL1*.

The rationale behind these chemotherapy regimens in the borderline resectable and locally advanced setting stems from survival benefit shown in large phase III studies for metastatic pancreatic cancer. The MPACT trial randomized patients with metastatic pancreatic cancer to gemcitabine and nab-paclitaxel versus gemcitabine alone. There was improved survival in the gemcitabine and nab-paclitaxel group (8.5 months vs. 6.7 months, hazard ratio 0.72, 95% CI 0.62–0.83). This survival benefit comes with increased neutropenia (38% vs. 27%) and peripheral neuropathy (17% vs. 1%). The PRODIGE4/ACCORD11 trial randomized patients with metastatic pancreatic cancer to FOLFIRINOX versus gemcitabine. There was improved survival in the FOLFIRINOX group (11.1 months vs. 6.8 months, hazard ratio 0.57, 95% CI 0.45–0.73). This survival benefit comes with increased neutropenia (45.7% vs. 21%) and peripheral neuropathy (9% vs. 0%).

The PREOPANC trial as mentioned previously found significantly higher R0 resection with neoadjuvant chemoradiotherapy therapy compared with immediate surgery (71% vs. 40%). However, survival benefit was not statistically significant (16 months vs. 14.3 months, hazard ratio 0.78, 95% CI 0.58–1.05). The ESPAC-5F trial randomized for patients with borderline resectable cancer to immediate surgery, neoadjuvant gemcitabine plus capecitabine, neoadjuvant FOLFIRINOX, or chemoradiotherapy with capecitabine. The preliminary report found 1-year survival rate higher in neoadjuvant therapy compared with immediate surgery (77% vs. 42%). The R0 resection rate was 23% vs. 15% for neoadjuvant therapy compared with immediate surgery.

The data with regard to adding radiotherapy to neoadjuvant chemotherapy is mixed. The Phase II Study of Preoperative FOLFIRINOX Followed by Accelerated Short Course Radiation Therapy for Borderline-Resectable Pancreatic Cancer selected patients with borderline resectable cancer and ECOG 0-1 to be treated with eight cycles of neoadjuvant FOLFIRINOX. After restaging imaging, patients with resolution of vascular involvement were treated with short-course chemoradiotherapy with capecitabine, and those with persistent vascular involvement were treated with long-course chemoradiotherapy with fluorouracil or capecitabine. Ultimately, 27 patients (56%) had short-course chemoradiotherapy and 17 patients (35%) had long-course radiotherapy. R0 resection was obtained in 31 study patients (65%) and obtained in 97% of the patients who underwent resection. The median overall survival of all patients was 37.7 months. The Alliance A021501 trial randomized patients with borderline resectable cancer and ECOG 0-1 to neoadjuvant modified FOLFIRINOX with radiotherapy or to neoadjuvant modified FOLFIRINOX alone. Preliminary results from the trial found the R0 resection rate was greater in the neoadjuvant chemotherapy alone group compared with neoadjuvant chemoradiation (42% vs. 25%). The median overall survival was also greater in the neoadjuvant chemotherapy alone group compared with neoadjuvant chemoradiation (31 months vs. 17.1 months).

Neoadjuvant chemotherapy remains the best option to improve the likelihood of a R0 resection. FOLFIRINOX or modified FOLFIRINOX are the most promising chemotherapy options for those who can tolerate it. The exact timing and duration of neoadjuvant chemotherapy and the benefit of radiotherapy are being studied in several ongoing trials and will help optimize treatment for this stage of pancreatic cancer.

LOCALLY ADVANCED PANCREATIC CANCER

Locally advanced pancreatic cancer is nonmetastatic but unresectable due to the tumor's location relative to critical local vasculature.

The goal is to potentially obtain a R0 resection given its curative potential. Several studies have shown that intensive chemotherapies may result in downstaging of the tumor for resection in a small proportion of patients. The preferred chemotherapy regimens are the same as in borderline resectable pancreatic cancer, which are FOLFIRINOX, modified FOLFIRINOX if ECOG 0-1, or gemcitabine plus nab-paclitaxel. For patients with known germline or tumor *BRCA1/2* or *PALB2* mutations, then the preferred regimens are FOLFIRINOX, modified FOLFIRINOX if ECOG 0-1, or gemcitabine plus cisplatin.

The NEOLAP trial randomized patients with localized pancreatic cancer to induction gemcitabine plus nab-paclitaxel followed by gemcitabine plus nab-paclitaxel versus induction gemcitabine plus nab-paclitaxel followed by FOLFIRINOX. Median overall survival was statistically unchanged (18.5 months vs. 20.7 months), and R0 resection rate was not statistically different. However, the overall conversion rate to surgical resection was 32%. This was the first clinical trial that required explorative laparotomy in all patients without radiographic evidence of disease progression, which may have also contributed to high surgical conversion rates. The LAPACT trial was a single-arm trial with patients with locally advanced pancreatic cancer who were treated with induction chemotherapy gemcitabine plus nab-paclitaxel followed by investigator's choice of continued chemotherapy, chemoradiation, or surgery. Of the patients in the study, 15% underwent surgical resection (7% R0, 8% R1 resection) demonstrating some feasibility of downstaging. For patients with poor performance status with ECOG ≥2, single-agent gemcitabine is a reasonable alternative.

The role of radiotherapy is controversial, and clinical trials have found no survival benefit to initial neoadjuvant chemoradiotherapy versus initial neoadjuvant chemotherapy alone. There may be a role for chemoradiotherapy after initial chemotherapy. Several single center institutional retrospective studies have found improved resection rates and modest survival benefits, but this has not borne out in randomized trials yet. The LAP07 trial randomized patients with locally advanced pancreatic cancer at two different points. First, the patients were randomized to neoadjuvant gemcitabine versus neoadjuvant gemcitabine and erlotinib. The patients were randomized again to the same chemotherapy or chemoradiotherapy if they had 4 months of progression-free survival. Chemoradiotherapy was associated with decreased locoregional tumor progression (32% vs. 46%). However, there was no statistically different survival between chemotherapy versus chemoradiotherapy (16.5 months vs. 15.2 months, hazard ratio 1.03, 95% CI 0.79–1.34).

If a patient has good performance status with a significant radiographic response and stable or decreasing CA19-9, then surgery should be strongly considered if the patient meets resectability criteria.

CONCLUSION AND FUTURE DIRECTIONS

The paradigm of treatment for pancreatic cancer has evolved significantly. One integrated approach based on the most recent evidence and guidelines is summarized in Figure 2 and Table 2. There are several ongoing clinical trials aimed at addressing several of the questions posed earlier in the chapter. These include neoadjuvant chemotherapy for resectable pancreatic cancer, the optimal adjuvant and neoadjuvant therapies, and the role of radiation therapy. The only possibility of a long-term cure for pancreatic adenocarcinoma involves an R0 resection. Even with an R0 resection, the overall survival rates are quite poor given relatively high risk of recurrence and presence of micrometastatic disease.

There is ongoing development of novel therapeutics for systemic disease, which has resulted in significant research in systemic therapies targeting multiple mechanisms including angiogenesis, receptor tyrosine kinases, and insulin-growth-factor-1. However, these therapies have largely been unsuccessful. Besides the FOLFIRINOX and gemcitabine regimens mentioned previously, there have been a few other promising regimens in a limited set of circumstances. Immunotherapy with pembrolizumab should be considered if the patient's tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR). Poly(ADP-ribose) polymerase (PARP) inhibitors such as olaparib should be considered in patients with germline BRCA1/2 or PALB2 mutations. Neurotrophic tyrosine receptor kinase (NTRK) inhibitors such as larotrectinib or entrectinib should be considered if the tumor is positive for NTRK gene fusion. Unfortunately, these promising therapies apply to a very small minority of pancreatic cancer patients.

Overall, there have been tremendous advances in chemotherapy regimens and timing, standardized staging systems, and imaging

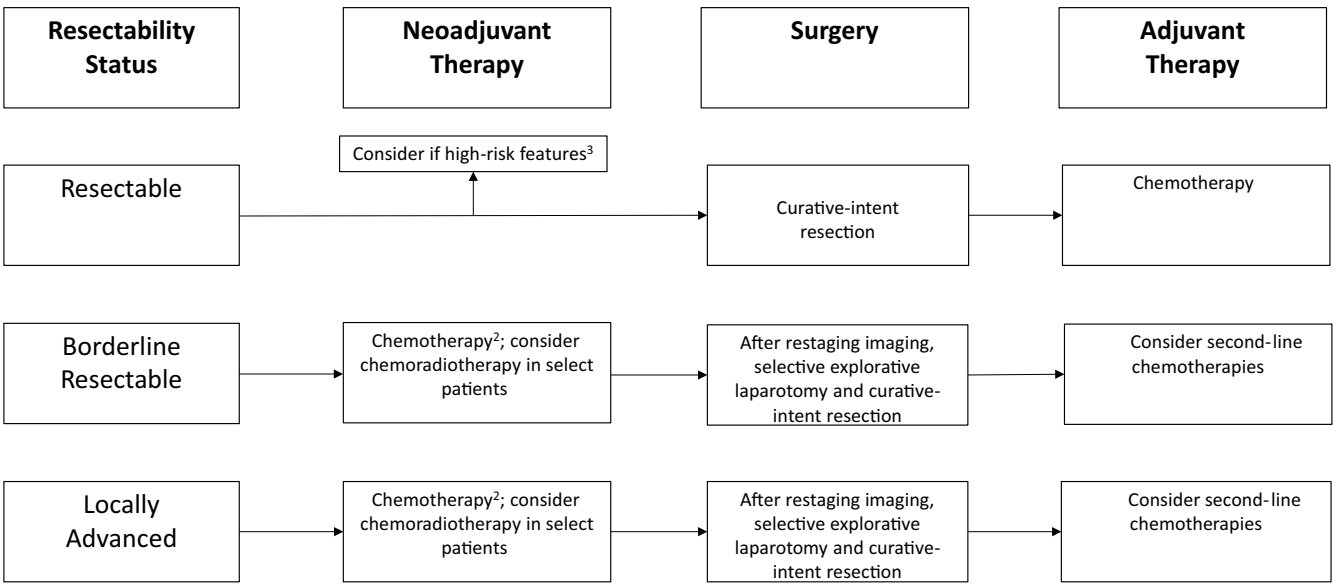


FIG. 2 Integrated approach to pancreatic cancer based on resectability. In all cases, consider enrollment in clinical trial.
[1]Modified FOLFIRINOX or gemcitabine plus capecitabine if good performance status.
[2]FOLFIRINOX or modified FOLFIRINOX, or gemcitabine plus nab-paclitaxel if good performance status.
[3]Highly elevated CA19-9>200, large primary tumors, large regional lymph nodes.

TABLE 2 Key Clinical Trials in Pancreatic Cancer

Study (Year)	Patient Number	Resectability	Intervention	Key Outcomes
ESPAC-1 (2004)	289	Resectable	1. Observation 2. Chemotherapy with fluorouracil + leucovorin 3. Chemoradiation with 20-Gy in 10 daily fractions and fluorouracil 4. Chemoradiation followed by chemotherapy	Worse survival in patients treated with any chemoradiotherapy compared with no chemoradiotherapy (15.9 months vs. 17.9 months)
ESPAC-4 (2017)	732	Resectable	1. Adjuvant gemcitabine and capecitabine 2. Adjuvant capecitabine	Improved survival 28.0 months vs. 25.5 months
PRODIGE-24/CCTG PA-6 (2018)	493	Resectable	1. Adjuvant modified FOLFIRINOX 2. Adjuvant gemcitabine	Improved survival 21.6 months vs. 12.8 months
EORTC 40013-22012/ FFCD-9203/ GERCOR (2010)	90	Resectable	1. Chemoradiation with gemcitabine 2. Adjuvant gemcitabine alone	Decreased local recurrence (11% vs. 24%) Disease-free survival and overall survival were not statistically different
APACT (preliminary results) (2021)	866	Resectable	1. Adjuvant gemcitabine plus nab-paclitaxel 2. Adjuvant gemcitabine	Improved survival 41.8 months vs. 37.7 months
Alliance A021501 (preliminary results) (2021)	126	Borderline resectable	1. Neoadjuvant chemotherapy with modified FOLFIRINOX 2. Neoadjuvant chemoradiotherapy with modified FOLFIRINOX	R0 resection rate higher in neoadjuvant chemotherapy alone (42% vs. 25%) Overall survival improved with neoadjuvant chemotherapy alone (31 months vs. 17.1 months)
PREOPANC (2020)	246	Resectable and borderline resectable	1. Neoadjuvant chemoradiotherapy with gemcitabine 2. Immediate resection followed by adjuvant gemcitabine	R0 resection rate was significantly higher with neoadjuvant therapy (71% vs. 40%) No statistically significant improvement in median survival
LAP07 (2016)	449	Locally advanced	1. Neoadjuvant gemcitabine with chemoradiation 2. Neoadjuvant gemcitabine with additional chemotherapy	No statistically significant survival difference
NEOLAP (2021)	165	Locally advanced	1. Gemcitabine and nab-paclitaxel followed by gemcitabine and nab-paclitaxel 2. Gemcitabine and nab-paclitaxel followed by FOLFIRINOX	High overall R0 resection rate (32%)
MPACT (2013)	861	Metastatic	1. Gemcitabine + nab-paclitaxel 2. Gemcitabine	Overall survival improved (8.5 months vs. 6.7 months)
PRODIGE 4/ACCORD 11 (2011)	342	Metastatic	1. FOLFIRINOX 2. Gemcitabine	Overall survival improved (11.1 months vs. 6.8 months)

modalities. These advances will serve as the backbone for ongoing research and further development of therapeutics in this field.

Suggested Readings

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Rare and Unusual Pancreatic Tumors

Jon M. Harrison, MD, and Carlos Fernandez-del Castillo, MD

INTRODUCTION

Although pancreatic ductal adenocarcinoma (PDAC), intraductal papillary mucinous neoplasm (IPMN), and pancreatic neuroendocrine tumor (PNET) are the most common indications for pancreatectomy, rarer pancreatic neoplasms and masses may warrant resection. These include cystic, epithelial, and mesenchymal tumors as well as inflammatory processes and other malignancies, all of which can masquerade as a more sinister pathology. As such, recognizing these less common pancreatic lesions is important for proper clinical management. In this chapter, the relevant clinical, histopathologic, and management options for several rare and unusual pancreatic lesions will be discussed (Box 1).

BOX 1 Rare and Unusual Pancreatic Tumors

Cystic Lesions

Benign
- Serous cystadenoma (SCA)
- Lymphoepithelial cyst (LEC)

Neoplastic
- Mucinous cystic neoplasm (MCN)
- Solid-pseudopapillary neoplasm (SPN)

Epithelial Cell Tumors
- Acinar cell carcinoma (ACC)
- Pancreatoblastoma (PBA)

Mesenchymal Cell Tumors
- Perivascular epithelioid cell tumor (PEComa)
- Solitary fibrous tumor (SFT)

Inflammatory Masses and Additional Malignancies

Inflammatory masses
- Groove pancreatitis
- Autoimmune pancreatitis

Additional malignancies
- Pancreatic lymphoma (PL)
- Metastases

BENIGN PANCREATIC CYSTS

Serous Cystadenoma

Serous cystadenoma (SCA) is a benign, nonmucinous lesion that accounts for 33% of pancreatic cysts. They are distributed throughout the pancreas and generally occur in postmenopausal females. The more common microcystic variant has a distinctive honeycomb appearance (Fig. 1) or central, calcified scar, which can be appreciated on axial imaging. A less common macrocystic variant lacks this characteristic appearance. The epithelial lining of either type, however, is composed of cuboidal, glycogen-rich cells that are thought to arise from the centroacinar cells of the pancreatic ductal system (see Fig. 1). Although most SCAs are sporadic, the lifetime risk for development in patients with von Hippel-Lindau syndrome approaches 40%.

The majority of SCAs are discovered incidentally, but some patients may present with nonspecific abdominal pain, a palpable mass, or obstructive symptoms. In instances of the macrocystic variant, a more extensive workup with endoscopic ultrasound (EUS), fine-needle aspiration (FNA), and cyst fluid sampling may be necessary to rule out similar-appearing pathologies such as IPMN, mucinous cystic neoplasm (MCN), or cystic PNET. In general, SCA fluid has low carcinoembryonic antigen (CEA) and amylase levels; however, cytologic atypia is a common finding that may confound the diagnosis.

In terms of management, SCAs should be considered for resection in patients with pain or obstructive symptoms. A Whipple procedure is required for proximal lesions, whereas a middle or distal pancreatectomy without splenectomy can be considered for body and tail SCAs. Although an exceedingly rare invasive form of SCA (serous cystadenocarcinoma) has been historically described, updated series question the authenticity of this tumor. As a result, formal lymphadenectomy is not necessary for complete resection.

Lymphoepithelial Cyst

First described in 1985, the lymphoepithelial cyst (LEC) is a much rarer (0.5%) and often incidentally discovered benign cystic lesion. Unlike SCAs and other pancreatic cysts, LECs are more common in middle-aged males, and its histologic hallmarks include a keratinized stratified squamous epithelium, which produces caseous cyst contents, and a subepithelial germinal center full of monomorphic lymphocytes (Fig. 2). This latter feature suggests that LECs may arise from tertiary lymphoid structures; however, other etiologies including cystic degeneration, pancreatic duct metaplasia, or a teratoma-like origin have also been purported. On imaging, an LEC appears as a well-circumscribed, unilocular or multilocular lesion but can occasionally become secondarily infected or rupture (see Fig. 2). Some LECs may also have elevated tumor markers or be mistaken for MCNs given their similar imaging characteristics. Management of LECs consists of segmental resection or enucleation

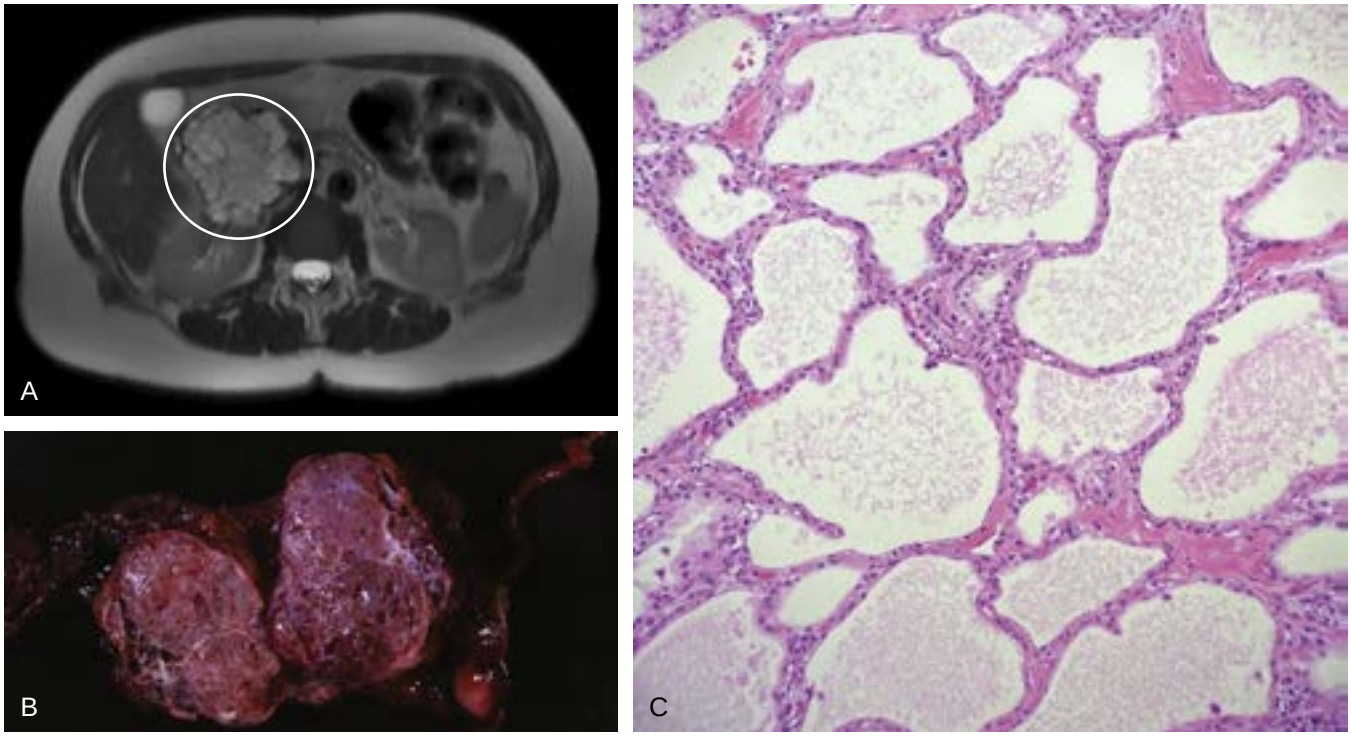


FIG. 1 Serous cystadenoma (SCA). **(A)** T2 MRI reveals an 8.5-cm multilobulated pancreatic head cyst. **(B)** SCA gross pathology demonstrates many small cysts in a honeycombing pattern. **(C)** Large, multicystic spaces lined by bland cuboidal cells on SCA histopathology.

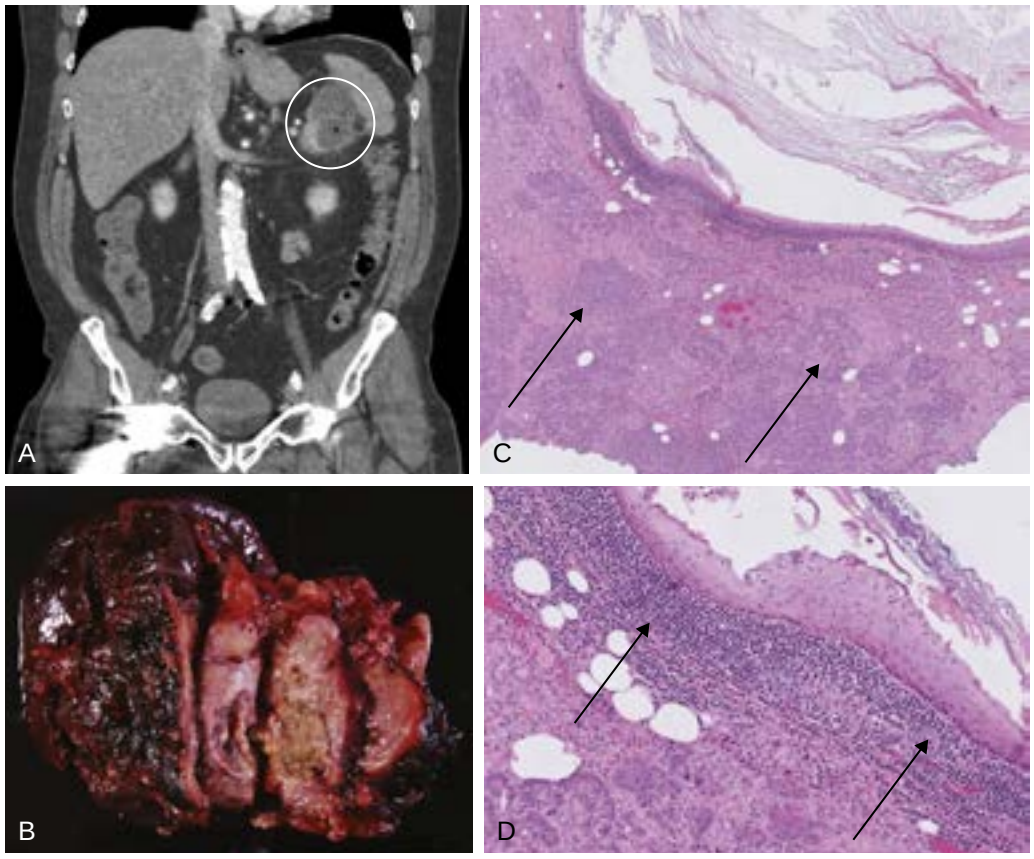


FIG. 2 Lymphoepithelial cyst (LEC). **(A)** CT shows a 6.6-cm multilobulated pancreatic tail cyst with foci of intralesional air and pericystic inflammation, **(B)** Gross pathology shows caseous material extruding from the cyst core formed from a keratinized epithelial lining. **(C)** Prominent germinal centers *(arrows)* characteristic of LEC histology. **(D)** Magnified view reveals a subepithelial layer *(arrows)* composed of monomorphic lymphocytes.

depending on anatomic location. Internal drainage may also be considered for poor surgical candidates.

NEOPLASTIC PANCREATIC CYSTS

Mucinous Cystic Neoplasm

MCNs represent 25% of pancreatic cysts and 2% of all pancreatic neoplasms. They are commonly found in the pancreatic body and tail and occur almost exclusively in perimenopausal females. This gender predisposition is related to the pathophysiology of MCNs as this neoplasm is thought to arise from the gonadal tissue that abuts the fetal pancreas before descending into the pelvis. These tumors are hormonally sensitive, and histologically, a classic subepithelial layer of ovarian-type stroma differentiates MCNs from IPMNs and other pancreatic cysts (Fig. 3). Although *KRAS* or *RNF43* mutations can be found on MCN fluid or tissue biopsy, the *GNAS* mutation found in IPMNs is not seen in MCNs.

Patients with MCNs often present with nonspecific abdominal pain and undergo axial imaging with either CT or MRI. Radiographically, they appear as well-encapsulated, unilocular or multilocular cystic lesions (see Fig. 3). In equivocal cases, EUS with FNA can be performed to sample cyst fluid, which usually reveals an elevated CEA level. Because MCNs do not communicate with the pancreatic ductal system, amylase levels are often low; however, cases of elevated levels have been reported. Adequate sample cytology may also reveal atypia or dysplasia, and roughly 5% to 15% of MCNs harbor malignancy (see Fig. 3). Additional concerning features for mucinous cystadenocarcinoma include a solid component, mural nodule, or calcifications.

Because of the lifetime risk of malignancy, all MCNs should be considered for formal resection, and only in rare instances of invasive carcinoma is surgery noncurative. Because this neoplasm does not metastasize through the lymphatic system, formal lymphadenectomy and splenectomy are not necessary. Care, however, must be taken not to violate the capsule and spill cyst contents intraoperatively.

Solid Pseudopapillary Neoplasm

The solid pseudopapillary neoplasm (SPN) is another neoplastic lesion that represents about 5% of resected pancreatic cysts and 1% of pancreatic tumors. Before its current designation by the World Health Organization (WHO) in 1996, historic names for SPN included *Frantz tumor, Hamoudi tumor,* and *papillary cystic neoplasm.* SPNs are characteristically well-circumscribed lesions found in the pancreatic body and tail of young females (Fig. 4), and although they are grouped with other pancreatic cysts, SPNs are in fact a cavitary lesion that forms as the tumor grows and necroses. Histologically, the epithelial lining of SPNs is composed of foamy histiocytes as well as polygonal cells that organize into stalks and pseudopapillae (see Fig. 4). Curiously, the origin cell type for this tumor remains unknown, and no pathologic equivalent has been described in other organ systems. On molecular analyses, 90% of SPNs harbor WNT/B-catenin pathway mutations, and these tumors stain positive for neuron-specific enolase (NSE), vimentin (VIM), alpha-1 antitrypsin (A1AT), and the membrane metallopeptidase, CD10.

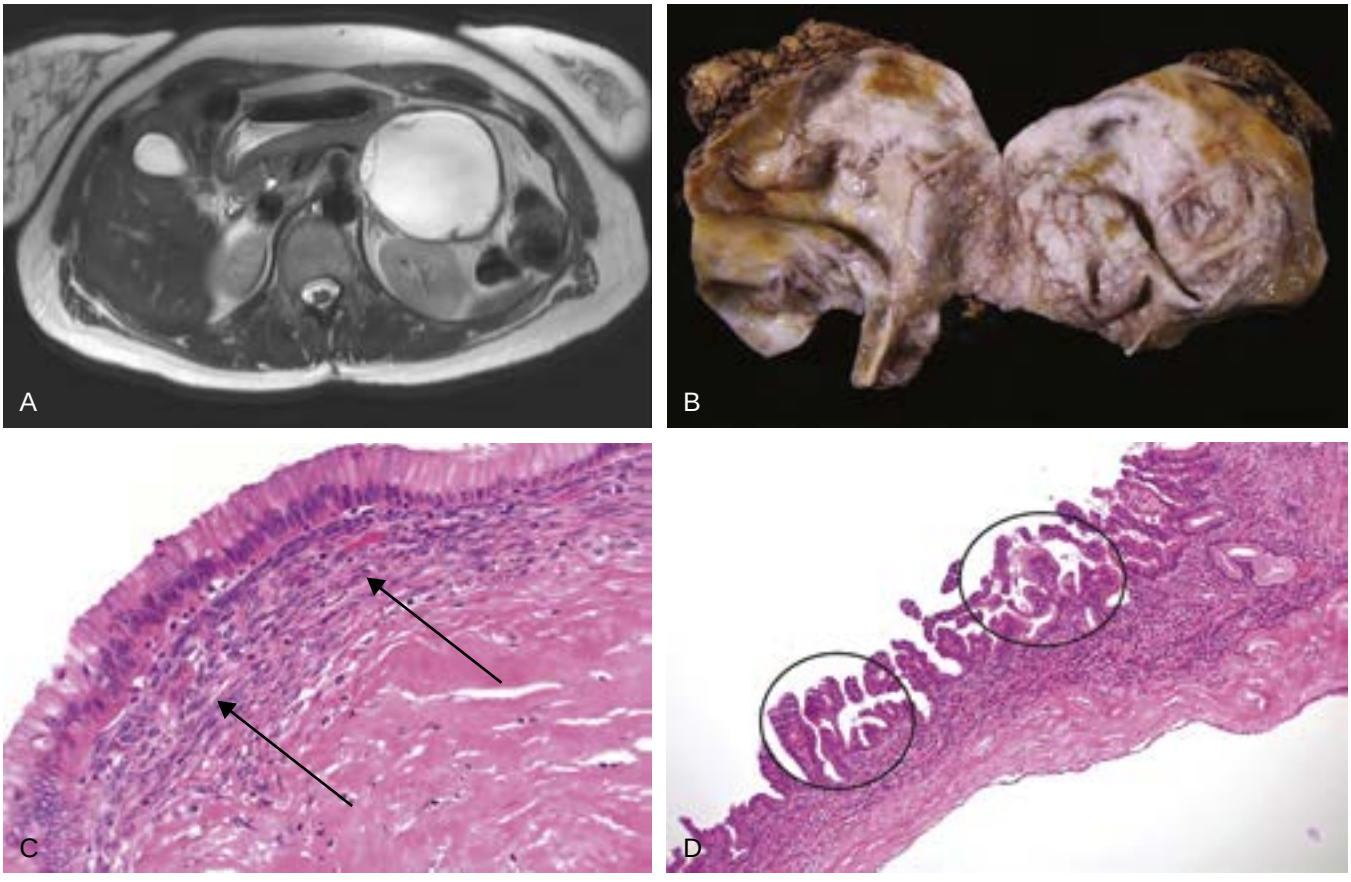


FIG. 3 Mucinous cystic neoplasm (MCN). **(A)** T2 MRI reveals an 8.4-cm pancreatic tail cyst with thin, peripheral septations. **(B)** Gross pathology shows bivalved MCN with a smooth epithelial lining. **(C)** Foveolar-type mucinous epithelium and prominent subepithelial ovarian-type stroma *(arrows)* characteristic of MCN. **(D)** Tubulopapillary projections and nuclear pleomorphism consistent with mucinous cyst adenocarcinoma in situ.

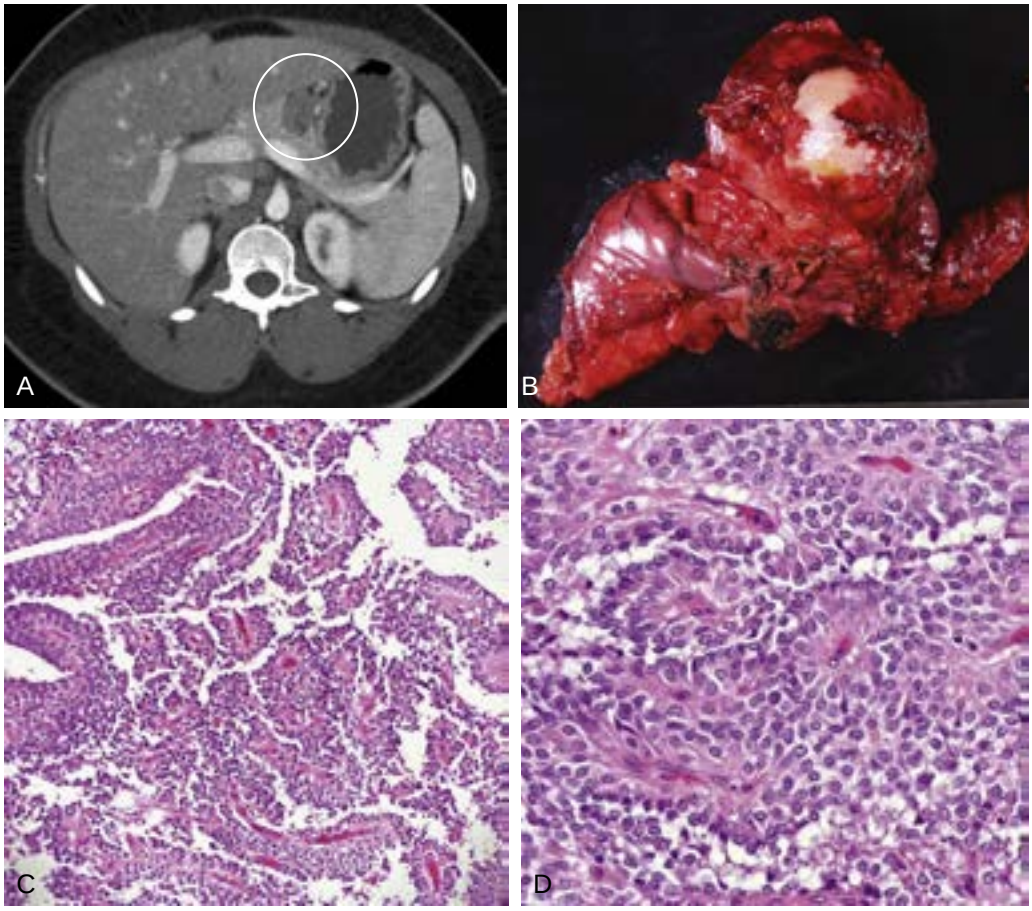


FIG. 4 Solid pseudopapillary neoplasm (SPN). **(A)** CT demonstrates a 2.6-cm hypoenhancing pancreatic body cyst abutting the posterior wall of the stomach. **(B)** A well-circumscribed tan-colored pancreatic mass consistent with SPN. **(C)** Fibrovascular cores engulfed in poorly cohesive sheets of neoplastic cells. **(D)** Monomorphic tumor cells organized in a pseudopapillary pattern around intervening capillaries.

Like MCNs, SPNs usually present with nonspecific abdominal pain or are found incidentally during workup for another pathology. Given its unique clinical features, EUS and FNA are usually not necessary for diagnosis. Patients should undergo formal oncologic resection, and a minimally invasive or robotic approach can be considered if technically feasible. Although a complete resection is generally curative, the recurrence rate for SPN is approximately 4.4%, and instances of distant metastatic spread have been reported. Surveillance is therefore an important component of the management for patients with SPN. For recurrent disease, attempts at surgical management should be pursued.

EPITHELIAL CELL TUMORS

Acinar Cell Carcinoma

Acinar cell carcinoma (ACC) represents 1% to 2% of pancreatic tumors and is more common in males. The pancreatic acinar cells, which comprise >90% of the pancreatic parenchyma, normally synthesize and secrete digestive enzymes such as lipase, trypsin, and chymotrypsin. As neoplastic ACC cells proliferate, a paraneoplastic syndrome caused by lipase hypersecretion may manifest as extremity erythema nodosum, polyarthralgia, and eosinophilia. Together, these symptoms constitute Schmid's triad, which is seen in roughly 10% to 15% of ACC patients. As such, lipase levels can be followed as part of disease surveillance, while other markers alpha fetoprotein (AFP) serum levels can also be followed. Histologically, tumor cells are organized into one of two patterns. In the acinar pattern, cancer cells organize to form small lumina, whereas in the absence of luminal structures, sheets of neoplastic cells coalesce to form a solid pattern. Both patterns, however, are commonly mixed within an individual tumor. A cystic variant, which can be mistaken for other pancreatic cystic lesions, can be appreciated on imaging or histology, and importantly, other nonductal epithelial components found within the ACC tumor mass can be mistaken for pancreatoblastoma (PBA) or PNET.

All patients with ACC should undergo formal oncologic resection for definitive management, though many ACC tumors present large and exophytic masses with locoregional disease. In such instances, neoadjuvant FOLFIRINOX-based chemoradiotherapy can effectively downstage the tumor and increase resectability. In terms of outcomes, overall survival for resected ACC is better compared with PDAC: 92% and 53% at 1 and 5 years, respectively. Because of its metastatic potential, however, postoperative surveillance should be continued in a similar manner to PDAC. Adjuvant chemoradiation is also recommended for all patients who did not receive up-front therapy as well as for recurrent or metastatic disease. In very select instances of isolated ACC metastases, metastectomy can also be considered.

Pancreatoblastoma

PBA is another rare pancreatic exocrine malignancy that accounts for 25% of pediatric pancreatic tumors and can be associated with other syndromes such as Beckwith-Wiedemann syndrome and familial adenomatous polyposis. Albeit uncommon, these tumors can also occur in young and middle-aged adults, and the prognosis is often poorer in these cases.

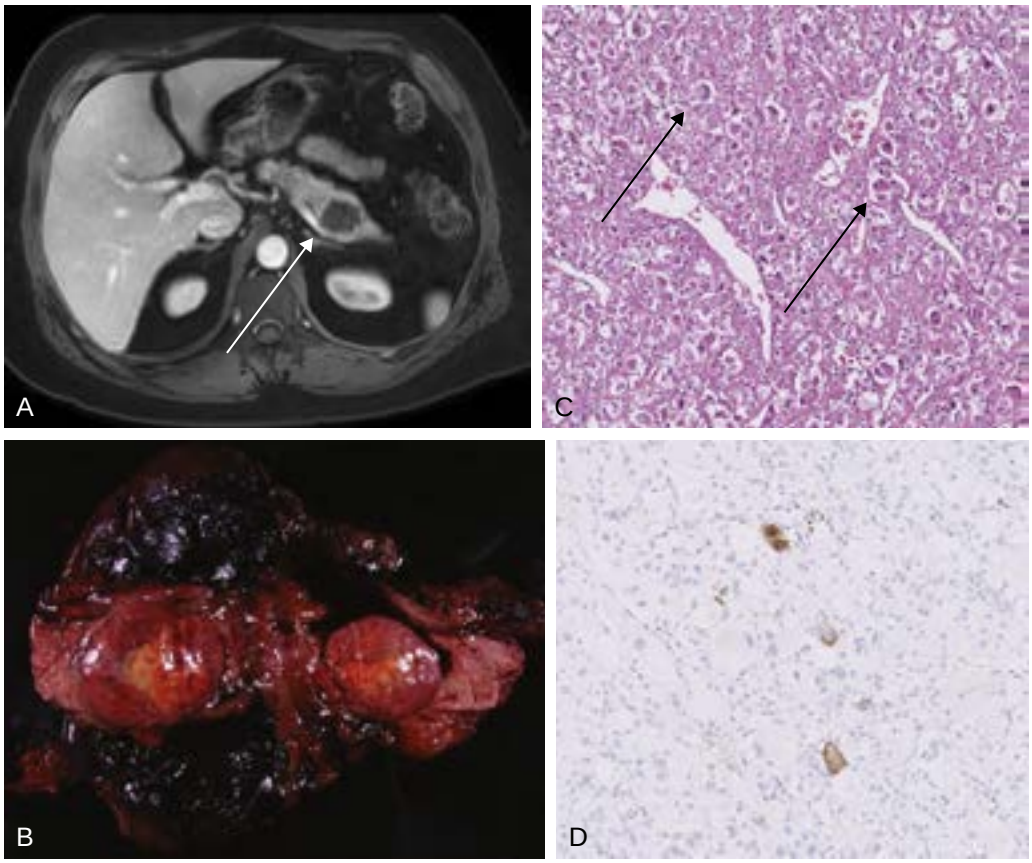


FIG. 5 Perivascular epithelioid cell tumor (PEComa). **(A)** MRI shows a 3.2-cm hypoenhancing mass *(arrow)* in the pancreatic tail with distal atrophy. **(B)** Gross pathology shows a well-circumscribed mass with a fibrotic capsule and yellowish central nodules consistent with PEComa. **(C)** Large epithelioid cells with prominent nucleoli *(arrows)* and clear cytoplasm among small blood vessels. **(D)** HMB45 staining *(brown)* characteristically seen in PEComa.

PBAs arise from primordial epithelial cell nests that form cores of keratinized spindle cells called *squamoid corpuscles*. For diagnostic and surveillance purposes, AFP is the most reliable biomarker for PBA and is seen in up to 70% of cases; however, other markers including alpha-1 antitrypsin (A1AT) and lactate dehydrogenase (LDH) may also be elevated. Infrequently, PBAs secrete adrenocorticotropic hormone (ACTH), resulting in a Cushing-like paraneoplastic syndrome.

Regarding presentation, PBAs are usually found in the pancreatic head and cause persistent abdominal pain or obstructive symptoms. In children, an abdominal mass may be palpated on physical examination, and calcifications are a common finding on axial imaging. Overall survival rates for PBA mirror ACC; however, recurrence is more common. For unresectable or recurrent disease, patients treated with cisplatin and doxorubicin-based chemotherapeutic regimens can achieve long-term survival.

MESENCHYMAL PANCREATIC TUMORS

PEComa

First described in 1996, the perivascular epithelioid cell tumor (PEComa) is a rare pancreatic mesenchymal tumor that is thought to originate from the pericyte or myofibroblast cells enveloping capillaries and small blood vessels. These tumors can arise in any organ system and are related to the clear cell or sugar tumors found in tuberous sclerosis patients. The link between pancreatic PEComa and tuberous sclerosis, however, remains unclear.

On imaging, PEComas are well-circumscribed and hypoenhancing (Fig. 5). Histologically, these tumors are notable for large epithelioid cells suspended among a trabecula of fine vessels (see Fig. 5). Necrosis and hyalinization are other common histologic features, and spindle-shaped cells can also be seen. Positive staining for melanin 45 (HMB45), alpha smooth muscle actin (ACTA2), and desmin (DES) are additional histologic features found in PEComas (see Fig. 5).

Although very rare, these tumors have malignant potential, and metastases have been reported in larger (>5 cm) and highly mitotic (>1/50 high-power fields [HPF] or Ki-67 index >5%) gynecologic PEComas. Pancreatic PEComas, although potentially benign, should be formally resected given their unclear natural history or in instances of diagnostic uncertainty.

Solitary Fibrous Tumor

The solitary fibrous tumor (SFT) is another mesenchymal tumor composed of spindle-shaped cells. This tumor can arise from the pancreas or metastasize from primary lesions in the pleura, extremities, or head and neck region. These tumors can arise throughout the pancreas and have a characteristic fleshy texture on gross pathology (Fig. 6). Common histologic markers for SFT include transmembrane protein CD34, transcription factor STAT6, and survival protein BCL2. Although malignancy has been described in large (>10 cm) and highly mitotic (>4 mitoses/10 HPF) forms of metastatic SFT, no cases of malignant pancreatic SFT have been reported. Even in cases of SFT metastases to the pancreas, long-term survival is possible after partial pancreatectomy or tumor enucleation.

Schwannoma and Paraganglioma

Found adjacent to or within the pancreatic parenchyma, schwannomas are benign and well-circumscribed masses arising from the

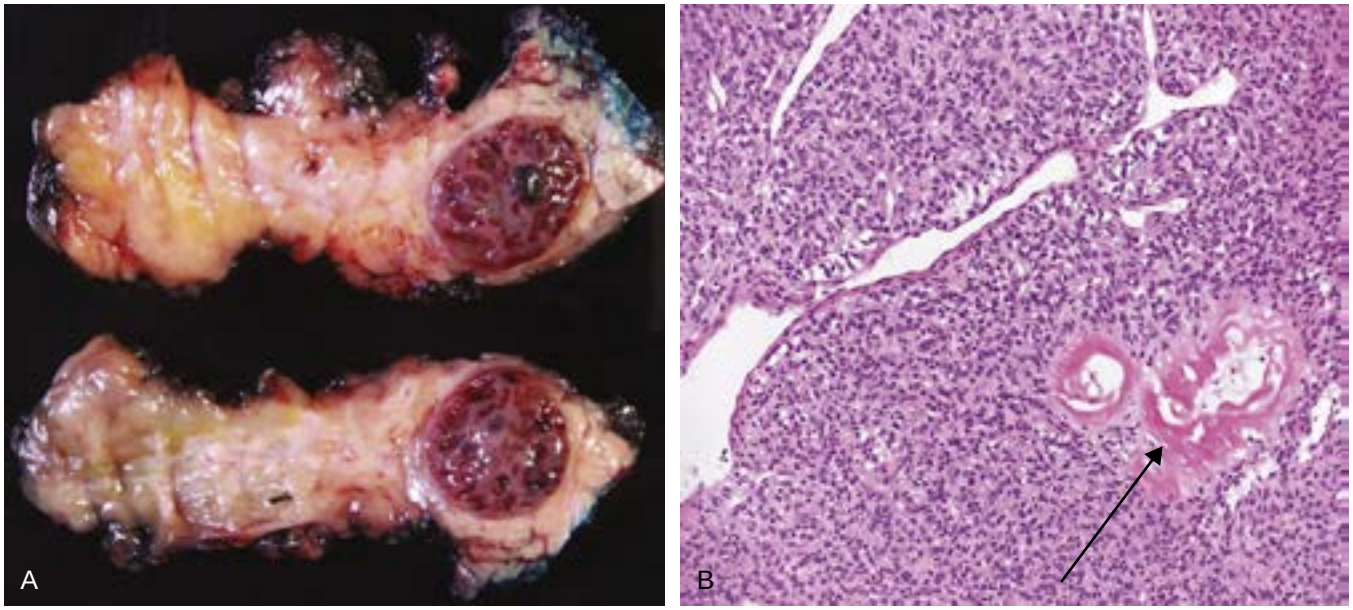


FIG. 6 Solitary fibrous tumor (SFT). **(A)** Fleshy pancreatic tail mass consistent with SFT. **(B)** Densely packed spindle cells amidst staghorn-like blood vessels. Notable perivascular hyalinization is also seen *(arrow)*.

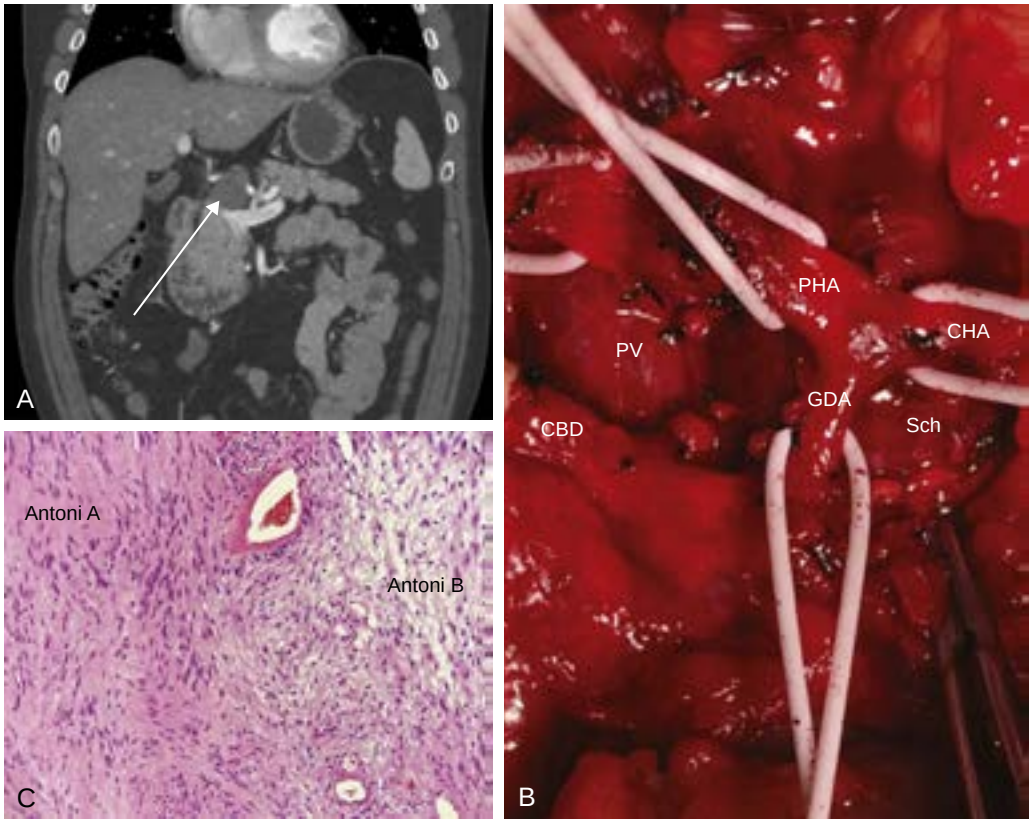


FIG. 7 Peripancreatic schwannoma. **(A)** CT demonstrates a 3.2-cm homogenous mass abutting the common hepatic artery, portal vein, and pancreatic neck. **(B)** Intraoperative image of solid peripancreatic mass *(forceps tips)* posterior to common hepatic artery trifurcation. **(C)** Antoni A area composed of spindle cell fascicles, and Antoni B area characterized by scattered cells within a loose matrix. *CBD,* Common bile duct; *CHA,* common hepatic artery; *GDA,* gastroduodenal artery; *PHA,* proper hepatic artery; *PV,* portal vein; *Sch,* schwannoma.

sheath of peripheral nerves (Fig. 7). Although an association between von Recklinghausen's disease and pancreatic schwannomas has been reported, most cases are sporadic. Histologically, these lesions can be solid, cystic, or contain focal areas of hemorrhage, calcifications, or xanthomatous debris. Staining for S100 proteins, NCAM1 (CD56), and transcription factor SOX10 are common, and either tumor enucleation or formal resection is appropriate, especially for larger lesions (>6 cm), which may have an increased risk of malignancy.

Although similar to schwannomas, paragangliomas arise from rests of extraadrenal chromaffin cells, and patients must undergo hormonal testing to identify features of catecholamine excess before resection. Paragangliomas appear to be a nonneoplastic entity and tend to occur in the pancreatic body and tail. Importantly, histologic markers for paragangliomas such as synaptophysin (SYP), chromogranin (CHGA), and anti-insulinoma protein 1 (INSM1) may be mistaken for a neuroendocrine tumor. Tumor enucleation or simple excision through a laparoscopic or robotic approach are adequate forms of treatment.

INFLAMMATORY MASSES AND SECONDARY MALIGNANCIES

Groove (Paraduodenal) and Autoimmune Pancreatitis

Various forms of pancreatic inflammation such as groove and autoimmune pancreatitis can present as a pancreatic mass. In groove, or paraduodenal, pancreatitis, chronic inflammation occurs at the interface of the duodenum and the pancreatic head between the major and minor pancreatic papillae (Fig. 8A). As in other forms of pancreatitis, groove pancreatitis is more common in males and in patients with a history of alcohol or tobacco abuse. Presenting symptoms may include obstructive jaundice or gastric outlet obstruction, which prompt further workup. Although tumor markers are often negative, axial imaging may reveal a hypodense mass in the pancreatic head or ampulla. A subtle but classic radiographic finding for groove pancreatitis is the presence of a curvilinear collection or lesion; however, a segmental form of the disease that infiltrates the pancreatic head is indistinguishable from more sinister pathologies. Although treatment is supportive in cases of biopsy-proven groove pancreatitis, cytology may be misleading and lead to pancreatoduodenectomy to rule out cancer.

Autoimmune pancreatitis (AIP) is another inflammatory condition that presents as a pancreatic mass. Two forms of this disease have been described, and a careful history and physical examination may reveal xerostomia, obstructive uropathy, biliary cirrhosis, or other stigmata of the systemic form (AIP I). This form tends to occur in older male patients and is mediated by IgG4, which is elevated in up to 70% of patients. Histologically, infiltrative IgG4-positive plasma cells engulf the pancreatic acini and cause the lymphoplasmacytic sclerosing pattern of inflammation characteristic of this form of AIP. On axial imaging, the pancreas may appear congested or "sausage-like"; however, a hypoenhancing mass may be seen and mistaken for pancreatic cancer (Fig. 8B). Main pancreatic duct structuring or common bile duct dilation can also be seen in AIP I and raise further concerns for a neoplastic process. By contrast, AIP II is more common in younger patients and commonly associated with inflammatory bowel disease. IgG4 levels are usually normal, and on histology, the lymphoplasmacytic infiltrate targets pancreatic ducts rather than acini and forms hallmark granulocyte epithelial lesions (GELs).

Workup with EUS and FNA may be necessary for patients with a pancreatic mass who lack features of AIP however, resection for diagnostic purposes is not uncommon. For confirmed cases, treatment includes high-dose (0.6–1 mg/kg) corticosteroids. Importantly, relapses occur in 60% of AIP1 cases compared with 10% in AIP2,

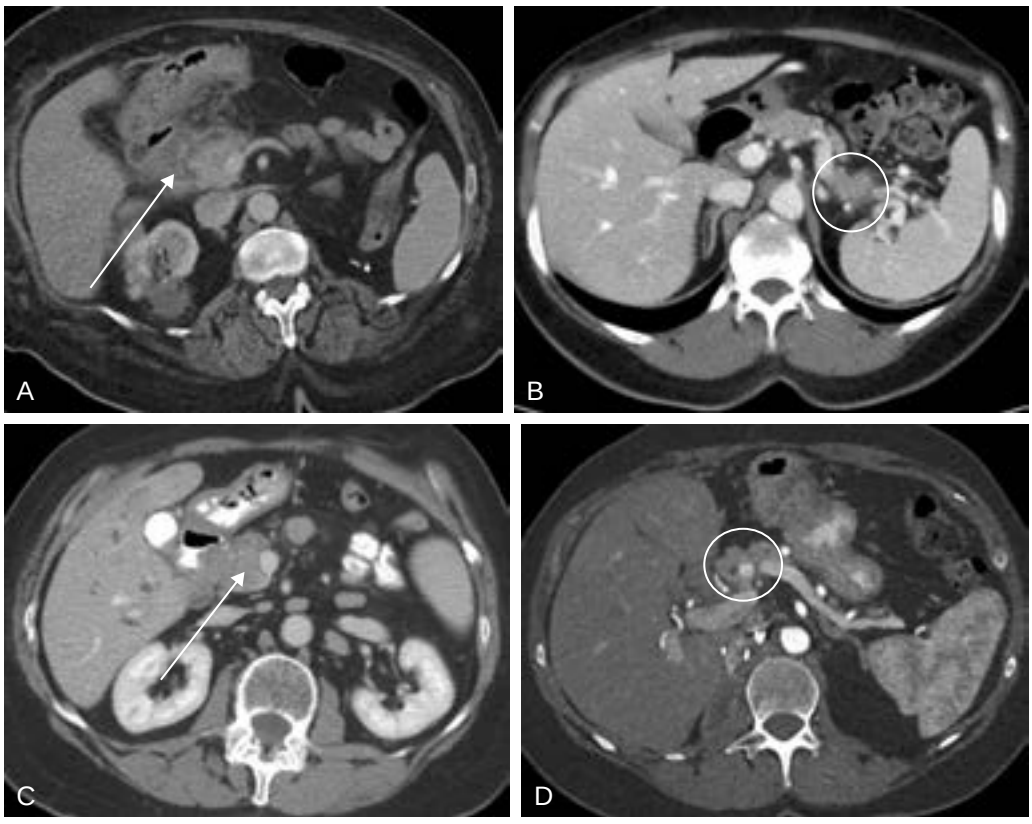


FIG. 8 CT shows inflammatory processes and additional malignancies. **(A)** Groove pancreatitis: diffuse stranding and inflammatory changes surrounding the first portion of duodenum and pancreatic head in addition to a 2.9-cm hypodense fluid collection *(arrow)*, **(B)** Autoimmune pancreatitis type I: 2-cm infiltrative pancreatic tail mass with associated narrowing of the splenic vein. **(C)** Pancreatic lymphoma: a bulky 2.9-cm mass arising along the porta hepatis and extending into the pancreatic head causing intrahepatic biliary ductal dilatation *(arrow)*. **(D)** Metachronous renal metastasis: 1.1-cm hyperenhancing pancreatic head mass in a patient with history of renal cell carcinoma.

and azathioprine can be incorporated into the treatment of refractory cases.

ADDITIONAL MALIGNANCIES

Primary Pancreatic Lymphoma

Primary pancreatic lymphoma (PPL) is a duplicitous mimicker of PDAC, yet this rare pathology represents only <1% of extranodal lymphomas and 0.5% of pancreatic neoplasms. Most PPLs are non-Hodgkin, diffuse B-cell lymphomas that respond to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. For B-cell PPL, the anti-CD20 monoclonal antibody, rituximab, can also be incorporated into the treatment regimen. PPL often presents in older males with weight loss, abdominal pain, and occasionally obstructive jaundice, all of which clinically resemble PDAC. Tumor markers are usually normal, however, LDH and beta-2 microglobulin levels are used to distinguish PPL from other pancreatic processes. Imaging features suggestive of lymphoma include a large, exophytic pancreatic mass with prominent peripancreatic and retroperitoneal lymphadenopathy (Fig. 8C), and these are also FDG-avid tumors on positron emission tomography (PET). EUS and FNA are essential in the management of PPL because the treatment is nonsurgical. The complete response rate after chemotherapy is 75% for PPL, and the median overall survival is approximately 6 years. Laparotomy is reserved for equivocal cases or palliation in instances of gastrointestinal bleeding or obstruction.

Pancreatic Metastases

Collectively, pancreatic metastatectomy represents 1% of all pancreatic resections, and renal cell carcinoma (RCC), breast cancer, lung cancer, colon cancer, and melanoma are the most common tumors to metastasize to the pancreas. The head and uncinate process is the most common site for metastatic disease, which is usually detected as part of routine surveillance or symptom workup. In patients with a suspected pancreatic metastasis, a full oncologic history and staging workup are necessary to rule out disseminated or multifocal disease.

Of these pancreatic metastases, RCC is both the most common and the most likely to benefit from pancreatectomy as the 5-year overall survival ranges between 70% and 80%. Interestingly, metastatic RCCs often are metachronous and develop many years after the initial tumor diagnosis. On axial imaging, RCCs are hypervascular and may mimic PNETs (see Fig. 8D). For other pancreatic metastases, survival post-resection remains poor, and palliative chemotherapy should be considered in lieu of surgery. For lesions causing gastric outlet obstruction or jaundice, a surgical bypass may be necessary.

CONCLUSION

In conclusion, there are many rare pancreatic lesions that should be considered during the workup of a pancreatic mass. Recognizing those that do not require formal resection may prevent a larger operation, and in some instances, surgery altogether. In cases of diagnostic uncertainty, however, surgical extirpation is necessary to rule out cancer.

Suggested Readings

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Intraductal Papillary Mucinous Neoplasms of the Pancreas

Gabriel D. Ivey, MD, and Richard A. Burkhart, MD

Described initially in 1982 by Ohashi and colleagues, the management of intraductal papillary mucinous neoplasm (IPMN) of the pancreas has changed considerably over the past four decades. This intraductal epithelial cystic neoplasm—characterized by (1) mucin production, and (2) diffuse or segmental dilation of the main pancreatic duct and/or branch ducts—has varying malignant potential that can be clinically stratified by characterizing factors that include the portion of duct involved, maximal size of the cystic component, radiographic appearance, and co-occurrence of clinical syndromes such as pancreatitis. Historically, initial management strategies were centered solely around surgical resection. As the capacity to quantify malignant risk has evolved, nonoperative management strategies for select patients have since been developed and formalized. Perhaps the most common strategy adopted internationally for management of patients with IPMN was published following a consensus meeting in Sendai, Japan, of the International Association of Pancreatology in 2006. These guidelines have been refined and published twice more, following the Fukuoka consensus in 2012, and most recently as the revised Fukuoka guidelines in 2017. Despite the growth of nonoperative management strategies, however, surgical resection remains a cornerstone of treatment for lesions at the highest risk for harboring high-grade dysplasia or malignancy.

Although the exact population-based incidence of IPMN is unknown, IPMN is the most commonly resected cystic neoplasm of the pancreas. Approximately 10% of all pancreatectomies in the United States are performed for presumed IPMN. Improved cross-sectional imaging has led to increased detection of these often asymptomatic lesions. In turn, our understanding of IPMNs has improved and, at present, there are at least nine separate guidelines and/or statements published to guide management. Several controversies remain when reflecting on these nine expert groups' recommendations. Timing and indication for resection, and the criteria for safe observation of IPMNs with lower malignant potential,

remain greatly debated areas as the risk-benefit profile for resection varies across both patient demographics and regional standards of care. Consider that while resection of high-grade dysplasia is often thought of as a perfect management strategy, a resection specimen demonstrating cancer in a patient who had previously elected for surveillance imaging is an unfortunate occurrence. Current evidence suggests that roughly one quarter of resected IPMNs are found to harbor high-grade histology or invasive disease. An additional area of considerable debate is the extent of resection when pancreatectomy is indicated, especially when there is residual cystic disease at the pancreatic resection margin.

CLINICAL CLASSIFICATION OF MALIGNANT POTENTIAL

IPMNs can be classified as one of three types based on duct involvement: main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), and mixed type (Figs. 1 and 2). MD-IPMN is characterized by segmental or diffuse dilation of the main pancreatic duct greater than 5 mm without other causes of obstruction. Pancreatic cysts that are greater than 5 mm in diameter and that communicate with, but do not directly involve, the main pancreatic duct are termed BD-IPMN. Patients with clinical findings that meet the criteria for both MD-IPMN and BD-IPMN meet classification criteria for mixed type IPMN. This classification scheme correlates well with biology of disease, with MD-IPMN having a higher likelihood for malignant degeneration. Invasive adenocarcinoma is identified in ≤18% of BD-IPMN and up to 64% of MD-IPMN.

Histologically, IPMN can be further classified into *gastric, oncocytic, intestinal,* and *pancreatobiliary* subtypes (Fig. 3). Much like the duct involvement classification scheme, each of these histologic subtypes is associated with a unique risk of malignant transformation. The gastric subtype is most commonly associated with BD-IPMNs and is often characterized by dysplastic features that demonstrate low grade histology. As a result, the incidence of invasive disease is limited in those found to have gastric histopathology. Similarly, though oncocytic histology tends to be associated with large cystic disease during clinical workup, it is rare to find invasive disease in this relatively small cohort. An intestinal histologic subtype is commonly associated with MD-IPMN and, particularly when disease is large and complex, this subtype is more apt to harbor foci of invasive carcinoma than the gastric or oncocytic subtypes. Finally, although the pancreatobiliary type is the least common in most large data sets, the biology can be particularly aggressive. This subtype is most commonly found in patients with MD-IPMN, and invasive disease can be common, even in cases of relatively small cystic lesions of the main pancreatic duct.

Pathogenesis

The potentially malignant epithelial lining (Fig. 4) that characterizes the cystic evolution of IPMN disease is thought to arise from stem cell precursors along the native epithelial lining of pancreatic ducts. The progression of IPMN, from low-grade dysplasia to invasive cancer, is associated with the acquisition of mutations in key oncogenes such as *KRAS* or *GNAS*. Despite these known molecular features,



FIG. 1 **(A)** Sagittal multidetector computed tomography showing main duct intraductal papillary mucinous neoplasm with notable dilation *(arrow)* of the main pancreatic duct. **(B)** Axial multidetector computed tomography showing a small cystic lesion in the pancreatic tail *(arrow)* consistent with a branch duct intraductal papillary mucinous neoplasm. No dilation is observed in the main pancreatic duct. **(C)** Mixed type intraductal papillary mucinous neoplasm on computed tomography. There is notable diffuse dilation of the pancreatic duct in the head and body of the gland *(arrowheads)* and multiple small branch duct lesions throughout the body and tail *(arrows)*.

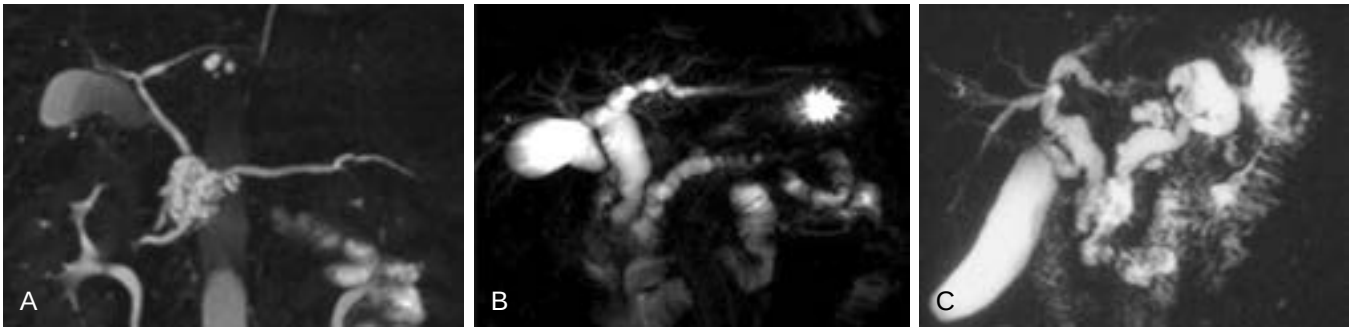


FIG. 2 Radiographic appearance of **(A)** branch duct, **(B)** main duct, and **(C)** mixed type intraductal papillary mucinous neoplasms. *(From Tanaka M. International consensus on the management of intraductal papillary mucinous neoplasm of the pancreas.* Ann Transl Med. *2015;3:286.)*

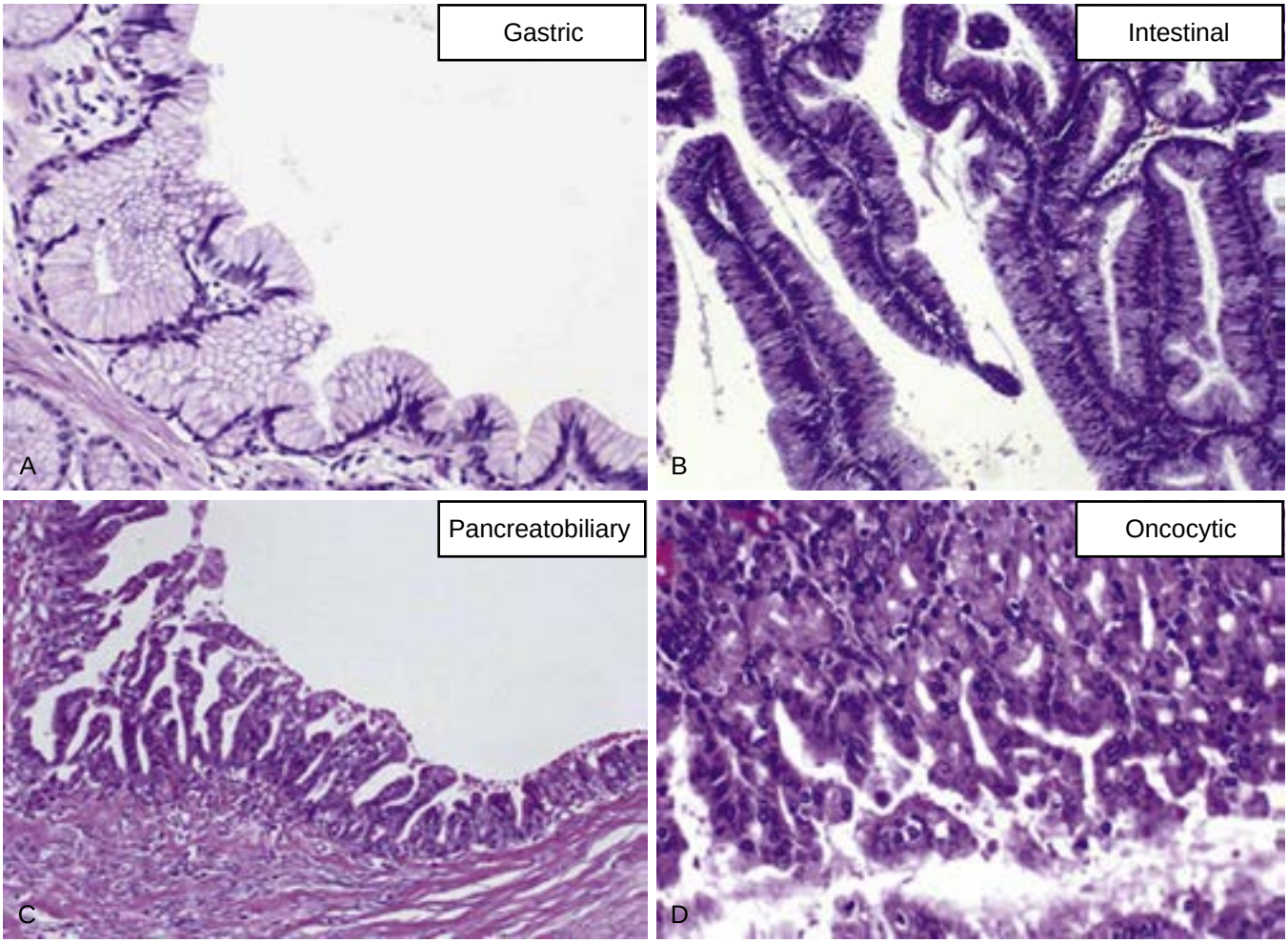


FIG. 3 The four histologic classifications of intraductal papillary mucinous neoplasm are **(A)** gastric, **(B)** intestinal, **(C)** pancreatobiliary, and **(D)** oncocytic. *(From Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas.* Pancreatology. *2012;12:183–187.)*

the underlying drivers that dictate progression along a broad spectrum of disease ranging from low-grade dysplasia to invasive cancer remain unknown. The accumulation of mutations in other key oncogenes and tumor suppressors, including RNF43, P16/INK4A, SMAD4, and TP53, likely play an important role.

Clinical Presentation

The discovery of a patient's IPMN is often the result of an imaging abnormality identified during workup for nonpancreatic pathology. Thresholds for utilizing high-quality cross-sectional imaging for workup of a variety of medical conditions have lowered in recent years. Concomitantly, improvements in cross-sectional technology have increased, and together the two have led to increased detection of incidental pancreatic cysts like IPMNs. Less commonly, IPMN is discovered during the workup for related clinical symptoms, including jaundice, unexplained weight loss, acute pancreatitis, and/or vague abdominal pain.

Workup and Management

The clinical workup for IPMN is designed to guide toward a management strategy that balances risk for intervention with the level of concern for underlying invasive disease and/or mitigation of associated symptoms. This balance is heavily reliant on characteristics elucidated by high-quality cross-sectional imaging, endoscopic characterization, and potentially, endoscopic tissue and fluid sampling. Key to effective management is the capacity to differentiate between IPMN disease and the nonmucinous cysts of the pancreas that lack malignant potential. This differentiation generally relies on identification of communication/involvement of the cyst with the main pancreatic duct or the presence of mucin, or high carcinoembryonic antigen (CEA) value on examination of cyst fluid. An assessment of the molecular or genetic features of the cyst fluid, including genetic mutational profiling, remains an area of emerging interest and can be particularly helpful in cases where the diagnosis remains uncertain.

Once a diagnosis of IPMN can be made with relative certainty, optimal management in many high-volume centers is typically guided by the international consensus criteria defining the presence of worrisome features or high-risk stigmata as outlined in the current International Association of Pancreatology consensus Fukuoka guidelines (Fig. 5). Although clinical trials for the nonoperative "active" management for IPMN are currently underway (including clinicaltrials.gov: NCT04207944), the core management strategies remain active surveillance or surgical resection.

As noted earlier, the decision to embark on surgical management of IPMN must balance the concern for underlying malignancy, presence or absence of symptoms, and patient-specific operative risk. To the latter, it should be noted that a patient's own goals for care may affect the decision to proceed to the operating room. In addition, a

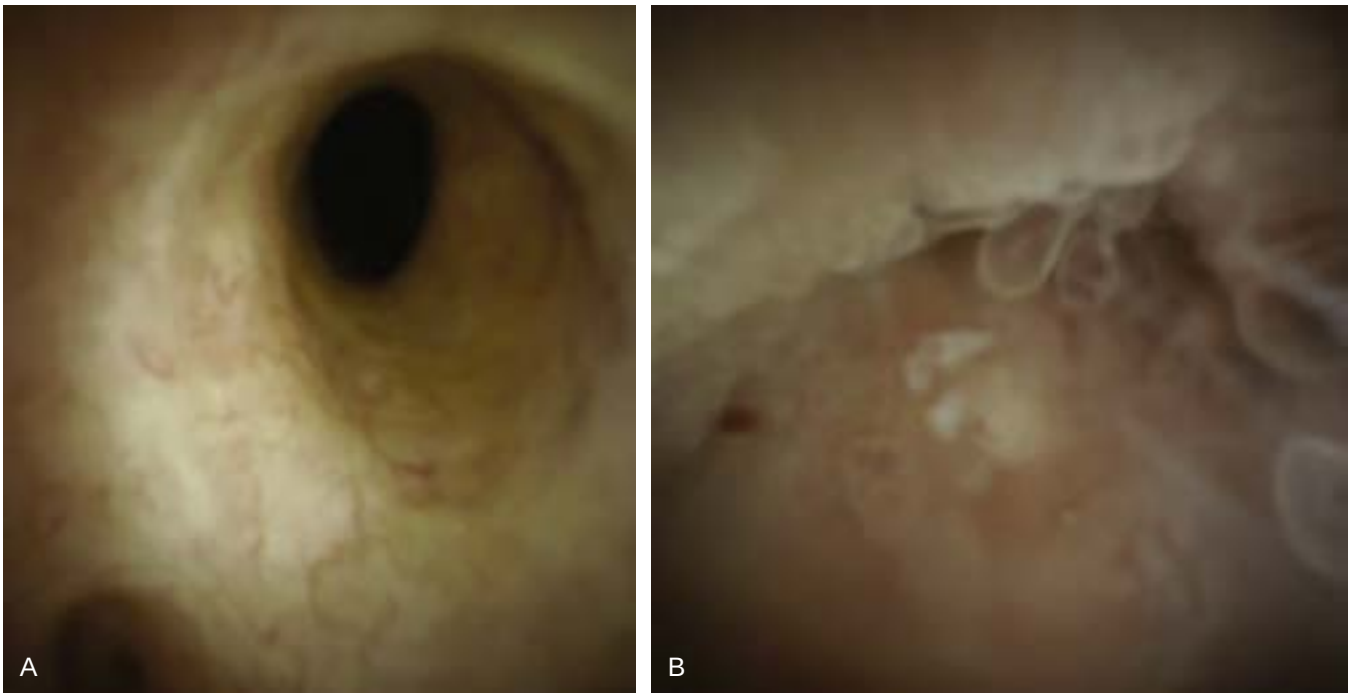


FIG. 4 Intraoperative pancreatoscopy. **(A)** Normal duct with smooth epithelial lining. **(B)** Cystic duct with dilation, papillary protrusions, neovascularization, and mucinous fluid.

strong family history of pancreatic cancer may affect the decision to intervene. Regardless of radiographic features, resection should be offered if cysts are symptomatic and affecting a patient's quality of life, if resection is likely to ameliorate these symptoms. Symptomatic cysts, when assessed overall, have a greater than two-fold risk of harboring invasive carcinoma or high-grade dysplasia. Weight loss and jaundice are the two most common clinical features associated with invasive IPMN.

In the absence of symptoms, risk assessment and management can be rapidly guided by a consultation that follows the Fukuoka guideline schema. When high-risk stigmata are identified (see Figure 5) in a patient with appropriate surgical risk stratification, resection should be offered. In the absence of high-risk stigmata, a clinical and radiographic workup should be completed to evaluate for worrisome features. These include cyst size ≥ 3 cm, an enhancing mural nodule < 5 mm, thickened/enhancing cyst walls, a main duct size of 5 to 9 mm, an abrupt change in caliber of the pancreatic duct with distal pancreatic atrophy, lymphadenopathy, increased serum CA 19-9 level, and a cyst growth rate of ≥ 5 mm/2 years if the lesion has previously been visualized on similar imaging studies. Worrisome features should prompt further investigation with endoscopic ultrasound (EUS), while their absence, in most cases, necessitates interval imaging based on the size of the largest cyst.

In centers with expertise in EUS with fine-needle aspiration (FNA) and cytologic interpretation, EUS can be used for detecting mural nodules and invasion. The addition of FNA and cytologic and/or molecular analysis adds value, especially for small BD-IPMNs without worrisome features. The identification of high-grade epithelial atypia may be a more sensitive predictor than positive cytology for invasive carcinoma or high-grade dysplasia. The identification of a *KRAS* or *GNAS* mutation may help distinguish BD-IPMN from nonmucinous cysts and mucinous cystic neoplasms, as positive *GNAS* mutations are observed only in IPMNs and not in MCNs.

Operative Management

There are several surgical options for patients with IPMN if criteria for resection is met: pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy. Each option includes the standard oncologic lymph node dissection that is considered in the setting of malignancy. The determination of the appropriate operation is dependent on the site and extent of disease, especially if dysplasia or a component of invasive disease is identified preoperatively. Employing more limited resections, like enucleation in the setting of BD-IPMN, remains somewhat controversial. Though these proposed techniques have the capacity to preserve parenchyma and decrease long-term complications of resection, they are associated with a higher incidence of short-term complications such as pancreatic fistula, risk of recurrence if there is residual disease adjacent to the resection margin, and pseudomyxoma peritonei if there is leakage of mucin. Further, when performed in the setting of a possible malignancy, the operation does not meet an oncologic standard should invasive disease be found on histopathologic analysis.

When performed in a center with dedicated pancreatic pathologists, surgical margins should be assessed at the time of surgery using a frozen section. If the resection margin demonstrates invasive cancer or high-grade dysplasia, an additional resection should be performed until the margin is negative. The intraoperative management of a patient found to have cancer in the main specimen and high-grade dysplasia at the margin, however, is debated, although most high-volume centers do not pursue additional margins as long as there is no suspicion of invasive disease in the remaining gland. A finding of low- or intermediate-grade dysplasia at the margin does not require additional resection. When surgical margin assessment is used to dictate the extent of resection, it is important to counsel a patient preoperatively regarding the possibility of a total pancreatectomy as significant lifestyle modifications can be anticipated; type 3c diabetes mellitus and exocrine insufficiency are universal and can be difficult to manage. Judgment in these clinical scenarios is important as the impact of a total pancreatectomy on patient outcome can vary depending on the underlying patient age, medical comorbid disease, and overall determinants of health.

Though not considered standard of care at present, the use of intraoperative pancreatoscopy (fiberoptic endoscopy of the pancreatic duct), with or without tissue sampling, provides a unique opportunity for the identification of occult high-grade dysplasia or invasive disease

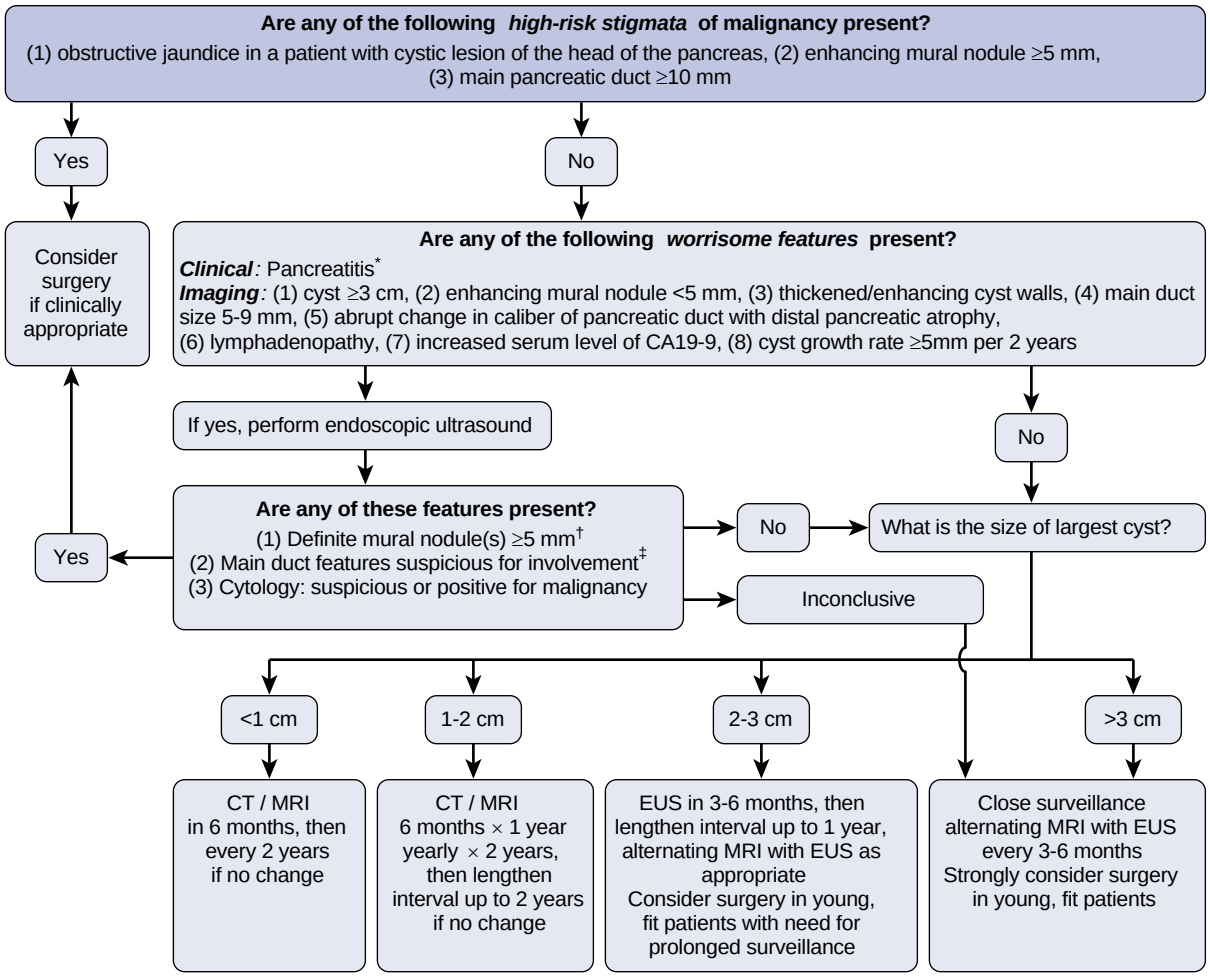


FIG. 5 Algorithm for the management of suspected branch duct intraductal papillary mucinous neoplasm. *Pancreatitis may be an indication for surgery for relief of symptoms. †Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage, and does not have Doppler flow. Features of true tumor nodule lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue. ‡Presence of any one of thickened walls, intraductal mucin, or mural nodules is suggestive of main duct involvement. In their absence, main duct involvement is inconclusive. *EUS*, Endoscopic ultrasound; *FNA*, fine-needle aspiration; *MRI*, magnetic resonance imaging. *(From Tanaka M, Fernandez-del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for management of IPMN of the pancreas.* Pancreatology. *2017;17:738–753.)*

in the setting of extensive or multifocal MD-IPMN (see Fig. 4). With the use of pancreatoscopy, the intraoperative course for 20% to 25% of patients is modified as a result. The impact of pancreatoscopy on long-term prognosis and survival outcomes remains unknown.

Postoperative Care

The postoperative management of patients undergoing resection for IPMN is similar to the management strategy used for patients undergoing pancreatic resection for other etiologies. We, like other high-volume centers, rely upon standardized perioperative care pathways designed to optimize high-value care. The surgeon should be mindful for the potential development of pancreatic endocrine and/or exocrine insufficiency, pancreatic fistula, post-pancreatectomy hemorrhage, and delayed gastric emptying. In many patients with cystic disease of the pancreas, the gland's parenchyma is found to be soft, and it is our practice to utilize drains in postoperative management.

Postoperative Surveillance

IPMN recurrence in the remnant gland after pancreatectomy occurs in up to 20% of individuals who are without histopathologic evidence of invasive carcinoma following resection. These data have led to the concept of IPMN serving as a marker for whole-gland field defect. As a result, surveillance following resection is a critical facet of long-term management; the remnant pancreas is at risk for the development of new IPMNs, progression of a preexisting IPMN, or the development of pancreatic cancer unrelated to a clinically detected IPMN.

The degree of dysplasia can be utilized as a guide for surveillance intervals and thresholds to offer reoperation for patients having undergone resection. IPMNs with high-grade dysplasia have a 13% to 31% risk of recurrence with completion pancreatectomy frequently being offered at a relatively low threshold (when compared with lesions resected with less dysplastic features). We currently entertain surveillance with MRI or EUS for these patients beginning at 6-month intervals. IPMNs with low- or intermediate-grade dysplasia have a 0% to 22% risk of recurrence, and the surveillance paradigms are less well-defined. For these patient populations, surveillance programs can vary from 6- to 12-month intervals all the way to 24 months. The decision to stop surveillance is also controversial, and our approach at Johns Hopkins has been to favor a conservative strategy and follow lifelong, particularly when high-grade dysplasia was found prior on surgical pathology. MRI—or even

high-quality CT—is frequently employed with less reliance on EUS in this cohort. For patients in whom an IPMN reveals an invasive component, the risk of local and/or distant recurrence of malignancy is 17% to 65%, and these patients are best managed and followed per guidelines outlined by the National Comprehensive Cancer Network.

CLINICAL EVALUATION FOR EXTRAPANCREATIC MALIGNANCIES

The potential association of IPMN with extrapancreatic malignancies has been a controversial area of study. Most studies that have evaluated this association are retrospective in nature and have been subject to some degree of bias. The reported prevalence of extrapancreatic malignancies in patients with IPMN ranges from 10% to 52%. The one prospective study that has evaluated this potential association, however, observed no increased risk of extrapancreatic malignancies in patients with IPMN compared with patients without IPMN. A systemic review of the current data was unable to draw a definitive conclusion on the topic because of the paucity of high-quality evidence. Screening paradigms for extrapancreatic malignancy, beyond normal screening guidelines, lack robust study and are generally not advised.

Prognosis

The long-term prognosis for patients with IPMN is dependent on the risk of underlying malignancy and, for those undergoing resection, the final pathology and margin status. While the development of IPMN is considered a whole-gland field defect that subsequently places a patient at increased risk for the development of malignancy, many IPMNs never manifest worrying clinical signs/symptoms of dysplasia, and segmental resection confers a high rate of risk reduction when performed before the development of cancer. Still, disease recurrence after segmental resection can occur, but current surveillance guidelines outline excellent strategies that help mitigate this risk. Alternatively, total pancreatectomy can be curative and eliminate long-term risk; however, it can be associated with a lower quality of life given the resultant pancreatic insufficiency, which must be carefully weighed during shared decision-making given the lifelong medication needs that result.

Published survival rates following resection of IPMN are based on histology classification—low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive IPMN. Five-year overall survival rates for LGD, HGD, and invasive IPMN are 89%, 84%, and 48%, respectively. Five-year overall survival rates with negative, LGD, or malignant margins are 80%, 83%, and 30%, respectively.

CONCLUSION

The management of patients with IPMN requires an astute awareness of the nuances of this clinical entity. The current treatment algorithm takes into account numerous factors that in turn help guide diagnostic, operative, and surveillance strategies. IPMN harbors a risk for malignant progression, and options for resection must be weighed against morbidity and mortality risks in a shared decision-making fashion. When patients present with one or more high-risk stigmata, surgery should be considered. If there are no high-risk stigmata but at least one worrisome feature is present, EUS is often performed to assess the underlying risk of malignant transformation and guide the consideration of resection. Operating principles follow oncologic standards, with partial pancreatectomy and lymphadenectomy remaining the standard approach. Perioperative and postoperative management should follow standardized clinical pathways for care using a high-volume team-based approach. Surveillance strategies reflect individualized risk and are tailored on clinicopathologic features of disease.

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PANCREATIC NEUROENDOCRINE TUMORS OF THE PANCREAS EXCLUDING GASTRINOMA

Mohammad R. Khreiss, MD, and Taylor S. Riall, MD, PhD

INTRODUCTION

First described in 1869 and previously referred to as islet cell tumors, pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of tumors that arise from precursor cells in the pancreas. PNETs account for approximately 7% of all neuroendocrine tumors, but only 1% to 3% of pancreatic neoplasms. Their incidence has been on the rise and is estimated at 0.5 per 100,000 persons per year. This is likely multifactorial, but primarily caused by the increased utilization and improved sensitivity of cross-sectional imaging for a variety of diagnoses leading to incidental findings of asymptomatic, nonfunctional PNETs. Eighty to ninety percent of PNETs are sporadic, while 10% to 20% are associated with familial disorders such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau (VHL) syndrome, tuberous sclerosis complex, and neurofibromatosis type 1. PNETs are broadly classified into functional PNETs (F-PNETs) and nonfunctional PNETs (NF-PNETs) based on whether they produce unregulated hormones that cause well-described syndromic symptoms. The majority of PNETs (60%–90%) are nonfunctional and are discovered incidentally during cross-sectional imaging done for other purposes. PNETs exhibit a wide range of malignant potential, ranging from slow-growing, discrete tumors to locally invasive, rapidly metastasizing ones. The classification of PNETs has evolved over the decades, but given the wide range of biologic behavior, standardization of the diagnosis, management, and follow-up

surveillance is difficult. In this chapter, we will discuss both F-PNETs and NF-PNETs, except for gastrinomas, which are covered elsewhere in this book.

CLASSIFICATION

The classification of PNETs has evolved through the years. The most widely used classification system was developed by the World Health Organization (WHO) in 2017 (Table 1). This classification system relies mainly on histopathologic criteria and includes the use of Ki-67 proliferative index and mitotic index to predict tumor grade and biologic behavior. In the WHO classification, PNETs are divided into well-differentiated and poorly differentiated tumors, with well-differentiated tumors subdivided into low-grade, intermediate-grade, and high-grade tumors. In the WHO classification, the term *pancreatic neuroendocrine neoplasm* (panNEN) refers to the entire heterogeneous group of PNETs; the term *pancreatic neuroendocrine tumor* (panNET) refers to well-differentiated, nonmalignant tumors, and the term *pancreatic neuroendocrine carcinoma* (panNEC) refers to poorly differentiated large and small cell tumors. This classification system is useful because it addresses the significant heterogeneity in the biologic behaviors of PNETs and has implications on patient selection for surgery, surveillance, and treatment of metastatic disease, which will be described in detail.

PRESENTATION

The presentation of PNETs varies across a broad spectrum including completely asymptomatic and incidentally found NF-PNETs, to F-PNETS causing a well-defined syndrome, to widely metastatic disease. Overall, PNETs are equally distributed between the head, body, and tail of the pancreas; however, certain types of PNETs have a predilection to occur in the pancreatic head versus body/tail. NF-PNETs are usually found on cross-sectional imaging of the abdomen that is done for symptoms such as abdominal pain or found incidentally on cross-sectional imaging done for other purposes (e.g., evaluation after blunt abdominal trauma or during workup for acute abdominal pain in the emergency department). Large PNETs can cause mass effect on the stomach or other abdominal organs and result in a feeling of early satiety, abdominal distension, or pressure, and PNETs of the head of the pancreas can cause biliary obstruction and jaundice as the initial presenting symptom, but this is much less common than is seen in pancreatic adenocarcinomas. Patients with poorly differentiated tumors often present with synchronous metastatic disease and symptoms including weight loss, abdominal distention, and abdominal pain. In very rare instances, fulminant liver failure is the first presentation in poorly differentiated PNETs resulting from replacement of liver parenchyma with disease.

F-PNETs present with specific symptoms related to the type of hormone that is being overproduced (Table 2). Hormone-producing tumors include insulinomas, gastrinomas, vasoactive intestinal peptide (VIP)-secreting tumors, glucagonomas, somatostatinomas, PNETs resulting in carcinoid syndrome caused by production of serotonin, and even less common tumors that make hormones like adrenocorticotrophic hormone (ACTH), calcitonin, growth hormone–releasing factor, and parathyroid hormone–related peptide (PTHrP). Because of the hormone-related syndromes, F-PNETs are usually detected earlier.

Once identified, the diagnostic workup is similar for both F-PNETs and NF-PNETs. Diagnostic workup should focus on determining if the tumor is functional, complete staging, and evaluation for associated familial syndromes, which may lead to screening for other associated cancer and potentially change the timing of operative management for the PNET.

TABLE 1 2017 World Health Organization Classification of Pancreatic Neuroendocrine Tumors

Classification/Grade	Ki-67 Proliferation Index (%)	Mitotic Index/HPF (%)
Well-differentiated panNEN: panNET		
PanNET grade 1	<3	<2
PanNET grade 2	3-20	2–20
PanNET grade 3	>20	>20
Poorly differentiated panNEN: panNEC grade 3 (small cell and large cell type)	>20	>20

HPF, High-power field; *PanNEC,* pancreatic neuroendocrine carcinoma; *PanNEN,* pancreatic neuroendocrine neoplasm; *PanNET,* pancreatic neuroendocrine tumor.

DIAGNOSTIC EVALUATION

The diagnosis of PNETs is multifaceted. Patients most often present to surgeons with cross-sectional imaging already done, with a tumor that has specific characteristics consistent with a PNET. The surgeon should complete a thorough history and physical examination focusing on clinical signs and symptoms that accompany F-PNETs and NF-PNETs. Physicians should assess general symptoms associated with pancreatic neoplasms, including jaundice, dark urine, acholic stool, weight loss, abdominal pain, and back pain. Furthermore, they should inquire about symptoms associated with hormone-related syndromes with PNETs. These include hypoglycemic episodes, tremors, palpitations, anxiety, hunger, confusion, seizures, diarrhea, refractory peptic ulcer disease, gastroesophageal reflux, rashes, new-onset diabetes, gallstones, venous thrombosis, wheezing, flushing, weight loss, or weight gain. They should also look for physical examination findings such as migratory erythema, central obesity, jaundice, hirsutism, facial fullness, cardiac murmurs, and wheezing.

If a patient is referred for hormonal syndromes classic for F-PNETs without cross-sectional imaging, triple-phase CTMRI with and without contrast should be obtained. Once the diagnosis of PNET is suspected, the patient must be completely staged. Cross-sectional imaging of the chest and abdomen allows for evaluation of the relationship to major vascular structures and assessment of the liver, lungs, and intraabdominal lymph nodes for obvious metastatic disease. Recently, functional imaging has been more commonly used in the diagnostic and staging evaluation. It is also useful in the setting of occult PNETs that present with hormonal syndromes but no identified tumor on cross-sectional imaging. Biochemical markers are used to confirm the diagnosis and evaluate for functional symptoms. Endoscopic ultrasound with fine needle aspiration (EUS/FNA) is the most common modality used to establish a tissue diagnosis when necessary. Often, the characteristic imaging findings are enough to proceed to surgical management without a tissue diagnosis and EUS/FNA is reserved for instances in which the diagnosis is in question, resection is not possible, or the tumor pathology (grade) will change management, as in the setting of metastatic disease. Figure 1 provides an algorithm for evaluation, staging, and management of PNETs.

Cross-Sectional Imaging

Cross-sectional imaging with multiphase CT of the abdomen and pelvis or MRI with and without contrast play a vital role in the diagnosis, staging, and assessment of resectability in patients with PNETs. CT and MRI are helpful in evaluation of vascular involvement, which would preclude resection of the primary tumor. When water is used as oral contrast, pancreatic protocol CTs can also identify small

TABLE 2 Clinical Presentation of Pancreatic Neuroendocrine Tumor Subtypes

Tumor	Hormone	Symptoms
Nonfunctional PNET	Varies (pancreatic polypeptide, chromogranin A, others in small quantities)	Asymptomatic, abdominal/back pain, nausea/vomiting, pancreatitis, obstructive jaundice
Insulinoma	Insulin	Hypoglycemic symptoms (tremor, palpitations, anxiety, hunger, cognitive impairment, seizure, coma), fasting hypoglycemia, rapid correction with glucose (Whipple triad)
Gastrinoma	Gastrin	Severe, medically refractory peptic ulcer disease, gastroesophageal reflux, diarrhea (Zollinger-Ellison syndrome)
VIPoma	Vasoactive intestinal peptide (VIP)	Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome, pancreatic cholera or Verner Morrison syndrome)
Glucagonoma	Glucagon	Necrolytic migratory erythema, weight loss, diabetes mellitus, diarrhea, venous thrombosis
Somatostatinoma	Somatostatin	Diabetes, gallstones, steatorrhea, weight loss
Pancreatic carcinoid	Serotonin, tachykinins	Flushing, diarrhea, bronchospasm, valvular heart disease (carcinoid syndrome)
ACTHoma	Adrenocorticotropic hormone (ACTH)	Obesity, facial plethora, round face (moon facies), hirsutism, hypertension, bruising, fatigue, depression, dorsal fat pad, glucose intolerance, stria, proximal weakness, menstrual irregularities, decreased fertility (Cushing syndrome)
GRFoma	Growth hormone–releasing factor (GRF or GHRF)	Coarse facial features, enlarged hands and feet, macroglossia, deepening of voice, skin thickening, sleep apnea, arthritis, cardiovascular disease, insulin resistance, fatigue, weakness (acromegaly)
PTHrPoma	Parathyroid hormone–related protein (PTHrP)	Nephrolithiasis, weakness, bone pain, nausea, constipation, polyuria, depression (hypercalcemia)

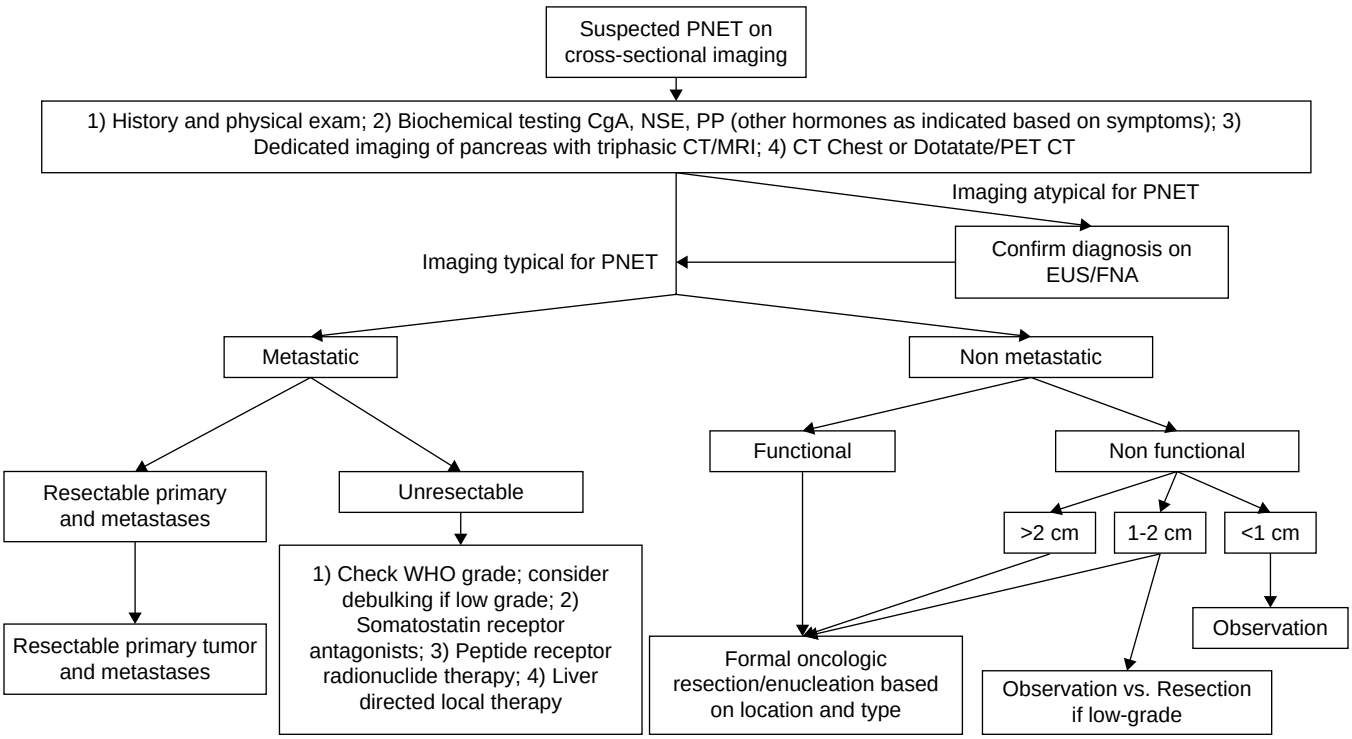


FIG. 1 Algorithm for the diagnosis and subsequent management of pancreatic neuroendocrine tumor.

duodenal primary tumors, as are sometimes seen with gastrinomas, especially in the setting of MEN-1. PNETs have a characteristic appearance on contrast-enhanced multiphase CT or MRI. The arterial phase is considered the gold standard in localizing PNETs as they are usually hypervascular and hyperenhancing in the arterial phase. Because of their contrast washout in the venous phase, PNETs may be isodense with respect to the surrounding parenchyma (Fig. 2).

Both multiphase abdominal CT and contrast MRI aid in detecting intraabdominal liver, lymph node, or other metastatic disease (Fig. 3); on CT/MRI, liver metastases are best seen in the arterial phase because of the characteristic arterial supply of metastatic lesions. On initial imaging with CT/MRI, evaluation of PNET size, vascular involvement, regional lymphadenopathy, and distant metastasis has significant implications for subsequent treatment decisions. If functional imaging is not utilized, cross-sectional imaging of the chest is important to complete staging (see Fig. 1).

Functional Imaging

Functional imaging has long been used for diagnosis and staging of PNETs. Somatostatin receptors are expressed by 80% to 100% of PNETs except insulinomas, where the rate drops to 50% to 70%. Historically, the functional imaging test of choice was Indium-111 somatostatin receptor scintigraphy. This was used both to localize PNETs not found on routine cross-sectional imaging and to detect distant metastasis. Recently, somatostatin receptor-PET imaging using gallium-dotatate has become the standard of care in patients with suspected PNETs. Relative to indium-111 somatostatin receptor scintigraphy, dotatate PET/CT has several advantages such as shorter scan time, lower radiation dose, improved image quality, decreased bowel activity, improved sensitivity, and better ability to quantify uptake. It is most useful in detecting occult lesions and evaluating for metastatic disease outside the field of intended resection. It is also useful in detecting disease recurrence and is used for follow-up to confirm suspicious lesions present on surveillance cross-sectional imaging or when hormone levels are elevated without obvious recurrent disease on CT/MRI. It may also be helpful to monitor disease progression and response in patients receiving treatment who were originally diagnosed with dotatate PET/CT (Fig. 4). Functional imaging should always be done in patients with MEN-1 and other genetic syndromes to evaluate for multifocal disease.

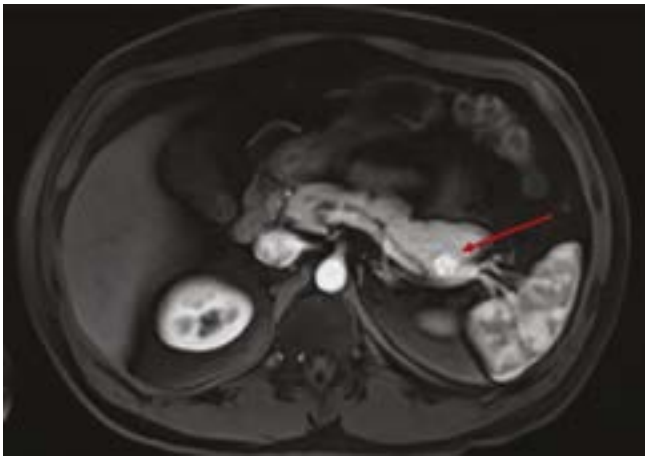


FIG. 2 Cross-sectional MRI of a 1.3-cm pancreatic neuroendocrine tumor *(arrow)* in the tail of the pancreas seen in the arterial phase. Note the hyperintense appearance of the mass on arterial phase imaging in relation to surrounding pancreatic parenchyma.

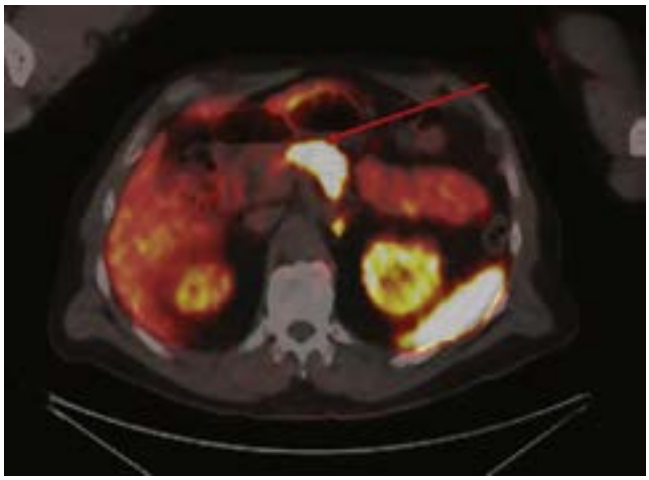


FIG. 4 Dotatate PET/CT of a patient with cystic neuroendocrine nonfunctional pancreatic neuroendocrine tumor. The patient presented with pancreatitis secondary to stricture of the pancreatic duct at the level of the neck of the pancreas. The dotatate PET/CT fused images show diffuse fluorodeoxyglucose avidity of the pancreatic neck and body *(arrow)*.

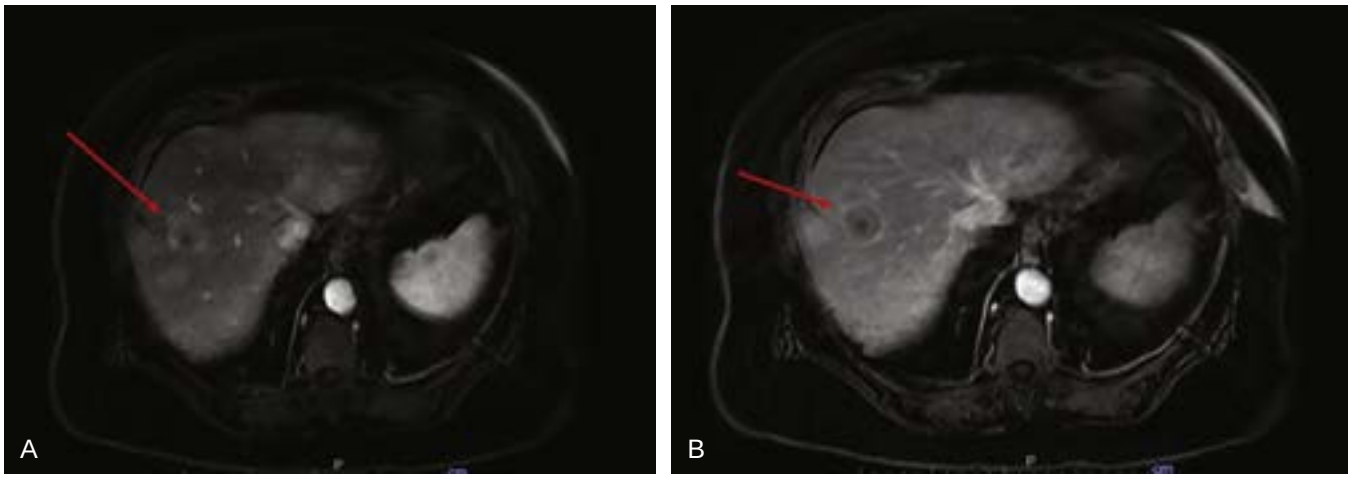


FIG. 3 MRI of the abdomen with and without contrast demonstrating a metastatic PNET to the liver in a 75-year-old female patient with metastatic poorly differentiated PNET to the liver and Ki-67 >20%. **(A)** The mass appears hyperenhancing in the arterial phase *(arrow)* **(B)** The same mass is shown in the venous phase *(arrow)* with washout of contrast.

Biochemical Markers

We do not recommend sending a wide panel of biochemical markers on all patients with PNETs, but rather sending biochemical tests based on symptoms. Such markers are confirmatory but often do not aid in the diagnosis given the distinct radiographic characteristics of these tumors. Chromogranin A (CgA) is considered one of most understood general clinical biomarkers of neuroendocrine tumors. It has a sensitivity of 66% and specificity of 95% and overall accuracy of 71% in PNETs. Serum chromogranin A is recommended both as a marker for diagnosis and for clinical follow-up in NF-PNETs after surgical resection. After surgical resection, return of chromogranin A to normal confirms complete resection, and chromogranin A has an established role in detecting recurrent or metastatic disease and serves as an independent marker for progression-free survival (PFS) and overall survival (OS). Chromogranin A can be falsely elevated in patients with inflammatory bowel disease, renal failure, liver failure, and chronic use of proton-pump inhibitors.

Neuron-specific enolase (NSE) is a glycolytic enzyme produced in the neurons of neuroendocrine cells. Elevated NSE levels are associated with poor differentiation and shorter PFS. In conjunction with chromogranin A levels, NSE levels may be used to predict outcomes when response occurs after treatment.

Pancreatic polypeptide (PP) is produced by pancreatic islet cells in the head and uncinated process of the pancreas. The combination of PP with chromogranin A improves the sensitivity for detection of PNETs from 25% to a total of 93% in patients with nonfunctioning PNETs. Its diagnostic sensitivity ranges from 41% to 68% in patients with PNETs. We recommend sending chromogranin A, NSE, and PP for all suspected NF-PNETs and sending specific hormone levels based on symptoms only as described later (see Fig. 1).

In patients with insulinomas, insulin levels are found to be elevated inappropriately in the setting of low serum glucose levels. Insulin is secreted by the beta cells of the pancreas. Patients with insulinomas develop Whipple triad, which includes (1) fasting hypoglycemia, (2) associated hypoglycemic symptoms including tremors, palpitations, anxiety, hunger, weight gain, confusion, seizures, and coma, and (3) resolution with glucose administration. In the patient with symptoms consistent with insulinoma syndrome, a 72-hour monitored fast documenting low serum glucose and high serum insulin levels at the time of hypoglycemic symptoms confirms the diagnosis. Patients with suspected insulinoma should also be screened for serum C-peptide levels and urine sulfonylurea levels. The absence of C-peptide at the time of hypoglycemia with inappropriately high insulin levels implies exogenous insulin administration. High urine sulfonylurea levels imply the use of inappropriate oral antihyperglycemic agents. Most insulinomas are benign and rarely metastasize.

Glucagon is secreted by the alpha cells of the pancreas. It plays a counterregulatory role to insulin, and a level greater than 500 pg/mL is usually detected in patients with glucagonomas. Glucagonoma is rare; patients may present with necrolytic migratory erythema caused by amino acid deficiency, weight loss, diabetes mellitus, and poor glucose tolerance. Glucagonomas have high malignant potential and may be part of MEN-1. Glucagon levels should be sent in the setting of the classic necrolytic migratory erythema rash and/or new-onset diabetes mellitus in the presence of a NET.

VIP is a hormone that plays an important role in gastrointestinal contraction and pancreatic exocrine function. It has a classic clinical presentation of watery diarrhea, hypokalemia, and achlorhydria (Verner-Morrison syndrome). VIPomas are usually malignant and often present with synchronous metastasis to the liver and regional lymph nodes. Elevated VIP levels are highly specific to VIPomas when present in patients with PNETs. This syndrome is profound, and it is unlikely that a tumor without profound diarrhea is secreting VIP, and it should not be seen in patients without such symptoms.

Somatostatin is a hormone that inhibits the endocrine secretion and motility of the stomach and gallbladder. Patients may be symptomatic or may present with an often subtle triad of hyperglycemia, cholelithiasis, and indigestion. Somatostatinomas are a rare form of PNETs that are usually difficult to diagnose in the preoperative setting.

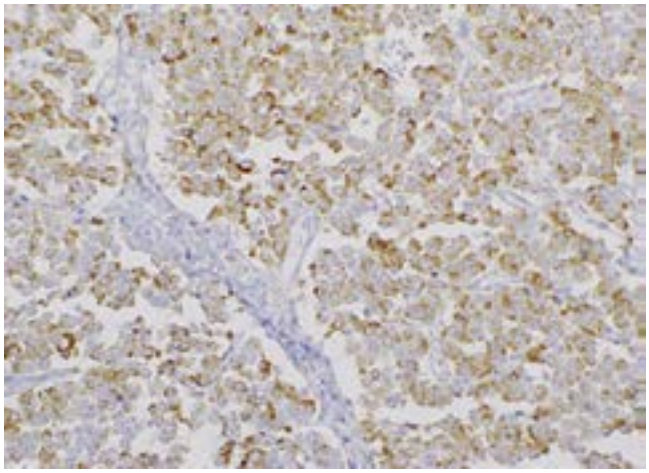


FIG. 5 Glucagonoma staining *(brown)* seen microscopically at 20× magnification in a patient who did not have classic syndromic symptoms. The diagnosis of functional pancreatic neuroendocrine tumor is confirmed by histopathologic staining for various hormones.

Gastrin is usually present in patients with gastrinomas. This topic will be covered extensively in a separate section of this book. PNETs can also secrete rare hormones, including serotonin, parathyroid hormone–related protein (PTH-rp), ACTH, and growth hormone–releasing factors. These instances are incredibly rare. In many cases, the functional syndromes are clinically obvious, but in some cases hormone secretion is found only on histopathologic staining (Fig. 5).

EUS/FNA

Definitive tissue diagnosis of a PNET can be established through pathologic examination of tissue obtained through needle biopsy. This is most useful in cases in which the preoperative imaging is not classic and the diagnosis remains in question. This may be the case in cystic neuroendocrine tumors, which differ in radiographic appearance.

The use of EUS/FNA is not necessary in all patients with PNETs. Because of their typical appearance on cross-sectional imaging and the presence of functional imaging, EUS/FNA should be utilized only when the diagnosis of PNET is not certain or there is a high suspicion for mixed tumors. It is also used when the grade of tumor would affect clinical management, such as in the setting of metastatic disease. In this case, establishment of high-grade, poorly differentiated tumors would represent a contraindication to resection or debulking, while low-grade, well-differentiated tumors mandate an aggressive approach with resection of the primary and complete resection or debulking of metastatic disease. However, EUS/FNA has limitations. On EUS/FNA, there is poor correlation of the FNA-determined grade with final pathology because of significant tumor heterogeneity. In 50% of patients with grade 2/grade 3 tumors, the final pathologic grade differs from the FNA biopsy. EUS/FNA biopsy is also utilized in the setting of clinical trials when tissue diagnosis is necessary for enrollment.

EUS can also be utilized to help in sampling regional lymph nodes and detecting vascular invasion, but this adds little over modern cross-sectional imaging. EUS is also important in patients with MEN-1, as is dotatate PET/CT, where it aids in detecting multifocal disease. The use of EUS/FNA should be used judicially as it carries the risks of gastrointestinal tract perforation, pancreatitis, and bleeding.

MANAGEMENT OF PNETS

The management of PNETs depends on many factors including: (1) tumor functional status, (2) tumor location in the head, body, or tail of the pancreas, (3) tumor size, (4) tumor grade and differentiation, and (5) presence of regional lymph node metastasis or distant metastasis (see Fig. 1). Assessing the tumor grade and risk of lymph node metastasis is of paramount importance when making management decisions, especially in the setting of metastatic disease.

Functional PNETs

With the exception of insulinomas, F-PNETs are usually malignant. In addition, they secrete hormones that cause symptoms. As such, surgical resection is the standard of care for all nonmetastatic, functional, sporadic PNETs. Surgical resection improves patient survival and allows for control of the endocrine syndromes associated with the specific PNET. Surgical resection provides curative intent therapy and decreases the risk of future problems. The development of metastatic disease is least common in insulinomas (approximately 15%) ranging to up to 90% in gastrinomas, glucagonomas, and VIPomas. Cure rates vary with surgical resection and range from 90% for insulinomas to around 40% with gastrinomas. Surgical planning in the setting of F-PNETs should consider the presence of metastasis to regional lymph nodes. Formal oncologic resection with local lymphadenectomy through either a pancreaticoduodenectomy or distal pancreatectomy with splenectomy is usually utilized based on the location of the tumor. Regional lymphadenectomy increases the chances of biochemical cure and improves OS. However, because insulinomas have low malignant potential, as do small incidentally found NF-PNETs, enucleation may be considered in these cases. For enucleation to be considered, the PNET must be at least 2 to 3 mm from the main pancreatic duct.

Nonfunctional PNETs

Surgical management of NF-PNETs depends on multiple factors including size, location, presenting symptoms, proximity to the pancreatic duct, presence of regional lymphadenopathy, presence of metastatic disease, and the grade and degree of differentiation of the tumor. All NF-PNETs greater than 2 cm in size should undergo formal oncologic resection with regional lymphadenectomy because 50% of NF-PNETs greater than 2 cm will have nodal metastasis. PNETs have a more favorable prognosis than tumors of the exocrine pancreas, even in the setting of node-positive disease. Multiple meta-analyses have shown survival benefit in surgically resected patients, even in the setting of node-positive disease.

The management of NF-PNETs less than 2 cm remains controversial. Sharpe and colleagues reviewed the national cancer data base (NCDB) and found that OS was improved with resection of patients of PNETs of all sizes. Surgical resection provided improved OS at 3 and 5 years in patients with NF-PNETs less than 2 cm in size who underwent surgical resection. However, many other studies have shown that small, asymptomatic tumors can be safely observed. For tumors this size, tumor grade and differentiation play a big role in decision making as the risk of malignant behavior is presumably higher in high-grade tumors. The current literature divides small NF-PNETs into those less than 1 cm and those with size between 1 and 2 cm. PNETs that are less than 1 cm in size are usually benign and have an indolent course. In these instances, surveillance without surgical resection is indicated. However, there are no clear-cut guidelines regarding the frequency of surveillance. We usually perform cross-sectional imaging with multiphase CT or MRI every 6 months for the first 2 years and then annually thereafter. It is unclear when or if such imaging should be stopped in the setting of a stable NF-PNET over a significant period. In patients undergoing surveillance, indications for resection would include increase in size, development of regional lymph node enlargement, or, in rare instances, patient anxiety.

The management of PNETs that are 1 to 2 cm in diameter carries even more controversy. Toste et al. reported a 7% incidence of metastasis to regional lymph nodes in patients with PNETs less than 2 cm. In a recent study from 16 European centers, 210 patients underwent surgical resection of NF-PNETs less than 2 cm in diameter. The incidence of lymph node metastasis was 10.6%. Only 3% of patients had lymph node metastasis in grade 1 tumors; this number increased to 16% in grade 2 tumors and 100% in grade 3 tumors. Therefore, in the setting of 1- to 2-cm PNETs, biopsy with determination of grade may help guide management, with the caveat mentioned regarding the limitation of FNA for determining tumor grade because of tumor heterogeneity. For PNETs less than 2 cm, the presence of biliary obstruction or pancreatic duct obstruction warrants resection. Also, in young patients who have a potential long period for observation, resection should be considered. Enucleation can be considered in low-grade tumors without proximity to the main pancreatic duct. In higher-grade tumors, larger tumors, and those close to the pancreatic duct, formal resection is achieved with pancreaticoduodenectomy or distal pancreatectomy with or without splenectomy.

Metastatic Disease

The liver is the most common site of metastasis of PNETs, with 65% of patients with metastasis having disease in the liver. The 5-year OS for PNETs is 75% to 90% in the setting of localized disease and is decreased to 13% to 50% in patients with metastatic disease to the liver. This wide range of survival reflects the heterogeneity in presentation. In the setting of metastatic disease, determining tumor grade and differentiation is critically important in management decisions.

Complete resection or debulking of liver metastasis should be considered in patients with symptomatic disease and low-grade, well-differentiated histology. The goal is to achieve complete resection while keeping an adequate functional liver remnant. R0/R1 resection is preferred over R2 resection (debulking) and is associated with higher 5-year survival. Debulking of liver disease up to 80% is an acceptable treatment strategy for well-differentiated, low-grade disease. However, debulking is not indicated in the setting of high-grade, poorly differentiated disease. The use of microwave ablation, radiofrequency ablation, and enucleation are strategies employed to provide a liver parenchyma–sparing approach in the setting of unresectable liver metastases. In addition to resecting metastatic disease, primary tumor resection in this setting shows improved survival and should be considered. This is usually done at the same time.

SURGICAL APPROACHES

Minimally Invasive Approaches

PNETs are often small without vascular involvement and ideal for minimally invasive approaches. Minimally invasive approaches have been proven to be safe and effective in management of all pancreatic tumors with oncologic outcomes on par with open approaches. In fact, minimally invasive distal pancreatectomy has become the standard of care for management of disease in the body and tail of the pancreas and provides several advantages over the open approach. The LEOPARD trial supported these findings clearly in patients with left-sided pancreatic tumor. This is not as clear with respect to right-sided tumors. Zeureikat et al. reported on 1028 patients who underwent either robotic or open pancreaticoduodenectomy. They concluded that in the hands of experienced robotic surgeons, the robotic approach was associated with longer operative times, but also a reduction in blood loss and in major complications. There was no difference in 90-day mortality, wound infection, clinically relevant postoperative pancreatic fistulas, or readmission rates.

Enucleation

Enucleation carries the theoretical advantage of improved endocrine and exocrine postoperative function. It can be used in patients with

benign tumors with smaller size and small insulinomas. The proximity to the pancreatic duct or involvement of it precludes enucleation. A 2- to 3-mm distance from the pancreatic duct is needed to avoid injury and pancreatic leak. Although enucleation has been proven to have similar outcomes to formal resection with respect to mortality, morbidity, and return to work in carefully selected patients, it is associated with increased risk of postoperative pancreatic fistula. Resection margins for both formal resection and enucleation have not been clearly defined in the literature, but current teaching suggests that any negative margin is acceptable.

MANAGEMENT OF UNRESECTABLE PNETS

Use of long-acting somatostatin analogues is warranted in the setting of symptomatic disease in patients who show positive expression of somatostatin receptors. Somatostatin receptor antagonists show an antiproliferative effect and are associated with prolonged PFS. Two somatostatin receptor antagonists are most commonly used: lanreotide and octreotide long-acting release (LAR). The use of octreotide LAR has been associated with longer times to tumor progression compared with placebo. In the CLARINET trial, treatment with lanreotide was associated with prolonged PFS in patients with advanced PNETs. Somatostatin receptor antagonists are also the treatment of choice for patients with excessive hormone secretion before surgery or if surgical resection cannot be performed, and they can significantly improve symptoms related to hormonal syndromes.

Targeted therapies have been employed for management of locally advanced, metastatic unresectable PNETs. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, and sunitinib, a tyrosine kinase inhibitor, are generally recommended as second-line therapies after somatostatin receptor antagonists in patient with positive expression of somatostatin receptors. They are used as first-line therapies if there is no expression of somatostatin receptors. Everolimus and sunitinib have been shown to improve PFS to 11 months on average compared with placebo. Other agents being investigated include cabozantinib, sulfatinib, and lenvatinib.

Chemotherapy may be used in patients with poorly differentiated PNETs, high tumor burden, and/or elevated Ki-67 index. Temozolomide and streptozocin are used for well-differentiated tumors, whereas platinum-based regimens are used in the setting of poorly differentiated disease. They can help in decreasing tumor burden to allow surgical resection when indicated.

Recently, peptide receptor radionuclide therapy (PRRT) has shown great promise in patients with metastatic disease. Peptide receptor radionuclide therapy is applied in patients with advanced neuroendocrine tumors. It usually incorporates a radioisotope like Yttrium-90 or Lutetium-177 and a somatostatin receptor antagonist. This allows for delivering targeted radiation to the tumor. Several studies have demonstrated the role of PRRT in patients with advanced PNETs with an overall response rate ranging between 16% and 61%. The phase 3 Lu-DOTATATE PRRT trial showed an overall response rate of 39% in all NETs of the midgut. PNETs showed the highest response rates in other studies involving patients with a NET. For this reason, PRRT may be attempted in patients with high expression of somatostatin receptors.

CONCLUSION

PNETs are a heterogeneous group of tumors that present treatment challenges. Treatment of patients with PNETs should be tailored based on size, location, tumor grade and differentiation, presence of symptoms, and distant metastasis. It should be approached in a multidisciplinary fashion with the goal to control symptoms and provide long term OS. Cure should be considered feasible in patients with low-grade tumor, even in the setting of metastatic disease to the liver. Further work is needed to better understand this disease entity.

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Intraoperative Radiation for Pancreatic Cancer

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INTRODUCTION

Although intraoperative radiation therapy (IORT) for pancreatic cancer has a long history of inquiry, improvements in systemic control with multiagent chemotherapy have increased the enthusiasm for aggressive local therapy, including more frequent exploration and attempts at radiation dose escalation. As such, there has been renewed enthusiasm surrounding the potential use of IORT. Indeed, IORT provides an opportunity for the focused delivery of high doses of radiation while shielding radiosensitive structures that often limit the dose of external beam radiation therapy (EBRT). Nevertheless, considerable challenges exist surrounding the development of a successful IORT program. Beyond the need for a shielded operating room and delivery system, successful administration of IORT requires a coordinated effort between the radiation oncology and surgery teams. As such, it is critical that surgeons interested in administering IORT have an in-depth understanding of both the scientific and technical underpinnings of this treatment modality.

REVIEW OF EXISTING LITERATURE

Early exploration of IORT for pancreatic cancer came from Japanese investigators. In the 1970s, Kyoto University investigators described their experience with IORT for locally advanced disease, in which doses of 20 to 40 Gy resulted in improvements in tumor-related pain. These findings subsequently prompted investigators at the

Massachusetts General Hospital (MGH) and the Mayo Clinic to further study IORT for pancreatic cancer in both the unresectable and resectable setting. In 1984, MGH reported outcomes among unresectable patients treated with IORT and EBRT, noting high rates of pain improvement and a median survival of 16.5 months. Three years later, Mayo investigators retrospectively reported outcomes among resected patients who received either postoperative EBRT alone or IORT followed by postoperative EBRT, noting higher rates of 1- and 2-year local control in patients who received both modalities. Since then, encouraging data have been reported in both the unresectable and resectable settings, as outlined in the following sections.

IORT for Unresectable Disease

Multiple subsequent series, including reports from Mayo and Japan, further explored IORT in the locally advanced setting, suggesting improvements in local control with the use of both IORT plus EBRT compared with EBRT alone. These findings prompted a multi-institutional US study through the Radiation Therapy Oncology Group, namely Report 8505, in which locally advanced pancreatic cancer patients were treated with IORT to 20 Gy followed by 50.4 Gy of EBRT. Unfortunately, median survival in this cohort was only 9 months, which dampened enthusiasm for the role of IORT. Since then, however, other institutions have published positive long-term results with the use of IORT, with MGH reporting the most robust experience. An analysis of long-term outcomes among 194 locally advanced patients who were treated at MGH with IORT between 1978 and 2010 showed decent outcomes, particularly among well-selected patients with smaller tumors, with a 2-year overall survival of 16% and with a small fraction of patients (3%) experiencing long-term survival more than 5 years. These findings have renewed interest in IORT as a component of therapy for locally advanced pancreatic cancer, particularly with more patients with more advanced disease now undergoing attempted exploration in an era of better systemic control with multiagent chemotherapy. The most modern experience is from MGH, where patients were treated with multiagent FOLFIRINOX and chemoradiation followed by surgical exploration and IORT. The majority of patients (86/132, 65%) underwent resection and IORT, while 46 (35%) underwent IORT alone. Among the 46 patients who underwent IORT alone, 1-year, 2-year, and 5-year overall survival rates were promising at 98%, 49%, and 9%, respectively, which are much more favorable than those from the initial MGH report.

IORT for Resected Disease

Following the results of the Mayo study of resected patients, the National Cancer Institute conducted a small, randomized trial of 24 patients comparing resection alone to resection with IORT. Patients in the IORT arm experienced improvements in local control and survival. Since then, subsequent institutional reports (see the Suggested Readings) have also suggested improvements in local control with the administration of IORT. A recent study from MGH reported on outcomes among patients with borderline resectable disease or locally advanced patients who were managed with a modern regimen of up-front multiagent systemic therapy (primarily FOLFIRINOX or gemcitabine/Abraxane), chemoradiation to a median dose of 50.4 Gy, and surgical exploration with or without IORT. The report analyzed 68 patients who made it through the neoadjuvant regimen without progression, of whom 41 successfully (60%) underwent resection, 18 (27%) had unresectable disease, and 9 (13%) had metastatic disease. Among the 41 patients who underwent resection, 22 were treated with IORT to a dose of 10 Gy. Patients treated with IORT experienced improved survival without additional toxicity or complications. Furthermore, unresectable patients who were treated with IORT to a dose of 15 Gy experienced an encouraging median survival of 24.8 months. The most modern experience with IORT in the postoperative setting also comes from MGH, where patients with borderline or locally advanced pancreatic cancer were treated with FOLFIRINOX and chemoradiation (median dose of 50.4 Gy) followed by surgical resection with or without IORT. In the no-IORT group, R1 resection was associated with poorer overall and disease-free survival. However, in the IORT group, there was no difference in overall and disease-free survival between patients who underwent R0 versus R1 resection, suggesting that IORT may mitigate the negative effects of R1 resection.

PATIENT SELECTION

As reflected in the literature, well-established guidelines for the use of IORT for pancreatic cancer are lacking. Nonetheless, institutional data support consideration of IORT in instances (1) when close or positive margins are expected at the time of resection or (2) when disease may be unresectable, both of which are frequent scenarios with pancreatic cancer. Certainly, the decision to consider IORT should be discussed in a multidisciplinary setting, and its potential use should be defined ideally from the outset of therapy. Importantly, it is unlikely that intraoperative radiation alone is sufficient to achieve tumoricidal doses for either gross or microscopic disease, and as such, IORT should be used in combination with either preoperative or postoperative radiation therapy. Although postoperative radiation can be considered with the use of surgical clips for guidance of radiation fields, preoperative radiation is often preferred for a number of reasons, including the following.

1. Better definition of the intact tumor target in the preoperative setting as compared with the often-ill-defined surgical bed in the postoperative setting.
2. Displacement of bowel by the intact tumor in the preoperative setting compared with filling of the surgical bed by bowel in the postoperative setting.
3. Improved oxygenation of target tissue in the preoperative setting, rendering the target potentially more radiosensitive compared with the postoperative setting.
4. Removal of irradiated tissue with the preoperative approach.

EQUIPMENT

IORT can be administered using multiple devices, including LINAC-based electron beam radiation therapy (intraoperative electron radiation therapy [IOERT]), low-energy photon therapy, low-dose-rate brachytherapy, or high-dose-rate (HDR) brachytherapy. Each of these modalities are viable strategies with their own relative merits. HDR-based IORT delivers a more concentrated dose at the surface of the target with sharp fall-off, which may be optimal for a surgical cavity/margin, whereas IOERT delivers a more homogenous dose of radiation to a greater depth. A significant advantage of an HDR-based technique lies in its method of delivery through the use of customized applicators that can allow delivery of radiotherapy to irregular surfaces compared with the rigid cone applicators that are required for IOERT or IORT with low-dose photons. At our institution, we have primarily used an HDR technique to take advantage of the flexible applicators; therefore, the technique described in this chapter will primarily focus on the administration of HDR-based IORT. Newer applicators that allow the delivery of low-dose-rate brachytherapy such as the CivaSheet are also under investigation. As noted, HDR-based IORT requires the use of a flexible flap applicator along with an HDR-based after-loader system. The Freiburg flap is the applicator used at our institution and consists of silicone balls that are 1 cm in diameter and are connected to form a flexible planar sheet through which 6Fr catheters can be inserted. The size and shape of the Freiburg flap can be customized at 1-cm intervals based on the dimensions of the target site. The after-loader system used at our institution is the Nucletron system by Elekta ; however, other applicators and after-loader systems are available.

TECHNIQUE

The first step of HDR-based IORT is for the surgeon to try to retract as much radiosensitive normal tissue such as bowel (see Normal Tissue Toxicity later in this chapter) out of the field and protect these structures by placing lead shields in front of them. Subsequently, the surgeon and radiation oncologist should jointly identify the high-risk surgical bed and/or gross disease. The target area is measured to inform the size of the applicator. The target area can also be marked with a marking pen to aid in accurate positioning of the applicator. Once the dimensions of the applicator have been finalized and the prescription dose and depth have been selected, the radiation oncologist's physics team can subsequently begin developing the radiation plan, which primarily consists of determining the amount of time that the radioactive source will spend in each silicone ball. While the radiation plan is being developed, the radiation oncologist can preselect an applicator that is closest to the desired size. If an exact match is not available, the applicator can be cut to the appropriate size. Before proceeding further, it is a good idea to place the applicator in the surgical field to ensure that the chosen dimensions are optimal and that the applicator fits well into the surgical field. Additionally, the entrance route of the catheters from the after-loader into the surgical cavity and subsequently into the applicator should also be considered to ensure that the catheters will not be kinked as a result of sharp angling. Thereafter, 6Fr catheters are thread through the applicator and secured on either side of the applicator. The catheters are subsequently labeled in numeric order. It is helpful to place labels on the catheters both at a point near the applicator (at our institution, we use the labels as one of the mechanisms of securing the catheters to the applicator) as well as at a point a distance away from the applicator. These labels are critical because they allow accurate identification of the catheters, even after the applicator can no longer be visualized once packing has been placed. At this point, the applicator and catheters can be positioned into the surgical field in the location that had been previously defined (Fig. 1). Wet lap sponges can be packed on top of the applicator to help ensure its stability (Fig. 2). If need be, sutures can also be considered to further secure the applicator in place. Additional lead shields can be placed to minimize radiation dose to surrounding structures, with 3 mm of lead roughly reducing the dose by 70%. Of note, it is important to remember to cover lead shields with wet gauze to minimize the backscatter dose. Distance from the applicator also helps reduce the radiation dose, with the prescribed dose dropping to 70%, 50%, and 35% at 1, 2, and 3 cm, respectively. Thereafter, the catheters are connected to the after-loader, and a dry run is performed without a radiation source to ensure that there are no kinks or other obstacles to successful delivery. The room is evacuated, and appropriate video surveillance of the patient is confirmed. Radiation delivery can subsequently commence. Total treatment time is dictated by the prescription dose, the size of treatment area, and the activity of the source. At our institution, we use an ^{192}Ir source, which has a half-life of 73 days.

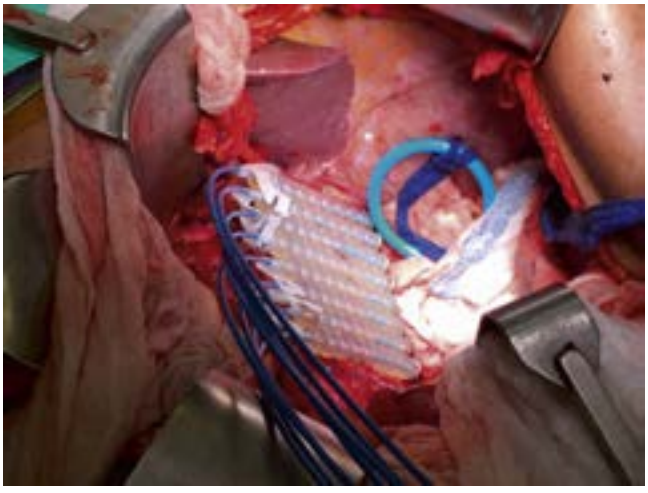


FIG. 1 Freiburg flap in the surgical bed connected with catheters to an after-loader *(not shown)*.

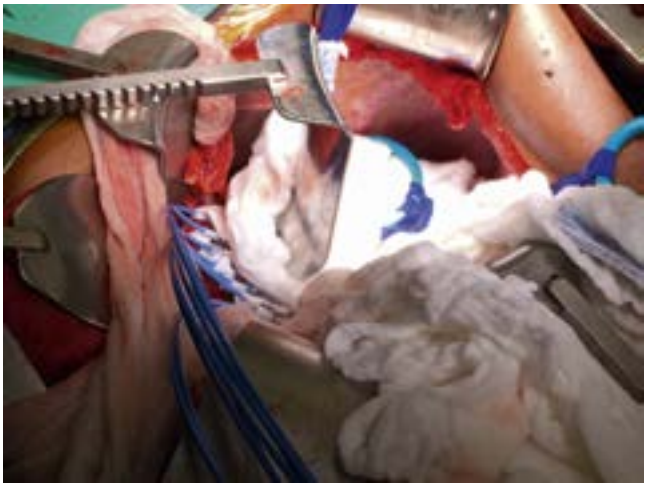


FIG. 2 Packing over the Freiburg flap to ensure stability.

TARGET VOLUME DELINEATION

There is no consensus on optimal field design in the setting of IORT. Currently, IORT is most commonly targeted to the vascular margin at risk for microscopic residual disease in the setting of gross total resection or residual gross tumor in the setting of unresectable disease. Whether "elective" irradiation of larger volumes of tissue at risk for microscopic, subclinical residual disease in peripancreatic perineural tracts or lymph node basins should be pursued, particularly in the setting of gross total resection, is an open question.

DOSING

Given that IORT consists of high doses of radiation administered at one time, the biological effective dose of a given IORT prescription dose is significantly higher than an equal EBRT dose administered in a fractionated manner. Conversion factors between IORT and fractionated EBRT doses are primarily derived from in vitro data and animal studies and therefore must be interpreted with some caution. Nevertheless, Table 1 provides helpful estimates for IORT dose conversions. In general, multiplication of an IORT dose by 2.2 to 2.5 yields a rough estimate for an equivalent fractionated EBRT dose to tumor, whereas multiplication of an IORT dose by 3 yields a rough estimate for an equivalent fractionated EBRT dose to normal tissue.

TABLE 1 Conversion Estimates Between IORT and EBRT Doses

IORT Dose	EBRT Tumor Dose	EBRT Normal Tissue Dose (Acute)	EBRT Normal Tissue Dose (Late)
10 Gy	17 Gy	20 Gy	30 Gy
15 Gy	31 Gy	37 Gy	65 Gy

NORMAL TISSUE TOXICITY

Data describing normal tissue toxicity from IORT come primarily from canine models. In general, EBRT for pancreatic cancer will approach the radiation tolerance of bowel, so great effort should be made to limit any further bowel exposure from IORT to minimize the risk of late bowel toxicity such as obstruction, ulceration, perforation, or fistula. Sites used for anastomotic creation should be avoided in particular. As opposed to HDR brachytherapy, IOERT may allow for minimization of dose to anastomotic sites. Dose to the ureter, although usually less relevant to the treatment of pancreatic cancer, should also be minimized because excessive dose to the ureter can result in ureteral stenosis. In canine models, IORT doses above 18 Gy in combination with EBRT doses of 50 Gy led to significant risk of ureteral stenosis. Although typical IORT prescription doses tend to be below 18 Gy, effort should still be made to shield the ureter. Vascular structures have a higher radiation tolerance compared with bowel and ureter. Nonetheless, at high IORT and EBRT doses, clinically significant intimal hyperplasia and medial wall fibrosis have been described, with the potential for subsequent complications including arterial thrombus. Although these risks tend to be less apparent at the IORT and EBRT doses used in the abdomen, caution should nonetheless be taken, particularly if the patient has received prior courses of radiation. Last, patients should be counseled on the risk of neuropathy, which tends to occur with IORT doses in excess of 15 Gy. For pancreatic IORT, the effect on wound healing should be less relevant compared with IORT in more superficial sites, with modern series from MGH showing no increase in wound complications in patients receiving IORT.

CONCLUSION

IORT represents a potential treatment option for decreasing local recurrence in pancreatic cancer patients with resected or unresectable disease, particularly when administered as a boost in combination with either preoperative or postoperative EBRT. Successful delivery of IORT requires a joint effort between the surgical oncologist and radiation oncologist to ensure appropriate targeting and minimization of radiation exposure to surrounding structures. In the era of contemporary multiagent systemic therapy leading to better systemic control, IORT can serve as a tool to provide more durable local control for this disease.

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Transplantation of the Pancreas

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INTRODUCTION

Type 1 diabetes mellitus, formerly known as *juvenile diabetes,* is characterized by hyperglycemia resulting from destruction of the insulin-producing beta cells of the pancreatic islets of Langerhans. This loss of beta cells is caused by T-lymphocyte–mediated autoimmune destruction that typically occurs during childhood or early adolescence. Insulin replacement can lead to acceptable control of blood glucose levels; however, affected individuals are subject to the development of various secondary complications, including cardiac disease, stroke, retinopathy and blindness, nephropathy and renal failure, peripheral and autonomic neuropathy, and peripheral vascular disease. Although careful blood glucose control has been demonstrated to decrease the number of diabetes-related secondary complications, it has also been shown to lead to an increased number of dangerous hypoglycemic episodes. Technologic advances (insulin pumps and continuous glucose sensors) may help reduce the incidence of secondary complications and the number of hypoglycemic episodes.

Transplantation therapy for type 1 diabetes was developed as an alternative to insulin administration, with the goal of reducing or eliminating the development of secondary complications of the disease by perfecting glycemic control. The pancreas—both the whole organ and isolated pancreatic islets—is being transplanted into individuals with type 1 diabetes. Clinical islet transplantation has been an experimental therapy available at only a few academic centers for the past 20 years. However, in 2021, the US Food and Drug Administration granted regulatory approval to CellTrans as the first entity approved to supply pancreatic islets as a commercial product for transplantation into highly select diabetic individuals with severe hypoglycemia unawareness. In contrast, whole-organ pancreas transplantation is an established and widely available therapy for the treatment of individuals with type 1 diabetes and also a highly select group of individuals with type 2 diabetes. Whole-organ pancreas transplantation is the main focus of this chapter.

WHOLE-ORGAN PANCREAS TRANSPLANTATION

History and Early Results

On December 20, 1893, Dr. P. Watson Williams grafted pieces of a sheep pancreas into the subcutaneous tissues of a diabetic child who died 3 days later of unrelenting diabetic ketoacidosis. This first attempt to treat diabetes with transplantation, although unsuccessful, preceded decades of animal experimentation in which investigators developed the methods necessary to perform a vascularized pancreas transplant.

The first vascularized pancreas transplant in a patient was performed on December 17, 1966, by Drs. William Kelly and Richard Lillehei at the University of Minnesota. The patient achieved temporary insulin independence but eventually required graft removal and ultimately died of postoperative complications. The subsequent early experience with pancreas transplantation was characterized by some technical success, but no graft functioned beyond 1 year. Most pancreas grafts that were successful from a technical perspective were lost as a result of rejection. The initial enthusiasm for this procedure dwindled so much that it was nearly abandoned by the mid-1970s. However, further technical refinements and the introduction of more potent immunosuppressive medications (first cyclosporine and then tacrolimus) allowed for more favorable outcomes after pancreas transplantation. Throughout the 1980s and early 1990s, the number of pancreas transplants performed in the United States increased dramatically, peaking at nearly 1500 transplants during 2004. However, this number has declined since, with fewer than 1000 pancreas transplants performed in the United States during 2021.

Indications and Patient Selection

The majority of patients undergoing pancreas transplantation have type 1 diabetes mellitus and end-stage renal disease. In these individuals, pancreas transplantation is performed with simultaneous kidney transplantation (simultaneous pancreas and kidney [SPK] transplantation) or after successful kidney transplantation (pancreas after kidney [PAK] transplantation). The normal blood glucose control achieved by the transplanted pancreas should protect the transplanted kidney from recurrent diabetic nephropathy and is beneficial from an overall quality-of-life perspective. In a small proportion of patients with difficult-to-control diabetes but with preserved renal function, pancreas transplantation alone (PTA) is performed. In the United States for the 3-year period ending in 2021, 85% of pancreas transplantations were SPK, 6% PAK, and 9% PTA. SPK and PAK recipients require immunosuppressive therapy to protect both the kidney and pancreas from rejection, whereas in the case of PTA recipients, the need for immunosuppression is solely for the pancreas itself. For this reason, careful individual risk-to-benefit consideration is essential in selecting PTA recipients.

Potential pancreas recipients are carefully screened for contraindications to transplantation, such as an ongoing infectious process or malignancy. These candidates almost always have medical comorbid conditions resulting from secondary complications from diabetes; therefore, a thorough assessment of a candidate's cardiovascular status is essential. Cardiac contraindications to pancreas transplantation include the presence of noncorrectable coronary artery disease, ejection fraction of less than 40%, or myocardial infarction within the previous 6 months. Recipient age is also important, although there is no consensus as to what an upper age limit should be for undergoing pancreas transplantation. National data indicate that almost all pancreas transplants in the United States are performed in recipients younger than 65 years of age.

The Donor Operation

Selection of an appropriate deceased donor for pancreas procurement includes standard donor selection criteria. In addition, there is a bias toward using organs from younger, leaner, and hemodynamically stable deceased donors. Donor organs that require high doses of vasopressor are considered higher risk for complications in the recipient. In addition, pancreata with significant infiltration of fat in the parenchyma are usually avoided because they are associated with a greater likelihood of postoperative complications such as pancreatitis, peripancreatic fat necrosis, and infection. On the basis of these relatively stringent selection criteria, only a fraction of deceased donors are deemed suitable for whole-organ pancreas donation. In the United States, there were 13,863 deceased donors during 2021; however, only 976 pancreata were transplanted from 7% of all deceased donors, in comparison with 8666 livers (63%) and 19,843 kidneys (72% of all deceased donors).

Pancreas procurement from a deceased donor is performed in careful conjunction with liver procurement. The blood supply to the liver is identified to ensure that both organs can be removed and transplanted. In most cases, aberrant blood supply should not preclude the transplantation of both organs. Initial dissection involves division of the gastrocolic ligament to expose the anterior surface of the pancreas. Visual inspection is considered an important element in pancreas procurement because this is an opportunity to assess the organ for the presence of infiltrating fat, fibrosis, or hematoma that might preclude transplantation. The portal triad is carefully dissected, with division of the common bile duct and the gastroduodenal artery. In addition, the common hepatic, the proximal left gastric, and the proximal splenic arteries are all dissected free from surrounding lymphatic tissues. Further dissection of the pancreas includes performing Kocher's maneuver to mobilize the pancreatic head and dividing the lienophrenic and lienocolic ligaments to mobilize the pancreatic body and tail. Of note, the spleen is left in continuity with the pancreas to minimize manipulation of the gland, and it is removed later during backbench preparation. The duodenum is decontaminated by flushing of a solution containing povidone-iodine, an antibiotic, and an antifungal through a nasoduodenal tube.

After the donor has been prepared with heparin, the abdominal aorta is ligated at the iliac bifurcation, and a cannula is placed in a retrograde direction for perfusion. The liver surgery team may also place a cannula into a portal vein tributary, such as the inferior mesenteric vein, for portal perfusion. The supraceliac aorta is cross-clamped, the vena cava is vented, and the abdominal organs are flushed in situ with preservation solution (Belzer UW Cold Storage Solution) at 4°C. In addition, topical cooling of the organs is performed. Once the organs have been adequately flushed, the liver and pancreas are removed either en bloc and divided on the back table or removed separately from the donor. In the latter situation, the liver is removed first, by division of the portal vein 1 cm cephalad to the superior margin of the pancreatic head (at the level of the coronary vein) and division of the splenic artery 5 mm beyond its origin, which thus preserves the entire celiac axis with the liver. Next, removal of the pancreas proceeds. The proximal duodenum (just beyond the pylorus) and the distal duodenum (near the ligament of Treitz) are divided with a GIA stapler. The small bowel mesentery and transverse colon mesentery that lie inferior to the pancreas are divided. The superior mesenteric artery is divided just above its origin from the aorta. Long segments of iliac arteries and veins are removed for vascular reconstruction on the back table.

Backbench Preparation of the Pancreas

In relation to other solid organs, the pancreas requires more preparation before transplantation into the recipient. This back table preparation is performed in ice-cold preservation solution to minimize further ischemic injury to the organ. The duodenum is often shortened with a GIA stapler, with care to exclude any gastric

tissue and also not to compromise the opening of the ampulla of Vater. The small bowel mesentery is divided by firing a stapler across this mesentery and then reinforcing it with running Prolene suture. The transverse colon mesentery is divided in a similar manner. The spleen is removed by dividing the vessels in the splenic hilum, being careful not to injure the tail of the pancreas. Finally, the arterial inflow to the graft is reconstructed because the organ has two major sources of blood supply that are not in continuity: the splenic artery, which supplies the pancreatic body and tail, and the superior mesenteric artery, which supplies the pancreatic head. In most instances, arterial reconstruction can be performed with a donor iliac artery as a Y-graft. The internal iliac artery is joined to the splenic artery, and the external iliac artery is joined to the superior mesenteric artery. Both anastomoses are performed in an end-to-end manner with fine Prolene (6-0) sutures. The common iliac artery of the Y-graft can then be anastomosed to the recipient artery to provide the arterial inflow to the pancreas. In rare instances, it is necessary to create a portal vein extension graft on the backbench with donor iliac vein; however, this technique is avoided when possible because it may increase the risk of venous thrombosis of the pancreas graft.

The Recipient Operation

Unlike the techniques for most solid-organ transplantations, those for transplanting the pancreas have evolved significantly. Partial segmental grafts containing only the pancreatic body and tail were once common; however, this technique is rarely used now. Exocrine secretions were previously managed by pancreatic duct ligation or by injection of a polymer that would cause duct obliteration; today the exocrine secretions are handled by internal drainage.

The two significant areas in pancreas transplantation in which current techniques differ are the drainage of exocrine secretions and the venous drainage of the graft. Exocrine drainage is performed either via the intestinal tract or via the bladder. Throughout most of the 1980s and 1990s, drainage of the pancreatic secretions into the recipient bladder was the most common form of exocrine drainage. This technique is convenient for monitoring organ function by measurement of amylase levels in the urine. However, problems with hematuria, cystitis, bicarbonate loss, and dehydration are all associated with bladder drainage. These complications necessitate surgical revision to enteric drainage in 20% of bladder-drained pancreas recipients. Because of these issues and the lower rejection rates observed with newer immunosuppressive medications, the vast majority of transplant centers now perform enteric drainage of exocrine secretions. This enteric drainage is either directly into a loop of jejunum in a side-to-side manner or into a Roux limb of jejunum.

The venous drainage of the graft is either to the systemic circulation (via an iliac vein or the inferior vena cava) or to the portal circulation. Portal venous drainage has the advantage of delivering insulin in a more physiologic manner inasmuch as insulin undergoes a "first pass" through the liver, and the hyperinsulinemia that results from systemic drainage is avoided. An immunologic advantage of portal drainage has also been observed in several experimental studies in which the delivery of foreign antigen via the portal system results in diminished immune responses. Despite these theoretical advantages, there has been no demonstrable difference in outcomes between portal and systemic venous drained pancreatic transplants in humans, and systemic venous drainage is how the preponderance of pancreas transplants are performed.

There are two common locations in the abdomen where a pancreas transplant is placed, on the basis of the type of venous drainage planned: either in the pelvis (most commonly the right side) for systemic venous drainage or in the midabdomen for portal venous drainage. When the graft is placed in the pelvis, the donor portal vein is anastomosed to the external iliac vein, the common iliac vein, or the inferior vena cava. In this pelvic position, the graft is oriented with the duodenum inferiorly if bladder drainage is planned (Fig. 1A) or with the duodenum in either the superior (Fig. 1B) or inferior direction if enteric drainage is planned. Alternatively, for portal venous drainage, the pancreas is placed in the midabdomen below the transverse colon with the duodenum oriented superiorly. The portal vein of the pancreas is anastomosed to the major branch of the superior mesenteric vein found in the small intestine mesentery in an end-to-side manner (Fig. 2). Enteric drainage for exocrine secretions must be used with portal venous drainage. With either technique, the arterial Y-graft of the pancreas is anastomosed in an end-to-side manner with either the recipient's iliac artery (common or external) or distal aorta.

COMPLICATIONS

The major complications after pancreas transplantation are often technical in nature. Thrombosis (arterial or venous) is more frequent in pancreatic grafts than in other solid-organ transplants, and the reported incidence is approximately 5% to 10%. Thrombosis often occurs within the first week after transplantation and is characterized by a sudden increase in serum glucose levels. In most instances of thrombosis, graft removal is necessary. Early pancreatitis occurs in 10% to 20% of cases and is largely a reflection of ischemic damage to the gland during preservation and subsequent reperfusion injury. Elevated serum amylase levels and graft edema are characteristic, and graft pancreatitis is usually treated with octreotide. Leakage at the site of pancreatic exocrine drainage is another early complication, with management often dictated by the method of drainage. Bladder-drained transplants with a small leak at the duodenocystostomy can often be managed by Foley catheter drainage of the bladder, which allows the site of leakage to heal over time. Leaks at the duodenojejunostomy in transplants with enteric drainage usually result in peritonitis, and operative intervention is necessary to control the leak.

Rejection after pancreas transplantation was once very common. The diagnosis of pancreas rejection is often difficult, and a variety of indicators are used to help establish the diagnosis. These include increased serum amylase levels, decreased urinary amylase excretion (if bladder drainage is used), biopsy of the pancreas, and the presence of hyperglycemia. Hyperglycemia is a late indicator of rejection, however, and the pancreas is often difficult to salvage once hyperglycemia has occurred. If SPK transplantation is performed, then renal allograft dysfunction can often assist with the diagnosis of pancreatic rejection because the rejection process is usually occurring in both organs. As a result of the high incidence of rejection and the difficulty in establishing the diagnosis, pancreas transplant recipients usually receive potent induction immunosuppression with a T-cell–depleting agent and maintenance therapy with tacrolimus, mycophenolate mofetil, and corticosteroids.

The total amount of immunosuppression that pancreas transplant recipients receive is among the highest for any solid-organ transplant. As a result, they are more susceptible to the complications of immunosuppressive therapy. These complications include infection with opportunistic bacteria, viruses, and fungi; malignancy; and gastrointestinal complications. The high incidence of these complications highlights the importance of effective prophylaxis strategies.

RESULTS

Patient and graft survival after pancreas transplantation have improved significantly since the 1990s. The rates of patient survival are approximately 98% at 1 year and 92% at 5 years after SPK transplantation. Similar patient survival rates are reported for PAK and PTA recipients. Graft survival is variable, depending on the type of pancreas transplant performed (Fig. 3), and the reliability of the data is variable because of the lack of a widely accepted definition of pancreas graft failure. Nonetheless the reported 1- and 3-year pancreas graft survival rates for SPK recipients are 89% and 80%, respectively.

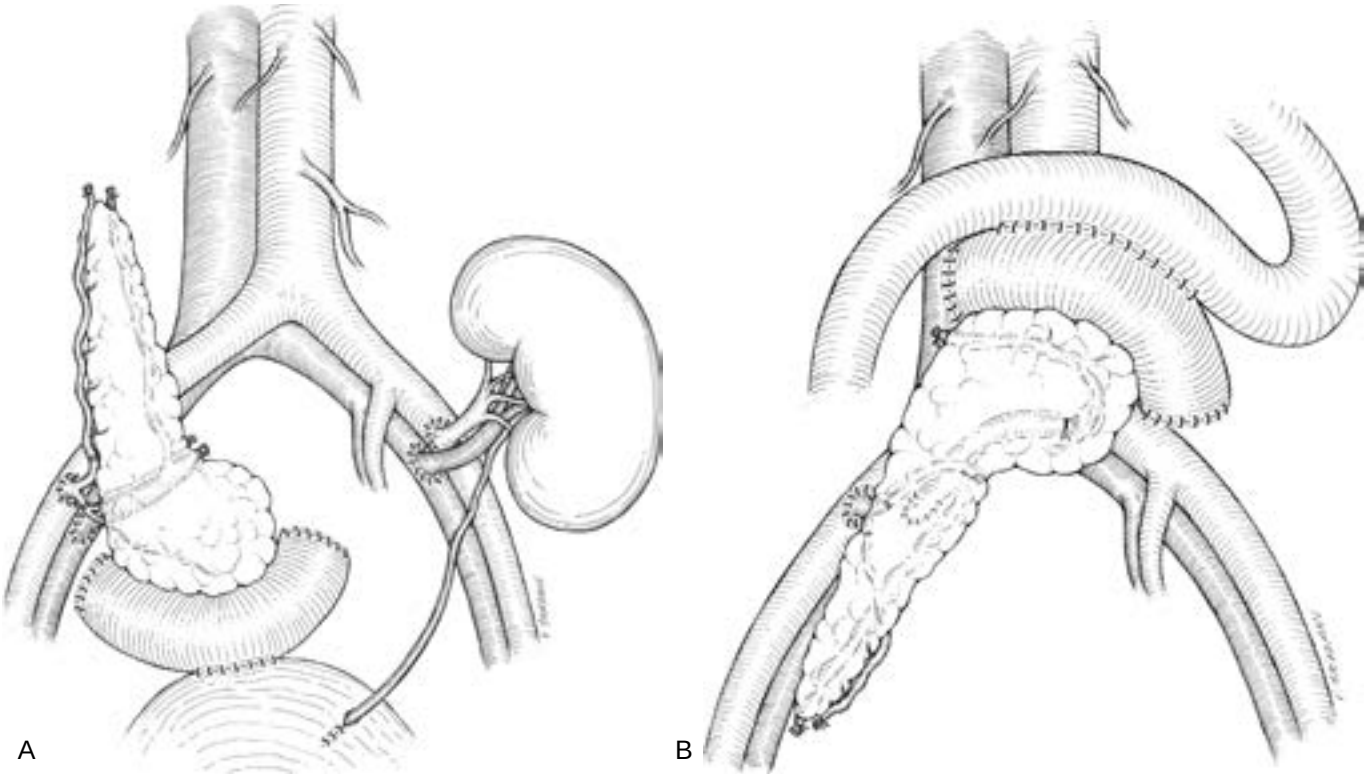


FIG. 1 Whole-organ pancreas transplantation with systemic venous drainage. The pancreas is placed on the right side of the pelvis with anastomosis of the donor portal vein to the recipient iliac vein for venous drainage. The donor iliac artery Y-graft is sewn to the recipient iliac artery for arterial inflow to the graft. Kidney transplantation can be performed simultaneously with the left-sided iliac vessels. **(A)** The donor duodenum is oriented inferiorly to allow anastomosis to the recipient bladder *(shown)* or to the recipient small intestine *(not shown)* for pancreatic exocrine drainage. **(B)** Alternatively, the donor duodenum is oriented superiorly to allow anastomosis to the recipient small intestine for pancreatic exocrine drainage.

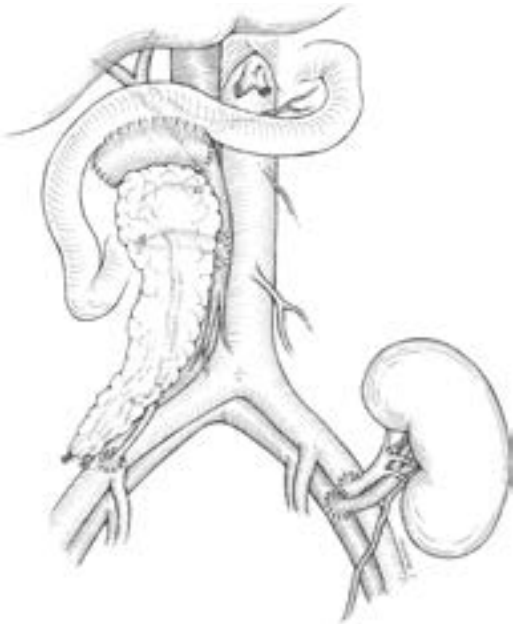


FIG. 2 Whole-organ pancreas transplantation with portal venous drainage. The pancreas is placed in the midabdomen with anastomosis of the donor portal vein to the major branch of the recipient superior mesenteric vein for venous drainage. The donor iliac artery Y-graft is sewn to the recipient iliac artery for arterial inflow to the graft. The donor duodenum is oriented in the superior direction for anastomosis to the recipient small intestine. Kidney transplantation can be performed simultaneously with either the left *(shown)* or right *(not shown)* iliac vessels.

For PAK and PTA recipients, 1- and 3-year pancreas graft survival rates are 84% and 66%, respectively.

The effect of a successful pancreas transplant on the complications associated with diabetes mellitus is debated. Because the successful transplant restores euglycemia and normal hemoglobin A1c levels, most proponents argue that diabetic complications should cease and the damage perhaps be reversed. Neuropathy appears to stabilize and often improve after pancreas transplantation, whereas retinopathy progression is slowed after several years of graft function. The

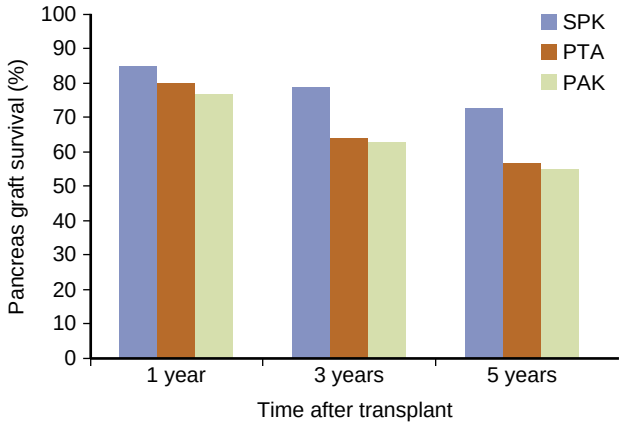


FIG. 3 Pancreas graft survival rates at 1, 3, and 5 years after whole-organ transplantation by transplantation category. *PAK,* Pancreas-after-kidney (transplantation); *PTA,* pancreas transplantation alone; *SPK,* simultaneous pancreas and kidney transplantation.

development of diabetic nephropathy in the transplanted kidneys of SPK and early PAK recipients appears to be prevented by successful pancreas transplantation. In PTA recipients, diabetic nephropathy appears to stabilize after the transplant; however, the renal benefit is probably outweighed by the detriment to renal function caused by the maintenance immunosuppressive agents, specifically tacrolimus or cyclosporine.

RISK-TO-BENEFIT CONSIDERATIONS

Considerable evidence suggests that a pancreas transplant can stabilize the secondary complications of diabetes and, in some cases, reverse the damage. Despite this evidence, the procedure is considered appropriate for only a subset of patients with type 1 diabetes because of its highly invasive nature in comparison with insulin therapy and because of the potential for significant surgical complications. Therefore, risk-to-benefit considerations are of utmost importance in pancreas transplantation and play an essential role in the recipient selection process.

In several important studies, researchers have evaluated the survival benefit of pancreas transplantation by examining large data sets to compare the survival of pancreas recipients with that of patients who were on a waiting list for transplantation but did not receive a pancreas. In this study design, the two patient groups were as similar as possible. Because the indications, risks, and benefits differ depending on whether a patient has underlying renal failure, these analyses were stratified according to whether a patient remained waitlisted or underwent an SPK, PAK, or PTA procedure. All studies revealed a marked survival benefit for patients who received SPK transplants, with a greater than 50% reduction in mortality at 4 years in comparison with similar patients who remained on the waiting list.

In contrast with the clear survival benefit of SPK transplantation, the data for PAK and PTA recipients are less clear. In one study, the mortality rate among both PAK and PTA recipients was increased 4 years after transplantation; compared with the patients who remained on the waiting list, PAK recipients exhibited a 42% increase in mortality, and PTA recipients exhibited a 57% increase in mortality. However, another study demonstrated no difference in mortality rates among PAK and PTA recipients, with a trend toward improved survival in the PAK and PTA recipients in comparison with patients who remained on the waiting list.

There are two important caveats to these risk-to-benefit studies. The first is that the effect of pancreas transplantation on quality of life was not evaluated in these nonrandomized retrospective analyses and would probably heavily favor the PAK and PTA recipients. Whether this factor would outweigh any survival disadvantage in the short term and the significant cost of these complex procedures has not been evaluated. A second critical outcome measure that is lacking from these studies is the long-term effect of successful pancreas transplantation on the secondary complications of diabetes. There is considerable evidence that diabetic nephropathy, neuropathy, and retinopathy may be positively affected by the long-term normoglycemia conferred by transplantation.

These results substantiate the marked clinical benefit observed in the care of patients who receive SPK transplants. The relative contributions of the transplanted kidney and of the transplanted pancreas to the overall survival benefit have not been differentiated. This issue is significant because of the marked survival benefit that has been documented in the setting of kidney transplantation alone in diabetic recipients.

Although the survival benefit for SPK recipients is clear, the data demonstrating a lack of survival benefit for PAK and PTA recipients remain controversial. At a minimum, the studies available to date suggest a narrow therapeutic margin for PAK and PTA recipients. Perhaps the most meaningful conclusions that can be drawn at present are that recipients should be selected with the utmost care, donor organs should be optimal, and the surgery should be performed at transplantation centers with favorable outcomes. The field is dynamic as a result of both improvements in surgical techniques and in perioperative management.

FUTURE DIRECTIONS

Continued advancements in the care of individuals with type 1 diabetes may eventually render pancreas transplantation obsolete. Ongoing improvements in glucose sensing with continuous glucose monitoring (CGM) and insulin delivery via insulin pumps have improved the lives of countless individuals by making insulin delivery constant, thereby allowing more precise glycemic control. Improvements in software algorithms combined with wireless connectivity now allow closed-loop systems to automatically adjust the amount of insulin being delivered via a pump based on glucose readings obtained from a CGM, thus creating an "artificial pancreas."

Cellular therapy with embryonic stem cell–derived pancreatic beta cells has moved from the laboratory to early clinical trials. At least two products are undergoing testing in phase 1/2 clinical trials, with some early success being observed. A stem cell–derived product offers the hope of a limitless source of pancreatic beta cells that would be available to all individuals with type 1 diabetes seeking an alternative treatment option to exogenous insulin. In addition, a stem cell–derived product has the potential for genetic manipulation before differentiation using advanced techniques such as CRISPR. Genetic manipulations could be used for a variety of reasons, including enhancement of cellular function and reduction or elimination of immunogenicity. Although still several years from becoming an available treatment, stem cell–based therapy appears to be the ultimate transplant option for individuals with type 1 diabetes.

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Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis

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INTRODUCTION

Proper patient selection is a critical part of surgical therapy with any operation, but patient selection is especially challenging in the case of total pancreatectomy with islet autotransplantation (TPIAT). All of us who have performed this procedure for many years have regrets about offering the procedure to patients who technically met the criteria but ended up having a poor outcome because of poor social support, opioid addiction, or underestimation of a patient's ability to manage severe diabetes later in life when it occurs.

TPIAT is an option for a very small subset of patients being considered for surgical therapy for chronic pancreatitis (CP). We find that the Frey procedure is the procedure of choice for most patients with chronic pain and a dilated pancreatic duct, unless they have a precancerous gene mutation as the etiology. As a result, genetic testing has become a standard of care in these patients. We do not perform TPIAT procedures for patients with alcoholic pancreatitis (AP) or patients with mild symptoms. Instead, we reserve this highly morbid procedure for patients with debilitating pain and a genetic mutation or idiopathic cause for pancreatitis.

The procedure is intended to achieve the desired outcome of pain improvement and prevent or temper the effects of endocrine insufficiency. It has now been adopted at numerous centers worldwide, with the number of procedures being performed annually across the United States more than tripling in the past 20 years.

PATIENT SELECTION

Over the past several years, we have narrowed our criteria for performing a TPIAT procedure. In addition to setting a high bar with patient selection, we work hard to ensure that patients understand what it is like to have severe brittle diabetes that may result from the procedure and what it is like to take pancreatic enzymes with each meal. Even though insulin-dependent diabetes can be averted for several years after the procedure, we tell all patients that they will develop diabetes as a result of the procedure. For those who already have diabetes, we tell them that it may result in brittle diabetes because the autotransplanted islets do not have good longevity in many patients. In short, we only offer the procedure to those who understand what it means to have brittle diabetes in the short term and in the future when they may be older and frail. Some surgeons even inform all TPIAT patients that they will develop diabetes; it's just a matter of how long after the procedure.

As a starting point, no patient should undergo TPIAT unless they are able and motivated to regularly check their blood glucose levels, inject themselves with insulin three times a day, and take oral pancreatic enzymes with each meal. Surgeons should not only consider if a patient can be compliant with this regimen in their current state of health and age, but also if they will still be able to do so in 20 or 30 years. For example, if a 50-year-old patient has some cognitive slowing, it should be anticipated that they will not be able to comply with an insulin regimen in 20 years' time, when they are 70 years of age. Missing one dose of insulin in a patient with brittle diabetes can result in death. The physiologic disabilities created by the procedure are often permanent and should be taken very seriously.

EVIDENCE

Before considering patient selection, it is important to have an understanding of the potential outcomes of the procedure and the factors that may affect this.

Pain Control

Review of data from the past 50 years has demonstrated favorable results in terms of pain control following TPIAT for CP. Significant improvements in pain can be achieved in the form of reduction in opiate requirements or freedom from opiate use in most patients. Studies describe improvements in pain scores in approximately 70% of patients, with the largest study from the University of Minnesota demonstrating pain improvements in 85% to 92% of patients. There is limited data on long-term pain outcomes; however, two studies looking at the longer-term durability of this operation suggest up to 82% of patients freedom from persistent pain at 5 or 10 years post-TPIAT. Given these results, we inform all patients that there is a 20% chance that they may have the operation (possibly with a complication such as brittle diabetes) and have zero pain relief after the operation. In other words, patients should understand that there is a roughly 20% risk that they will be in the exact same pain that they started with. Proper informed consent for this procedure requires several clinic visits over time.

Endocrine Function

TPIAT is associated with postoperative lifelong insulin requirements in two-thirds of patients. This is typically from a baseline of no diabetes or non–insulin-dependent diabetes, which can represent a significant change for patients and must be weighed against the potential for pain relief during preoperative counseling. However, in the natural course of CP without surgery, 83% of patients will develop some degree of diabetes within 25 years of diagnosis regardless, albeit usually mild.

The prospect of post-TPIAT insulin dependence lies in stark contrast with the type IIIc (brittle) diabetes that would result from total pancreatectomy (TP) alone. TP alone is associated with "difficult-to-control" brittle diabetes in over 75% of patients, and the removal of glucagon-containing α-cells can result in unpredictable responses to exogenous insulin and episodes of dangerous hypoglycemia. Glucagon-containing α-cells are important in insulin regulation. Without them, swings in blood glucose levels are magnified and more difficult to control.

Several large-scale studies have documented C-peptide levels as a measure of graft (islet) function as well as different classes of insulin dependence after autologous islet transplantation. Approximately 90% of patients have evidence of islet function following transplantation. This translates into varying degrees of glucose tolerance or insulin dependence, with patients falling approximately into a rule of thirds: one-third of patients (30%) are insulin independent at 3 years post-TPIAT; one-third (33%) require supplementation with once-daily or intermittent insulin doses; and one-third (37%) require a more intensive basal-bolus–style regimen of insulin.

Limited data looking at hypoglycemic events after TPIAT have shown that patients may have difficulties with glucose homeostasis postoperatively, even if they retain insulin independence. In a study of 14 patients, 11 reported frequent hypoglycemic events, with 50% of these having daily episodes of hypoglycemia. Patients also tend to suffer from muted or absent symptom responses during these episodes. It is hypothesized that because of hepatic gluconeogenesis and

glycogenolysis, local hyperglycemia impairs the detection of systemic hypoglycemia by the islets. Several studies have suggested, however, that this may be ameliorated by additional non-hepatic sites of islet transplantation.

Some element of exhaustion of transplanted islets occurs over time, with notable increases in patients' insulin requirements over the years following TPIAT. Initial small-scale studies looking at long-term graft function demonstrated that all patients maintain evidence of C-peptide production at 10 years posttransplant. However, recent long-term data from the University of Minnesota found that of 140 patients with data at 10 years posttransplant, only 20% maintained insulin independence. In this study, the proportion of patients requiring basal-bolus insulin increased from 23% to 52% after 10 years.

Overall Quality of Life

Importantly, the improvements in pain scores and opiate requirements are translated into noticeable improvements in quality of life (QoL) for these patients. After TPIAT, 84% of patients report improvement in QoL, with further increases after the first year postoperatively. These improvements are sustained at 5 and 10 years on long-term follow-up. QoL has also been shown to improve even if patients are still requiring some opiates and, significantly, QoL improvements are maintained regardless of postoperative insulin requirements. However, the highest percentage of improvement is understandably seen in patients who achieve both pain control and insulin independence.

Factors Predictive of Outcome

Unfortunately, despite success in the majority of patients, 10% to 20% of patients will see no improvement in pain or QoL. Furthermore, if these patients fall on the worse end of the spectrum of postoperative glycemic control or suffer complications of the operation, it may worsen their QoL in a significant way. As a result, many groups have attempted to tease out which patients derive success from the operation and which do not. A landmark study from the University of Alabama at Birmingham in 2013 assessed outcomes according to underlying etiology of the disease. This study found that patients with AP showed no meaningful improvement in pain scores or QoL following surgery, and they were also more likely to have a low islet yield and higher insulin requirements at follow-up.

Factors that influence islet yield include low body weight (BMI <23) or obesity (BMI >30); personal or family history of diabetes; longer duration of disease (>5 years); more progressive disease as evidenced either by atrophy, calcifications, or ductal dilation on imaging or by endocrine or exocrine insufficiency; and previous pancreatic resection. The greatest predictor of postoperative endocrine function across a number of studies has been transplanted islet mass, with a 28-fold increased risk of graft failure among patients with <2000 islet equivalents/kg (IE/kg) transplanted compared with those with >5000 IE/kg transplanted. Unfortunately, islet yield cannot yet be accurately predicted preoperatively.

PREOPERATIVE EVALUATION

Any personal history of genetic risk factors for recurrent AP or CP (e.g., *CFTR, SPINK1,* or *PRSS1*) is important to note as the lifetime risk of pancreatitis and pancreatic cancer may warrant stronger consideration of TPIAT. Marked portal hypertension is a contraindication to islet infusion because of intraoperative increases in portal pressure.

Investigations

Preoperative laboratory testing should include further assessment of endocrine function. This typically includes glucose tolerance testing, HbA1c measurement, and C-peptide measurements. Exocrine function is sometimes assessed via fecal elastase testing and fat-soluble vitamin levels, but these tests are not essential. Imaging should be obtained to confirm features of CP, assess the extent of fibrosis, and establish the vascular anatomy in the area.

The location of disease in the pancreas should also be evaluated for consideration of localized resection. It is also important to rule out any evidence of pancreatic neoplasm, as this is a direct contraindication to IAT. Further imaging assessment of any pancreatic lesions noted during workup should be performed using endoscopic ultrasound. Significant ductal dilation (>5 mm) seen in patients without a precancerous genetic mutation to provide strong indication for prophylactic resection may warrant consideration of a decompressive operation in place of TPIAT.

SURGICAL PLANNING

Our practice is to offer TPIAT to patients with debilitating chronic pain of pancreatic origin who either have a genetic mutation or are not a candidate for a hybrid resection/drainage operation.

Timing of Surgical Intervention

Our practice is to have found the following triggers to be milestones to discuss surgery for eligible patients with CP with debilitating pain or multiple episodes of acute pancreatitis each year for multiple years:

1. Development of prediabetes or any evidence of exocrine insufficiency
2. Identification of a genetic cause of recurrent acute pancreatitis
3. A person's inability to be in school or work as a result of recurrent attacks of acute pancreatitis

COUNSELING AND DECISION MAKING

Patients should be adequately counseled on the statistical outcomes in terms of both pain control and postoperative endocrine function. They should also be counseled on the potential complications of the operation and postoperative care, including diabetic and nutritional monitoring as well as lifelong pancreatic enzyme replacement. Given the considerable risks behind TPIAT, especially the risks of nonimprovement in pain and loss of glycemic control, patients are generally recommended to undergo evaluation by a multidisciplinary team including a gastroenterologist, a hepatopancreaticobiliary surgeon, an endocrinologist, an anesthesia pain specialist, and/or a neuropsychologist as part of their preoperative assessment. As part of guidance from PancreasFest 2012 on TPIAT in CP, review by this team is intended to "review alternative interventions, assess the likelihood of success in reducing pain and preventing or minimizing diabetes, follow the patient through the procedure and provide guidance for long-term care."

At our institution, we schedule multiple clinic visits before scheduling surgery to ensure that patients are comfortable with the decision. We have multiple discussions to prepare the patient for the possibility of failed pain control as well as the development of diabetes. We generally discuss with patients that diabetes is inevitable, regardless of initial postoperative function, and that islet autotransplantation is intended to delay this. Transplanted islets rarely maintain enough insulin production to keep a patient insulin-free beyond 10 years.

OPERATIVE TECHNIQUE

TPIAT involves performance of TP followed by isolation and processing of islets before islet infusion. At our institution, minimally invasive TP is the procedure of choice when appropriate. This may either be laparoscopic or robotic, depending on surgeon experience. Our conversion rate is approximately 10%, usually resulting from

extensive scarring from recurrent episodes of pancreatitis. Approximately 30% of our cases are planned open because of surgical history or other factors.

The operative approach for TP varies among centers. Duodenal-sparing TP was previously performed but has been largely abandoned. Our preference is to perform a traditional pre-pyloric resection. We sometimes perform a splenectomy to be able to perfuse the tail of the pancreas after it is removed.

In contrast with TP performed for pancreatic cancer, the surgical resection during a TPIAT is modified to minimize warm ischemic time. As a result, full mobilization of the pancreas should be achieved before vascular ligation, with the exception of the gastroduodenal artery (GDA), which has good backflow. To achieve this, we generally perform a Whipple procedure if allowed by scarring and process the pancreatic head while then dissecting out the body and tail of the pancreas. The body and tail are subsequently processed after vessel ligation as a final step.

Preparation

Islet isolation techniques vary among centers. These variations include same-day intraoperative isolation and transplant versus laboratory isolation with next-day transplant in interventional radiology. Intraoperative islet isolation allows for immediate processing of the pancreas and a patient-centered approach. It also minimizes cold ischemia time and maximizes efficiency of the operation as well as islet yield.

Total Pancreatectomy

After entry to the abdomen has been achieved (whether laparoscopic or open), the following steps are performed (Fig. 1):

- Mobilization of the right colon and hepatic flexure and takedown of the greater omentum from the greater curvature of the stomach
- Release of the lesser curve of the stomach from the lesser omentum and stapled transection of the stomach just proximal to the pylorus
- Performance of an extended Kocher maneuver to mobilize the pancreatic head and expose it to the superior mesenteric artery (SMA)
- Dissection of the hepatoduodenal ligament to isolate the portal structures and the GDA, and clipped transection of the GDA
- Creation of a tunnel underneath the neck of the pancreas from the superior mesenteric vein cephalad
- Performance of a cholecystectomy
- Transection of the common hepatic duct
- Transection of the neck of the pancreas
- Mobilization of the first portion of the jejunum through the defect in the ligament of Treitz and stapled transection of the jejunum
- Dissection of the head of the pancreas off of the SMA
- Delivery of the Whipple specimen and processing by the transplant team
- Medial-to-lateral mobilization of the body and tail of the pancreas
- Stapled transection of the splenic artery and vein
- Delivery of the distal pancreatectomy specimen and processing by the transplant team
- Mobilization and resection of the spleen
- End-to-side hepaticojejunostomy
- Antecolic side-to-side gastrojejunostomy
- Intraportal infusion of islets via angiocatheter
- Closure of venotomy
- Surgical drain placement and abdominal closure

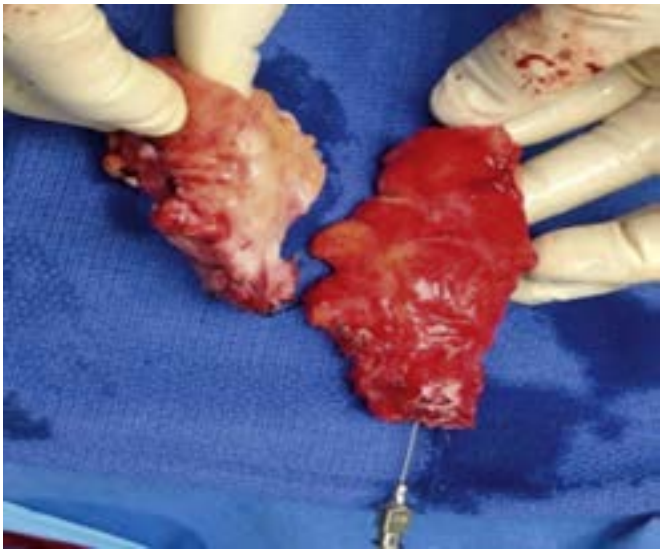


FIG. 1 Representative image of separate Whipple and distal pancreas specimens with cannulation of the pancreatic duct of the distal pancreatectomy specimen.

Islet Processing and Infusion

As described, the separate Whipple and distal pancreatectomy specimens are delivered to the transplant team and processed in parallel to completion of surgical resection. Steps for processing each of the specimens are as follows (Fig. 2):

- Flushing of the arterial system (the Whipple specimen via the GDA and the distal pancreatectomy via the splenic artery) with cold preservation solution
- Removal of peripancreatic tissues from the specimen
- Cannulation of the pancreatic duct with an angiocatheter (if not permitted by scarring, enzyme solution may be injected directly into the parenchyma at multiple sites)
- Distension of the duct with combined solution of collagenase and thermolysin



FIG. 2 Laparoscopic infusion of islet isolate into the portal vein.

- Sectioning of the pancreas into pieces less than 1 cm^3 in size
- Placement of sections into a Ricordi digestion chamber with additional enzyme solution (pulmozyme)
- Collection of isolate and measurement of the final islet count

Portal pressure is measured via the angiocatheter during infusion with the aim of maintaining this below 15 to 20 mm Hg. If portal pressures remain persistently elevated above this level or the volume of isolate exceeds 20 mL, remaining tissue can be injected into the peritoneal cavity, mesentery, or stomach wall.

INTRAOPERATIVE CARE

Blood glucose levels should be closely monitored throughout the case, with maintenance of serum glucose of 100 to 120 mg/dL. Multiple animal studies have demonstrated that hyperglycemia is detrimental to transplanted islet engraftment; therefore, euglycemia may be important for initial graft survival.

POSTOPERATIVE CARE

At our institution, patients are typically transferred to the surgical intensive care unit postoperatively. The patient is also kept on an insulin drip overnight for tight control. Following this, endocrinology is consulted to provide recommendations on further glycemic control and assist with the transition to subcutaneous insulin injection. Daily C-peptides are measured at this point to monitor graft function. Patients are then generally maintained on intravenous insulin for the first 1 to 3 months postoperatively (goal glucose in the range of 100–120) as strict normoglycemia is thought to reduce stress on the transplanted islets and allow for maximal engraftment. We generally consult the acute pain service postoperatively also in patients with high preoperative opiate requirements. They will see the patient and provide recommendations throughout their recovery.

A nasogastric tube is placed in the operating room and maintained for at least the first night following surgery. Thereafter, when the patient is demonstrating evidence of bowel function, we advance the diet until tolerating a regular diet. Creon is added when tolerating semisolid food. If there are no other issues, a surgical drain is monitored postoperatively and removed when drainage is consistently <50 mL in 24 hours. Patients are able to go home when blood glucose is well controlled, they are tolerating a regular diet, and pain is under control. They will receive postsplenectomy vaccinations before discharge if their spleen was removed.

Risks of the procedure include those associated with TP alone. There is a high readmission rate (upwards of 40% given accompanying motility disorders), with a 30-day mortality rate of 2% and a 1-year mortality rate of 4%. Up to 50% of patients will experience a postoperative complication, with the most common complications including pneumonia, delayed gastric emptying, deep venous thrombosis, and wound infection. TPIAT-specific complications can include portal vein thrombosis as a result of decreased portal flow during islet infusion.

OTHER CONSIDERATIONS

Future work should focus on attempting to quantify preoperative pancreatic function and to further clarify appropriate candidates. TPIAT has the potential to be a life-changing operation in the right patient, but it should not be undertaken without due consideration.

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Splenectomy for Hematologic Disorders

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INTRODUCTION

Splenectomy may be indicated in a wide variety of hematologic diseases that lead to hypersplenism. It may also be performed more generally to relieve the mass effect and symptoms of splenomegaly, to control infection or traumatic hemorrhage, and, finally, a surgeon may decide to remove the spleen to diagnose splenic pathology. Despite a broad range of disease processes affecting the spleen, the most common indications for elective splenectomy are hematologic autoimmune disorders such as idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), and malignancy. For the purposes of this chapter, which is focused primarily on hematologic disorders for which splenectomy may be used for cure or palliation, we divide the indications into the following categories: (1) benign conditions, including red blood cell disorders, hemoglobinopathies, and platelet disorders; (2) malignant conditions, including white blood cell disorders, myeloproliferative disorders, and tumors of the spleen; and (3) miscellaneous conditions. Although not an exhaustive list, we highlight the most common hematologic disorders of the spleen that are clinically relevant from a surgeon's perspective. We also touch on perioperative considerations of the splenectomized patient, and finally we discuss current surgical techniques.

BENIGN CONDITIONS

Red Cell Disorders

Glucose-6-Phosphate Dehydrogenase Deficiency

The most common red blood cell enzyme deficiency is glucose-6-phosphate dehydrogenase (G6PD) deficiency. It is an X-linked genetic disease of the glutathione pathway. It is estimated that over 400 million people are affected worldwide. Clinical manifestations occur after oxidative stress (acute infections, trigger foods such as fava beans, and several medications) and vary in severity from acute and chronic intermittent hemolytic episodes to no hemolysis depending on the variant of G6PD deficiency. Transfusions are often required in cases of symptomatic anemia. Conventional wisdom suggests that the majority of patients with G6PD deficiency will not progress or benefit from splenectomy, however case series do exist supporting splenectomy for severe and refractory clinical presentations including massive splenomegaly, transfusion dependence, or medication side effects.

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is the most common type of hemolytic anemia for which splenectomy is indicated and a common type of congenital hemolytic anemia. Its estimated prevalence in Western populations is roughly 1 in 2000. HS results from an autosomal dominant deficiency or dysfunction in one of the many erythrocyte membrane proteins (including but not limited to alpha or beta spectrin, ankyrin, or protein 4.2). This results in destabilization of the membrane lipid bilayer, and the red blood cell assumes a more spherical, less deformable shape causing sequestration and destruction in the spleen and resulting in hemolytic anemia. Common clinical manifestations include mild jaundice and palpable splenomegaly. Indications for splenectomy often include moderate to severe cases of symptomatic hemolytic anemia including growth retardation, skeletal changes, leg ulcers, and extramedullary hemopoietic tumors in young patients. Because HS can affect children, the timing of splenectomy is important and is aimed at reducing the possibility of post-splenectomy sepsis. Unless the anemia and hemolysis are rapidly accelerating, delaying splenectomy until 4 to 6 years of age is generally recommended, as is consideration for a near-total splenectomy in children. If gallstones coexist with spherocytosis, cholecystectomy should be strongly considered. Prophylactic cholecystectomy in this population without gallstones remains controversial.

Pyruvate Kinase Deficiency

Pyruvate kinase (PK) deficiency is the most common glycolytic defect causing congenital non-spherocytic hemolytic anemia. PK deficiency affects people worldwide, with a slight predisposition for those of Northern European or Asian descent. Its estimated prevalence in the Caucasian population is roughly 50 per 1 million. Clinical manifestations of the disease also vary widely, from severe transfusion-dependent anemia in early childhood to well-compensated mild to moderate anemia in adolescents or adults. Prenatal hydrops fetalis has also been reported. PK enzyme activity remains the gold standard for initial diagnostic testing (and a favorite among standardized tests). Splenomegaly is common, and in severe cases splenectomy is recommended to alleviate transfusion requirements. As with HS, splenectomy should be delayed in children, if possible, to at least 4 years of age to reduce the risk of post-splenectomy infection.

Warm-Antibody Autoimmune Hemolytic Anemia

AIHAs are characterized by the destruction of red blood cells, whose erythrocyte life span is diminished by autoantibodies. AIHA is classified as either *primary* or *secondary*, depending on whether the underlying cause, such as a disease or toxin, is clearly identified and either *warm* or *cold* based on the temperature at which the autoantibodies exert their effect. In cold-agglutinin disease, severe symptoms are uncommon, and splenectomy is almost never indicated. Warm-antibody AIHA has clinical manifestations with which the

surgeon should be most familiar. Warm AIHA can affect individuals of all ages and both sexes but most commonly affects women in midlife. Clinical manifestations include mild jaundice, signs and symptoms of anemia, and roughly 30% to 50% of patients will have palpable splenomegaly on physical examination. Although the mainstay treatment of both primary and secondary AIHA remains long-term corticosteroid administration, newer therapies such as anti-CD20 antibody therapy exist and may be of benefit to specific subpopulations of patients. Splenectomy remains third-line therapy after failure of medical management. Notably, some unfortunate patients experience hemolytic episodes, even post-splenectomy.

Hemoglobinopathies

Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal dominant disorder causing chronic hemolytic anemia that results from a mutant sickle cell hemoglobin S (HbS) within the red blood cell. Those who inherit an *HbS* gene from one parent are heterozygous carriers, and those who inherit *HbS* genes from both parents are homozygous and have sickle cell anemia. Deoxygenated HbS is insoluble and becomes polymerized and sickled. The lack of deformability of the red blood cell results in microvascular congestion, which may lead to thrombosis, ischemia, and tissue necrosis that manifest clinically as painful intermittent episodes. Abnormal red cell sequestration occurs within the spleen, and splenomegaly can result early in the disease course. In a large percentage of patients, infarction of the spleen and autosplenectomy will occur. The most common indications for splenectomy are recurrent acute sequestration "crises," hypersplenism, and splenic abscess. Transfusions are often indicated for anemia and for moderate to severe episodes of acute chest syndrome, which include new infiltrate on chest radiograph associated with new symptoms of fever, cough with sputum production, or hypoxia. The occurrence of just one major acute sequestration crisis, which is characterized by rapid painful enlargement of the spleen and circulatory collapse, is generally considered sufficient to strongly consider splenectomy. Although both partial and total splenectomy have been shown as viable options in children, partial splenectomy may not be sufficient to control hematologic abnormalities. Preoperative preparation should include special attention to adequate hydration and avoidance of hypothermia.

Thalassemia

Thalassemias are a group of inherited disorders of hemoglobin synthesis found in all populations, but they appear to be most prevalent among individuals of Mediterranean descent and those from the Arabian Peninsula, Turkey, Iran, India, and southeastern Asia. In these populations the prevalence appears to be 2.5% to 15% of the population. Collectively, thalassemias are the most common genetic diseases that arise from a single gene defect. They are classified according to the hemoglobin chain (alpha, beta, or gamma) affected, with both underproduction of hemoglobin and excessive production of unpaired hemoglobin subunits leading to clinical manifestations. In all forms of thalassemia, the primary defect is reduced or completely absent hemoglobin chains causing reduced function of hemoglobin tetramers (which leads to hypochromia and microcytosis) and unbalanced biosynthesis of the individual alpha or beta subunits, resulting in insoluble red blood cells that cannot release oxygen normally and may increase cell aging. The clinical presentation of thalassemia varies, with heterozygous carriers usually asymptomatic and homozygous individuals usually presenting before 2 years of age with pallor, growth retardation, jaundice, and hepatosplenomegaly. Thalassemia major, a severe form of the disorder, may also present with intractable leg ulcers, head enlargement, frequent infections, and dependence on blood transfusions. Although blood transfusions and parenteral chelation therapy with deferoxamine are mainstays of treatment, splenectomy is indicated for patients requiring excessive transfusions, with splenomegaly or splenic infarction. Notably and unexplainably, thalassemia patients are at risk for pulmonary hypertension following splenectomy, which mandates careful and thorough preoperative discussion. As with other disorders that may require pediatric splenectomy, it should be delayed, if possible, until 4 years of age and consideration for partial splenectomy has also been explored.

PLATELET DISORDERS

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by low platelet count leading to mucocutaneous and petechial bleeding. It is one of the most common indications for elective splenectomy (and a favorite question on many standardized tests). ITP carries an estimated incidence of 100 persons per 1 million annually, of which 50% are children. Premature removal of circulating platelets opsonized by antiplatelet immunoglobulin G (IgG) autoantibodies produced in the spleen results in the disorder's characteristic thrombocytopenia. The severity of bleeding frequently, and not unexpectedly, corresponds to the platelet count level. Levels > 50,000 mm^3 usually have mild bleeding, and levels < 10,000 mm^3 put patients at the greatest risk for major internal bleeding. Interestingly, children often present at around the 5 years of age with sudden onset of petechiae or purpura several days or weeks after an infectious illness. In contrast, adults seem to experience a more insidious and chronic form. Notably, splenomegaly is generally regarded as uncommon in ITP for both children and adults. Its presence warrants alternative diagnoses to be explored. The medical workup for ITP and symptomatic thrombocytopenia is quite extensive and should include the exclusion of other common disease processes such as systemic lupus erythematosus (SLE), antiphospholipid syndrome, human immunodeficiency virus (HIV), and hepatitis C (Hep C), to name a few. Although the first-line therapy for ITP is oral prednisone, there still remains no good consensus on the duration of therapy. However, on average most responders, which account for 50% to 75% of patients, will see dramatic improvements within 3 weeks. For severe cases with confirmed or presumed internal bleeding, intravenous immunoglobulin is indicated. Splenectomy is indicated in failure of medical management including prolonged steroid use with undesired effects, relapse after treatment to maintain platelet count levels >30,000 mm^3, and in rare cases for life-threatening acute bleeding. Splenectomy in children with ITP remains controversial as their clinical courses are usually self-limited, and complete remission is seen in more than 70% of children regardless of medical therapy selected.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a serious medical condition characterized by thrombocytopenia, microangiopathic hemolytic anemia, and neurologic, renal, or cardiac complications. Its incidence is reported to be approximately 4 individuals per 1 million. Abnormal clotting of platelets occurs in arterioles and capillary beds, predisposing the patient to microvascular thrombotic events. The reduction in lumen size caused by clumping of platelets also leads to deformation of red blood cells, which are then subjected to hemolysis by the spleen. Clinical manifestations of TTP are hallmarked by petechial hemorrhages in the lower extremities, fever, neurologic symptoms (from generalized headaches to altered mental status or seizures), renal failure, and infrequently heart failure or cardiac arrythmia. Patients may also demonstrate flulike symptoms, malaise, or fatigue, making its differential diagnosis often broad. The diagnosis is confirmed by peripheral blood smear, which shows classic schistocytes, nucleated red blood cells, and basophilic stippling. In conjunction with thrombocytopenia and a negative Coombs test, the diagnosis of TTP is however often easy to make. Although plasma exchange is the first-line therapy for TTP, splenectomy should be considered in patients who experience a relapse or who require multiple plasma exchange therapies to control severe symptoms.

MALIGNANT CONDITIONS

White Cell Disorders

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is considered a subtype of NHL highlighted by progressive accumulation of old and nonfunctioning lymphocytes. Although the most common presentation of CLL includes lymphadenopathy, clinical presentations of CLL can be nonspecific and include weakness, fatigue, fever, and night sweats, along with frequent bacterial and viral infections. Splenomegaly may be present, and if massive, splenectomy may be indicated to also help improve cytopenias and facilitate chemotherapy in patients whose cell counts are prohibitively low.

Hairy Cell Leukemia

Hairy cell leukemia (HCL) is an uncommon white cell disorder representing only 2% of all adult leukemias. HCL is characterized by pancytopenia, a large number of abnormal lymphocytes in the bone marrow, and splenomegaly. These lymphocytes contain irregular hairlike cytoplasmic projections, as the name implies. Splenectomy for HCL was historically performed as a palliative procedure (especially in pregnancy), alleviating symptoms of splenomegaly and normalizing peripheral blood counts, but it may not lead to morphologic bone marrow remissions. Asymptomatic patients with HCL require no specific therapy.

Hodgkin's Lymphoma

Hodgkin's lymphoma (HL) is a disorder of the lymphoid system characterized by the presence of Reed-Sternberg cells. More than 90% of patients with HL present with lymphadenopathy above the diaphragm. Massive lymphadenopathy within the mediastinum can lead to shortness of breath, cough, and pneumonia. Lymphadenopathy below the diaphragm is uncommon but often suggests advanced disease. Although the spleen is often an occult site, massive splenomegaly with HL is uncommon, and therefore the role of splenectomy may be limited.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) encompasses all malignancies derived from the lymphoid system except classic HL. A proliferation of any one of the three predominant lymph cell types (natural killer cells, T cells, or B cells) may be included in the category of NHL. Because of the varied cell types, the clinical subtypes also vary, including but not limited to nodal versus extranodal, indolent versus aggressive, and very aggressive types. Clinical presentations may include mild lymphadenopathy or no symptoms to more aggressive symptoms such as pain, fever, and night sweats. Splenomegaly also exists in some, but not all forms of NHL. Although splenectomy does not alter the natural history of disease in NHL, it is indicated in cases in which a diagnosis cannot be established in peripheral tissue or for the management of an enlarged spleen.

MYELOPROLIFERATIVE DISORDERS

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) involves abnormal growth of stem cells in the bone marrow with a rapid and dramatic presentation. The incidence of AML in the United States is approximately 10,000 new cases each year and accounts for just over 1% of all cancer deaths. Death from AML may be seen within weeks to months if untreated. Presenting symptoms are nonspecific and include viral-like illness with fever, malaise, and bone pain caused by expansion into the medullary space. Standard treatment includes systemic therapy and stem cell transplantation. Because of concerns of post-splenectomy infection in neutropenic patients on chemotherapy, splenectomy may be considered in AML only when massive splenomegaly leads to left upper quadrant abdominal pain and/or early satiety from mass effect.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) involves abnormal growth of the primitive pluripotent stem cells in the bone marrow that result in significant increases in erythroid, megakaryotic, and pluripotent progenitors on peripheral blood smear. It has a much more indolent course compared with AML and is hallmarked by transposition between the *BCR* gene on chromosome 9 and the *ABL* gene on chromosome 22. CML accounts for roughly 15% of all leukemias, with an incidence in the United States of 1.5 per 100,000. Although often asymptomatic, CML can cause fatigue, anorexia, left upper quadrant pain, and early satiety. Roughly one-half of patients will have splenomegaly, with splenectomy indicated to relieve symptoms associated with mass effect. Notably, splenectomy has no impact on blast crises and does not alter disease progression.

Chronic Myelomonocytic Leukemia

Chronic myelomonocytic leukemia (CMML), like AML and CML, is characterized by proliferation of hematopoietic elements in the bone marrow and blood. CMML differs histologically from CML as it is hallmarked by monocytosis in the peripheral smear and in the bone marrow. Like CML, roughly 50% of patients will present with splenomegaly, for which splenectomy may be indicated to relieve symptoms associated with mass effect.

Essential Thrombocythemia

Essential thrombocythemia (ET) occurs from abnormal growth of the megakaryocytic cell line, resulting in increased levels of platelets in the bloodstream, as the name implies. Diagnosis is made by first excluding other conditions that can cause thrombocytosis (such as CML and polycythemia vera). Clinical manifestations of ET include vasomotor symptoms as well as thrombohemorrhagic events including recurrent fetal loss in women of childbearing age. Although hydroxyurea can be used to reduce thrombotic events, it unfortunately does not reduce the risk of myelofibrosis or conversion to AML. Although splenomegaly may occur in one-third to one-half of patients, it is not believed to be helpful in the early stages of ET and is only reserved for the later stages of disease, when myeloid metaplasia may have developed.

Myelofibrosis (Agnongenic Myeloid Metaplasia)

Agnongenic myeloid metaplasia (AMM) can be referred to as *myelosclerosis, idiopathic myeloid metaplasia,* or *osteosclerosis.* It may be associated with a number of benign or malignant disorders and present with or without splenomegaly. Histologically, nucleated red blood cells and immature myeloid elements in the blood are present in nearly 100% of cases and strongly suggest the diagnosis of AMM. Teardrop poikilocytosis may also be present. AMM must be differentiated from primary neoplasms such as lymphoma; adenocarcinoma of the GI tract, lung, prostate, and breast; and conditions such as tuberculosis in which myelofibrosis may occur secondarily. Treatment depends on symptoms, with splenomegaly symptoms being treated with splenectomy.

Polycythemia Vera

Polycythemia vera (PV) is a progressive myeloproliferative disorder characterized by an increase in all cell lines to include red blood cells, white blood cells, and platelets. PV is rare, with an annual incidence of 5 to 17 per 1 million individuals. Physical examination findings are hallmarked by hypertension, conjunctival plethora, ruddy cyanosis, and hepatosplenomegaly. Treatment will depend on

disease characteristics and may include simple phlebotomy, aspirin, or chemotherapy for more severe disease. As with ET, splenectomy may not be helpful in early disease and is best reserved for patients with later-stage disease.

PRIMARY TUMORS OF THE SPLEEN AND METASTASIS

The most common primary tumors of the spleen are sarcomas, many of which are linked to environmental and occupational exposures (such as vinyl chloride or thorium dioxide). Lung carcinoma is the tumor that most commonly metastasizes to the spleen, although melanoma and colorectal and ovarian carcinoma can spread to the spleen as well. Splenectomy can be considered in isolated splenic metastasis.

MISCELLANEOUS CONDITIONS

Amyloidosis

Amyloidosis is a disorder of abnormal extracellular protein deposition. Like NP, there are multiple forms of amyloidosis, each with its own clinical presentation from mild asymptomatic to those that lead to multiorgan system failure. Only 5% of patients with amyloidosis will experience splenomegaly, and a smaller percentage of patients with secondary amyloidosis may even present with splenic rupture. Splenectomy may be indicated in symptomatic patients.

Gaucher's Disease

Gaucher's disease is a lipid-storage disorder characterized by the deposition of glucocerebroside in the cells of the macrophage-monocyte system. The underlying abnormality is a deficiency in the activity of lysosomal hydrolase in which abnormal glycolipids storage results in organomegaly such as hepatosplenomegaly. Thus symptoms including abdominal pain and early satiety may be seen in addition to normocytic anemia, thrombocytopenia, leukopenia, bone pain, pathologic fractures, and jaundice. Hematologic findings occur as a result of sequestration of formed blood elements in the spleen for which splenectomy may be indicated, although it may not correct the underlying disease process.

Niemann-Pick Disease

Niemann-Pick (NP) disease is another inherited disorder that includes four subtypes (A, B, C, and D), each with its own unique clinical presentation. NP results from abnormal lysosomal storage of sphingomyelin and cholesterol in cells of the macrophage-monocyte system. Splenomegaly is common, and splenectomy is indicated for symptomatic patients.

Sarcoidosis

Sarcoidosis is an inflammatory disease characterized by noncaseating granulomas. Signs and symptoms of sarcoidosis range in severity and are typically nonspecific including fatigue and malaise. Although the most common organ involved are the lungs, the spleen is the second most common and occurs in approximately 25% of patients. Massive splenomegaly, however, is rare, with a reported incidence around 3%. Splenectomy effectively relieves symptoms of splenomegaly and may correct hematologic manifestations such as anemia and thrombocytopenia often seen in sarcoidosis.

PERIOPERATIVE CONSIDERATIONS

Vaccination

Vaccinations directed at encapsulated pathogens are the mainstay of preventive therapy for the asplenic patient. Although rare, overwhelming post-splenectomy sepsis (OPSI) remains the most dreaded and extreme infectious complication of splenectomized patients. OPSI is seen more commonly in the pediatric population, therefore strong risk-benefit analysis must be undertaken when considering total splenectomy in children and adolescents. Although the risk of OPSI is seen more frequently within 2 years of splenectomy, asplenic patients remain at risk for OPSI lifelong. Recommended vaccinations include an annual influenza vaccine but also must include therapy against the encapsulated bacteria: *Streptococcus pneumoniae* (which is responsible for >50% of OPSIs), *Haemophilus influenzae* type B, and *Neisseria meningitidis*. Ideally, patients will receive their vaccines 2 weeks before elective splenectomy. If splenectomy is performed emergently, although vaccinations can be administered immediately postoperatively (especially in a poorly compliant trauma patient!), strong consideration should be given to delayed administration for 2 weeks to avoid the transient immunosuppression seen with surgery, which has been shown to reduce vaccine efficacy.

Deep Vein Thrombosis Prophylaxis

Deep vein thrombosis (DVT) can be seen after splenectomy, especially in myeloproliferative disorders requiring splenectomy, with portal vein thrombosis arising in as many as 50% of these patients. Therefore all patients undergoing splenectomy should be given sequential compression devices (SCDs) and considered for subcutaneous heparin preoperatively. For patients at the highest risk, such as obese patients, smokers, or patients with cancer, postoperative DVT prophylactic therapy with low-molecular-weight heparin should be strongly considered on discharge.

SPLENECTOMY TECHNIQUES

Open

During open splenectomy, the patient is positioned on the operating table in the supine position. Although an upper midline incision may be more commonly selected in the case of traumatic spleen rupture or when massive splenomegaly is anticipated to make the exposure attained by a subcostal incision suboptimal, our preference is to use a left subcostal incision for the vast majority of elective splenectomies. This incision is made paralleling the left costal margin and two fingerbreadths below. Once entered into the peritoneal cavity, our preference is to use a Bookwalter retractor for exposure. The first steps of the procedure involve dividing the ligamentous attachments. In patients with significant splenomegaly, once lesser sac access has been achieved by either the gastrosplenic or gastrohepatic attachments, early ligation of the splenic artery found along the superior border of the pancreas may be preferable before full mobilization of the spleen is attempted (as in the case of traumatic spleen rupture in which timely control of the arterial blood supply may be needed). In other more elective cases, we typically begin our dissection by dividing the splenocolic ligament. Further medial mobilization of the spleen can then be achieved by incising its lateral peritoneal attachments, notably the splenophrenic ligament, and gently retracting the spleen into the midline. The short gastrics then may be taken individually with an energy device such as a LigaSure, or by individual clamps and silk ties, with care to avoid retraction of a vessel and bleeding as well as avoiding injury to greater curve of the stomach. When possible, during the dissection of the splenic hilum, we recommend individual identification and ligation of the splenic artery and then vein (in that order) and conscious awareness of the tail of the spleen to avoid injury. Once the spleen is passed off the field as the specimen, meticulous hemostasis should be confirmed with irrigation and suction. Faint retroperitoneal ooze can be touched up with electrocautery and gentle packing as needed. A nasogastric tube to decompress the stomach overnight may be considered.

Laparoscopic

Laparoscopic splenectomy remains the gold standard for elective splenectomy procedures for patients with normal-size spleens. In experienced hands, these procedures are associated with decreased blood loss, shorter hospital stay, and overall lower morbidity compared with open splenectomy. Although initially performed via an anterior approach with the patient supine (Fig. 1), the lateral approach with patients in the right lateral decubitus position was popularized for adult and pediatric patients by Skinner et al. in the early 1990s. The lateral approach routinely involves the use of four trocars including the use of two working ports for the operating surgeon, a 10- to 12-mm camera port, and an assistant port (Fig. 2). As with open splenectomy, the splenocolic ligament and lateral peritoneal attachments are divided with resultant medial mobilization of the spleen. Next, the short gastric vessels are usually taken with a bipolar energy device such as a LigaSure. With gentle retraction of the spleen, the splenic hilum is then accessed for application of clips or stapler to both the splenic artery and then the vein individually when possible. Using this approach, the operating surgeon can easily visualize the tail of the pancreas and avoid injury. The spleen may then be removed in an endoscopic retrieval bag and meticulous hemostasis ensured before desufflation and port removal.

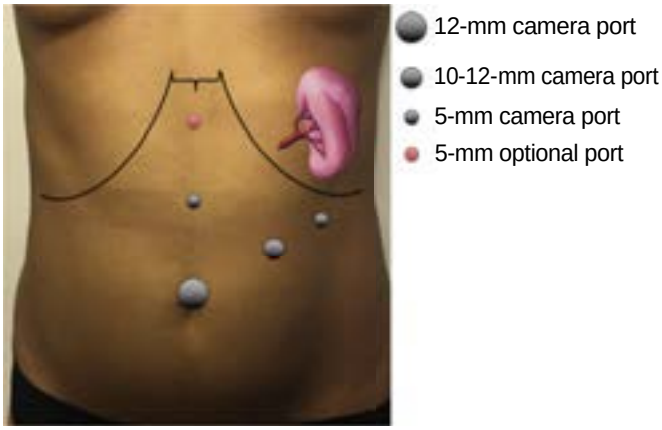


FIG. 1 Laparoscopic anterior approach.

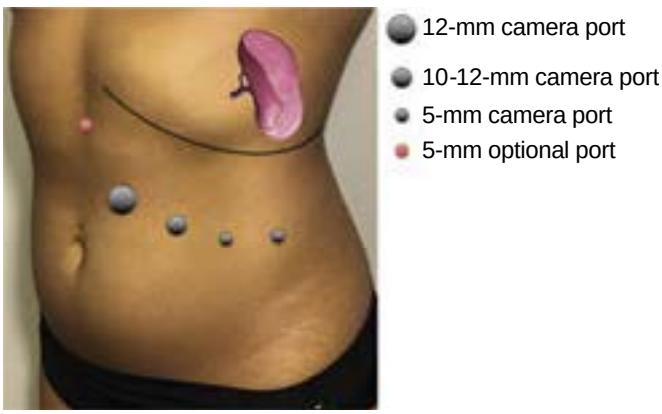


FIG. 2 Laparoscopic lateral approach.

Robotic

Robotic splenectomy procedures were first cleared by the US Food and Drug Administration (FDA) in 2002, for which the daVinci surgical system (Intuitive Surgical, Sunnyvale, CA) remains one of few robotic platforms that can be used for splenectomy procedures. Generally speaking, these procedures are most commonly performed in the right lateral decubitus position with trocar placements similar to their laparoscopic counterparts (described earlier). The reported advantages of robotic surgery have inspired many surgeons to explore these procedures. Although notably, the patient experiences seen with laparoscopic and robotic procedures have largely been comparable as the procedural steps, number of incisions, and anticipated postoperative recovery are similar. Strong proponents of robotic surgery argue that ergonomic benefits for the surgeon and technologic advances seen with surgical robotics (e.g., motion-scaling, tremor reduction, and improved optics including surgeon control of the camera) make robotic procedures preferable when choosing between straight-stick laparoscopy and robotic platforms. However, these potential benefits to the surgeon remain difficult to objectively quantify and generally have been poorly supported (or studied) in the literature to date to offset the significantly higher costs seen with robotic splenectomy. The entry into the market for competing devices with newer and potentially better technology as well as potential cost improvements, which may be seen with increased competition entering the market, may alter these considerations in the future.

CONCLUSIONS

Splenectomy for hematologic disorders remains an important procedure in the armamentarium of the foregut surgeon and is indicated to treat a broad range of clinical conditions, as discussed in this chapter. As with all surgical procedures, careful risk-benefit analysis, preoperative planning, and patient education are the hallmark of ensuring favorable outcomes for our patients.

Suggested Readings

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Management of Cysts, Tumors, and Abscesses of the Spleen

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SURGICAL ANATOMY OF THE SPLEEN

The operative surgeon must have a full knowledge of spleen anatomy. The spleen is positioned in the upper left quadrant of the abdomen and is protected by ribs 9 to 12. In a healthy, normal person, it is 10 to 12 cm in length and weighs approximately 100 g. The anatomy of the splenic vasculature differs among patients. The splenic artery usually arises from the celiac axis; however, in rare instances it may originate from the aorta, the superior mesenteric artery, the middle colic artery, the left gastric artery, the left hepatic artery, or the accessory right hepatic artery. The splenic artery's branching pattern is likewise varied and has traditionally been classified into two types: *distributed* and *magistral*. The less frequent magistral type is composed of a long splenic trunk that separates closer to the hilum into three or four bigger branches that enter the hilum in a more compact bundle, making dissection of the individual vessels more difficult. The splenic trunk also gives rise to the left gastroepiploic artery, which runs along the stomach's greater curvature and should be preserved throughout the procedure. The inferior polar arteries, which come from the left gastroepiploic artery, are, nevertheless, ligated during the initial phases of a splenectomy. The short gastric vessels arise from the stomach fundus and connect to the superior polar artery of the spleen. During the procedure, these vessels are taken in order to expose the splenic hilum. In addition to its variable vascularity, the spleen's complex architecture is supported by many ligaments that sustain it. A detailed knowledge of these ligaments aids in the laparoscopic execution of the surgery, and their anatomy should be routinely reviewed by the staff before to each operation. Anteriorly, the gastrosplenic ligament includes the short gastric and gastroepiploic vessels. The splenic vessels and pancreatic tail can be located posteriorly within the splenorenal ligament. Laterally, the spleen is connected to the diaphragm superiorly by the phrenicosplenic ligament, which is part of the phrenicocolic ligament, and to the splenic flexure of the colon inferiorly by the splenocolic ligament. The phrenicocolic and splenocolic ligaments are typically avascular structures that may be safely separated during surgery.

SPLENIC CYSTS

Splenic cysts are uncommon and frequently discovered by chance; however, because of the widespread use of abdominal imaging nowadays, the prevalence of splenic cysts is estimated to be as high as 1%. Several classification systems for splenic cysts have been proposed. Martin classified splenic cysts into type 1 (or true cysts), which are cysts with an epithelial lining, and type 2 cysts (or false cysts), which are cysts that lack an epithelial lining. Pseudocysts are usually posttraumatic and originate in an organized subcapsular hematoma that failed to reabsorb. Rarely, splenic pseudocysts are secondary to a prolonged splenic abscess or an infarct. Other classification systems are based on pathogenesis or the etiology of splenic lesions. Fowler classified splenic cysts as *parasitic cysts* and *nonparasitic cysts* (Fig. 3). Parasitic cysts are caused mainly by *Echinococcus granulosus* and usually are seen in endemic areas. Calcification in the cyst wall or daughter cysts might be used to make a radiologic diagnosis. Serologic tests can help in diagnosis. For parasitic splenic cysts, the management is typically surgical. If the patient's risk factors make surgery unreasonably risky and the cyst is smaller than 5 cm in diameter, a method known as *PAIR* (*puncture* of cyst; *aspiration* of cyst contents; *injection* with 3% hypertonic saline, alcohol, or 0.5% silver nitrate to sterilize the cyst; and *reaspiration,* in conjunction with anthelminthics) has been described. Typically, parasitic cysts should not be drained percutaneously because of the risk of seeding or anaphylaxis. Spleen preserving surgery can be done if there is a small solitary cyst on the periphery; however, because of the invasive nature of the infection, care must be given to ensure that there are 1-centimeter margins from the cyst. If preserving the spleen does not appear to be an option, a splenectomy should be performed. Extreme caution should be used to avoid rupture or spilling of the cyst contents into the abdominal cavity; in fact, anaphylactic shock and death have been reported as a result of cyst contents spilling and spread.

Primary splenic true cysts account for 10% of all nonparasitic cysts; they are lined with squamous epithelium and are considered to be congenital. They are identified in children and teenagers accidentally and are typically asymptomatic. They are benign in nature and have elevated cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA). The majority of other nonparasitic cysts

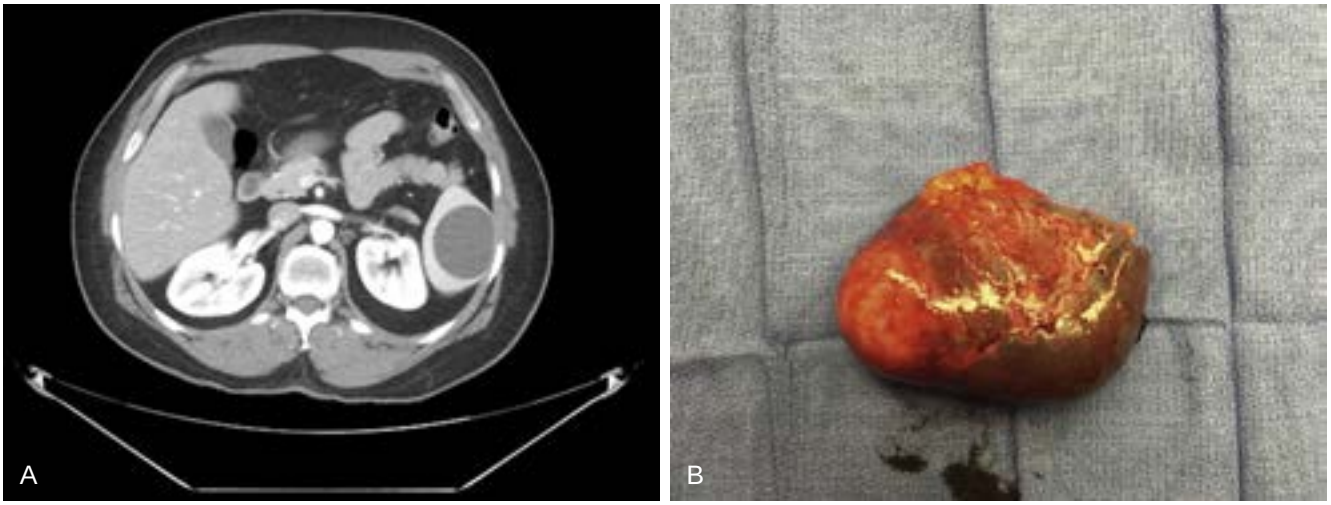


FIG. 3 **(A)** Patient with a symptomatic splenic cyst found on computed tomography. **(B)** The spleen was removed with the cyst intact.

are pseudocysts caused by trauma. Other extremely rare primary nonparasitic cysts are of mesothelial and dermoid origin. The clinical importance of splenic cysts is mostly caused by the mass effect (i.e., affecting surrounding organs) and their ability to rupture and bleed profusely. Small, asymptomatic, nonparasitic splenic cysts or pseudocysts can be monitored, whereas symptomatic cysts would typically enlarge, necessitating surgery. When operative, simple cysts can be managed in a variety of ways, from total splenectomy to simple deroofing of the cyst. The trend is moving toward spleen preservation whenever possible, with partial splenectomy, decapsulation, cyst fenestration, or deroofing. There is also the option for percutaneous drainage. This topic is controversial, and some recommend it, while others have found that it should not be attempted because of high recurrence rates. The technique for decapsulation involves suctioning out the cyst, opening the anterior cyst wall, and then circumferentially excising the cyst wall using an energy device. This is preferred over simple unroofing, which has a higher recurrence rate. In patients with recurrent splenic cysts or initial splenic cysts, partial splenectomy is recommended because the recurrence rate is lower than after decapsulation.

SPLENIC PELIOSIS

Splenic peliosis is a benign disease that has been observed in the liver. Sinusoidal dilation leads to the appearance of multiple blood-filled "cystic" cavities scattered within the splenic parenchyma in the parafollicular red pulp. The rupture of these cavities might result in hemorrhagic shock and death. HIV, systemic steroid use, oral contraceptives, and persistent hematologic diseases such as Hodgkin's lymphoma and multiple myeloma are also risk factors for peliosis. Both the liver and spleen are involved in the majority of these cases. The occurrence of isolated splenic involvement is exceedingly unusual, and it usually manifests as hemoperitoneum. Even when peliosis is discovered accidentally, complete splenectomy should be performed to eliminate the risk of bleeding.

SPLENIC TUMORS

Primary splenic neoplasms are uncommon tumors that are classified according to their origin tissue (Box 1). Lymphoid neoplasms arise from the white pulp, whereas vascular neoplasms arise from the red pulp. In addition to this classification, primary neoplasms can be classified into benign and malignant tumors. Benign tumors include hemangioma, lymphangioma, hamartoma, and littoral cell angioma. Malignant tumors include lymphoma and angiosarcoma. Other tumors such as lipoma and inflammatory pseudotumors have been described but are exceedingly rare, with very few reports in the literature. Secondary neoplasms also occur within the spleen, with melanoma, breast, lung, ovary, colon, stomach, and pancreatic neoplasms all being reported as metastasizing to the spleen.

BOX 1 Splenic Neoplasms

Benign tumors
- Hemangioma
- Lymphangioma
- Hamartoma
- Littoral cell angioma

Malignant tumors
- Lymphoma
- Angiosarcoma

Nonvascular, nonhematopoietic tumors
- Inflammatory pseudotumor
- Mesenchymal tumors

Metastatic tumors

Benign Tumors

Hemangioma

Hemangiomas originate from the vascular endothelium and are the most common benign primary tumors of the spleen. Most patients are asymptomatic and identified incidentally on radiographic imaging for other indications. The majority are solitary and less than 2 cm in diameter; however, hemangiomatosis and generalized angiomatosis syndromes can occasionally show numerous and widespread disease lesions. Splenic hemangiomas are classified as either *capillary* or *cavernous*, with the latter being more frequent. These two patterns have slightly different appearances on imaging. On CT, cavernous hemangiomas appear larger in size and have a cystic appearance with intermittent areas of hypodensity, which enhance peripherally with contrast administration. The capillary subtype demonstrates smaller hypodense or isodense masses on CT with homogeneous enhancement with contrast administration. Hemangiomas larger than 2 cm have an associated risk of bleeding and may be considered for complete or partial splenectomy.

Lymphangioma

Lymphangiomas are less frequent and are believed to be congenital lymphatic abnormalities. These abnormalities can fill with eosinophilic proteinaceous material, causing increased weight of the spleen, and they become symptomatic as a result of the mass effect. The absence of the cystic look associated with hemangiomas distinguishes them from the latter. These lesions, like hemangiomas, can be unifocal or part of a systemic lymphangiomatosis syndrome that affects several organs. They can be multiloculated, lobulated, and cystlike, unlike hemangiomas. Lymphangiomas detected in adulthood are typically incidental on imaging, and patients remain asymptomatic. Three histologic subtypes are capillary, cavernous, and cystic. On ultrasound, multiple hypoechoic cysts are separated by hyperechoic septate, and calcifications can be seen. They are more common in a subcapsular location and may have enhancing septa and peripheral rim calcification (Fig. 4). Although splenectomy has traditionally been the gold standard of treatment for suspected splenic lymphangiomas, partial splenectomy is becoming increasingly common.

Hamartoma

Splenic hamartomas are uncommon benign tumors characterized by red pulp malformation without organized lymphoid follicles. They are generally tiny and found by chance on imaging, although they can occasionally appear as a big mass or diffuse splenomegaly. Although most patients are asymptomatic, this entity has been associated to spontaneous splenic rupture, especially in larger masses. Ultrasonography shows a well-circumscribed homogeneous solid mass, whereas CT shows early enhancement with intravenous contrast and uniform delayed enhancement of an isodense mass. Because of stagnation inside the red pulp sinusoids, larger hamartomas may show more heterogeneous contrast uptake and longer contrast retention. Although imaging is helpful in determining a diagnosis, it is not always accurate, and percutaneous biopsy is recommended when possible. If biopsy is not possible, splenectomy is indicated for definitive diagnosis and management.

Littoral Cell Angioma

Littoral cells, the cells that line the red pulp, can cause littoral cell angioma, a benign vascular tumor of the spleen. The spleen is involved in a diffuse nodular pattern in this condition. As a result, patients may have splenomegaly and hypersplenism symptoms such as anemia, tiredness, and bleeding. Hemoperitoneum and splenic rupture have also been reported. Multiple isodense masses of various sizes can be seen on noncontrast CT. Following contrast administration, the masses appear hypodense on the early portal phase, returning to an isodense appearance on the delayed phase. When littoral cell angiomas are found, splenectomy is recommended because of

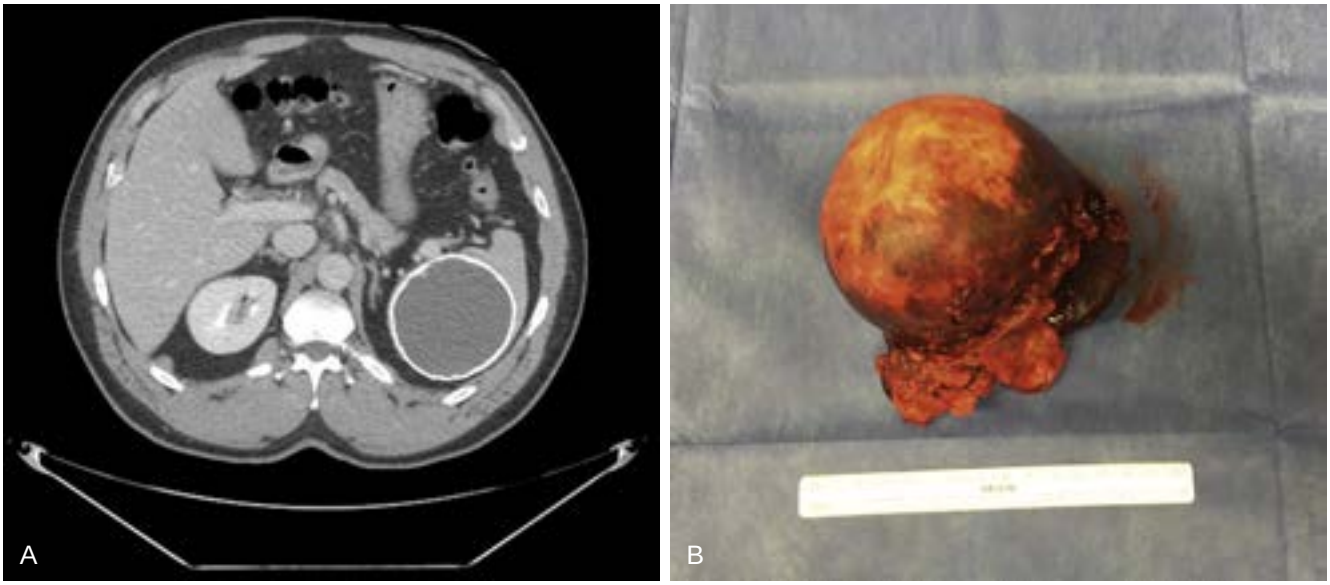


FIG. 4 **(A)** Large (>5 cm) calcified splenic lesion was identified on computed tomography. **(B)** The thin calcified wall is noted on the surgical specimen after splenectomy.

the danger of splenomegaly and hypersplenism. Pathologic specimens reveals small vascular channels connecting cystic areas with papillary projections on histology, confirming the diagnosis.

Malignant Tumors

Lymphoma

The most common primary malignant tumor of the spleen is lymphoma. Primary splenic lymphoma is rare, occurs in approximately 1% to 2% of all lymphomas, and is most commonly diffuse large B-cell lymphoma. Diagnosis of primary splenic lymphoma relies on imaging techniques. A primary splenic lymphoma will appear as a single large mass or multiple focal splenic masses. The masses are generally well defined and hypoechoic. Primary splenic lymphoma patients typically present with nonspecific symptoms, including fever, night sweats, and weight loss, and sometimes specific symptoms, such as splenomegaly and left upper quadrant pain. Secondary lymphoma of the spleen is considerably more frequent than primary lymphoma of the spleen. The most prevalent feature on examination for primary splenic lymphomas is splenomegaly, which occurs in more than two-thirds of patients. Disease confined to the spleen and hilar nodes with no recurrence following splenectomy has traditionally been used as a diagnostic criterion. Fine-needle aspiration and core needle biopsy were formerly avoided because of fears that puncturing the hypervascular, fragile spleen may result in hemorrhagic consequences. Most subsequent research studies have disproved this, and it is now considered a safe practice. Splenic marginal zone lymphoma, in particular, is a slow-growing subtype that nearly invariably manifests as splenomegaly. Hepatitis C virus infection is linked to it. Splenectomy has been the standard treatment for this subtype of primary splenic lymphoma, but more recently, rituximab monotherapy has been proven to be effective as a first treatment for this subtype of primary splenic lymphoma. With appropriate treatment, the prognosis is favorable, with an estimated 5-year overall survival rate of 80% to 95%.

Angiosarcoma

The rare angiosarcoma is the most frequent primary nonhematopoietic malignant tumor of the spleen. These tumors, also known as *hemangiosarcomas,* are very aggressive and have a poor prognosis. Splenomegaly and evidence of metastasis, most often to the liver, regional nodes, bone marrow, and lungs, are common in patients with advanced disease. Because of the aggressive nature of the cancer, these patients may develop cachexia in addition to the clinical manifestations associated with splenomegaly. Less common findings include ascites and pleural effusion. Spontaneous rupture can be the first symptom, and it is a terrifying, although extremely rare, and potentially fatal consequence. On imaging, there are several complicated heterogeneous and hypervascular masses. Calcifications are uncommonly observed. Biopsy, like lymphoma, has been avoided in the past because of concerns about bleeding, but it is now regarded safe if precautions are taken. When possible, splenectomy is used to treat the condition.

Other Nonvascular, Nonhematopoietic Splenic Tumors

An inflammatory pseudotumor is a rare benign splenic tumor. The cause is unknown, although it is thought to be linked to an inflammatory reparative response following traumatic or viral damage. Patients are generally asymptomatic but may present with symptoms from mass effect, which is usually an incidental finding on imaging. These pseudotumors show as a hypodense mass with delayed contrast enhancement and central scarring on CT. Splenectomy should be performed if the patient is symptomatic or if the diagnosis is in doubt. The presence of spindle cell growth and plasma cells in the pathology report will confirm the diagnosis. Mesenchymal tumors such as fibroma, fibrosarcoma, lipoma, angiomyolipoma, leiomyosarcoma, and malignant fibrous histiocytoma have been described in the literature and are very rare. Apart from the characteristic presence of fat in lipoma, there are no specific pathognomonic features on imaging with these neoplasms. Patients are frequently asymptomatic, and the diagnosis is made after splenectomy.

Metastatic Tumors

In metastatic disease, splenic involvement is uncommon. Splenic metastases are seen in less than 10% of all cancers that go untreated. There are several theories as to why the spleen appears to be immune to metastases. There are no afferent lymphatics, the splenic arteries have a sharp angle, and the splenic lymphoid tissue itself has anticancer activity. Hematogenous spread is the most likely route when

splenic metastases do occur. The most common primary malignancies to metastasize to the spleen are melanoma and breast, lung, and ovarian cancers. Rarely, metastases from colon, stomach, and pancreas primary tumors are also found. Though infrequent, these latter tumors may spread via direct invasion into the spleen. Diffuse infiltration is rare. More commonly, metastatic disease is seen as solitary or multiple masses. Radiologic findings vary with the primary neoplasm. Cystic and necrotic degeneration can occur, particularly with melanoma. Calcifications may be noted with mucinous adenocarcinomas. Carcinomatosis and pseudomyxoma peritonei may manifest as serosal implants on the splenic surface, also visualized as splenic margin scalloping.

SPLENIC ABSCESS

Splenic abscess is uncommon, yet it can be deadly if left untreated. According to a large series of Western autopsies, the incidence of this disease ranges from 0.14 % to 0.7%. They are most commonly spread hematogenously in the presence of bacteremia or fungemia, although they can also spread contiguously. Splenic abscess has traditionally been associated to endocarditis, although it has also been linked to urinary tract infections and gastrointestinal infections. As a result of changing lifestyle trends, the prevalence of diabetes mellitus, HIV/AIDS, and liver illness is increasing, predisposing individuals to splenic abscesses. Ultrasonography or CT are the best ways to make a diagnosis. Antibiotic treatment should be designed to cover the organisms that are most often cultivated. The most common isolates are gram-positive cocci, such as *Staphylococcus* and *Streptococcus* species, and gram-negative enteric organisms, such as *Salmonella* species. Coverage for *Mycobacterium* and *Candida* species should be considered in immunocompromised patients, especially those who may present in septic shock. In most recent studies, definitive treatment of splenic abscesses with percutaneous draining has had satisfactory results. Patients with unilocular abscesses are the most likely to achieve complete resolution with percutaneous or image-guided drainage. Splenectomy is recommended for individuals who do not improve clinically, have multiloculated abscesses, or have partial resolution after first drainage.

SURGERY

Splenectomy is one of the most common procedures performed by general surgeons, and it is used to treat trauma and hematologic disorders. Because of its position in the abdomen, the spleen is highly susceptible to damage caused by trauma because it lacks a protective anatomic cage. The most frequent indications for splenectomy are grade 4-5 spleen injury, symptoms of massive splenomegaly, cysts, abscesses and tumors of the spleen, and diagnosis and treatment of hematologic diseases. Splenectomy can be done by an open or laparoscopic procedure. The surgical team's experience and the patient's history of previous abdominal operations are two criteria that influence the decision. Laparoscopic splenectomy remains the gold standard of surgical treatment for elective patients. When compared with open splenectomy, laparoscopic splenectomy has the advantages of a shorter hospital stay, less postoperative discomfort, and lower morbidity. We describe laparoscopic splenectomy, as it is the most common surgery performed today for splenic lesions.

Preoperative Considerations

Preoperative evaluation includes a detailed history and physical examination with focus on abdominal symptoms, a complete blood count, and a CT scan of the abdomen. Preoperative imaging is critical for surgical planning. For measuring the size of the spleen, CT and ultrasonography are also viable options. The former is likely to be preferred because it provides a better view of anatomic connections and anatomy (e.g., auxiliary spleens) and lymphadenopathy, and it provides a clear interpretation of the vascular anatomy. Medical comorbidities, splenic size, blood counts, concurrent coagulopathy, previous splenic irradiation, and percutaneous manipulation are all factors to consider before undergoing surgery. In particular, planning includes correction of any coagulopathy to the degree possible. Steroids and intravenous immunoglobulin are used to increase platelet counts preoperatively for patients with idiopathic thrombocytopenic purpura (ITP). Nevertheless, laparoscopic splenectomy can be performed safely and effectively in patients with ITP who have platelet counts as low as 20,000/μL. In fact, recent studies support the notion that laparoscopic splenectomy is feasible with platelet counts below 20,000/μL without transfusion. Before performing a skin incision, appropriate pretreatment antibiotics are administered. Despite the risk of bleeding, there is also a chance of splanchnic thrombosis following splenic artery manipulation; therefore it is advisable to administer low-molecular-weight heparin before induction of anesthesia and maintain it for up to 1 month postoperatively as prophylaxis. When the short gastric arteries are dissected along the larger curvature, gastric decompression via an orogastric or nasogastric tube can minimize gastric distention and enhance visibility. Intraoperative blood products should be available, especially in patients with severe thrombocytopenia. After ligation of the splenic artery, platelets are transfused only as needed and are rarely required. To reduce the risk of overwhelming post-splenectomy sepsis, patients are immunized against encapsulated organisms (*Haemophilus influenzae* B, polyvalent pneumococcus, and meningococcus vaccines) 2 weeks before splenectomy in the elective context. If the splenectomy is an emergency procedure, the patient should be immunized within 30 days after being discharged from the hospital.

Laparoscopic Splenectomy

Although anterior, lateral, and posterior methods to laparoscopic splenectomy have been proposed, we believe that a semilateral approach provides the surgeon with more versatility and adaptability to spleens of various sizes and forms.

Laparoscopic Access and Initial Port Placement

An orogastric tube is placed to decompress the stomach after induction of anesthesia and general endotracheal intubation. Because insertion of an orogastric tube while the patient is in the lateral decubitus position is difficult and generally ineffective, this is performed before the patient is positioned. Invasive monitoring with a central line or an arterial line is desirable but not necessary in most individuals. In every case, a Foley catheter is inserted. The strategy for additional perioperative hydrocortisone dosage is discussed with the anesthesiologist if the patient has been treated continuously with significant doses of steroids.

Positioning of the Patient

The patient is positioned in the right semilateral decubitus posture (at a 45-degree angle to the operating table) on a beanbag on the operating room table. Positioning the patient in this manner, with the added stability provided by the beanbag, allows for correct adjustment during surgery, allowing the surgeon to reach a completely supine (anterior approach) or entirely lateral (lateral or posterior approach) posture at his or her choice. A more anterior approach is employed for spleens that are longer and larger and for those in which the splenocolic ligament is positioned more inferiorly. Furthermore, to successfully increase the space between the left costal margin and the anterior superior iliac spine of the pelvis, the patient is placed with his or her costal margin just hanging from the break of the operational table. This gives the most lateral port, which is implanted in the patient's left flank, more mobility. The padding is then liberally applied to all pressure points.

Port Placement

A 5-mm incision is made 3 cm below the center of the left costal border after full neuromuscular paralysis. A Veress needle is placed, the abdomen is insufflated with 14 mm Hg of carbon dioxide, and a water drop test is done (CO_2). The Veress needle is then withdrawn, and a 5-mm port is introduced into the abdominal cavity, followed by a 5-mm, 0-degree laparoscope. Following that, the laparoscope is replaced with a 5-mm, 30-degree laparoscope, and the additional trocars are inserted under direct view. Three 5-mm trocars are inserted anteriorly along the costal margin, spaced 10 cm each, and one 11-mm trocar that fits the endoscopic stapler is placed in the left flank, typically after the splenic flexure of the colon has been mobilized correctly, as is the case with longer spleens.

Mobilization of Splenic Ligaments

For mobilization of the splenic ligaments, a vessel-sealing device is generally used. The surgery begins with the splenocolic ligament being divided, which contains the spleen's inferior polar vessels. The ligaments are mobilized to the left once the inferior pole of the spleen has been fully mobilized by separating the most lateral part of the gastrocolic ligament to access the gastrosplenic ligament medially. The dissection proceeds superiorly and medially, dividing the short gastric vessels. As progress is made toward the apex of the spleen, the dissection proceeds upward toward the left pillar of the crus, with gentle medial retraction of the fundus of the stomach. The whole stomach is next folded medially to reveal the splenic hilum in its entirety. The orogastric tube, which was inserted preoperatively and left on low, continuous suction, considerably facilitates this maneuver. The superior pole of the spleen is totally mobilized at this point by dividing the highest part of the splenorenal ligament. The full mobilization of the spleen's superior pole will therefore make vascular control of the splenic hilum easier. Following these procedures, a thorough search is conducted for accessory spleens, which are removed and put between the folded stomach and the left lobe of the liver for retrieval with the main specimen later. A clear view of the splenic hilum, upper pole, and lower pole is finally achieved at this point because of the use of proper operating table positioning, the effective use of gravity for retraction and exposure, and suspension of the spleen primarily by the splenorenal and phrenocolic ligaments, leaving the surgeon with the best strategy for addressing the hilar structures.

Management of Splenic Hilum

The tail of the pancreas is first identified in connection to the hilar components of the spleen. The zone for transection of the splenic arteries is short when the tail of the pancreas reaches closer to the hilum of the spleen. Small (0.5-cm) hilar vessels can be sealed using the vessel sealing system in this scenario or when a scattered anatomy is present. In all other cases (e.g., difficult cases with a large amount of visceral fat and larger hilar vessels), we prefer applying careful serial firings of an endoscopic stapler loaded with vascular cartridges. Conversely, when a clear anatomy is present, the hilum is taken with one firing of an endoscopic stapler loaded with a vascular cartridge, provided that the tail of the pancreas is protected and that all hilar structures can be included between the jaws of the cartridge. The superior and inferior poles of the spleen must be sufficiently mobilized to allow a posterior window to form behind the hilum to accommodate the stapler. These steps can be accomplished by mobilizing the spleen anteriorly or posteriorly by tilting the operating table to the left or right and utilizing the stability provided by the beanbag. The surgeon can then choose the optimal approach to the splenic hilum based on the size, shape, vascular architecture, and connection of the spleen to the pancreatic tail. Finally, a major splenic artery and vein can be readily dissected separately. Energy devices are used to complete the remaining dissection of the splenorenal ligament and associated vascular structures away from all staple lines in all patients.

Extraction of the Spleen

An effective manipulation of both the spleen and the bag can make this step a very rewarding conclusion to the operation. First, the spleen is separated from all of its attachments and carefully positioned away from the left diaphragmatic dome, often using operating table positioning. Then, through the most lateral, 11-mm port site, a strengthened, large plastic bag is introduced. The bag is unfolded and positioned in the shape of a "scorpion tail," with the open end held superiorly by the assistant and inferiorly by the surgeon's left hand, and the tail curled up slightly and nestled in the left upper quadrant. The spleen is then directed into the bag with a grasper held in the surgeon's right hand (which holds the severed ligaments of the spleen, not its parenchyma), and the patient is placed in the Trendelenburg position. The spleen is guided into the open bag in this scenario, and the bag's "tail" unfolds as the spleen enters. The strings of the bag are grabbed using an instrument inserted via the 11-mm port once the spleen has been safely put into the bag. The port is then withdrawn, allowing the bag to be opened and ring forceps to be inserted for morcellation and extraction. In known cases of ITP, it is always preferred to morcellate the spleen. In other cases, when an intact spleen should be sent to the pathology department, the surgeon can resort to one of two options. It is preferable to widen downward the most medial trocar incision, which is always positioned at the midline in the epigastrium, to execute a laparotomy small enough to recover the specimen in elderly patients. In young patients, the surgeon may offer the option of doing a Pfannenstiel incision before surgery for aesthetic reasons. Following the removal of the specimen, the abdomen is reinsufflated, and the dissection region is examined again to confirm hemostasis and rule out damage to the stomach, pancreas, diaphragm, and colon. All trocars are removed once the wound has stopped bleeding and the port sites have been appropriately managed. The 11-mm port site is always closed and infiltrated with local anesthesia using a figure-of-eight 2-0 absorbable suture. Drains are rarely used on a regular basis unless the pancreas has been accidentally damaged.

Posterior Approach

The truly posterior approach is performed with the patient in a fully lateral position. It could be used for spleens that are more prominent anteriorly, obscuring the view to the hilum, and those in which a magistral branching pattern of the splenic artery is present. The lateral ligaments of the spleen (phrenicocolic and splenocolic) are transected to allow the spleen to descend and rotate medially, exposing the hilar arteries straight from behind. In some situations, this procedure is considered to enable a safer and less difficult dissection of the individual vessels.

Postoperative Care

At the conclusion of the procedure, the orogastric tube and Foley catheter are removed. Intermittent parenteral opioids are used to manage pain before the patient is switched to oral pain medication. Patients are urged to walk as much as possible and are allowed an unrestricted diet as soon as feasible. The majority of patients are discharged on the first or second postoperative day and are encouraged to tailor their activities to their degree of comfort. Patients are often visited in the clinic two weeks after surgery for a full blood count. Administration of preventive immunization against overwhelming post-splenectomy infection (OPSI) and sepsis is warranted if the patient did not receive it before surgery.

Robotic Splenectomy

Robotic surgery has been used in clinical practice for a number of laparoscopic purposes in recent years. Doubts have been raised regarding the suitability of laparoscopic splenectomy for patients with splenomegaly, advanced liver cirrhosis, and splenic tumors and

for those who will undergo a partial splenectomy. The benefits of robotic surgery have encouraged some of the most skilled laparoscopic surgeons to research its potential and expand its use in the minimally invasive surgery paradigm. Both straightforward splenectomies and complicated splenectomies in patients with cirrhosis or patients with splenomegaly have been described, and the high resolution of the robotic system allows safe and precise dissection of the splenic hilar vessels. The robotic system provides a stable camera platform with a better view as a result of three-dimensional imaging, instruments with more degrees of freedom, and a comfortable position for the surgeon. Concern was raised about the ability to control significant bleeding using the current limitation of three arms, with the need to convert emergently to open surgery in cases of major bleeding. In partial splenic resections requiring precise vascular dissection, recent research has revealed the advantages of robotic splenectomy.

Outcome and Complications

Based on the time after the operation, post-splenectomy complications are usually classified into early and late complications. Surgery-related and non–surgery-related early complications include intraoperative and postoperative bleeding, left lower lobe atelectasis and pneumonia, left pleural effusion, subphrenic collection, and iatrogenic pancreatic, gastric, and colonic damage. Reactive thrombocytosis is a common side effect after splenectomy. Although post-splenectomy deep vein thrombosis, pulmonary embolism, and acute myocardial infarction have all been documented, the significance of post-splenectomy thrombocytosis and its role in the etiology of these events is still debated. Prophylactic antiplatelet therapy is not advocated. Mesenteric vein thrombosis is a well-documented complication of splenic vein ligation, occurring in up to 30% of cases in certain studies. The most common deadly late splenectomy consequence is OPSI. After a splenectomy, it can happen at any moment. The majority of infections that have been documented occur more than 2 years following surgery. The most frequently involved organisms are *Streptococcus pneumoniae, H. influenzae, Neisseria meningitidis,* and *Salmonella* spp. The standard of care today for post-splenectomy prophylaxis includes administration of pneumococcal vaccine polyvalent (Pneumovax 23), *H. influenzae* type b conjugate, and meningococcal polysaccharide vaccine within 2 weeks of splenectomy or before surgery.

Suggested Readings

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Management of Inguinal Hernia

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More than 20 million inguinal hernia repairs are performed every year around the globe, placing this operation among the most common general surgical procedures (HerniaSurge Group, 2018). Although the use of mesh in inguinal hernia repair parallels a dramatic reduction in recurrence rates, chronic post-herniorrhaphy pain syndrome has simultaneously emerged as an important cause of morbidity in these patients, affecting up to 18% of patients (Reinpold, 2017). Further, the rapid and widespread adoption of robotic-assisted techniques has carried with it a steep learning curve with a renewed emphasis on patient selection, identification of appropriate surgical indications, and technical mastery of a variety of approaches to the surgical management of this condition.

INDICATIONS AND TIMING OF REPAIR

Repair should be offered to all male patients with symptomatic inguinal hernias who are otherwise physically fit to undergo surgery. For those with no or minimal symptoms related to the presence of an inguinal hernia, it is well-accepted that watchful waiting is a safe and reasonable option for male patients. However, there is a time-dependent risk of development of nonemergent symptoms such as inguinal pain or progressive hernia enlargement, which will lead to a majority of patients seeking eventual surgical repair (Fitzgibbons et al., 2006). Other considerations that should influence the timing of repair include the increased complexity of repair associated with larger hernia defects as well as the greater risk of perioperative complications when performed in emergency settings, which is particularly relevant in patients with significant comorbidities or bleeding disorders.

Watchful waiting is not currently recommended for female patients. Although inguinal hernias are much less prevalent in females, the risk of emergencies associated with observation in this group appears to be higher than for males. A contributing factor is the higher rate of femoral hernias in female patients with groin hernias—historically double the rate for male patients. However, the higher acuity of presentation of female patients may be caused, in part, by diagnostic challenges unique to this population that can lead to presentation or diagnosis at more advanced stages of the condition. Multiple population studies have estimated that 3% of female patients have groin hernias. However, a Swedish herniography study of female patients younger than 40 years of age identified hernias in 24%, suggesting that we gravely underdiagnose this condition (Kesek and Ekberg, 1999). When imaging is needed to evaluate the female patient with nonacute groin pain, standard ultrasound may not be adequate. Pelvic magnetic resonance imaging is considered the best imaging modality in this population. It is important to note that evidence-based guidelines for female hernia patients are lacking, and future research efforts should focus on this demographic specifically.

CONSIDERATIONS IN SELECTING THE OPERATIVE APPROACH

A variety of surgical repairs have been developed, all with their own unique benefit and risk profiles as well as characteristic learning curves. Selection of the appropriate technique is largely surgeon-dependent and based on experience, with the most favorable outcomes associated with the repair most frequently performed. Additionally, characteristics unique to each patient and the hernia should inform decision making regarding procedural selection. Although there are no absolute contraindications to minimally invasive repair, patients who are not candidates for general anesthesia are perhaps better suited for open techniques, which can be performed under spinal or local anesthesia with or without sedation. While laparoscopic inguinal hernia repair can be performed under epidural anesthesia, inadequate muscular relaxation can impose severe limits on the available working space. Accordingly, a large majority of these repairs are conducted with general endotracheal anesthesia to avoid this frustration. The choice of total extraperitoneal repair (TEP) versus transabdominal preperitoneal repair (TAPP) may also be largely dictated by patient characteristics or surgeon experience. For example, in the case of a surgeon comfortable with both TAPP and TEP techniques, the choice of pursuing a totally extraperitoneal approach in a given patient might be entirely dictated by features of that patient's particular surgical or medical history. Individuals who have previously undergone abdominal surgery may have adhesions that make a transabdominal approach more challenging and perhaps even unsafe. Similarly, patients with a history of prostatectomy may have scarring of the preperitoneal space, rendering it unsuitable for an entirely extraperitoneal approach.

There is compelling evidence to support minimally invasive posterior inguinal hernia repair for patients with bilateral inguinal hernias as well as recurrent inguinal hernias after prior open inguinal hernia repair. For the majority of inguinal hernia patients, open and minimally invasive mesh repairs are equivalent.

OPEN INGUINAL HERNIA REPAIR

Tissue Repair

Several pure tissue repairs have been described over the past century, but they were largely abandoned in favor of repairs utilizing mesh reinforcement in modern times. Although direct comparisons are limited and available randomized controlled trials are of low quality with concerns regarding standardization of technique, the Shouldice repair is the best nonmesh inguinal hernia repair technique with

supporting level 1A evidence. Compared with other pure tissue repairs, the Shouldice confers lower recurrence, hematoma, and chronic pain rates (Shouldice 2003). Surgeon experience and meticulous technique have significant impact on outcomes. From a 2012 Cochrane systematic review, the recurrence rate for Shouldice was higher than Lichtenstein mesh repair, although substantial doubts about the uniformity of technique described in the Shouldice arms raise concerns about the validity of conclusions drawn from this review. Nevertheless, there was no significant difference in chronic pain, surgical site infection, or the incidence of postoperative seroma formation. Newer tissue repair techniques include the Desarda repair, a tension-free strategy that utilizes an autogenous patch of external oblique aponeurosis to reinforce the floor of the inguinal canal. Early data on recurrence and other traditional outcomes are promising for this repair. In a recent systematic review and meta-analysis of 14 randomized controlled trials comparing the Desarda or Shouldice with Lichtenstein repair, there were similar rates of recurrence for either tissue repair to Lichtenstein (Bracale, 2019). However, the recurrence rate was still higher for the tissue repair compared to Lichtenstein in these heterogeneous trials, with a threefold increased risk for the Shouldice repair (seven studies) and 40% higher for Desarda (three trials). Despite the higher rate of recurrence, public appetite for mesh-free repairs persists, and there remain circumstances in which the implantation of prosthetic mesh is inadvisable, such as contaminated cases and those involving strangulated bowel. All general surgeons should learn and maintain comfort with a pure tissue repair.

Lichtenstein Repair

The most common open, mesh-based treatment is the Lichtenstein "tension-free" repair, which relies on the use of prosthetic mesh to reconstruct the posterior wall of the inguinal canal. Initially described in 1989, the repair involves fixation of mesh, usually polypropylene, to the internal oblique aponeurosis or muscle superiorly, the pubic tubercle medially, and the inguinal ligament inferiorly. The approach is via an incision inferior and medial to the anterior superior iliac spine, which is extended medially and obliquely for approximately 6 to 8 cm, ending just lateral to the symphysis pubis. Dissection is then carried down to the aponeurosis of the external oblique muscle, taking care to ligate or cauterize the superficial epigastric veins before opening the inguinal canal. The aponeurosis is then opened in the direction of the underlying fibers using Metzenbaum scissors, and the incision is extended through the external inguinal ring medially. The ilioinguinal nerve can now be visualized as it courses the inguinal canal, and this should be preserved. The interior oblique fibers are dissected bluntly from the overlying external oblique muscle flap, revealing the shelving edge of the inguinal ligament. The iliohypogastric nerve can be located by elevating the external oblique superior to the inguinal canal. This nerve courses along the anterior body of the internal oblique muscle before dividing into two cutaneous branches: anterior and lateral.

The spermatic cord, along with an indirect hernia sac, if present, is commonly isolated using a Penrose drain for easy retraction. The hernia sac will usually be seen on the anterolateral surface of the cord structures and should be separated from the adjacent spermatic cord, which will often require division of surrounding fibers of the cremaster muscle. The genital branch of the genitofemoral nerve travels within the deep spermatic cord adjacent to the external spermatic vein, and it should be identified and preserved while separating the cord structures from the hernia sac. The posterior wall of the inguinal canal should be carefully assessed for weakness suggestive of the presence of a direct hernia. Repair of the hernia is initiated by securing the medial aspect of a prosthetic mesh to the aponeurotic tissue overlying the pubic tubercle with a single monofilament suture with an overlap of approximately 2 cm. The inferior edge of the mesh is then sewn to the inguinal ligament from medial to lateral. This can be done either in a running ("baseball stitch") fashion or with the use of interrupted sutures. A second line of suture is placed superiorly, securing the mesh to the aponeurosis of the internal oblique muscle or to the muscle itself. Interrupted suture limited to medial to the deep inguinal ring is recommended to limit the risk of nerve entrapment or injury. The mesh is divided along its long axis starting at the lateral edge, and these "tails" are then used to recreate the internal ring secured with a single nonabsorbable suture. The layers of the abdominal wall are then closed individually, starting with the aponeurosis of the external oblique muscle, Scarpa's fascia, and finally the skin.

Mesh fixation was initially described with nonabsorbable suture. Increasingly, long-acting absorbable monofilament suture is employed in an effort to limit the risk of chronic pain and inflammation. Alternatively, cyanoacrylate glue fixation and self-adherent mesh have been determined in randomized trials to be equal in hernia recurrence and chronic pain (Matikainen 2017, 2021).

A modification of the Lichtenstein repair uses the addition of a mesh plug that is placed through the internal ring in the case of an indirect inguinal hernia. For a direct hernia, the plug is sutured to Cooper's ligament (an extension of the inguinal ligament that forms the floor of the femoral canal), the inguinal ligament proper, and the internal oblique aponeurosis. International hernia guidelines note that the risk of mesh erosion and migration appear to be higher with the mesh plug versus flat mesh and therefore is not recommended (HerniaSurge Group, 2018). Additionally, bilayer mesh violates both the anterior and preperitoneal space, does not appear to be beneficial in reducing the risk of hernia recurrence, and may complicate future recurrence repair.

Local Anesthesia Block

A local anesthetic block is safe and cost-effective as the primary method of anesthesia delivery during open repair as well as for postoperative analgesia. Regardless of whether general anesthesia is used, preemptive local anesthetic injection before performing the surgical incision may decrease postoperative pain by blocking the stimulation of local nociceptors. Lidocaine (1% or 2%), or bupivacaine (0.25% or 0.5%) may be used with or without epinephrine additive. The longer half-life of bupivacaine may confer advantages with respect to postoperative pain mitigation. Attempts should be made to inject local anesthetic in the intradermal, subdermal, and deeper subcutaneous layers. Regional blockade can also be achieved with injection just medial to the anterior superior iliac spine, although this risks causing a direct nerve injury. Additionally, injection of local anesthetic under the aponeurosis of the external oblique muscle following its closure will confer temporary analgesia to the peripheral inguinal nerves (ilioinguinal and genital branch of the genitofemoral nerve). Finally, patients are also likely to benefit from injection near the pubic tubercle and in the space just anterior to the internal oblique where the iliohypogastric nerve resides.

MINIMALLY INVASIVE INGUINAL HERNIA REPAIR

Transabdominal Preperitoneal Repair

The transabdominal preperitoneal inguinal hernia repair is performed with the patient in the Trendelenburg position tilted toward the contralateral side, which facilitates visualization of the operative field by allowing gravity to pull intrabdominal viscera cephalad. The abdomen is accessed in accordance with the individual surgeon's standard practice. The presence of a concomitant umbilical hernia is not unusual and can be utilized for entry into the abdominal cavity. Although the existence of an umbilical hernia does not preclude a TEP repair, umbilical hernia repair is a convenient adjunct to the TAPP approach when the hernia is used for initial access to the abdominal cavity. Visual inspection of both inguinal regions allows for port placement adjustment to triangulate the instruments to the target surgical site. Bilateral hernias are approached via two 5-mm

working ports placed approximately 6 cm lateral and slightly inferior to the umbilical port. For the unilateral repair, the ipsilateral 5-mm trocar is placed at the level of the umbilicus, whereas the contralateral 5-mm trocar is placed several centimeters lower than the umbilicus for ergonomic optimization (Fig. 1).

Robotic-assisted TAPP can also be performed and has emerged as the preferred approach for adopters of this platform. The operation is typically performed with two working ports placed in mirror-image locations on either side of the abdomen, at least 8 to 10 cm lateral to the midline (often supraumbilical) camera port. To reduce the risk of midline port-site herniation, the port can be directed through the rectus abdominis sheath rather than the linea alba. The patient is placed in a flexed position to maximize the working space and clearance for the robotic arms. The operative and anesthesiology teams should be cognizant of the positioning of the arms during the procedure, and the patient's upper extremities and face should be padded and protected to avoid inadvertent injury or extubation. After visualization of both inguinal sites and confirmation of the hernia(s), the mesh and suture for peritoneal closure can be inserted as appropriate before docking the robot to eliminate the later need for camera removal and repositioning to a lateral port. The robotic-assisted inguinal hernia repair can be performed with the fenestrated bipolar forceps, monopolar scissor, and suture-cut needle driver. Some variation of this instrumentation may be preferred according to the level of experience of the surgeon and the characteristics of the hernia, which may require bowel reduction with the more gentle Cadiere forceps.

Regardless of the platform, wide exposure of the myopectineal orifice (MPO) is critical to safe and effective performance of this operation. The peritoneum is opened at least 4 cm above the internal inguinal ring, from just lateral to the anterior superior iliac spine to the medial umbilical ligament, and dissection is continued posteriorly until generous exposure of the psoas muscle is achieved. Dissection should take place in the avascular preperitoneal space, just deep to the transversalis fascia. Medially, the dissection is at the parietal layer of the transversals fascia, allowing the mesh to lay along the abdominal wall with separation from the bladder and full coverage over the obturator space. Laterally, the visceral and parietal transversalis fascia and fat overlying the nerve area should be preserved to reduce the risk of neuropathic postoperative pain. Recurrences of inguinal hernias commonly occur medially and posteriorly, so great care should be taken to ensure adequate posterior and medial dissection of the preperitoneal space, which in turn allows generous overlap of the mesh. Generally, if the spermatic cord structures lift up while the posterior peritoneal flap is elevated anteriorly, the posterior dissection is likely insufficient and should be continued until the cord structures have been completely freed from this layer. In the female patient, transection of the round ligament may be necessary to allow the peritoneal flap to come down adequately for wide mesh overlap. As the genital branch of the genitofemoral nerve may join the round ligament, transection should be performed close to the attachment at the peritoneum and not near the inguinal ring to limit the risk of nerve injury. The preperitoneal pocket should extend medially to the posterior surface of the symphysis pubis and laterally to just beyond the fibers of the transversus abdominis muscle as they come into the visual field superiorly and laterally near the anterior superior iliac spine. The preperitoneal "pocket" developed should be of sufficient size to allow identification of all hernia defects around the MPO and to facilitate wide mesh coverage of the area. Generally, all efforts should be made to ensure that this space is large enough to allow the mesh to lie flat, maximizing the surface area available for integration of the mesh into the abdominal wall. It may be useful to perform the medial and lateral dissections first as this will improve the mobility of the peritoneal flap and exposure, and it may assist in reduction of the hernia sac. A circumferential "margin" of 1 to 2 cm of clearance from the inner posterior edge of the peritoneum to the edge of the mesh will prevent folding of the mesh as the peritoneum is closed.

Lipomas, which consist of incarcerated preperitoneal fat, should be fully reduced from the hernia defect as these are theoretically a source of compression and potential postoperative discomfort. Moreover, the presence of a retained lipoma could give patients the impression of a persistent hernia, diminishing their satisfaction with the outcome. The white edge of the attenuated transversalis fascia can be seen at the intersection of the spermatic cord and the lipoma, and it offers a visual cue for the proper plane of dissection (Fig. 2). Caution should be exercised to identify and preserve the corona mortis, the variably present aberrant vessels linking the epigastric and obturator arteries located below the direct defect at the ligament of Cooper. The external iliac vein should also be visible at this point, and the presence of overlying fat suggests an occult femoral hernia. If present, this should also be fully reduced before placement of the mesh.

The hernia sac at the indirect space, if present, is then dissected from the cord structures while retracting the sac cephalad. One advantage of the TAPP approach, particularly during complex cases, is that it permits visualization of herniated viscera through both the preperitoneal and peritoneal spaces, which is often useful for

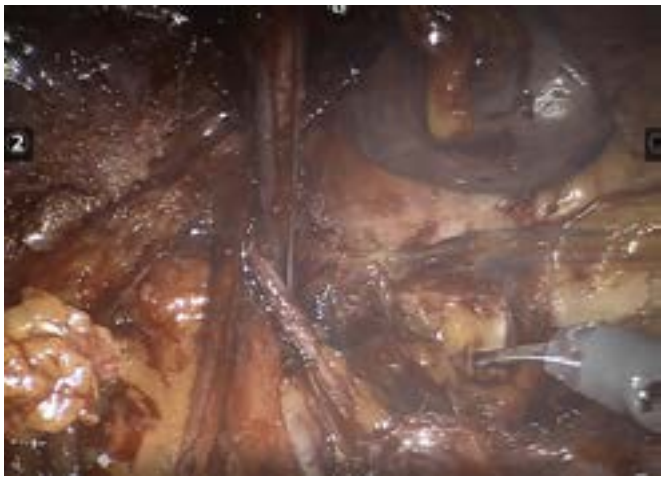


FIG. 1 Myopectineal orifice.

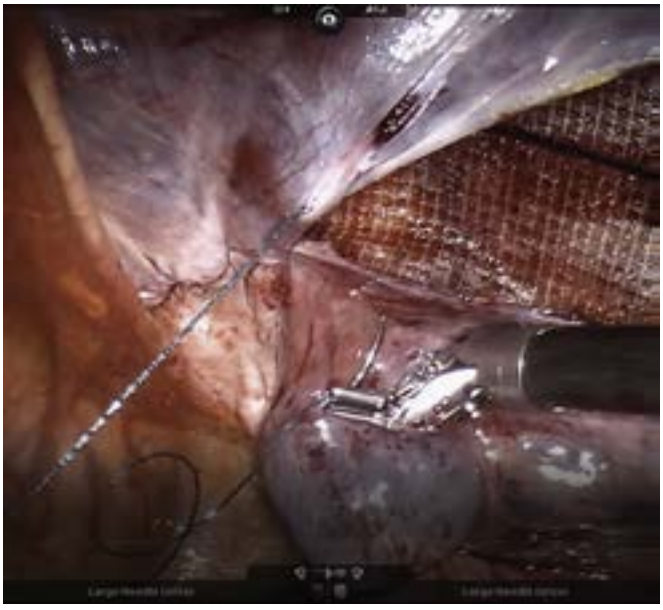


FIG. 2 The peritoneum is closed, taking care to leave no gaps through which mesh might be exposed to underlying bowel.

determining the boundaries of the sac. The cord structures should be completely freed from hernia sac attachments, which might contribute to a subsequent hernia recurrence. With large direct defects (M3 EHS designated hernia), primary closure of the hernia can be undertaken to secure the iliopubic tract, composed of thickened fibers of the inferior edge of the transversalis fascia and musculoaponeurotic transverses abdominis, to the transversalis arch superiorly with incorporation of the attenuated transversalis fascia of the direct defect. This strategy should be used with caution, however, as it risks nerve entrapment if performed too anteriorly through the muscle wall and may contribute to the development of chronic postoperative pain.

Meticulous attention to dissection can help reduce the risk of hernia recurrence. In the setting of larger direct hernias, inversion of the portion of transversalis fascia involved in the hernia not only decreases the likelihood of recurrence, but may also mitigate the potential for postoperative seroma formation. The size of the mesh selected should be large enough to offer wide coverage of the MPO as this may obviate the need for fixation in all but the largest defects. Additionally, although relatively pliant mesh is desirable, it should be substantial enough to resist herniation through the underlying defect. Lightweight mesh may not be adequate for a large indirect and particularly a large direct hernia. Mesh fixation in the setting of inguinal hernia repair is a matter of some controversy. No data currently exist that show a difference in recurrence rates directly attributable to the lack of fixation, regardless of the choice of platform. On the other hand, there exists some evidence associating fixation with both immediate and chronic postoperative pain. Given the current absence of definitive data supporting one strategy over the other, the decision to use fixation remains within the realm of surgeon preference at this time. For large defects, fixation may be prudent to prevent mesh migration or eventration.

Implanted mesh should be completely excluded from the peritoneal cavity, including the elimination of any gaps in the suture line closure of the peritoneal flaps. Tears or rents in the peritoneum that result in exposed mesh likewise should be individually closed with absorbable suture. Although popular because of the expediency of their use, the barbs characteristic of "self-locking" sutures may impose a risk of small bowel obstruction, and care should be taken to ensure that these are adequately covered with native tissue. In circumstances in which the peritoneum cannot be sufficiently closed to adequately cover the mesh, omentum can be secured over the mesh as an alternative, though there remains a risk of interparietal hernia between the peritoneum and the mesh. The medial umbilical ligament can also be mobilized and used to cover the most medial portions of the preperitoneal space if necessary.

Total Extraperitoneal Repair

Patient preparation is similar for both the TEP and TAPP approaches; the patient is placed in the supine Trendelenburg position, typically with the arms tucked as this is more convenient for pelvic laparoscopy. Patients should be asked to make an attempt to void before surgery, although some surgeons prefer the routine placement of a Foley catheter to ensure that the bladder is fully decompressed. Of note, postoperative urinary retention appears to be more common after laparoscopic and robotic-assisted repairs, particularly when bilateral repairs are performed. When this occurs, this may serendipitously denote the presence of underlying prostatic hypertrophy, and referral to a urologist might be prudent. There is also emerging evidence that the use of Sugammadex, which binds rocuronium and vecuronium, for reversal of anesthesia may prevent urinary retention. For the TEP approach, access to the preperitoneal space is gained via an infraumbilical 12-mm port. Under direct visualization, the anterior leaflet of the rectus sheath is incised just off of the midline, and the rectus muscle is split, revealing the underlying retrorectus space. This compartment is then developed bluntly, often through the use of commercially available balloon dissectors. Alternatively, this same space can be accessed while advancing an optical port under camera visualization and may be aided by ultrasound guidance. This approach is particularly useful for surgeons who prefer the use of a 5-mm port and camera. Inadvertent tears in the peritoneum during the preperitoneal dissection may occur and occasionally require closure in order to proceed. Sutures, endoscopic clips, or Endoloops may be useful for this purpose. Additionally, a Veress needle or 5-mm port can be inserted into the abdominal cavity for decompression, allowing for selective insufflation of the preperitoneal space. Large tears may prevent insufflation of the preperitoneal space altogether, necessitating conversion to a TAPP or open approach.

Insufflation pressures of 12 to 15 mm Hg are established before proceeding, and an angled laparoscope is recommended. Two 5-mm working ports are then placed in the midline under direct visualization, allowing for 5 cm between the lowest port and the symphysis pubis when possible, as well as adequate spacing between the ports. The lateral abdominal wall is identified first by bluntly dissecting away the filmy avascular tissue anterior to the hernia sac, but inferior to the epigastric artery and vein, which should be identified and preserved in situ anteriorly. Medially, Cooper's ligament is identified and cleared of any overlying fat while taking care to avoid the venous circle of Bendavid and the femoral canal inferiorly. If injury to the deep venous circulation is not recognized and addressed, the result can be hematoma formation following the release of insufflation, with substantial postoperative morbidity. The spermatic cord and hernia sac can be grasped and retracted cephalad, which facilitates dissection of the preperitoneal space and reduction of any cord lipomas that may be present.

Despite the notable benefits of a minimally-invasive procedure that does not violate the peritoneal cavity, the traditional TEP repair is limited by space constraints imposed by the architecture of the preperitoneum. These challenges are particularly exaggerated in patients with obesity, as well as those with large inguinal hernias. A modification of the conventional TEP was proposed in 2012 that substantially alleviates the difficulties associated with this limitation. (Daes, 2012) Known as the extended totally extraperitoneal repair (eTEP), this approach can be performed either laparoscopically or robotically. The primary innovation of this approach is the placement of a retromuscular optical port (12 mm laparoscopically or 8 mm robotically) in the upper quadrant on the same side as the hernia. This strategy takes advantage of the presence of the posterior rectus sheath above the arcuate line, which resists tearing, and promotes a much larger space in which to work. The retrorectus space is then dissected, either using a commercially available balloon dissector, or bluntly using the camera itself, taking care not to injure or disrupt the lateral neurovascular bundles or the linea semilunaris. Following this dissection, the space is insufflated to a minimum of 12 mm Hg pressure. In the original description of the procedure, 5-mm working ports were placed along the midline at the umbilicus and approximately halfway between the umbilicus and the symphysis pubis. However, a variety of port placement strategies can be successfully utilized depending on the presence of bilateral disease, a large unilateral hernia, or surgeon preference.

The next key step in the procedure is division of the arcuate line, granting access to the preperitoneal space in the lower abdomen and pelvis. The hernia can then be identified and reduced, and the mesh can be placed as with a traditional TEP. This approach results in a markedly expanded view of the preperitoneal space, with ample additional room in which to work. Though originally described in the endoscopic treatment of inguinal hernias, the approach has become the basis for a multitude of retromuscular repairs of other hernia types, including midline ventral, incisional, and lumbar. There are limitations to the approach, however. Under the best of circumstances, eTEP is technically challenging. Development of the retromuscular space can be especially problematic in patients in whom this space has been damaged, such as those with prior history of colostomy or ileostomy. Additionally, eTEP should not be attempted in patients in whom retromuscular mesh is present.

TAPP VERSUS TEP?

The International Guidelines for Groin Hernia Management published by the HerniaSurge Group in 2018 and subsequently endorsed by multiple international hernia societies largely considers TAPP and TEP equivalent operations with similar operative time and cost, complication profiles, and recurrence rates. Conversion to open is more likely with a TEP approach, although this remains a relatively infrequent occurrence. Visceral injuries, while rare, are more common with the transabdominal approach, while the risk of vascular injuries is increased with the totally extraperitoneal approach. Port-site hernias are quite uncommon but tend to occur at the umbilical port. Given the similarities between the two approaches described here, the choice of technique should consider the surgeon's skills, training, and experience.

Some situations may be better suited for one approach over the other, however. For example, recurrent hernias following laparoscopic TEP may be more easily addressed via TAPP or an open (anterior) approach. TEP may be favorable in the setting of bilateral hernias given that there is no need for a peritoneal closure. Patients with prior surgery on the lower abdomen or pelvis, particularly when performed through a midline laparotomy incision; patients with a scrotal hernia, prior prostatectomy, or recurrence after previous use of a mesh plug; and patients in whom diagnostic laparoscopy would be beneficial may be preferred candidates for a TAPP procedure.

Risk Factors for Inguinal Hernia Development and Recurrence

Patients with a family or personal history of inguinal hernia or prostatectomy, those of older age, male patients, and patients with collagen disorders resulting in decreased levels of mature type I collagen are at an increased risk of developing an initial inguinal hernia. Interestingly, obesity appears to be protective, as lower body mass index (BMI) is associated with a higher incidence of inguinal hernia, although this could be caused by a discrepancy in the rate of diagnosis. Factors related to surgical technique also appear to make a significant contribution to the overall risk of recurrence, as does surgeon volume, which is inversely related to recurrence rates. Direct and sliding hernias, in which part of the hernia sac is formed by the wall of a retroperitoneal organ, are likewise associated with poorer outcome. For reasons not completely understood, female patients are more likely to develop a recurrence.

CHRONIC PAIN AFTER INGUINAL HERNIA REPAIR

Chronic pain after inguinal hernia repair has emerged as the most common complication of this operation, with rates ranging from 11% to 18%. Conventionally known as chronic post-herniorrhaphy pain syndromes, these are defined by surgery-related pain that persists beyond 3 months after the initial operation. This risk is higher with open approaches, and an effort should be made to identify the ilioinguinal, iliohypogastric, and genital branch of the genitofemoral nerves during open repairs with the intent of avoiding direct retraction of the nerves or injury to the perineurium. An international group of hernia experts convened in 2011 for the purpose of developing guidelines for the prevention and management of chronic pain after inguinal hernia surgery. The group found in a literature review that identification and preservation of all three peripheral nerves of the inguinal region reduced the risk of postsurgical pain syndromes to less than 1% (Alferi, 2011). If an injury to one of these nerves is suspected at the time of repair, a neurectomy proximal to the site of injury should be considered and the cut end implanted into muscle if performed. When tacks are used for fixation during laparoscopic repairs, these should not be implanted too deeply into the muscle to avoid injury to superficial nerves not visible from the posterior approach. Similarly, surgeons should consider performing "air knots" if suture fixation is utilized as this may help prevent nerve entrapment.

CONCLUSION

Elective repair of symptomatic inguinal hernias is recommended; however, observation is appropriate in those patients with no discernible symptoms. The choice of minimally invasive or open techniques is primarily driven by surgeon preference, and the use of synthetic mesh significantly reduces the rate of hernia recurrence. The most common complication of inguinal hernia repair is the development of a chronic post-herniorrhaphy pain syndrome, the risk of which appears to be increased with the use of mesh and tack fixation. The risk of chronic pain must be balanced against that of recurrence in a thoughtful and transparent preoperative discussion with the patient regarding the necessity of repair and the available options.

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Management of Recurrent Inguinal Hernia

Britta Jean Han, MD, MS, and Bethany C. Sacks, MD, MEd

INTRODUCTION

Inguinal hernia surgery is one of the most common general surgery procedures performed in the United States. Recurrence rates after repair have been reported to be as high as 17%, with primary nonmesh repairs having even higher recurrence rates. Rates may be even higher than reported as long-term follow-up in the hernia population is often limited. Regardless, recurrent inguinal hernias are a problem that every general surgeon will encounter in training and practice (Fig. 1).

RISK FACTORS FOR RECURRENCE

The etiology of recurrent inguinal hernias is complex and often multifactorial. Risk factors for recurrence include nonmodifiable and modifiable categories. Nonmodifiable risk factors include genetics such as connective tissue metabolism disorders, the type and location of inguinal hernia (direct vs. indirect, femoral), and female gender. In the following sections, we detail modifiable risk factors for recurrence, which are categorized into (1) patient factors, (2) technical factors, and (3) mesh factors. All factors should be aggressively optimized before repair of the recurrent hernia as each subsequent repair will increase the risk of hernia recurrence.

Patient Factors

Several critical patient risk factors for hernia recurrence are those related to delayed wound healing. These factors include smoking, obesity, glucose control, and immunosuppression.

The deleterious effects of smoking on wound healing are well known and documented. Smoking affects tissue oxygenation and aerobic metabolism and prolongs the effect of inflammation on healing. This ultimately delays wound healing and increases the risk for surgical site occurrences such as wound infection, hematomas, or seromas, which all contribute to an increased risk of hernia recurrence. Of note, although nicotine replacement therapies seem to attenuate the inflammation phase of wound healing, these effects appear to be marginal according to a recent large observational cohort study and are also not associated with adverse postoperative outcomes. Thus, nicotine replacement therapies can be considered for patients who struggle with smoking cessation before undergoing redo repair.



FIG. 1 Recurrent inguinal hernia.

Obesity impacts risk of recurrence in two ways. First, increased mechanical strain and tension on the initial repair increase the risk of hernia recurrence. Second, obesity increases the risk of wound infection, another independent risk factor for recurrence. In fact, increasing body mass index (BMI) is associated with significantly increasing rates of surgical site infections.

Poor glucose control is also a well-known contributing factor to poor postoperative wound healing. Hyperglycemia impairs neutrophil bactericidal activity and increases the risk of wound infection. Data suggest that for every 40-point increase from normoglycemia, there is a 30% increase in the rate of postoperative infections. Similarly, the use of immunosuppressive agents affects wound healing and increases the risk of wound infection.

Technical Factors

Several key technical factors contribute to hernia recurrence. One is the failure to achieve a tension-free repair. The use of mesh is considered the gold standard because of its ability to provide a tension-free repair. Thus, primary tissue repair techniques such as Bassini, Halsted, and McVay have a 50% to 75% higher recurrence rate than mesh repairs. In recent meta-analyses and systematic reviews, recurrence rates by mesh weight are not significantly different.

Other technical factors include inadequate dissection and reduction of the hernia sac or failure to identify concurrent indirect or direct hernia during the primary repair. Additionally, failure to resect a cord lipoma can present as pseudo-recurrence, so lipomas should be resected or adequately reduced during the initial repair.

Finally, an ongoing debate centers around whether laparoscopic inguinal hernia repair is associated with higher rates of recurrence compared with the Lichtenstein open hernia repair. The data remain inconclusive. However, studies demonstrate that surgeon experience is most important in consideration for open versus laparoscopic repair. That is, recurrence rates for laparoscopic repairs decrease as surgeon experience with laparoscopy increases.

Mesh Factors

As previously mentioned, tension-free mesh repairs remain the gold standard. Additionally, mesh products have evolved since their first inception and use. However, there remain several mesh factors that may contribute to recurrence. These factors include mesh shrinking after placement, mesh migration, mesh resorption, and mesh folding. Although any of these mesh events can occur even under the best of repairs, they highlight the importance of thoughtful mesh placement in the primary repair.

PREOPERATIVE EVALUATION

Recurrent inguinal hernias are complex cases and warrant careful preoperative workup and operative planning. Native tissue planes and anatomy have often been distorted or obliterated because of scar tissue and prior mesh use, making repeat dissection challenging. This is particularly true in patients with multiple recurrent inguinal hernias.

Defining Recurrent Inguinal Hernia

Recurrent inguinal hernias that present within the first 3 to 6 months after primary repair are considered *early recurrences*. Patients presenting with recurrences after 6 months are considered *late recurrences*. Traditionally, early recurrences were often attributed to technical factors, and late recurrences were attributed to patient factors. However, this is not always the case. Both early and late recurrences can be caused by either technical, patient, or mesh factors (as described earlier).

Patient History and Physical Examination

When patients present with a chief concern of recurrent inguinal hernia, a careful history and physical examination is crucial. Although some patients will present with an acute change to the groin (e.g., new bulging sensation, groin pain, or visible bulge), other patients will be asymptomatic. A detailed history, physical examination, and judicious use of imaging can help delineate a recurrence from other diagnoses that can present with similar symptoms.

When a recurrent hernia diagnosis is confirmed, a thorough history of the inguinal hernia is important. The history should include any potential eliciting events to recurrence, number of prior recurrences with repair, history of mesh repair, and types of repairs performed. Ideally, the operative note(s) from the prior repair(s) will include details of the type of mesh used, the type of repair performed, and the dates of repairs. Finally, a history of surgical site infection and complex wound healing should be documented, especially a history of methicillin-resistant *Staphylococcus aureus* (MSRA). This should be accounted for in antibiotic prophylaxis if the patient undergoes recurrent inguinal hernia repair.

Other components of the patient history should assess for risk factors listed previously. These should subsequently be optimized if the patient undergoes redo repair. Furthermore, these risk factors, in conjunction with other parts of the patient history, may determine whether a patient should undergo a redo operation at all.

Although physical examination will be like that of a primary inguinal hernia, there are several examination maneuvers that may help distinguish a recurrent hernia from other diagnoses. In general, pain from a recurrent hernia can be elicited by palpating directly over the bulge or defect. Pain that is elicited with hip rotation or flexion/extension is generally not from a recurrent hernia. Constant pain can also have multiple etiologies that may be related to prior hernia repair (e.g., suture tacking, mesh fixation) but not actual hernia recurrence.

Role of Imaging

Although a history and physical examination may be sufficient to diagnose recurrent hernia, adjunct use of imaging can be helpful in both diagnosis and preoperative planning. When clinical diagnosis of recurrent hernia is difficult or the patient has a complex or unclear hernia history, imaging may be required.

Clinically difficult to diagnose hernias are defined as *occult hernias* in literature. These hernias can present with chronic pain without a recurrent or palpable bulge. In these patients, imaging will be crucial to diagnosis. Traditionally, ultrasound is used as first-line imaging with computed tomography (CT) as follow-up imaging if ultrasound is inconclusive. However, in particularly challenging diagnoses such as occult hernias or complex clinical presentation, magnetic resonance imaging (MRI) can be used to further elicit a diagnosis. In one study, MRI demonstrated the highest sensitivity, specificity, and negative predictive value for occult hernias when compared with ultrasound and CT. In addition, MRI has increased sensitivity for neuromas or issues with implanted mesh.

Management of Patient Expectations

Management of patient expectations is an important component for counseling patients with recurrent inguinal hernias. Patients should be made aware of the higher risk of complications in redo operations. Pain, particularly chronic pain, is a common symptom in both primary inguinal hernias and recurrent inguinal hernias. An honest conversation about pain will help prevent unrealistic postoperative expectations. Some patients will continue to experience chronic pain, even after a redo repair, or they may experience worsening pain because of the increased risk for nerve injury and damage to surrounding structures. Being realistic about the pain and potential for continued chronic pain can help allay patient disappointment or dissatisfaction after redo repair.

In addition to management of expectations around pain, patients should also be well informed that recurrence rates after redo operations are even higher, regardless of the type of technique or mesh used.

Management of Asymptomatic Recurrent Inguinal Hernia

Not all recurrent inguinal hernias must be repaired immediately. A randomized multicenter trial in 2006 demonstrated that watchful waiting is an appropriate option for male patients with asymptomatic or minimally symptomatic inguinal hernias. This study found strangulation risk to be rare, with no significant changes to rates of postoperative complications. Of note, this study did not follow female patients. In this select group of patients, there may be time for not only watchful waiting, but also careful planning and, if needed, prehabilitation and optimization before undergoing a redo operation. Symptomatic patients should undergo repair (Fig. 2).

TECHNIQUES FOR REPAIR OF RECURRENCE

Regardless of approach, all risk factors should be aggressively optimized, particularly smoking and obesity. If the patient is asymptomatic, more time is available for preoperative optimization.

Repair of a recurrent inguinal hernia is complex and often more difficult than the initial operation because of distorted tissue planes and scar tissue. The cornerstones of recurrent inguinal hernia repair include (1) reinforcement of the entire inguinal canal, regardless of the size and location of recurrence, and (2) approaching the repair through unviolated tissue planes when possible.

Minimally Invasive Approaches

Minimally invasive approaches are useful when a recurrence occurs following an open (anterior) inguinal hernia repair. This allows for surgeons to utilize unviolated native posterior tissue for dissection and mesh placement. However, as surgeons gain experience and comfort with laparoscopic approaches, many surgeons will approach a recurrent inguinal hernia with a laparoscopic approach regardless of the prior technique used. An additional advantage of laparoscopic re-repair is the ability to view all potential sites of recurrence and to examine the contralateral side for hernia presence. A recent retrospective study found that 96% of patients successfully underwent a second laparoscopic inguinal hernia repair for recurrent hernia with low rates of late re-recurrence.

The most frequently utilized laparoscopic techniques include transabdominal preperitoneal repair (TAPP), total extraperitoneal repair (TEP), or extended-view total extraperitoneal repair (e-TEP). The approach will depend on surgeon preference and experience, patient surgical history, and hernia size. In a recent randomized prospective study, no differences were noted between the TAPP

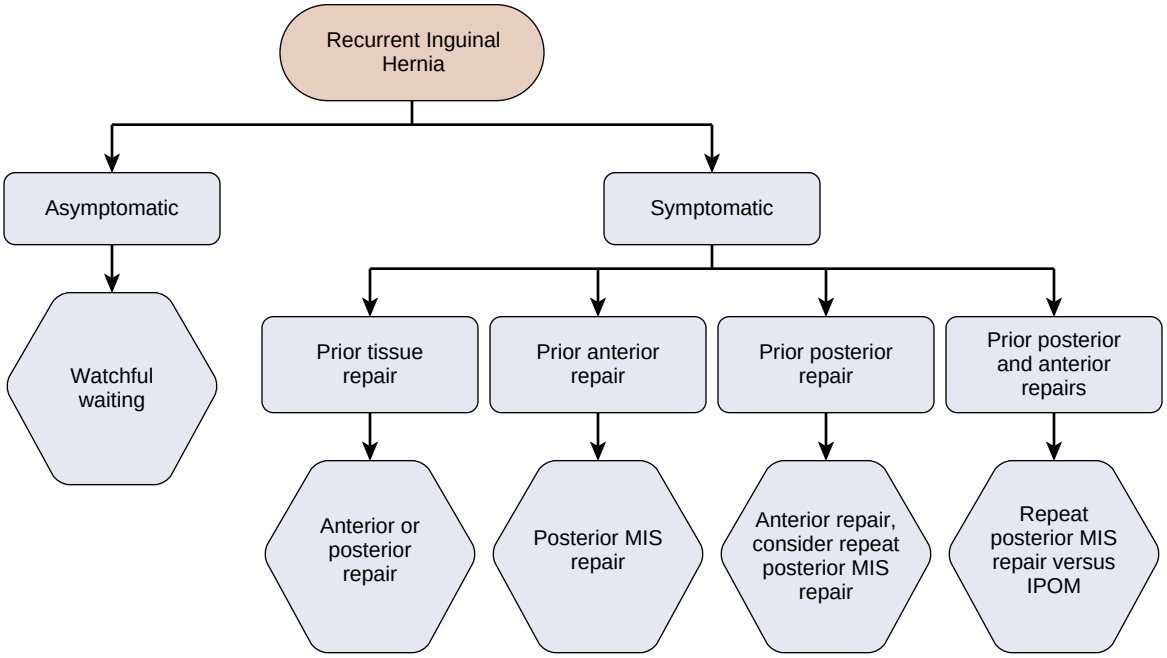


FIG. 2 Algorithm for management of recurrent inguinal hernia. *IPOM,* Intraperitoneal onlay mesh; *MIS*, minimally invasive surgery.

and TEP approaches in regard to quality of life, chronic groin pain, resumption of normal activities, or cost. TEP and e-TEP repairs minimize intraabdominal adhesions. Dissection of the preperitoneal tissue plane can be more challenging in patients with prior repairs and may lead to tearing of the peritoneum. In these cases, conversion to TAPP may be warranted. Thus, any surgeon attempting a TEP approach should be comfortable with both TEP and TAPP techniques. In particularly large and/or difficult to reduce recurrent hernias (e.g., inguinoscrotal), the TAPP approach provides improved visualization of incarcerated contents with concurrent ability to reduce the contents.

Finally, in the case of difficult exposure or dense adhesions, conversion to open anterior or posterior repair is an option.

Open (Anterior) Approaches

An open (anterior) approach can be considered for a patient with a prior posterior repair for the ipsilateral inguinal hernia (e.g., TAPP) to avoid previously dissected tissue. The most utilized technique is the Lichtenstein repair (tension-free mesh repair), though some surgeons will use an open preperitoneal repair (e.g., Stoppa).

Other tissue-based repairs should be avoided when possible unless mesh is absolutely contraindicated, such as in the case of an active infection.

The Complex Recurrent Inguinal Hernia Patient

Some patients will present with a multiply recurrent inguinal hernia. These patients may have undergone both open and laparoscopic repairs. Prior mesh may exist in more than one plane. Thoughtful preoperative evaluation should be completed with attempts to review all prior operative notes. These patients should undergo expectation management as risk of recurrence and postoperative complications increases with each subsequent repair. Additionally, these patients should be considered for referral to a high-volume, specialized hernia center for redo repair.

For these patients, a laparoscopic approach is recommended as the initial approach. A diagnostic laparoscopy is helpful in identifying the direct, indirect, and femoral spaces and can provide improved visualization.

Finally, an intraperitoneal onlay mesh (IPOM) repair can be considered in the event that a repeat TAPP repair is difficult or the peritoneum is insufficient for mesh coverage. The mesh for these repairs is coated permanent mesh with an anti-adhesive barrier. Generally, IPOM is often considered a last resort after open and other laparoscopic approaches.

Mesh Considerations

There is no clear consensus on the management of mesh from prior repairs. Some surgeons will advocate for removal of prior mesh whenever possible. If complete mesh resection is not feasible, it is ideal to remove as much as possible. This may facilitate new mesh placement. In our experience, the removal of prior mesh is often difficult, if not impossible, and often not necessary. Regardless, it is important to manage patient expectations around pain and discomfort thought to be secondary to either old mesh and/or recurrence.

Mesh should be used in repairs of recurrent inguinal hernias. Patients presenting with hernia recurrence will already have weaker tissue because of prior repair and have a high likelihood of wound-healing abnormalities. The rare case of infected mesh is the only situation that may preclude the use of mesh. Traditionally, biologic mesh has been reserved for use in contaminated cases. Lightweight polypropylene mesh is an ideal option because of decreased pain, decreased mesh sensation, and increased ingrowth of mesh, leading to a more durable repair. Standard weight polypropylene may be considered for larger hernias that require a wider bridged repair to minimize the risk of postoperative mesh eventration or recurrence.

Finally, there is no clear consensus on the role of mesh fixation in laparoscopic inguinal hernia repair. Some surgeons believe fixation can prevent mesh migration, folding, and recurrence, while other surgeons believe fixation only causes increased postoperative pain resulting from potential nerve injury. There is yet to be definitive data.

CONCLUSION

Recurrent inguinal hernia cases are complex and should not be taken lightly. Thoughtful preoperative evaluation and operative planning are crucial for recurrence risk optimization. Operative planning and approach should incorporate patient history and surgeon experience with plans for alternative intraoperative approaches if the initial selected approach cannot be safely completed. For patients with particularly complex recurrent hernias, consideration should be given to referring the patient to a high-volume specialized hernia center for evaluation and repair.

Suggested Readings

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Incisional, Epigastric, and Umbilical Hernias

Hien T. Nguyen, MD, MBA, and Katherine McDermott, MD

Incisional, epigastric, and umbilical hernias account for the majority of ventral abdominal wall hernias. Over 400,000 ventral hernia repairs occur annually in the United States, with a trend toward more minimally invasive and outpatient procedures. Incisional hernias may develop in up to 28% of patients who have undergone laparotomy, which leads to a hospital cost of over $3 billion per year in the United States. Though VHR is a common surgical problem, it includes a wide spectrum of hernia size, complexity, and morbidity. Surgeon experience of 40 or more cases per year is associated with a 30% to 40% lower rate of reoperation for recurrence compared with low-volume hernia surgeons.

Ventral hernias are generally repaired in the elective setting, and a watchful waiting approach may be appropriate for asymptomatic patients. Approximately 10% to 15% of patients under watchful waiting will cross over to require hernia repair. Factors associated with crossover include recurrent hernias, enlarging hernias, and BMI >30. There are no differences in outcomes and complications between patients who undergo initial surgery and elective crossover surgery, with low rates of emergent repair at 5 years among patients who participate in watchful waiting.

PATIENT SELECTION

Smoking, diabetes, obesity, and COPD are the four most consistently demonstrated modifiable patient factors associated with recurrence or wound complication. Chronic smokers have a risk of surgical site infection (SSI) up to 50% higher compared with nonsmokers, but smoking cessation 4 weeks preoperatively is associated with decreased SSI; nicotine replacement therapy does not seem to diminish this benefit. There is significantly increased risk of 30-day SSI in patients with HbA1c >8.0%, but no clear increased risk of long-term complications. HbA1c is a better indicator for infection than a single glucose reading or insulin dependence. In our practice, the ideal preoperative goal of HbA1c is less than 7.0%, with >8.0% being a relative contraindication for elective repair. Recurrence rate is approximately 30% among patients with a BMI of 30 to 40 and up to 50% among those with a BMI greater than 40. A total body weight reduction of 7% may lead to a 50% absolute risk reduction in wound complication rate. COPD carries a twofold increased risk for recurrence and fourfold increased risk for postoperative respiratory insufficiency; therefore, preoperative optimization by a pulmonologist is recommended.

Cirrhosis with ascites is associated with rates of umbilical and ventral hernia of up to 20% and a high risk of hernia complications as a result of poor nutrition and increased intraabdominal pressure. Inability to medically manage ascites is a relative contraindication to elective surgery, but elective repair of small and symptomatic hernias in optimized cirrhotic patients appears to be safe. Those who do not undergo elective repair have a 45% chance of requiring urgent repair, with a 15% mortality related to complications from urgent hernia surgery. Predictors of poor outcomes include high MELD or advanced Child classification, varices, age >65 years, and albumin <3.0. Synthetic mesh can be used in complicated hernias in cirrhotic patients with significant reduction in recurrence risk, but with slightly higher rates of SSI compared with primary nonmesh repair. In cirrhosis without ascites, laparoscopic ventral hernia repair may have fewer wound-related complications and shorter hospital length of stay compared with open repair, with similar rates of bleeding complications and reoperation or readmission. However, in patients with ascites, laparoscopic VHR is associated with higher mortality, complications, and reoperation compared with open hernia repair.

In pregnant patients with ventral hernias, the presence of a hernia is not associated with birthing complications. A nonmesh repair is appropriate for smaller primary ventral hernias in women who plan future pregnancies as mesh is associated with increased pain in subsequent third trimesters. It is safe to perform a primary repair concomitantly with cesarean section with no increase in rates of wound complications. Indications for emergent repair in pregnant patients are the same as in nonpregnant patients, with similar rates of complications and recurrence.

Nonelective VHR typically occur in the setting of incarceration or strangulation. Elevated white blood cells or lactic acid can aid in identifying patients with incarcerated hernias who require emergent surgery, but the specificity of a relatively normal white blood cell or lactic acid does not rule out ischemic bowel. Patients with strangulated hernias have lower postoperative complications and shorter operative times when taken to surgery within the first day of admission, with the goal of removing the source of sepsis. Bowel resection

with bridge repair is an acceptable strategy, as is a second-look laparotomy. Vicryl bridge mesh can be used if omentum can be placed between mesh and intestines to minimize the risk of fistulization. A biological mesh bridge may provide the best tensile strength and lower the risk of having a mesh nidus for infection. In some circumstances, it is safest to reapproximate the skin and intentionally leave a large fascial defect to allow the patient to recover before attempting a fascial repair.

SURGICAL CONSIDERATIONS

Medical and surgical history, amount of herniated tissue, quality of the deep fascial layers, and the width of the defect are considerations for choosing the optimal repair. Large hernia sacs, the need to remove extensive mesh, or the likelihood of forming a large lipocutaneous bulge after fascia reapproximation are best addressed via an open approach. Robotic surgery allows for more facile dissection and development of planes such as a pre-peritoneal approach versus laparoscopy; impact on clinical outcomes has not been demonstrated, but mesh placement in the pre-peritoneal space may decrease the risk of adhesions, enterocutaneous fistula, and mesh infection compared with intraperitoneal onlay mesh (IPOM). Defects that are less than 6 cm wide may be repaired with fascial reapproximation, while defects 7 to 9 cm wide may be good candidates for a retrorectus repair. Defects 10 to 14 cm wide may require a component separation, and anything wider than 16 cm may require a bridged repair. Changes in plateau pressure of more than 6 mm Hg or peak airway pressures more than 12 mm Hg after fascial reapproximation is associated with an increased risk of postoperative acute kidney injury, prolonged intubation, and abdominal compartment syndrome.

Hernias greater than 1 cm have lower recurrence rates with mesh reinforcement, and selection of mesh type and placement is based on the characteristics of the patient and the hernia (Fig. 1). Synthetic mesh is broadly characterized by weight (light to heavy) and level of porosity (microporous vs. macroporous), the combination of which will affect its strength, rigidity, elasticity, and ability to incorporate into tissue. It is ideal for clean cases but can be considered in some contaminated cases with mesh placement preferably in the retrorectus or pre-peritoneal space. Biologic mesh allows for rapid tissue ingrowth and is safe when placed in contact with intra-abdominal organs, even in contaminated cases, but it is more expensive and has a higher rate of seroma formation and recurrence after 3 years, especially when used as a bridge repair. Regarding mesh fixation, there is no difference in chronic pain, recurrence rate, or seroma/hematoma occurrence between tacking and transfascial suturing. There is also no difference in chronic pain or recurrence between absorbable and nonabsorbable tacks. Fibrin sealant has less acute postoperative pain, but higher recurrence rates at 1 year, and may be reasonable to use with epigastric hernias requiring mesh placement on portions of the diaphragm.

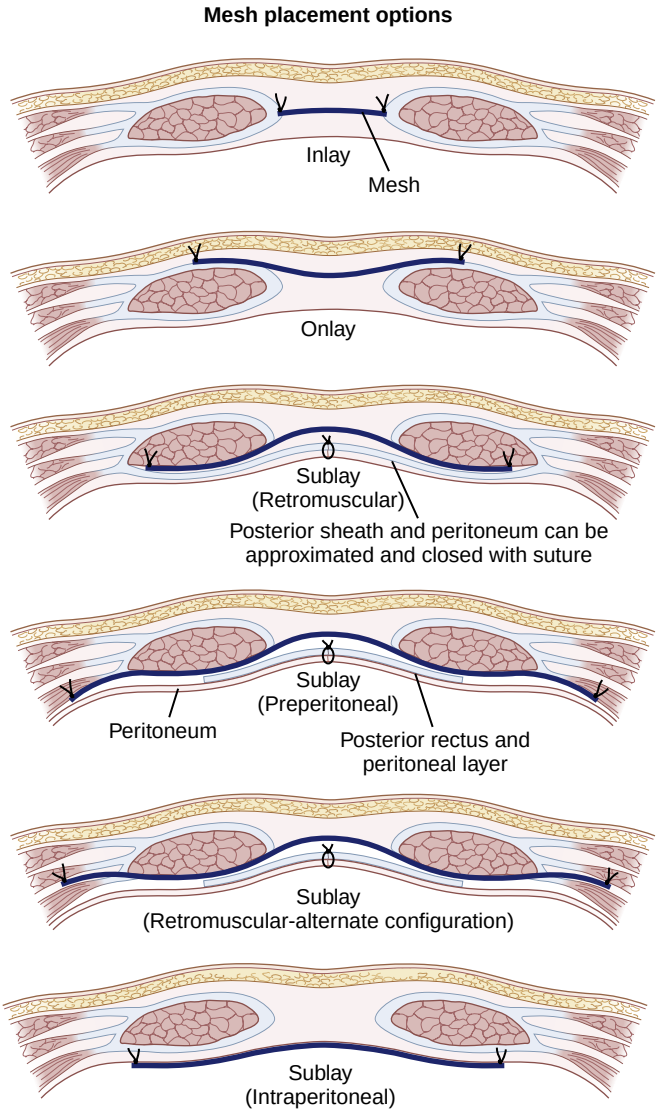


FIG. 1 Mesh placement options for abdominal wall hernia surgery. *(From Townsend CM, Beauchamp RD, Evers BM, Mattox KL, et al.* Sabiston Textbook of Surgery. *21st edition. St Louis: Elsevier; 2022.)*

OPEN SURGICAL REPAIR OF INCISIONAL HERNIAS

An open repair of smaller hernias has the advantage of allowing manual examination and reduction or excision of the herniated tissue. After reapproximation of the fascia, an onlay macroporous synthetic mesh can be secured to the myofascial layer with a 3- to 5-cm overlay.

An open retrorectus repair is appropriate for larger defects, whereby the posterior rectus fascia is divided off the rectus abdominis muscle along the length of the incision while preserving as much of the hernia sac as possible. Blunt lateral dissection toward the semilunar line can be performed, identifying and preserving the perforator vessels and the epigastric vessels adjacent to the semilunar line. Dissection below the arcuate line will include separation of peritoneum off the rectus muscle, and this plane will be continuous with the prevesical or retropubic space of Retzius medially and to the retro-inguinal space of Bogros laterally (Fig. 2). Bilateral separation of the posterior rectus sheath should allow re-creation of the linea alba with minimal tension. The posterior rectus sheath and peritoneum is reapproximated with 2-0 running polyglactin suture, and large gaps can be patched with omental tissue or polyglactin mesh. A retrorectus repair is commonly performed with mesh reinforcement placed within the retrorectus space. Typically, 4 to 6 polydioxanone (PDS) transfascial sutures are then placed on the periphery of the mesh to secure it to the anterior rectus sheath using a suture passer device. Drains should be considered with biologic mesh and should be placed between the mesh and rectus abdominis muscles. Running looped PDS is used to reapproximate the linea alba in patients with healthy fascia; otherwise, interrupted figure-of-8 sutures should be considered.

A component separation is appropriate if the retrorectus release does not allow for a tension-free repair. It is commonly performed via division of the external oblique aponeurosis or the transversus

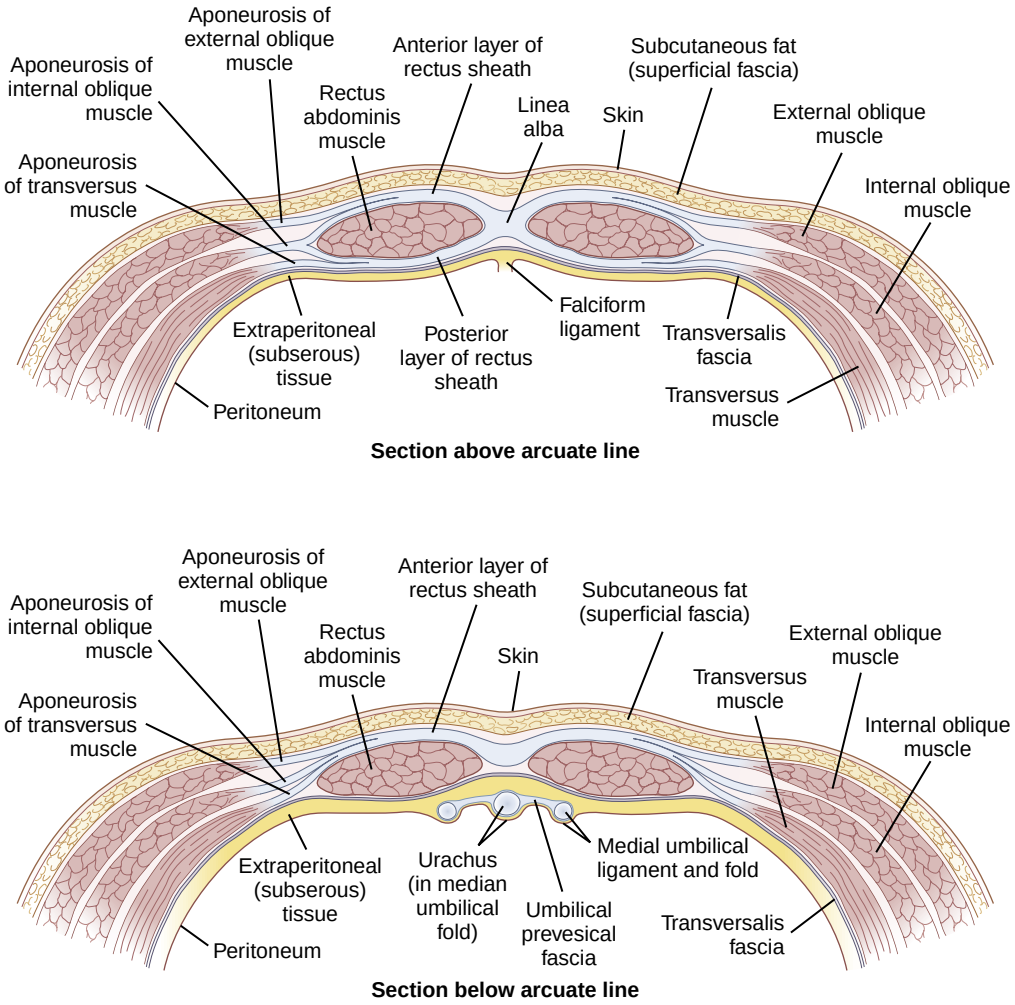


FIG. 2 Anatomic differences superior and inferior to the arcuate line. *(From Netter FT. Atlas of Human Anatomy. Summit, NJ: Ciba-Geigy; 1989: Plate 235.)*

abdominis, but never both at the same time in order to minimize destabilization of the abdominal wall. The anterior component separation involves elevation of lipocutaneous flaps laterally past the semilunar line and release of the external oblique aponeurosis longitudinally 2 cm lateral to the semilunar line (Fig. 3). Blunt separation of the external oblique muscle from internal oblique fascia is carried past the mid-axillary line, allowing rectus abdominus reapproximation with minimal tension. Mesh is secured to the divided lateral edges of the external oblique fascia using 0-PDS in interrupted fashion. Drains are placed above the anterior rectus sheath to evacuate the seroma that accumulates from the lipocutaneous flap. The dermal/subdermal scar tissue should be excised to healthy skin to minimize the risk of wound necrosis. Alternatively, a posterior component separation/transversus abdominus release (TAR) is performed by dividing the transversus abdominus muscle at the superior portion of the retrorectus release, looking for the transversus abdominis muscle extending medially past the semilunar line (Fig. 4). This posterior lamella of the internal oblique and transversus abdominus muscle body is then divided 2 cm medial to the semilunar line, avoiding the neurovascular bundles. Iatrogenic division of the semilunar line may cause a Spigelian hernia and denervation of the rectus muscle. Extension inferior to the arcuate line past the posterior rectus sheath requires dissection into the pre-peritoneal space and is continued inferiorly toward the prevesical space of Retzius to mobilize the bladder off the pubic tubercle as needed. Afterward, blunt dissection is used to separate the transversus abdominis muscle from the peritoneum laterally past the mid-axillary line. The posterior rectus sheath is then reapproximated as described in the retrorectus approach, and a 30-cm × 30-cm mesh in diamond configuration or 50-cm × 50-cm mesh in rectangular configuration is placed in the retrorectus space and secured to the divided lateral edges of the transversus abdominus muscle, requiring 6 to 8 transfascial sutures of 0-gauge PDS suture placed in the periphery of the mesh to secure it. Drains are placed between the rectus muscle and mesh, followed by reapproximation of the linea alba with running 0-looped PDS.

A bridge repair is necessary with extremely wide defects and can be performed with biologic or medium-weighted synthetic mesh secured to the fascial edge using interrupted PDS U-stitch suture with 1-cm suture distance. Reapproximation of healthy skin to cover the mesh is prioritized to minimize the risk of fistula and infection.

LAPAROSCOPIC/ROBOTIC APPROACH

Minimally invasive surgical techniques are ideal for midline hernias less than 6 to 8 cm wide. In a laparoscopic approach, entry at Palmer's point is used for midline hernias and obese patients. Additional trocars are positioned laterally on the abdominal wall with at least a 10-cm distance from the edge of fascial defect. After reduction of the herniated tissue, the fascia is reapproximated with a suture passer device and 0-PDS in interrupted figure-of-8 fashion. An IPOM repair is then performed by placing and tying a U-stitch in

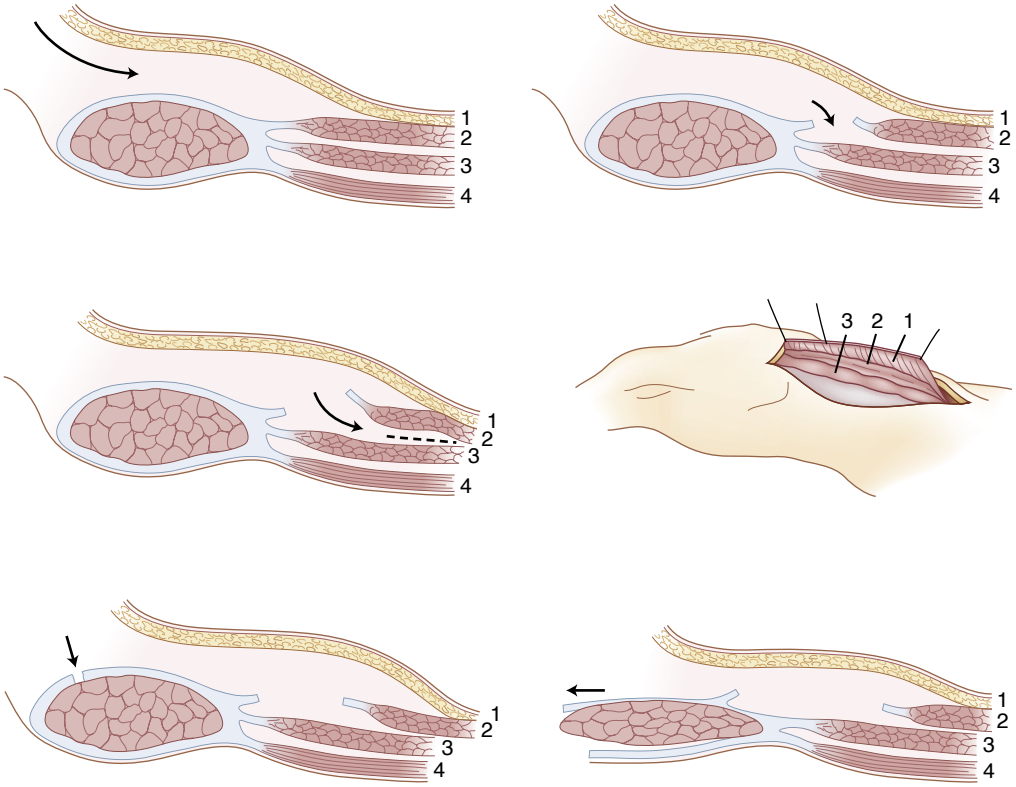


FIG. 3 Open external oblique release. *(From de Vries Reilingh TS, van Goor H, Rosman C, et al. Components separation technique for the repair of large abdominal wall hernias.* J Am Coll Surg. *2003;196:32–37.)*

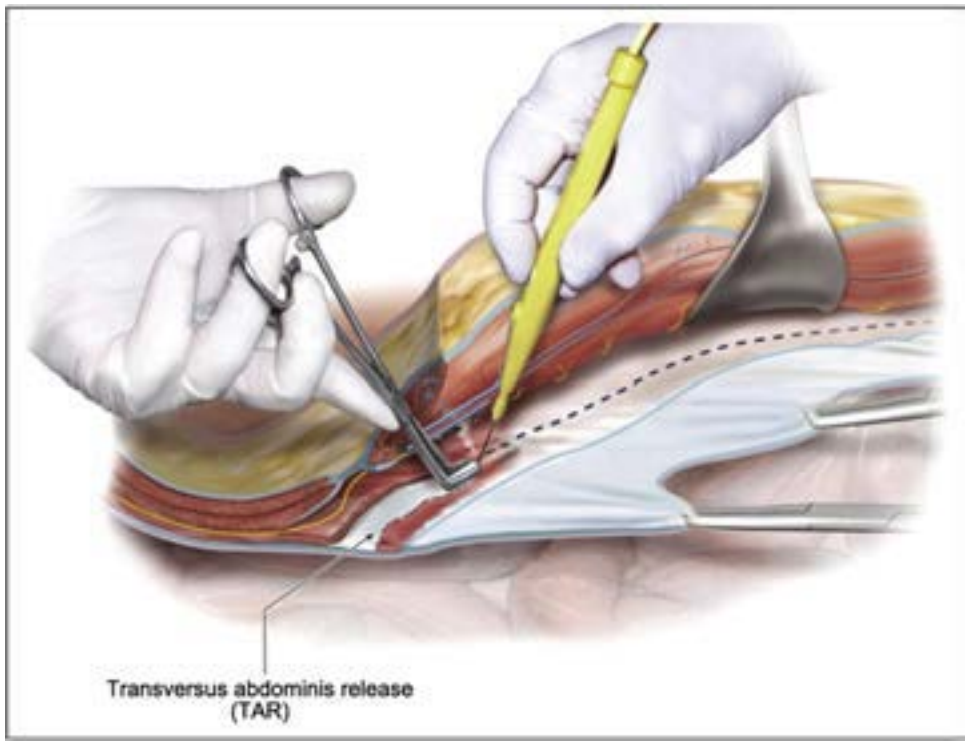


FIG. 4 Open transversus abdominis release *(TAR).* *(From Rosen M, ed.* Atlas of Abdominal Wall Reconstruction. *New York: Saunders; 2011).*

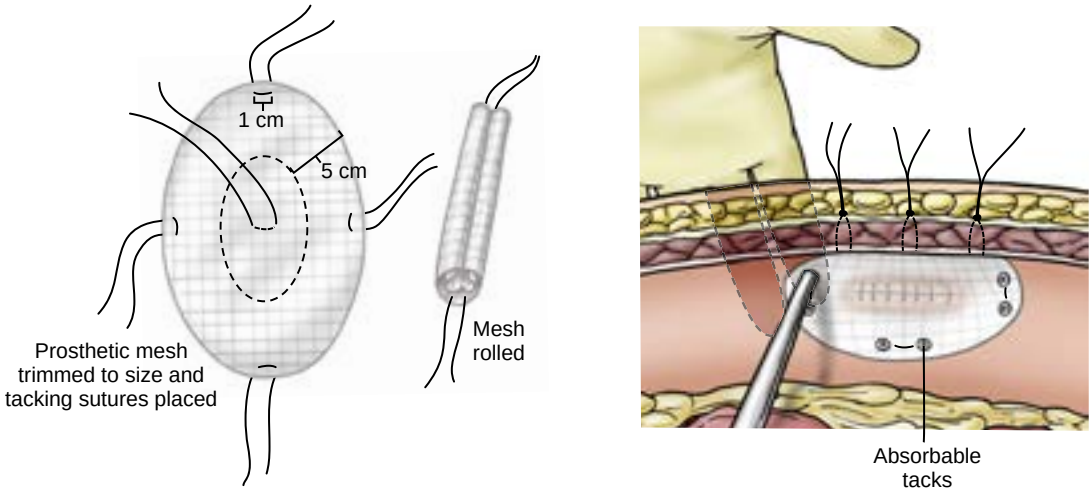


FIG. 5 Laparoscopic placement of intraperitoneal onlay mesh.

the center of the mesh on the noncoated side before introducing the mesh into the abdominal cavity; this can later be used to position the mesh directly posterior to the center of the reapproximated fascia. Additional sutures can be placed peripherally at the cardinal points on larger mesh to secure the mesh to the abdominal wall. Absorbable tacks can then be used to secure the mesh by placing the lateral tacks close to the edge of the mesh with 1-cm margins (Fig. 5). A second row of tacks is typically placed halfway between the center of the mesh and the edge to allow the mesh to lie flat with the abdominal wall. All trocar sites 10 mm or larger should be closed to minimize the risk of a port site hernia.

For robotic pre-peritoneal paraumbilical midline hernia repair, the patient's arm on the docking side is tucked, and three ports are placed lateral to the semilunar line, with the middle camera trocar placed more laterally to allow a wider viewing angle. Epigastric hernias may be approached more easily with trocar placement in the lower abdominal quadrants. After herniated tissue has been reduced, a curvilinear peritoneal incision 5 cm or more from the edge of the defect is made using monopolar scissors. The presence of pre-peritoneal fatty tissue will aid in dissecting pre-peritoneal space to minimize the risk of fenestrations in the thin peritoneum. This space is then dissected toward the contralateral side of the abdominal wall after the hernia sac is circumferentially mobilized and reduced. Visualization of the rectus muscle indicates that dissection has continued too anteriorly and the posterior rectus sheath has been divided. Once the pre-peritoneal dissection is complete, 0-absorbable barbed suture is used to close the fascial defect in running fashion. Decreasing intraabdominal insufflation to 10 mm Hg may facilitate reapproximation of the fascia. Any portion of diastasis or linea alba that was inadvertently divided during the pre-peritoneal dissection should be incorporated in the fascial reapproximation. Uncoated macroporous mesh with a 3- to 5-cm underlay is secured to the posterior rectus sheath using 2-0 absorbable suture at the center and in four cardinal points to ensure that it lays flat with the rectus sheath. The peritoneum is then closed with 3-0 absorbable barbed suture in running fashion to cover the mesh, and any fenestrations on the peritoneum should be closed to minimize the risk of bowel herniation or contact with mesh. In the event of multiple fenestrations in a thin peritoneum or for patients with a larger defect, a robotic IPOM using coated mesh can be performed. The center of the mesh is secured to the middle of the fascial reapproximation, and the periphery of the mesh is secured to the posterior rectus sheath using 2-0 absorbable running suture.

Robotic retrorectus repair is ideal for larger hernias, and robotic setup is similar to pre-peritoneal approaches. The posterior rectus sheath is divided no closer than 2 cm medially from the semilunar line to minimize the risk of injury to the neurovascular bundle, and the rectus abdominus muscle is immediately visualized. The length of dissection should allow mesh sublay of 3 to 5 cm from the edge of the fascial defect. As dissection continues medially, patients with a diastasis will manifest as a white fascial plane anteriorly between the rectus muscles and fatty tissues posteriorly between the posterior rectus sheath. The hernia sac is dissected circumferentially to allow complete reduction of the herniated tissue. Dissection continues to the contralateral retrorectus space by division of the fascial layers lateral to the diastasis to visualize the rectus muscle body on the contralateral side. The contralateral posterior rectus sheath is further mobilized off the rectus muscle for 3 to 5 cm past the edge of the hernia defect to allow appropriately sized mesh to be placed, while preserving the contralateral neurovascular bundles along the semilunar line. The anterior rectus sheath defect and portions of the diastasis that was inadvertently divided during dissection is reapproximated using 0 running barbed suture under lower insufflation pressure. Lightweight macroporous mesh is placed posterior to the rectus muscle and secured at the center and the cardinal points to the anterior rectus sheath using 2-0 absorbable suture. The posterior rectus sheath is then reapproximated using 2-0 running absorbable suture.

Extended totally extraperitoneal (eTEP) approaches are ideal for larger midline hernias or ones with multiple "Swiss cheese" fenestrations, with the intention of not entering the visceral space of the abdominal cavity. Therefore, preoperative CT examination to ensure that intestines are not within the hernia sac is advised as robotic dissection of the hernia sac may lead to disruption of the sac and injury of the herniated contents. A 1.5-cm incision is made in the left upper quadrant 2 fingerbreadths below the costal margin medial to the left midclavicular line, followed by incision of the anterior rectus sheath and blunt dissection past the rectus muscle to identify the posterior rectus sheath and placement of a dissecting balloon inferiorly toward

the pubis. For epigastric hernias, the initial incision is below the umbilicus but above the arcuate line in order to identify the posterior rectus sheath with blunt dissection after the anterior rectus sheath is divided, and the dissecting balloon is placed superiorly toward the costal margin. Optical trocars can also be used to identify the retrorectus space with blunt dissection used to separate the areolar tissue. Dissection continues toward the semilunar line with identification and protection of the neurovascular bundles found adjacent to the line. Additional trocars are placed medial to the semilunar line and neurovascular bundles. A diastasis is commonly encountered as dissection continues toward the contralateral side of the posterior rectus space. Dissection into this space will manifest as a widened linea alba anteriorly between the rectus muscles and fatty preperitoneal tissue posteriorly between the rectus sheath. Dissection continues laterally within the same plane to the contralateral semilunar line while preserving the neurovascular bundles. Inferior epigastric vessels are sharply dissected off the peritoneum and posterior rectus sheath, and minor bleeds can be effectively controlled with fenestrated bipolar graspers. The hernia sac is separated from the fascial defect and reduced, followed by closure of the anterior rectus fascial defect with 0 running barbed suture under lower insufflation pressure, incorporating any portion of diastasis that was divided during the dissection. Any fenestrations noted in the posterior rectus sheath or hernia sac should be closed to avoid bowel herniation or mesh contact with intraabdominal contents. Synthetic macroporous mesh is then placed into this retrorectus space and secured by application of tissue adhesives.

Robotic transversus abdominus release (rTAR) is relatively nascent, and published data are largely limited to hernias that traditionally have favorable results with retrorectus repair. Furthermore, larger defects that typically require component separation often also require excision of the excess hernia sac, skin, and fatty tissue, which is most efficiently performed via an open approach. Therefore, we currently do not perform rTAR.

EPIGASTRIC AND UMBILICAL HERNIAS

Umbilical hernias are defects found within a 3-cm radius of the umbilicus, and they are repaired when symptomatic. In an open approach, fascial reapproximation followed by sublay mesh is ideal, showing the lowest risk of SSI and/or recurrence. A horizontal incision is made in a semicircumferential fashion around the umbilicus and carried down to the fascial layer. Blunt dissection is then carried out circumferentially to isolate the hernia sac, which is divided to allow reduction or resection of herniated issue. The sac is closed with absorbable suture to enclose the abdominal contents. Defects smaller than 1 cm do not require mesh. Otherwise, a pre-peritoneal mesh placement should be attempted via a circumferential blunt dissection below the fascial layer of the umbilicus to create a pre-peritoneal space to allow placement of synthetic mesh with a 3- to 5-cm sublay. The mesh is secured to the fascial layer at the cardinal points using 2-0 absorbable suture. The fascial defect is then closed using 0-absorbable suture. A concave umbilicus is then reconstructed using 2-0 absorbable suture to secure the subdermal portion of the umbilicus to the fascia, followed by skin closure. Open epigastric hernias are fixed in the same fashion, ideally with pre-peritoneal synthetic mesh placement. Laparoscopic/robotic umbilical and epigastric hernia repair should include reapproximating the fascia with mesh underlay of 3 to 5 cm as IPOM, or as a pre-peritoneal technique. Dissection is similar to that described earlier for incisional hernia.

PERIOPERATIVE AND POSTOPERATIVE CARE

Enhanced recovery after surgery (ERAS) pathways have been shown to reduce cost, length of stay, and opioid use following surgery for ventral hernia repair (Table 1). Data are lacking to support the benefit of epidural catheters compared with regional plane blocks in terms of overall use of narcotic pain medication, but we favor epidural catheters for large complex open hernia repairs. Abdominal binders are routinely used and have been shown to improve patients' subjective experience postoperatively.

Negative pressure wound therapy (NPWT) may reduce the risk of surgical site occurrence (SSO) by up to 30% and has been shown to decrease 2- to 5-year recurrence rate in certain high-risk populations. It has demonstrated specific benefit in older adults (>65 years), patients with a history of wound infection, obesity, malnutrition, smoking, immunosuppression, and chronic inflammatory disease. For open hernia repair we selectively use incisional NPWT, especially in patients with the aforementioned risk factors, long incisions, or large musculocutaneous flaps. The skin is closed with absorbable braided interrupted deep dermal sutures, a nonadherent contact layer is placed in a strip over the incision to protect the surrounding skin, and a sponge is placed over the nonadherent contact layer with care not to place the sponge directly onto the skin. We leave this dressing in place until postoperative day 4, and wound closure strips are applied to the incision once this dressing is removed.

After discharge, patients are encouraged to optimize their level of activity with as much ambulation as possible. We also suggest a weight restriction of 15 lb for the first 2 weeks, and patients are asked to increase their maximal weight bearing by 5 to 10 lb per week until they are at their normal level of activity. Most patients are seen in the postoperative clinic 1 to 2 weeks after surgery. Additional follow-up is dependent on patient risk of developing an SSO. Any drains are typically removed by 2 weeks postoperatively when serosanguineous output is less than 25 mL/day.

COMMON COMPLICATIONS

Most patients will develop a seroma, but only 10% to 30% of these are clinically significant, defined as symptomatic or persisting after 6 months from the time of surgery. Primary fascial closure in mesh repairs is the most consistently demonstrated strategy to prevent seroma/hematoma, and it is our practice to routinely excise the hernia sac. There are no strong associations between anatomic position of mesh placement or method of adhering mesh and rates of clinically significant seroma. Drains may decrease the rate of seroma formation but have not been shown to decrease the rates of seromas needing intervention, rates of hernia recurrence, or mesh explantation. For symptomatic seromas or those that persist at 6 months, percutaneous drain placement with removal when output is serous and minimal (<25 mL/day), or sterile aspiration with interval CT or ultrasound have both demonstrated high rates of success. In the rare case of sterile seroma refractory to percutaneous drainage, chemical sclerosing agents (talc, doxycycline) have been described with high (>90%) reported rates of success.

Deep SSI, or "mesh infection," requires positive cultures from the mesh itself or from fluid directly in contact with mesh for diagnosis. Overall rates of mesh infection are low at 1% to 2%, with risk factors including urgent or emergent repair, immunosuppression, and superficial SSI. The presence of a sterile seroma is not associated with development of mesh infection. Mesh salvage can be attempted in nonseptic patients with lightweight or macroporous mesh, especially if the mesh is in the retrorectus position. Key components of salvage include early systemic antibiotics, superficial debridement, mesh irrigation with antibiotic solution if mesh is visible, and NPWT. Factors predicting failure of salvage include onlay position of mesh, urgent initial repair, and enterotomy at time of initial repair; additionally, PTFE, microporous, or heavyweight mesh are strongly associated with failure to salvage; thus, we typically excise these mesh types upfront rather than attempting long-term conservative

TABLE 1 Key Components of an Enhanced Recovery Protocol for Ventral Hernia Repair

Preoperative risk stratification/preoperative counseling	Structured counseling about protocol should be provided at clinic visit
Preoperative bowel preparation	Bowel preparation (clear liquids × 2 days before surgery) recommended only to patients with colostomy
Prophylaxis against thromboembolism	Preoperative and postoperative chemoprophylaxis and intraoperative and postoperative sequential compression devices ordered and utilized
Methicillin resistant *Staphylococcus aureus* (MRSA) prophylaxis	Preoperative MRSA nasal swab, and if positive mupirocin intranasal ointment BID × 5 days preoperatively
Nutritional preparation	Consider nutritional consultation and preoperative supplementation if albumin <3.0
Preoperative fasting and carbohydrate treatment	Gatorade (or diabetic alternative) 400 mL 4 hours before arrival time. No solid foods after midnight
Perioperative fluid management	< 5 mL/kg/hour or < 2 L of intravenous intraoperatively
Postoperative nausea and vomiting	Use of prophylactic antiemetics as appropriate
Nasogastric intubation	Nasogastric tube placed in the operating room removed before leaving the operating room
Urinary drainage	Removal of Foley catheter by postoperative day 2
Prevention of intraoperative hypothermia	Temperature ≥36°C intraoperatively
Multimodal pain management	No scheduled narcotics
	Multimodal therapy (epidural with hydromorphone and bupivacaine), scheduled acetaminophen (first dose preoperatively, then postoperatively IV transitioning to PO), ketorolac transitioning to ibuprofen, standing gabapentin, and oxycodone PRN after discontinuation of epidural)
Acceleration of intestinal recovery	Clear liquids immediately postoperatively with quick advancement to regular diet
	Multimodal standing bowel regimen
Early mobilization	Patient to be out of bed evening of surgery and ambulating by postoperative day 1
Postoperative glucose control	Blood glucose checked and sliding-scale insulin utilized per hospital protocol with goal < 180

Modified from Stearns E, Plymale MA, Davenport DL, et al. Early outcomes of an enhanced recovery protocol for open repair of ventral hernia. *Surg Endosc.* 2018;32(6):2914–2922.

management. When mesh excision is necessary, all foreign material should be excised if possible. Partial mesh excision is associated with approximately threefold higher rates of SSO and reoperation compared with complete mesh excision. We prefer primary fascial closure or bridged repair with biological mesh for cases of contaminated mesh excision.

Enterocutaneous fistula (ECF) may occur as a result of missed enterotomy or unplanned bowel resection at the index operation; it is more common with the use of synthetic mesh compared with primary repair or biologic mesh, though overall incidence of ECF remains low among all mesh repairs. ECF is typically preceded by chronic mesh infection, with an average time to presentation of 2 years after index hernia repair. In stable patients, we recommend initial nonoperative management: local wound care, nutritional optimization, and multimodal step-up therapy to limit fistula output, beginning with ensuring distal decompression and proceeding if necessary to NPO with parenteral nutrition and antisecretory agents. Antibiotics are indicated for cellulitis or presence of associated abscess, but there is no evidence to support the use of chronic suppressive antibiotics in the absence of clear active infection. Although ECF closure rates range from 15% to 65% with aggressive conservative management alone, there is a wide variation likely related to chronicity, output, anatomy, and duration of conservative management. If 6 months of conservative therapy has failed or if a patient presents with sepsis secondary to infection at the site of ECF, mesh explantation, excision of involved bowel, and primary abdominal wall closure should be considered. In the case of surgical treatment of ECF, complete excision of mesh and removal of all foreign material is recommended. Partial mesh excision is associated with higher risk of SSI, SSO, reoperation, and failure. Even after complete mesh excision, up to 50% of patients may develop additional wound complications.

CONCLUSION

Ventral hernias are a heterogenous surgical disease with high variability in complexity and morbidity. Though many factors contribute to likelihood of recurrence, surgeon experience of 40 or more cases

per year is associated with a 30% to 40% lower rate of reoperation for recurrence compared to 12 or fewer cases. Patient optimization, appropriate technique, and aggressive management of common complications are key to ensuring good outcomes.

Acknowledgment

The authors would like to acknowledge the contributions of Dr. Daniel Harris and Dr. Charis Ripley-Hager in the editing of this chapter.

Suggested Readings

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Management of Spigelian, Obturator, and Lumbar Hernias

Ajita S. Prabhu, MD

Spigelian, obturator, and lumbar hernias present a special challenge for surgeons because of their relative rarity and related lack of robust published surgical experience with their management. Intimate knowledge of abdominal wall anatomy is requisite to repair these defects and should be reviewed thoroughly before offering operative intervention.

SPIGELIAN HERNIA

Clinical Presentation

Spigelian hernias are uncommon, accounting for an estimated 0.1% to 2% of all ventral hernias. They are not clearly associated with gender, as is the case with femoral and inguinal hernias. They are most often diagnosed in the fifth or sixth decade of life, and they may be associated with connective tissue disorders, smoking, chronic cough, or increased intraabdominal pressure related to obesity. Although Spigelian hernias may be incidentally identified on cross-sectional imaging obtained for other reasons, patients with complaints of pain or tenderness along the linea semilunaris should prompt suspicion for a Spigelian hernia and should undergo a thorough physical examination and CT or ultrasound imaging to rule out its presence. A complete physical examination for Spigelian hernia should include examination in the supine and standing positions with the Valsalva maneuver. If present, the hernia may be palpated at the linea semilunaris, which correlates with the lateral aspect of the rectus abdominus muscle. Because the hernia typically does not disrupt the external oblique muscle, diagnosis may be challenging despite physical examination and CT or ultrasound imaging. There is some literature to suggest that CT has a slightly higher positive predictive value than ultrasound. Because of this finding and the operator-dependent and body habitus–dependent nature of ultrasound, the authors prefer cross-sectional imaging for workup of Spigelian hernia, although in some cases CT may fail to identify the presence of a Spigelian hernia because of its inherent interparietal nature and possible spontaneous reduction and protrusion of the hernia contents (Fig. 1). If high suspicion persists, diagnostic laparoscopy should be performed to rule out a hernia as Spigelian hernias are associated with a substantial risk of incarceration and strangulation and should be identified and repaired when possible.

Anatomy

Spigelian hernias occur through the Spigelian fascia, near the juncture of the arcuate line and the linea semilunaris. The arcuate line (also known as the *linea semicircularis or semicircular line of Douglas*) is the crescent-shaped demarcation where the internal oblique and transversus abdominus aponeuroses transition from passing posterior to the rectus abdominus muscle and instead pass anterior to the rectus abdominus, leaving only the transversalis fascia posteriorly. The location of the arcuate line can vary; however, it is estimated to be found roughly one-third to one-half of the distance from the pubic crest to the umbilicus. The deep inferior epigastric vessels perforate the rectus abdominus muscle at this point. Above (cephalad to) the arcuate line, the anterior rectus sheath is composed of the external oblique fascia and the anterior lamella of the internal oblique fascia. Here, the posterior rectus sheath is composed of the posterior lamella of the internal oblique fascia and the transversalis



FIG. 1 Spigelian hernia image. The hernia is located on the patient's left side in the lower abdomen at the lateral edge of the rectus abdominis and medial to the linea semilunaris.

fascia (Fig. 2). The linea semilunaris is formed by the convergence of the external oblique, internal oblique, and transversus abdominus aponeuroses. It is located at the lateral border of the rectus abdominus muscle, beyond the perforating intercostal neurovascular bundles from levels T7–T12 and L1–L2, which supply innervation to the abdominal wall. The Spigelian aponeurosis is bounded laterally by the linea semilunaris and medially by the lateral aspect of the rectus abdominus muscle, and it extends from the ninth rib to the pubic tubercle.

Operative Approaches

Minimally Invasive Surgical Approaches

Transabdominal Preperitoneal Approach

A Spigelian hernia can be easily appreciated from a minimally invasive transabdominal preperitoneal (TAPP) approach, either robotic or laparoscopic. There is no literature to suggest that either the robotic or laparoscopic approach is preferable from a clinical outcomes perspective. The patient is positioned supine with arms

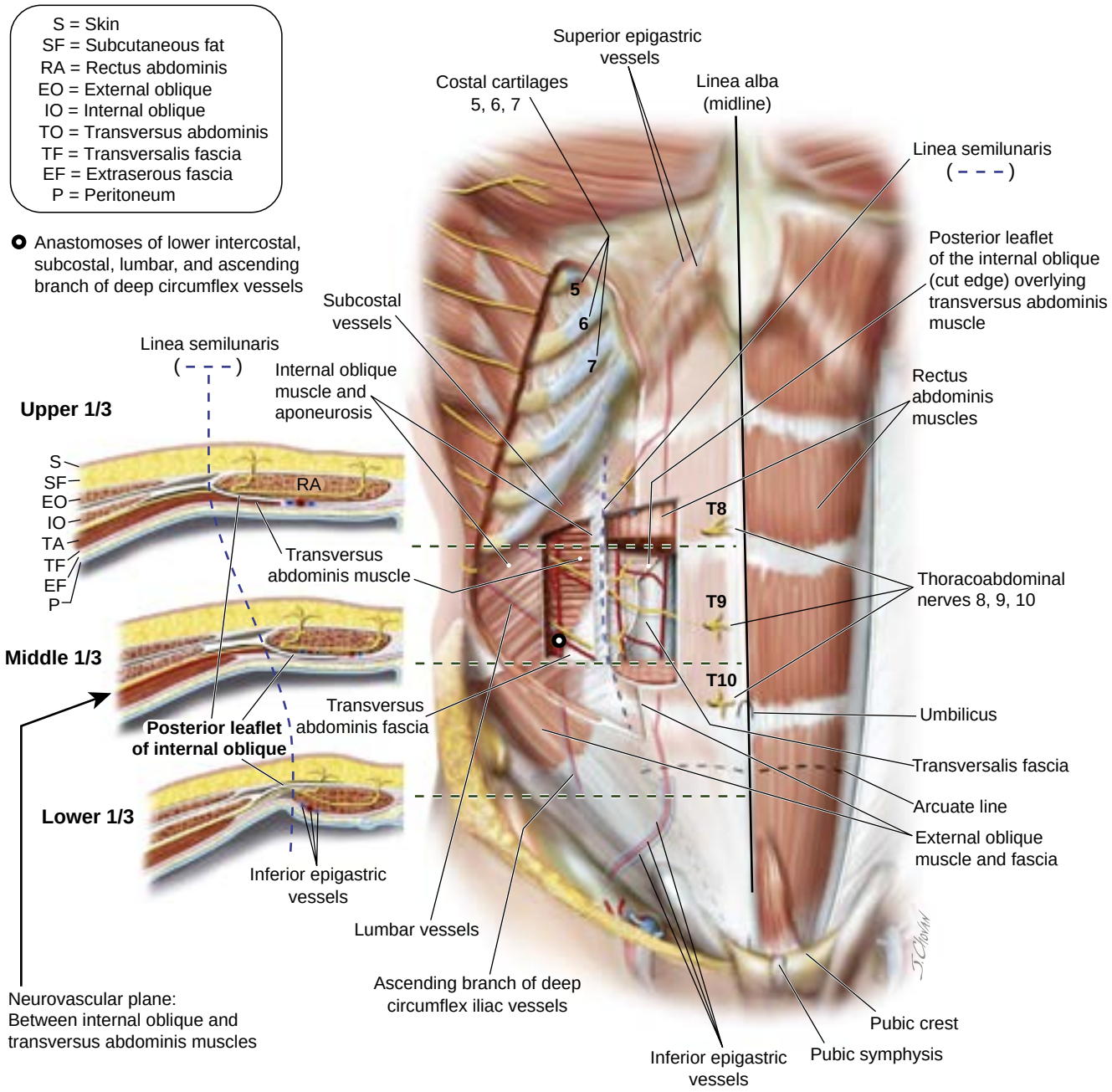


FIG. 2 Abdominal wall anatomy: myofascial relationships and neurovascular anatomy of the upper, middle, and lower thirds of the abdominal wall. *(From Rosen MJ. Atlas of Abdominal Wall Reconstruction. 2nd ed. Philadelphia: Elsevier; 2016.)*

tucked bilaterally for laparoscopic or robotic side-dock approach. Some robotic surgeons may prefer docking from a lithotomy position, which may be accomplished in standard fashion. For minimally invasive surgery (MIS) access to the abdomen, the authors prefer to perform a cut-down incision at the umbilicus to accommodate a 10-mm Hasson port. Once the abdomen is insufflated to a pressure of 15 mm Hg, a 5-mm trocar is placed on the side contralateral to the Spigelian hernia, toward the lateral aspect of the rectus abdominus muscle and roughly 2 cm in a cephalad direction. The laparoscopic camera is then moved to the 5-mm port, and a 5-mm port is placed on the side ipsilateral to the hernia. This port may be positioned more cephalad than the contralateral 5-mm port to allow adequate space to repair the hernia. Ports may be similarly placed for a robotic approach, with the port size adjusted to accommodate the specific robotic platform in use and the robotic scope placed at the umbilical location. (For the daVinci Si platform, the authors suggest a 12-mm port at the umbilicus and 5- or 8-mm ports as per surgeon preference for the lateral ports; for the daVinci Xi platform, the authors recommend 8-mm ports for all noted port sites.) The robot may be docked from the side or from the lithotomy position as noted earlier. If taking a laparoscopic approach, the surgeon will stand on the side contralateral to the Spigelian hernia. Once MIS access is established and ports placed, hernia contents are reduced back into the abdomen, taking care to avoid leaving behind any adherent fat within the defect space. The posterior rectus sheath (PRS) is incised at its medial juncture with the medial umbilical ligament, exposing the rectus abdominus muscle and allowing the surgeon to identify the deep inferior epigastric vessels to preserve them. The incision of the PRS is carried out, staying high in the abdomen and toward the anterior superior iliac spine. Next, the medial dissection is performed to expose the pubis and Cooper's ligament in the space of Retzius on the side ipsilateral to the Spigelian hernia. At the lateral aspect of the PRS, the surgeon will encounter some resistance in the tissue just medial to the linea semilunaris, which is the area where the posterior rectus sheath and the posterior lamella of the internal oblique may be incised in a vertical direction from cephalad to caudal to allow the preperitoneal space to become contiguous with the retromuscular space. The lateral dissection will proceed toward the arcuate line, which is divided to allow the hernia sac to be fully reduced. Once all of the hernia sac is reduced, a noncoated synthetic mesh can be introduced into the preperitoneal space and fixated as per the surgeon's standard MIS practice for inguinal hernia repair. The authors prefer to place a macroporous, heavyweight polypropylene mesh with titanium tack fixation. The mesh is introduced through the umbilical port and directly into the preperitoneal/retromuscular plane and is fixated circumferentially using titanium tacks. If the defect is lower in the abdomen, tacks are placed in a similar distribution to those utilized for inguinal hernia repair using the same approach (tacks are placed at the ipsilateral Cooper's ligament, the high-medial aspect of the mesh taking care to avoid the epigastric vessels, and at the high-lateral aspect of the mesh making sure that the tacker is palpable to avoid placing fixation within the ileopubic tract). If a robotic approach is utilized, the surgeon may prefer to close the defect before mesh placement and may also opt to fixate the mesh with suture as opposed to tacks. Regardless, the peritoneum is then reapproximated using absorbable monofilament suture or tacks to prevent the bare mesh from contacting the viscera. Care must be taken to avoid large gaps in the peritoneum, which may allow for internal hernias to occur, causing postoperative bowel obstruction. Ports are closed as per surgeon preference.

Totally Extraperitoneal Approach

If the surgeon prefers a totally extraperitoneal (TEP) approach, this is best performed laparoscopically as the robotic approach gives no advantage for this technique. Access to the retromuscular space is attained by creating an infraumbilical incision large enough for a port that will accommodate a balloon dissector. The PRS is incised to gain access to the retromuscular space, and a balloon dissector is passed into the retromuscular plane using a 0-degree scope and under direct vision. The dissector is passed toward the hernia defect, which is distinct from inguinal hernia TEP procedure in which the balloon is passed toward the pubis. After the space is sufficient to allow for mesh placement with 3 to 5 cm of mesh overlap from the edges of the hernia defect, two additional 5-mm ports are placed in the midline between the umbilicus and the pubic symphysis. A bare polypropylene mesh is introduced into the retromuscular space and positioned accordingly, with choice of fixation or no fixation as per surgeon preference. Ports are closed as per surgeon discretion.

Intraperitoneal Onlay Mesh Approach

For surgeons who are unaccustomed to preperitoneal or retromuscular approaches to hernia repair, intraperitoneal onlay mesh (IPOM) with barrier-coated mesh is another option. Barrier-coated mesh is required for this approach to prevent the mesh from adhering to the viscera. IPOM is carried out in standard laparoscopic (or robotic) fashion, with 3 to 5 cm of mesh overlap from the edges of the defect and mesh fixation as per surgeon discretion. Caution should be observed when approaching fixation near the inferolateral aspect of the repair, where the distribution of fixation may overlap with the iliopubic tract or so-called *triangle of pain,* leading to potential injury to the femoral branch of the genitofemoral nerve or lateral femoral cutaneous nerve.

Open Approach

For the open approach, the patient is placed in the supine position with arms out or tucked as per surgeon preference. Before induction of anesthesia, the site of the hernia should be marked with the patient awake and with ultrasound guidance as necessary. A transverse or oblique incision is made directly over the defect, and the skin and subcutaneous tissues are divided. In some cases, the hernia sac may be encountered in the subcutaneous space if the hernia has disrupted the external oblique muscle. Commonly, however, the hernia is in an interparietal position between the external and internal oblique musculature, and it is necessary to divide the external oblique muscle to appreciate the defect. In any case, a relaxing incision can be made toward the medial aspect of the defect if the contents are tightly incarcerated or strangulated. If no contamination is present and bowel resection is not required, the authors prefer to repair Spigelian hernias with mesh reinforcement. The mesh can be safely placed between the external and internal oblique muscles after repairing the defect in the internal oblique and transversus abdominus layer. We prefer slow-absorbing monofilament sutures for closure of these layers and a bare macroporous heavyweight polypropylene mesh for the reinforcement. Mesh overlap of the repaired defect of 3 to 5 cm is desirable. Fixation of the mesh may be avoided or utilized here as per the surgeon's discretion. The external oblique layer is then closed with slow-absorbing monofilament suture, and the skin is closed in absorbable layers. Although some authors may prefer preperitoneal or intraperitoneal mesh reinforcement through an open approach, blind preperitoneal mesh positioning may result in unanticipated buckling or folding of the mesh, and similarly blind intraperitoneal placement of a barrier-coated mesh patch may result in inability to confirm proper apposition of the mesh to the surrounding tissues, ultimately resulting in complications or hernia recurrence. For this reason, the authors prefer interparietal placement of the mesh if approaching a Spigelian hernia through an open incision.

OBTURATOR HERNIA

Clinical Presentation

Obturator hernias (hernias through the obturator foramen) are very rare and often go undiagnosed in the outpatient setting because of

their unusual location. Although obturator hernias represent <1% of all hernias overall, there is a distinct female preponderance (an estimated 85% occur in women) associated with this type of hernia, likely because of the presence of a wider obturator foramen in women than in men. Patients with an obturator hernia tend to be thin or emaciated elderly women, and most patients present with small bowel obstruction because preceding symptoms of groin pain radiating to the medial aspect of the thigh and the posterior knee are often misdiagnosed as nonspecific pain of aging or arthritic pain. Physical examination in the absence of bowel obstruction is challenging as the hernia is present between the pectineus and adductor longus muscles within the thigh, rendering it impossible to palpate. The Howship-Romberg sign is pathognomonic and is elicited if extension, adduction, or medial rotation of the ipsilateral hip causes inner thigh pain on the affected side, however it is only thought to be present in about 50% of patients with an obturator hernia. As noted, most patients will present with bowel obstruction and will therefore be diagnosed during surgery. Elderly female patients with groin pain and vague complaints of weight loss or intermittent bowel obstruction may benefit from CT or MRI, which may identify an obturator hernia. If identified incidentally, obturator hernias should be repaired electively because of a high risk of incarceration or strangulation.

Anatomy

The obturator foramen is in the pelvis and is formed by the union of the pubic bone and the ischium (Fig. 3). The obturator foramen is covered by the obturator membrane. The obturator canal is an opening in the superior aspect of the membrane that allows the obturator nerve, artery, and vein to pass. When the obturator canal becomes enlarged because of shrinking of the membrane, a hernia forms most commonly in the anteromedial aspect of the membrane. The defect is found medial to the femoral canal and inferior to the iliopubic tract and the Cooper's ligament.

Operative Approaches

The authors prefer a posterior approach for repairing obturator hernias, whether open or through a minimally invasive approach. Patients with incidentally identified obturator hernias and minimal pelvic surgery (below the level of the umbilicus) are ideal candidates for a minimally invasive approach. If obstruction is present, a laparoscopic or robotic approach may still be attempted if the patient has had minimal or no prior pelvic surgery, however caution must be taken to avoid bowel injury related to distended intestine causing poor visualization in the operative field. Mesh (permanent or absorbable depending on contamination) should be used in repair of every obturator hernia as primary repair is undesirable given the proximity of the obturator nerve and vessels to the hernia.

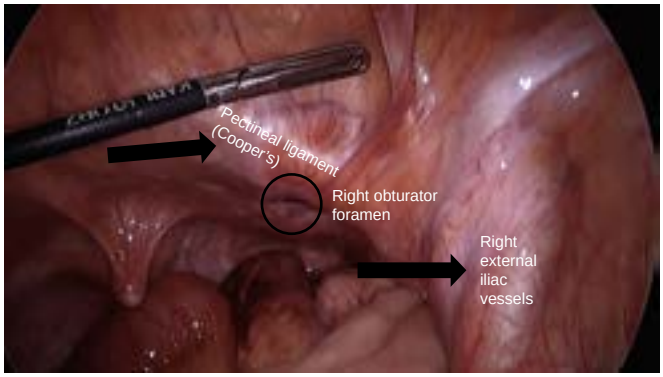


FIG. 3 Laparoscopic view of an obturator hernia defect. *(From Conti L Baldini E, Capelli P, Capelli C. Bowel obstruction in obturator hernia: a challenging diagnosis.* Int J Surg Case Rep. *2018;42:154–157.)*

Minimally Invasive Surgical Approaches

If attempting a laparoscopic or robotic approach, the patient should be positioned supine (or in the lithotomy position for surgeons who prefer lithotomy docking for a robotic approach; side dock is also acceptable for this approach) with both arms tucked and in Trendelenburg position. The authors prefer a cutdown approach, particularly in the setting of distended bowel related to obstruction, to avoid bowel injury and associated contamination. Port placement is like that for the TAPP approach for inguinal hernia repair as described earlier. Once the hernia is identified in the pelvis, any contents must be reduced. The intestine should be handled with caution as it may be friable resulting from obstruction and therefore prone to perforation. Attempts to grasp the bowel itself should be avoided in favor of grasping and manipulating the mesentery. Once the contents are reduced, if no bowel resection is indicated, a retromuscular/TAPP approach as described earlier for Spigelian hernias may be used to develop a wide preperitoneal plane for mesh placement (Video 1). The authors prefer bare macroporous heavyweight polypropylene mesh for this repair, and we typically secure it with titanium tacks to Cooper's ligament, high medial, and high lateral, taking care to avoid the deep inferior epigastric vessels and the iliopubic tract. The peritoneal flap and ports are closed as per surgeon discretion. If the operation requires bowel resection, the authors prefer an absorbable synthetic mesh for the repair as primary repair is complicated by the presence of the obturator nerve and vessels. Plugs should also be avoided for the same reason.

Open Approach

If attempting an open approach, the authors prefer supine patient positioning with arms out or tucked as per surgeon discretion. A low vertical midline incision starts at the umbilicus and is taken down to the suprapubic location. The peritoneum is opened, and the abdomen is entered to inspect the bowel. Once the abdomen is entered, with the patient in the Trendelenburg position, the surgeon may reduce the contents of the hernia, taking care to avoid leaving any nonviable preperitoneal fat in the obturator canal. Following this, the ipsilateral posterior rectus sheath is taken down with cautery, taking care to avoid injury to the deep inferior epigastric vessels. The dissection is carried out until the epigastric vessels are identified and mobilized from the posterior rectus sheath to stay with the rectus abdominus muscle. The posterior rectus sheath and posterior lamella of the internal oblique are divided in a vertical fashion, allowing entry to the preperitoneal plane laterally. This will allow room for mesh to be placed. Medially, the pubis and Cooper's ligament are identified in the space of Retzius, and the bladder is mobilized in a hemostatic fashion. The authors prefer to cross midline to the contralateral side in this plane and follow into the contralateral retromuscular or preperitoneal plane, allowing room for the mesh to overlap the midline, similar to a Stoppa procedure. Once adequate space has been created, the peritoneum and the posterior rectus sheath are closed together using a polyfilament absorbable suture and taking care to exclude the viscera. If there is tension on the closure of the posterior elements, the transversalis fascia on the contralateral side may also be incised to provide improved laxity for closure. Presuming that no bowel has been resected and there is no contamination, a macroporous heavyweight polypropylene mesh may be cut down to adequately cover the entire myopectineal orifice, including the direct and indirect inguinal spaces, the femoral space, and the obturator space. In the presence of contamination, an absorbable mesh may be placed in similar fashion. Fixation of the mesh is at the surgeon's discretion. Further closure of the abdominal

wall is usually performed by utilizing a slow-absorbing monofilament suture in a running fashion to close the anterior rectus sheath, and the skin is closed in absorbable layers. If the field is contaminated, the skin is packed.

LUMBAR HERNIA

Clinical Presentation and Anatomy

Lumbar hernias are relatively rare and occur in the lumbar region of the posterior, or dorsal, abdominal wall. Patients typically present with bulging and pain in the flank or lumbar region. These hernias can be congenital or acquired and typically occur through either the superior lumbar triangle (Grynfeltt triangle, bounded by the 12th rib, paraspinous muscles, and the internal oblique muscle) or less commonly through the inferior lumbar triangle (Petit triangle, bounded by the iliac crest, latissimus dorsi muscle, and external oblique muscle) (Figs. 4 and 5). CT imaging helps delineate between a denervation injury and associated eventration of the flank muscles, which is a nonoperative clinical entity, and a true hernia. Interpretation of CT imaging can be challenging because of a common presentation of interparietal lumbar hernia, in which the defect may not disrupt all three muscle layers (external oblique, internal oblique, transversus abdominis) of the lateral abdominal wall.

Mesh reinforcement is required for the repair of these hernias because of the presence of bony structures limiting primary closure of soft tissues. Elective repair of lumbar hernias is recommended regardless of symptomatic or asymptomatic nature because of the risk of incarceration and subsequent complications as well as a technically challenging operative approach.

Patient Positioning

Patient positioning is generally the same for lumbar hernia repair regardless of whether an open or minimally invasive operative approach is used. Although some very thin patients may be candidates for a midline approach, the typical scenario is challenged by both body habitus and the posterior location of the defect. Achieving adequate mesh overlap in every aspect of the hernia is most often best accomplished by taking a flank approach to the repair for this reason. A Foley catheter is recommended. The patient is placed in the lateral decubitus position on a beanbag with the affected side exposed and a pillow placed between the legs (Fig. 6). The patient's umbilicus should be aligned with the point of flexion, or "break" of the bed. Arms may be positioned using a double arm board or using pillows, and an axillary roll is placed in standard fashion. The bed is then flexed with the beanbag flaccid, and once the space between the costal margin and the anterior superior iliac spine has opened, the beanbag is desufflated to hold the position. Foam padding should be used to protect the skin from pressure points within the beanbag. Multiple points of circumferential tape fixation are utilized to ensure that the patient is adequately secured to the bed. It is important to ensure that the following landmarks are prepped into the field: the umbilicus, anterior superior iliac spine, pelvic brim, pubic tubercle, inguinal ligament, and lower costal margin.

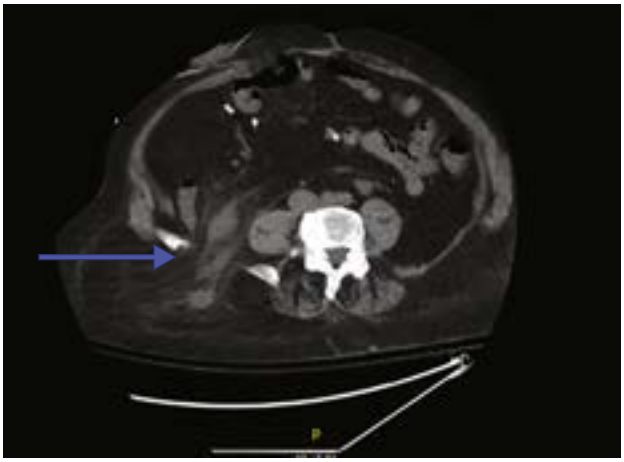


FIG. 4 Lumbar hernia on the patient's right side at the triangle of Petit.

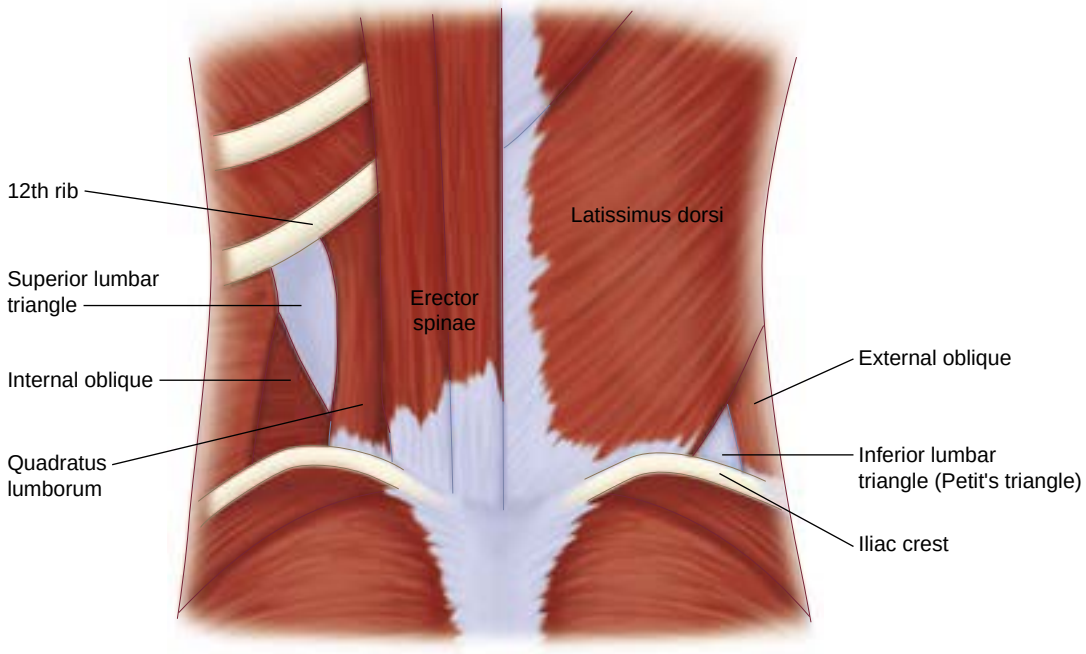


FIG. 5 Pertinent anatomy related to superior and inferior primary lumbar hernias. *(From Sundaramurthy S, Suresh HB, Anirudh AV, Prakash Rozario A. Primary lumbar hernia: a rarely encountered hernia.* Int J Surg Case Rep. *2016;20:53–56.)*

Laparoscopic Approach

When using the laparoscopic approach, the anterior superior iliac spine is identified, and a 12-mm incision is made roughly two fingerbreadths above this point and slightly medial to the mid-axillary line (Video 2). Dissection is carried down through the skin and subcutaneous tissues, exposing the external oblique fascia. This is divided, and the muscle is bluntly split in the direction of its fibers to reveal the internal oblique fascia, which is divided and the muscle split in a similar fashion. The final layer that must be divided is the transversus abdominis muscle and the transversalis fascia. Once these structures are divided, access is gained to the retroperitoneum. A balloon dissector is introduced into the retroperitoneal plane and insufflated under direct laparoscopic vision. The balloon dilator is removed, leaving the balloon port in place. An additional 5-mm port is placed approximately 2 fingerbreadths medial to the initial port, and the fat is dissected away from the retroperitoneal space until the edges of the hernia defect are identified and cleared. From this view, the psoas muscle, the iliac vessels, and the ipsilateral ureter may be identified and preserved. A ruler may be introduced through the larger port to measure the defect intracorporeally. The authors prefer macroporous heavyweight polypropylene mesh for this repair, which may be cut down to the appropriate size to allow 3 to 5 cm of overlap of the mesh from each aspect of the hernia defect. Desufflation is performed under laparoscopic vision to ensure that the mesh does not shift. Transfascial suture fixation or fixation with fibrin sealant are as per surgeon discretion. The cutdown incision is closed in the fascial layers using size 0 multifilament absorbable suture. Skin incisions are closed as per surgeon standard.



FIG. 6 Patient positioning for lumbar hernia repair. The break of the bed is aligned with the patient's umbilicus. Foam *(blue)* is used to pad any protuberances of the beanbag to prevent pressure injury to the skin. The patient is secured to the bed using a safety belt and 2 to 3 points of tape circumferentially placed.

Open Approach

With the patient in lateral decubitus position as described earlier, an incision is made about 2 to 3 cm cephalad to the anterior superior iliac spine, unless a prior incisional scar dictates otherwise. The dissection is carried down through the skin and subcutaneous tissue using cautery. The external oblique muscle is commonly encountered intact and must be divided to expose the hernia, which is commonly interparietal in location. This may be appreciated on CT before surgery (Fig. 7). The hernia sac is identified, and the edges are cleared. At this point, if it is possible to remain in the preperitoneal/retroperitoneal plane, respectively, the dissection may be completed in the extraperitoneal plane entirely. In the instance that scar or lack of anatomic clarity requires opening the hernia sac, this may also be done safely and can help reorient the surgeon as to the anatomic location of the dissection, and the dissection may be aided here by complete adhesolysis to release any viscera tethered to the hernia sac. With the surgeon standing on the patient's ventral side, the dissection is carried out in the retroperitoneal plane to expose the psoas muscle and then continued toward the medial aspect of the psoas muscle, where the ureter can be identified and preserved (Fig. 8). The genitofemoral, ilioinguinal, iliohypogastric, and lateral femoral cutaneous nerves are also identified from this aspect and avoided when securing the prosthetic. This plane is exploited bluntly toward the costal margin and toward the pelvic brim. The costophrenic aspect of the dissection is somewhat limited by the costal margin; however, peritoneum on the undersurface of the diaphragm can be mobilized here to obviate this issue. Once adequate lateral dissection is attained, the surgeon moves to stand on the dorsal or posterior side of the patient. The medial dissection is carried toward the ventral aspect of the patient in the preperitoneal plane. The preperitoneal dissection may be limited by very thin peritoneum at the lateral aspect of the rectus abdominis muscle, which is also the location of the linea semilunaris. In this scenario, adequate medial mesh overlap may be achieved by performing a retromuscular dissection and so-called *reverse transversus abdominis release* (reverse-TAR; Video 3). To do this, the surgeon first incises the fascial layer at the lateral-most aspect of the rectus abdominis muscle, revealing the lateral aspect of the muscle (Fig. 9). The dissection is carried out until the perforating intercostal and lumbar neurovascular bundles are identified and preserved where possible (Fig. 10). The retromuscular incision is carried out in a caudal and cephalad direction with the assistance of a right-angle dissector and cautery. The cephalad-most portion will become contiguous with the infradiaphragmatic preperitoneal plane.

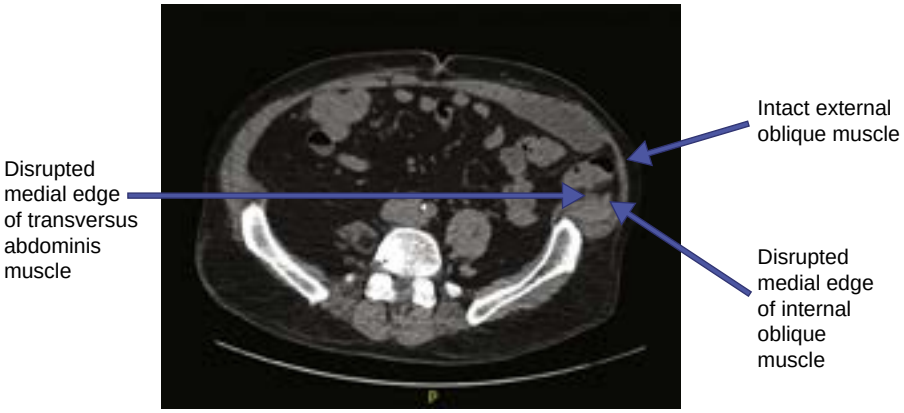


FIG. 7 Lumbar hernia CT scan showing a disrupted internal oblique and transversus abdominis with an intact external oblique.

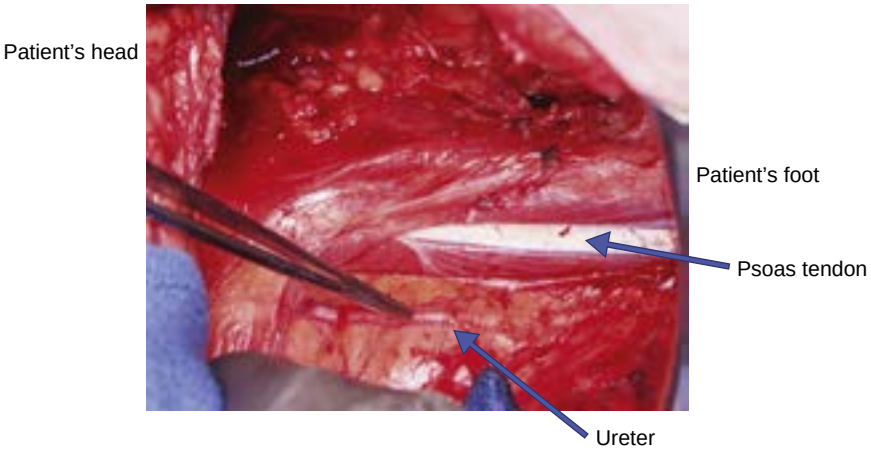


FIG. 8 Lateral dissection of a lumbar hernia.

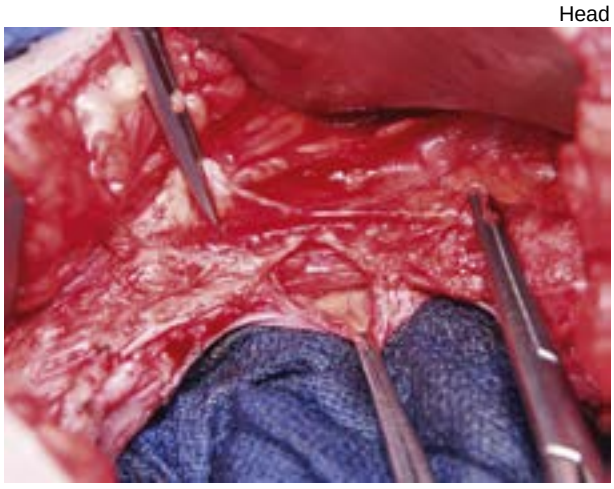


FIG. 9 Medial dissection of a lumbar hernia. The lateral-most aspect of the fascia abutting the rectus abdominis is incised, revealing the rectus abdominis muscle and the retromuscular plane.

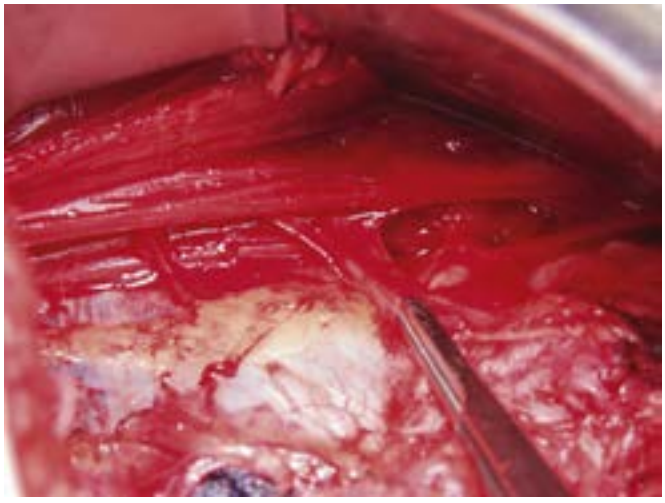


FIG. 10 Medial dissection of a lumbar hernia. The perforating neurovascular bundles are identified at the medial aspect of the dissection.

In the lower abdomen, care must be taken to preserve the deep inferior epigastric vessels and the spermatic cord in males. If the patient is female, the round ligament is identified and may be divided in a controlled manner to gain further space in the preperitoneal plane. The dissection is carried bluntly to the ipsilateral Cooper's ligament in the space of Retzius. This dissection plane can be taken all the way to the linea alba in the medial aspect if necessary. Once the dissection is sufficient in the retromuscular and retroperitoneal plane to allow the peritoneal sac to be closed if it was entered and to allow for at least 5 cm mesh overlap in every aspect of the repair, the mesh is selected and positioned within the extraperitoneal plane. The peritoneum must be completely closed to exclude the viscera from the mesh, and care must be taken to avoid leaving holes that may lead to visceral herniation and bowel obstruction deep to the mesh. The authors typically use macroporous heavyweight polypropylene mesh. The mesh will cover from the pelvic brim to underneath the costal margin, to the Cooper's ligament, the umbilical region ventrally, and toward the medial aspect of the psoas muscle laterally. It is placed in an arched configuration to follow the curve of the peritoneal sac. The inferior aspect of the mesh is fixated first, using No. 1 slow-absorbing monofilament sutures and a sharp suture passer. The sutures are placed several (8–10) centimeters in from the edge of the mesh, such that the mesh may overlap several centimeters beyond each fixation point. This will allow for adequate overlap beyond areas that are

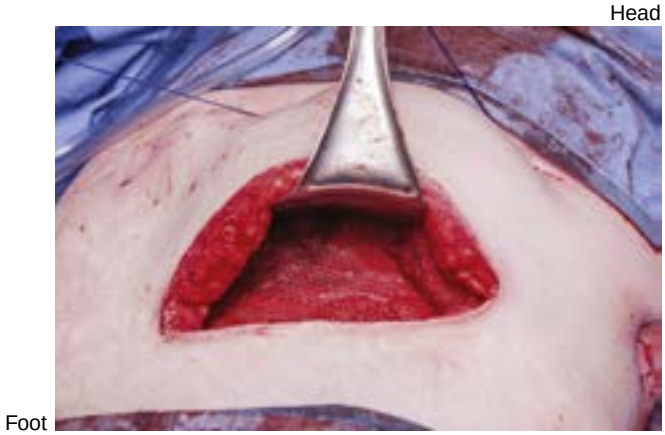


FIG. 11 Cephalad transfascial sutures with the bed unflexed.

not amenable to fixation, such as the space of Retzius and inside the pelvic brim. If there is a lack of soft tissue in the inferior aspect through which to fixate the mesh, the mesh may be fixated to the iliac crest utilizing bone anchors (Video 4). A cordless surgical drill

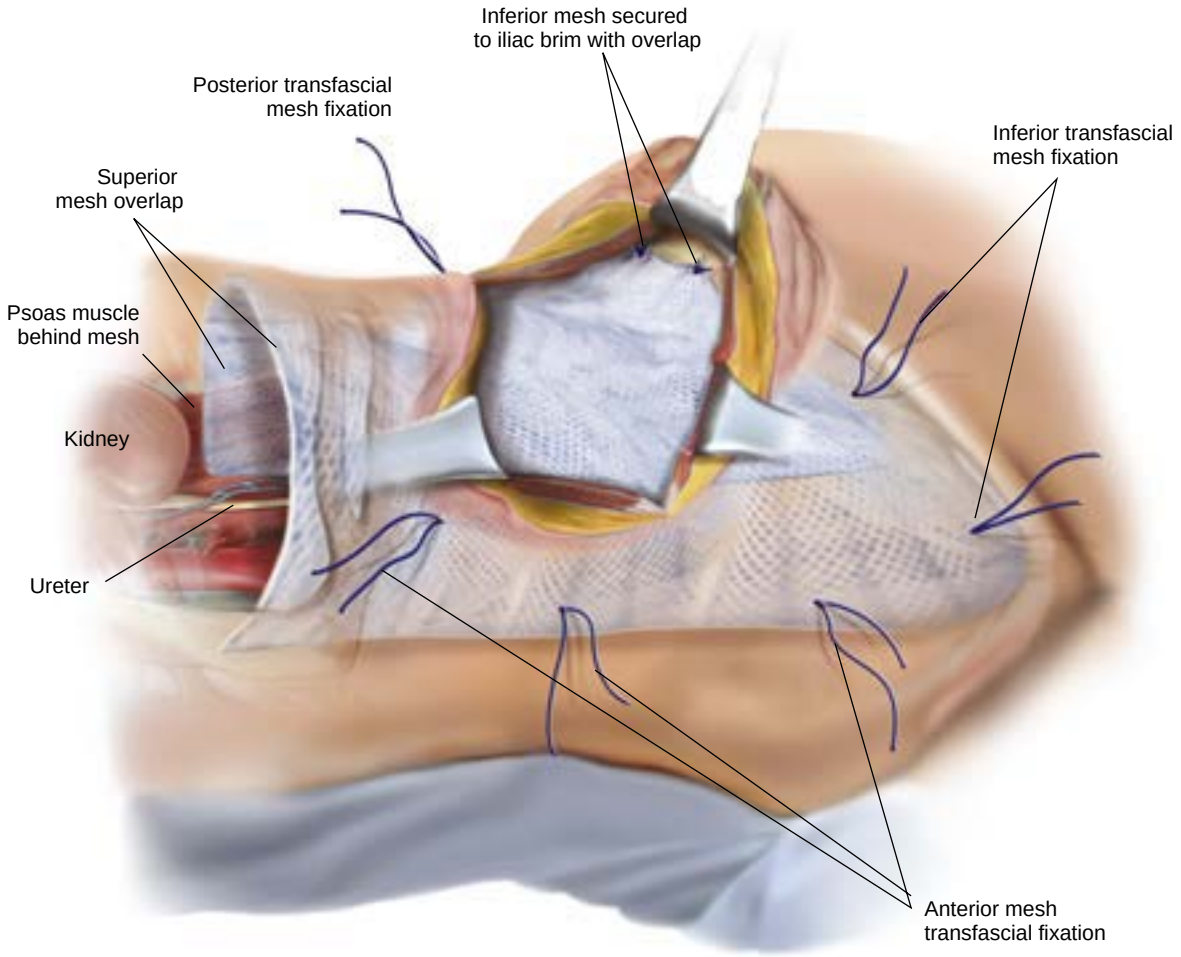


FIG. 12 **Final mesh placement.** *(From Rosen MJ.* Atlas of Abdominal Wall Reconstruction. *2nd ed. Philadelphia: Elsevier; 2016.)*

is used to create the desired number of holes for suture fixation to the iliac crest. Mitek bone anchors (Mitek Surgical Products, Westwood, MA) containing titanium anchors with double No. 2 braided polyester sutures are placed into the preplaced holes. Each arm of the bone anchor suture is passed through the mesh and tied, securing the mesh to the iliac crest. Two additional sutures attached to the bone anchor may be removed. A scalpel is typically required to cut these sutures. As noted earlier, the sutures should pass through the mesh several centimeters in from the edge of the mesh to allow for adequate mesh overlap of the pelvic brim. At this point, the beanbag is allowed to release, and the bed is then "unflexed" and returned to the neutral position. The superior aspect of the mesh is now fixated along the cephalad aspect utilizing No. 1 slow-absorbing monofilament sutures with a transfascial suture passer through stab incisions in the skin (Figs. 11 and 12). The mesh is now secured circumferentially, and the sutures are all tied down at this point to allow for the mesh to lay flat within the space. Returning the bed from the flexed to neutral position allows the mesh to be placed under tension so it remains flat for integration and contour. A Jackson-Pratt drain is typically left overlying the mesh and underneath the muscle. This is brought out medially, near the ventral aspect of the patient's incision, to minimize pain and avoid the patient lying on the drain after surgery. The overlying layers of lateral abdominal musculature are closed utilizing No. 1 slow-absorbing monofilament sutures. This can be accomplished in a running fashion if there is adequate laxity. Otherwise, interrupted figure-of-8 sutures may be placed sequentially and left untied until the entire area is incorporated, and then they can be tied down subsequently to mitigate tension on the repair. The skin is then closed in absorbable layers or as per surgeon discretion.

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Athletic Pubalgia

Samer Sbayi, MD, MBA, and Konstantinos Spaniolas, MD

The purpose of this chapter is to provide the best understanding possible of this surgical disease entity for the general surgeon, by identifying the involved elements that comprise it, through patient presentation, clinical history, physical examination, diagnostic workup, and interventions both nonsurgical and surgical that move the athletic patient from a place of limited function toward near complete function.

The patient is a professional, collegiate, or occasional athlete. The former two are constant and purposeful in their daily training, whereas the latter may be limited to time constraints based on work/life schedule and may not be as deliberate and consistent. The distinction is important as the mechanism is hinged on constant and repetitive bursts of activity versus the occasional not-as-frequent triggers in a not-as-conditioned body.

The symptomatic patient will shrug off the pain and ignore the inherent consequent limiting effects and push through to accomplish the task; the pain will inevitably worsen with activity. The mornings may be worse; symptoms may improve with the first few minutes of activity but often gets worse and more intense as the activity is continued. Many will report loss of their explosive nature. To understand how pervasive this is, a simple Google search for "athletic hernias for different sports" will yield multiple news reports.

Timing of the injury is critical but not specific. This can be preseason, midseason, or just before playoffs. Difficult decisions are at hand, as the athlete shares subjective and objective responsibility in the teams' goals and wishes to see them through. The physical limitations are too apparent to ignore, and the financial commitments and consequences of an ignored injury and absence for recovery for questionable outcomes of conservative and uncertain surgical interventions can be overwhelming. Online news boards detail athlete's health in terms of statistics and compare to previous years. The injury may be related to a trend in poor performance. Often contracts will be discussed (e.g., time left, player vs. team options) and how important it is for this player to be in excellent condition to fulfill their contractual obligations in the upcoming season.

Considering that many leagues have set games to get through, and the financial projections anticipated based on many investments, with the most expensive being the athletes, teams are continually heavily invested in their players for meaningful workups of the injury and dead-on interventions to plug them back into the game. Players are vetted on their athleticism and demonstrated mature experience but equally important on their health and injury-free history.

There is a statistically significant relationship seen with number of days out due to injury incurred by a team per season between the expected and actual rank achieved in the league standings. Meckel et al. reported that 271 injury days may cost a team one place in the rank. In the 2016–2017 English Premier League season, clubs suffered an average of 1410 injury days, dropping an average of six places in the rank table compared with their expected position. This translates into a financial loss of approximately 36 million pounds sterling.

Any treatment plan requires some intervention. However, current payers, mainly medical insurance companies, often consider surgical treatment of a legitimate groin injury "athletic pubalgia" based on history, clinical exam, and diagnostic imaging, defined as "experimental and investigational" and cannot guarantee payment. An online search of "athletic pubalgia" and your payer will lead you to that document. The patient and physician are left to make complicated financial transactions. The reason for this lies in the vagueness in defining a unified understanding and approach to groin injuries.

The surgeon should also understand the patient's potentially frustrating experience with treatments and consider participating in online chat rooms or blogs to get a better understanding that the correct diagnosis and management approach continues to evade most physicians. Patients will come armed with thorough online information and experiences ready to engage in lengthy conversations. This chapter will prepare the general surgeon for such interactions.

APPROACH TO GROIN PAIN

For the general surgeon, the approach to the groin pain patient utilizes traditional history-taking and physical examination tools. This is not a matter of the presence or absence of a hernia. The question here for the general surgeon is where do you begin to diagnose, using what workup, and if there is no hernia, then what is your next move? What will need to change is that the decision tree needs to move further once no hernia is identified. The history of the onset of pain needs to be deliberate in ascertaining the modifiable activities or inactivities that exacerbate the pain.

Definitions

Broad Categorization

1. Core muscle injury (athletic pubalgia)
2. Ball-in-socket hip joint injury
3. Other causes (Table 1)

Poor et al. define a core muscle injury as damage to any skeletal muscle within the area between the chest and the mid-thigh. The anterior pubic bone with muscle attachments and the pubic symphysis forms the center of core injuries. The elements that provide stability and injury that are core in nature are the caudal attachment of the rectus abdominis muscle to the pubis with fusion of the three adductors (adductor longus, adductor brevis, and pectineus), forming a musculoaponeurotic plate (Fig. 1).

Meanwhile, Weir et al. also define three categories:

1. Adductor-related, iliopsoas-related, inguinal-related, and pubic-related groin pain (Fig. 2)
2. Hip-related groin pain
3. Other causes of groin pain in athletes

Both categorizations are heavy on a well-elicited history and physical that focuses on resistive movements to define the injured elements.

Start With the Activity

These patients will mostly be the more active ones who push their individual limits as a high school, collegiate, university, or professional athlete. Consider the relevant sport to guide your triggers and localize the area of pain.

Consider the duration of recurrent pain, chronic versus acute, preseason, training camp, or playoffs. This can be a high-stakes visit, and trainers and coaches may also be present to provide a full picture of the problem and enhance the multidisciplinary approach.

Next, correlate the history with the physical findings. A ***thorough exam*** considers the area of pain and the possible secondary reasons for that. Patients should be examined standing and supine. Visual inspection is very telling, as hernias and ***asymmetries*** for inflamed or atrophied muscle groups can be identified. Your optical scan starts at the level of the anterior superior iliac spine (ASIS) from one side and runs to the opposite side across the navel. Then continue the scan in the caudad, examining groins, the genitals, and the thighs. Identify the area of pain and palpate for an inguinal hernia with and

TABLE 1 An Overview of Other Causes of Groin Pain in Athletes

Other Musculoskeletal Causes	Not To Be Missed
Inguinal or femoral hernia Posthernioplasty pain Nerve entrapment • Obturator • Ilioinguinal • Genitofemoral • Iliohypogastric Referred pain • Lumbar spine • Sacroiliac joint Apophysitis or avulsion fracture • Anterior superior iliac spine • Anterior inferior iliac spine • Pubic bone	Stress fracture • Neck of femur • Pubic ramus • Acetabulum Hip joint • Slipped capital femoral epiphysis (adolescents) • Perthes' disease (children and adolescents) • Avascular necrosis/transient osteoporosis of the head of the femur • Arthritis of the hip joint (reactive or infectious) Inguinal lymphadenopathy/Intraabdominal abnormality • Prostatitis • Urinary tract infections • Kidney stone • Appendicitis • Diverticulitis Gynecologic conditions Spondyloarthropathies • Ankylosing spondylitis Tumors • Testicular tumors • Bone tumors • Prostate cancer • Urinary tract cancer • Digestive tract cancer • Soft tissue tumors

From Weir A, Brukner P, Delahunt E, et al. Doha agreement meeting on terminology and definitions in groin pain in athletes. *Br J Sports Med*. 2015;49:768–774.

without Valsalva. The anterior palpation of the inguinal region is just as important as the scrotal invagination to examine the external ring. Also identify the femoral space and examine for a hernia. Remember, this is adjacent and lateral to the pubic tubercle and below the inguinal ligament. Palpate the pubis and tubercles at the rectus abdominis insertions in the ***neutral and engaged*** positions. For example, have the patient crunch their core and then relax. If the rectus abdominis muscle is symptomatic, it will be tender on palpation while engaged. Examine the adductors by sliding your hand up the medial side of the leg into the groin where it stops; you will feel the adductor tendon as it inserts on the pubis. Here you are examining for injuries to the adductor longus, brevis, and pectineus musculatures. Ask the patient to squeeze their knees to engage the adductors while you provide counterpressure; this may elicit pain, and it will be tender up on your palpation. In the supine position, repeat this exam—inspection and palpation—but now ask the patient to do a half-sit-up while you palpate the rectus abdominis insertion on the pubis and run your fingers in the cephalad toward the ASIS, palpating the obliques, across to the inguinal ligament and identifying any tenderness, while attempting to elicit the occasional entrapment of branches of the iliohypogastric, ilioinguinal, and genital branch of the genitofemoral nerve. If nerves are involved, you will be able to follow their affected areas. Injuries to the fibrocartilage musculotendinous plate of the rectus abdominis and adductor longus will likely put undue stress on the transversalis fascia and inguinal floor as rebalancing is sought by the body to compensate for the injury and some level of inflammatory edema is generated in this space. It becomes very important to palpate the inguinal canal for this reason where a patulous superficial ring may be appreciated. Pay attention to palpate across from the ASIS medially where Spigelian hernias are. If this is the problem, the patient will guide the exam in that direction.

GROIN PAIN CONSIDERATIONS

There could be as many as 70 causes for groin pain. The general surgeon should be aware of many of these. Compression neuropathies of nerves crossing the inguinal region can be triggered by repeated traumatic events of the area. Also included are findings of peripheral neurologic symptoms such as hypoesthesia, paresthesia, and weakness. Intervertebral disc diseases and spondylarthrosis may determine radiculopathy with radiation to the groin (T12-L1-L2); benign vertebral segmental dysfunctions, mechanical and reflex in nature, are generally reversible. Other involved etiologies can be femoris, pelvis, and hip boney pathologies. Also consider other medical differentials, such as urogenital and gastrointestinal.

Hip Pathologies

There is increasing evidence of association between hip pathologies, particularly femoroacetabular impingement (FAI) syndrome and athletic pubalgia (core muscle injury). FAI presenting as compromised hip motion can be commonly compensated by recruitment of peripubic muscular attachments and threatening them for injury if prolonged dependance is required without addressing this surgical disease. Hence, a complete evaluation of hip range of motion along with impingement testing is performed. Pain or loss of motion with flexion, adduction, and internal rotation or flexion, abduction, and internal rotation indicates FAI as a potential concomitant diagnosis. Patients may describe clicking, catching, locking, stiffness, restricted range of motion, or giving way. This can be severe and limiting in everyday life. When suspected, examine gait, single leg control, muscle tenderness around the hip, and hip range of motion including internal rotation in flexion and the FABER distance (flexion abduction external rotation) (Fig. 3).

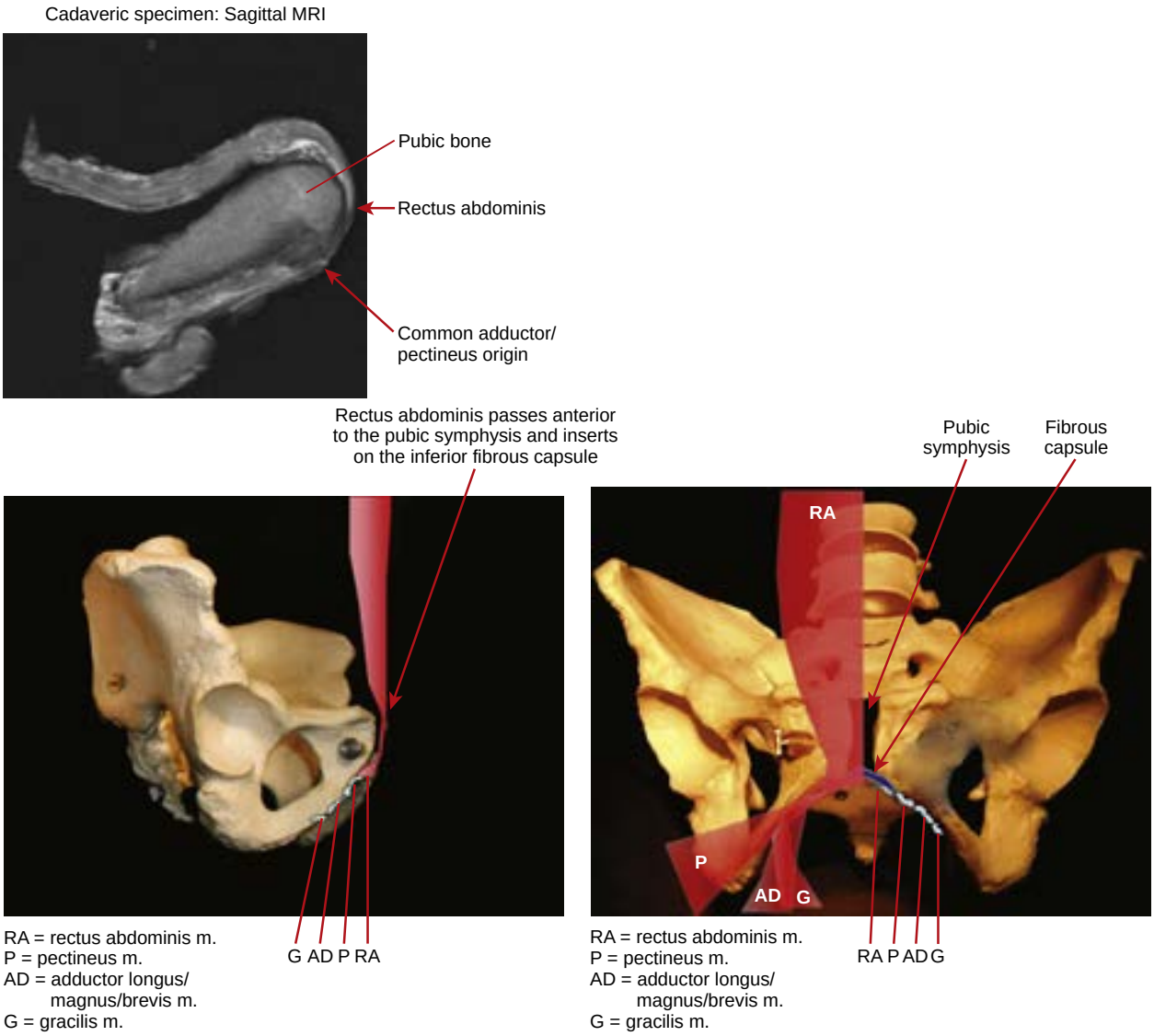


FIG. 1 The relationship of the common aponeurosis of the rectus abdominis and adductor longus demonstrated in the coronal and sagittal planes. *(From Morrison W.* Problem Solving in Musculoskeletal Imaging. *Philadelphia: Elsevier; 2010.)*

WORKUP/IMAGING

Although plain radiographs of the pelvis and hips can be very telling, visualizing the proximal femur requires orthogonal views of the neck such as the cross-table lateral, Dunn, and frog laterals. These views still can be limiting in properly visualizing three-dimensional shapes and limit pincer (acetabular) and cam (femoral neck) morphology. Cross-sectional imaging, either CT or MRI, is particularly more informative when considering surgical intervention, and MR arthrography is more accurate than plain MRI to assess the labrum and articular cartilage. Additionally, MRI provides more information about a soft tissue lesion that may result in hip and groin pain. The MRI can identify the tendon avulsion and tendinitis as increased signal and frank detachment. You should seek out a musculoskeletal radiology expert to review with you.

When comparing MRI to intraoperative findings, Zoga et al. found a sensitivity and specificity of 68% and 100%, respectively, for rectus abdominis injury and 86% and 89%, respectively, for adductor longus injury. Based on these findings, Zoga et al. identified that the most valuable diagnostic information is acquired utilizing a specialized MRI noncontrast protocol (Table 2).

The planes of imaging are optimized to evaluate the musculoskeletal core with high resolution noncontrast MR imaging in four planes with a phased array surface coil. This can be on 1.5 Tesla machines or later models where the peripheral elements can be turned off to acquire higher resolution sequences. Large field of view coronal and axial imaging as well as smaller field covers from the level of the umbilicus to the proximal third of the thighs are the basic framework for imaging. Furthermore, sagittal planes along with coronal and oblique planes prescribed along the arcuate line of the pelvis (anterior crest of the iliac bones) can reveal subtle abnormalities.

This workup will identify some common differentials to consider, adductor strains, osteitis pubis (fibrocartilage and musculotendinous plate detachment, plus or minus muscular injuries of the rectus abdominis and adductor longus), stress fractures, and FAI, as you develop your diagnosis and identify opportunities to intervene.

MANAGEMENT

Surgical and nonsurgical modalities are considered depending on acute versus chronic injuries. In-season athletes can consider a 6- to 8-week trial of conservative management to get through the season. This can include NSAIDs, heat/ice, massage, 6 to 8 weeks away from games, focused progressive resistance and stretching, sports-specific functional task, and gradual return to full activities. The physician

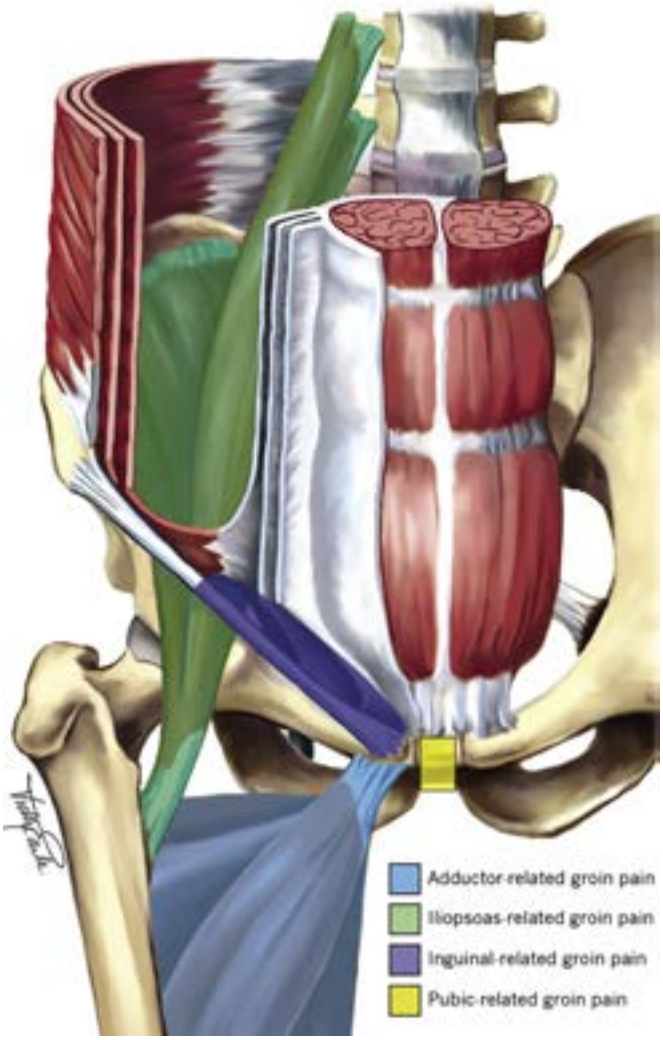


FIG. 2 Classification of groin pain. *(From Weir A, Brukner P, Delahunt E, et al. Doha agreement meeting on terminology and definitions in groin pain in athletes.* Br J Sports Med. *2015;49:768–774.)*

will work closely with coach, trainers, and patient to ensure that symptoms are not worsening.

Injection using ultrasound guidance with local anesthetic and a corticosteroid can provide initial relief by temporizing the inflammatory reaction and, in some studies, facilitate a return to preinjury activity. Anesthetic and corticosteroid combinations can be lidocaine, bupivacaine, ropivacaine with and without epinephrine, and triamcinolone acetonide or methylprednisolone. Relief may last as long as 14 days.

Percutaneous tenotomy for an adductor tendinosis, for example, with a 20G or 18G needle and lidocaine, while needling the tendon may loosen up the tendon and induce bleeding, recruiting platelets, growth factors, and cytokines. Prolotherapy may be used by injecting a local anesthetic acting as a proliferant, changing the chemical environment to assist with healing.

Platelet-rich plasma injection can be performed with needling to induce growth factor release to stimulate healing. However, heterotopic ossification of the area has been reported, which required debridement and compartment release.

SURGERY AND CLINICAL ENTITIES

Surgery is considered after conservative treatment has failed. Six to 12 weeks is agreed by most as satisfactory to offer surgery. This is the ongoing presence of symptoms and inability to perform at expected athletic ability.

Unilateral or Bilateral Rectus Abdominis/Adductor Aponeurosis Injury (U or B RA/AAI)

This is the most common core injury in athletic pubalgia identified on MRI. A dedicated athletic pubalgia protocol MRI can help with diagnosis. Clinical findings (point tenderness) mirror mostly a unilateral surgical disease and involve instability of the superficial ring with visualization of a subtle bulge on MRI, US, or clinical examination. These injuries could be found in baseball pitchers and hitters. Surgical approach is pelvic repair with inguinal floor stabilization and suture reinforcement/repair of the RA/AA.

Midline Rectus Abdominis/Adductor Aponeurotic Plate Injury (M RA/AAPI)

This injury is also identified on dedicated athletic pubalgia MRI protocol. This can be common to hockey goalies and females. A unilateral pelvic floor repair of the symptomatic side is offered, and a bilateral repair should be discussed because repair of the injury could threaten the unrepaired side.

Osteitis Pubis

This is identified as bone marrow edema secondary to the altered biomechanics due to a core muscle injury causing inflammation. Acute and chronic forms exist. This can exist in soccer and football players. Once the pelvic repair of the symptomatic side is undertaken, this finding tends to progressively improve over time with time away from activity.

This can also exist without soft tissue injury, which may be related to pregnancy or axial loading traumas. Image-guided steroid injections can be helpful.

Adductor Injury

This includes mostly the adductor longus, adductor brevis, and pectineus muscles that intimately blend into the pubic plate with the caudal rectus abdominis muscles. MRI with athletic pubalgia protocol can best interpret their involvement in injury. Injuries could be proximal and warrant pelvic repair. Acute injuries can be dramatic in presentation with varying degrees of avulsion with and without fragments of the bony pubis requiring surgical fixation. Chronic injuries exist distal to this and can be recurrent and warrant debridement and compartment decompression if conservative measures with time, physical therapy, and injection are not effective. An example of this is hockey players, and the lesion is called "baseball pitcher hockey goalie syndrome" (BPHGS).

Rectus Abdominis Strain

This refers to more caudal injuries to the pubis and are mostly treated conservatively with rest, physical therapy, image-guided injection, and rarely with debridement and compartment decompression.

Inguinal Hernia

True hernias can accompany muscular injuries that contribute to a core/athletic pubalgia injury. What is found more commonly is weakness causing instability and bulging in differing degrees that can be appreciated on imaging (US/athletic pubalgia MRI protocol) or physical exam along with the soft-tissue elements (e.g., RA/AAI). Precise diagnosis should be deliberately sought. A combination of clinical history, physical exam, and imaging must be considered to give this a complete assessment. Prone positioning during MRI or US with or without Valsalva maneuvers can be helpful.

A weak and wide superficial ring in addition to RA/AAI can be addressed during the pelvic floor repair.

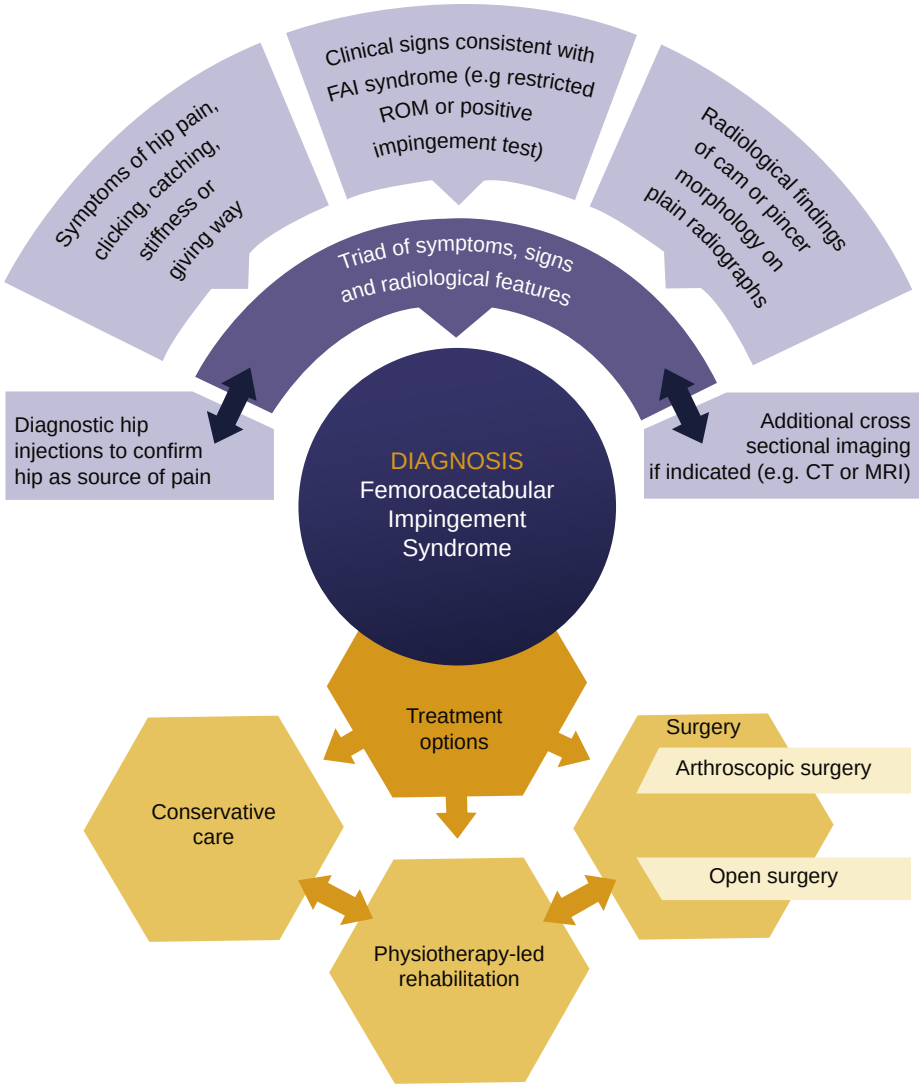


FIG. 3 Diagnostic algorithm for femoroacetabular impingement (FAI) syndrome. *(From Griffin DR, Dickenson EJ, O'Donnell J, et al. The Warwick Agreement on femoroacetabular impingement syndrome (FAI syndrome): an international consensus statement.* Br J Sports Med. *2016;50:1169–1176.)*

TABLE 2 Thomas Jefferson University 1.5 T MR Imaging Protocol for Athletic Pubalgia

Sequence	Plane	FOV (cm^2)	Matrix	Section Thickness/ Gap (mm)	TR (msec)	TE (msec)	TI (msec)	BW (kHz)	ETL
STIR	Coronal	28–36	256 × 192	4/1	>2000	20–40	150	160	8
T1-weighted SE	Coronal	28	256 × 256	4/1	400–800	Min	NA	16	NA
T2-weighted fat-suppressed FSE	Axial	28	256 × 192	5/1	>2000	50–60	NA	16	8
PD-weighted fat-suppressed FSE	Sagittal	20–20	256 × 256	4/0.5	>2000	20–40	NA	16	8
PD-weighted fat-suppressed FSE	Axial oblique*	20	256 × 256	4/0.5	>2000	20–40	NA	16	8
PD FSE nonfat-suppressed	Axial oblique*	20	256 × 256	4/0.5	3000	15–30	NA	16	4–6

Indications for MR imaging with this protocol include suspicion of a rectus abdominis injury, adductor injury, osteitis pubis, or athletic pubalgia. All sequences should be centered on the symphysis pubis.

*The use of the axial oblique plane is recommended to maximize sensitivity for the detection of rectus abdominis-adductor longus myotendinous injuries.

BW, Bandwidth; *ETL*, echo train length; *FOV*, field of view; *FSE*, fast spin echo; *NA*, not applicable; *SE*, spin echo; *STIR*, short inversion time inversion recovery; *TE*, echo time; *TI*, inversion time; *TR*, repetition time.

From Mizrahi DJ, Poor AE, Meyers WC, et al. Imaging of the pelvis and lower extremity, demystifying uncommon sources of pelvic pain. *Radiol Clin North Am*. 2018;56:983–995.

OTHER SOURCES OF GROIN PAIN

Hip Disorders

Approximately 16% of the time, hip disorders can occur with core/athletic pubalgia injuries and require orthopedic collaboration and subsequent dedicated imaging with direct MR arthrography with intraarticular contrast and anesthetic injection. Stress fractures, accessory flexor lesions, and apophysitis are some other findings in the workup.

Surgical Approach

The more common elements that need to be considered and addressed are repairing the site of injury and stabilizing the anterior pelvis. Stabilizing the pelvis with an inguinal hernia repair approach or adductor longus tenotomy and/or reimplantation of the rectus abdominis-adductor longus aponeurosis have not proven to be singularly successful in relief of symptoms. When all elements are addressed, a 95% success rate was observed in achieving resolution or enough recovery to allow return to baseline activity. Omar et al. referred to this as a pelvic floor repair. Meyers et al. describes this as a broad surgical reattachment of the inferolateral edge of the rectus abdominis muscle with its fascial investment to the pubis and adjacent anterior ligaments. It is a modified Bassini repair (Fig. 4): the first stitch includes the sheath of the rectus abdominis laterally to the pubic periosteum, then the inguinal ligament, then progresses in the direction of the ASIS with other interrupted sutures if there is

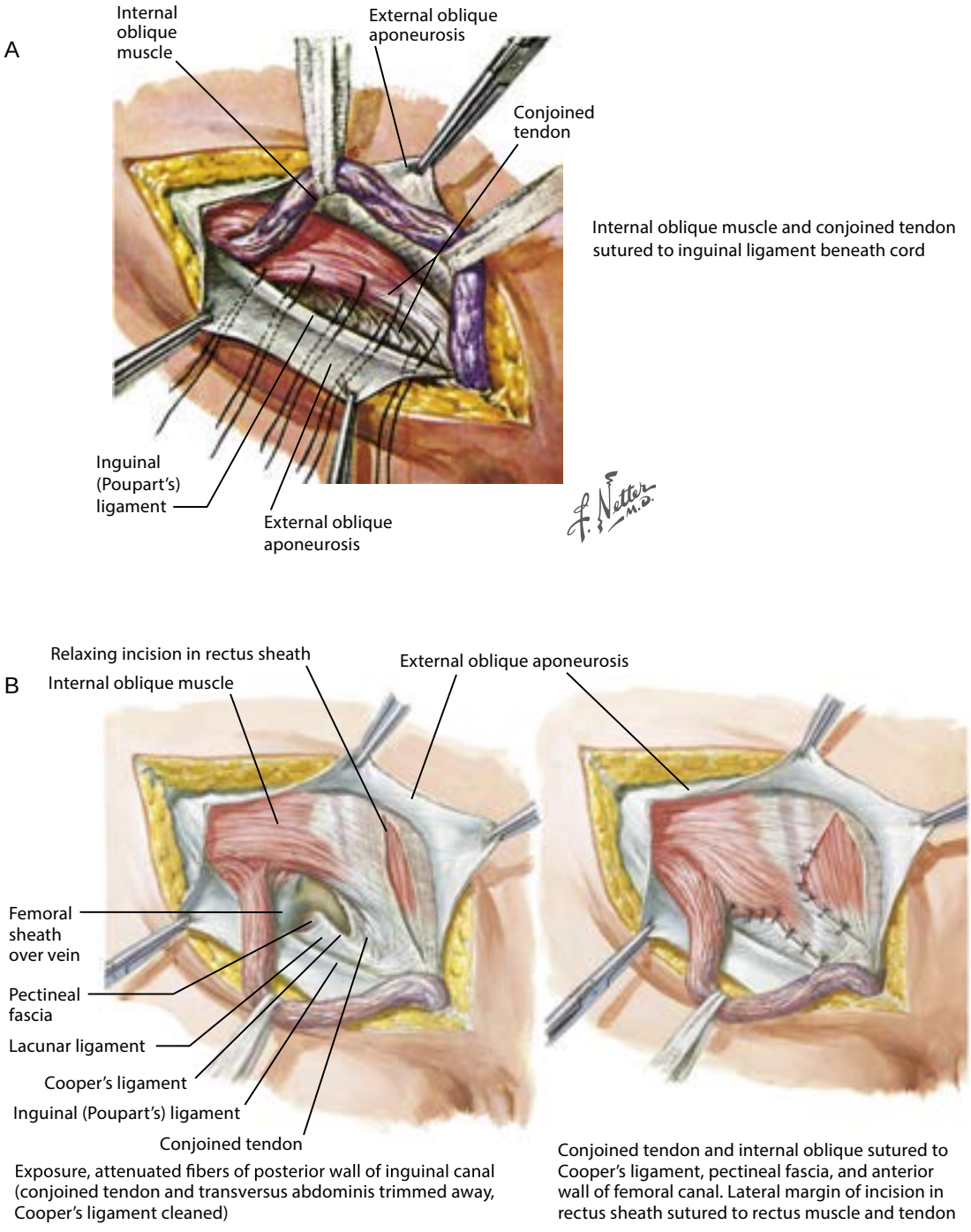


FIG. 4 **(A)** Bassini repair. **(B)** McVay repair. *(From Delaney:* Netter's Surgical Anatomy and Approaches, *Philadelphia: Elsevier; 2014.)*

continued bulging in the floor. This is combined with longitudinal incisions in the anterior and lateral epimysial fibers of the adductor longus (adductor compartmental decompression) at the pubic attachment or fractional lengthening and incomplete adductor longus tenotomy about 1 cm off the pubic origin and/or primary muscle suture repair.

Emblom et al. describes an adductor longus tenotomy 2 to 3 cm distal to its pubic attachment, releasing it, which will then fold the 1 cm flap off the pelvis onto the rectus aponeurosis with three nonabsorbable figure-of-8 sutures. The concern with this is the potential likelihood of pelvis imbalance incurred despite symptomatic relief. The authors report a 96% rate of return to sport, with a mean recovery time of 4.1 ± 2.3 months (range, 1–12 months).

If there is clear bulging in the direct space, the floor is opened, and a tissue repair or mesh repair is used to approximate it. If the bulge is identified preoperatively, a laparoscopic mesh repair has been used. In the open repairs, the genital branch of the genital femoral nerve is selectively transected (decompressed) along with the ilioinguinal nerve if involved with scarring. The cremasterics are preserved if feasible to preserve the cremasteric reflex, but these are usually heavily scarred and thickened causing the potential nerve entrapment. The iliohypogastric nerve is sought out, examined, and preserved if no surrounding inflammation or involved scarring is identified.

The Shouldice repair (Fig. 5) can also be used to address direct space bulging. The inferior portion of the incision is extended onto

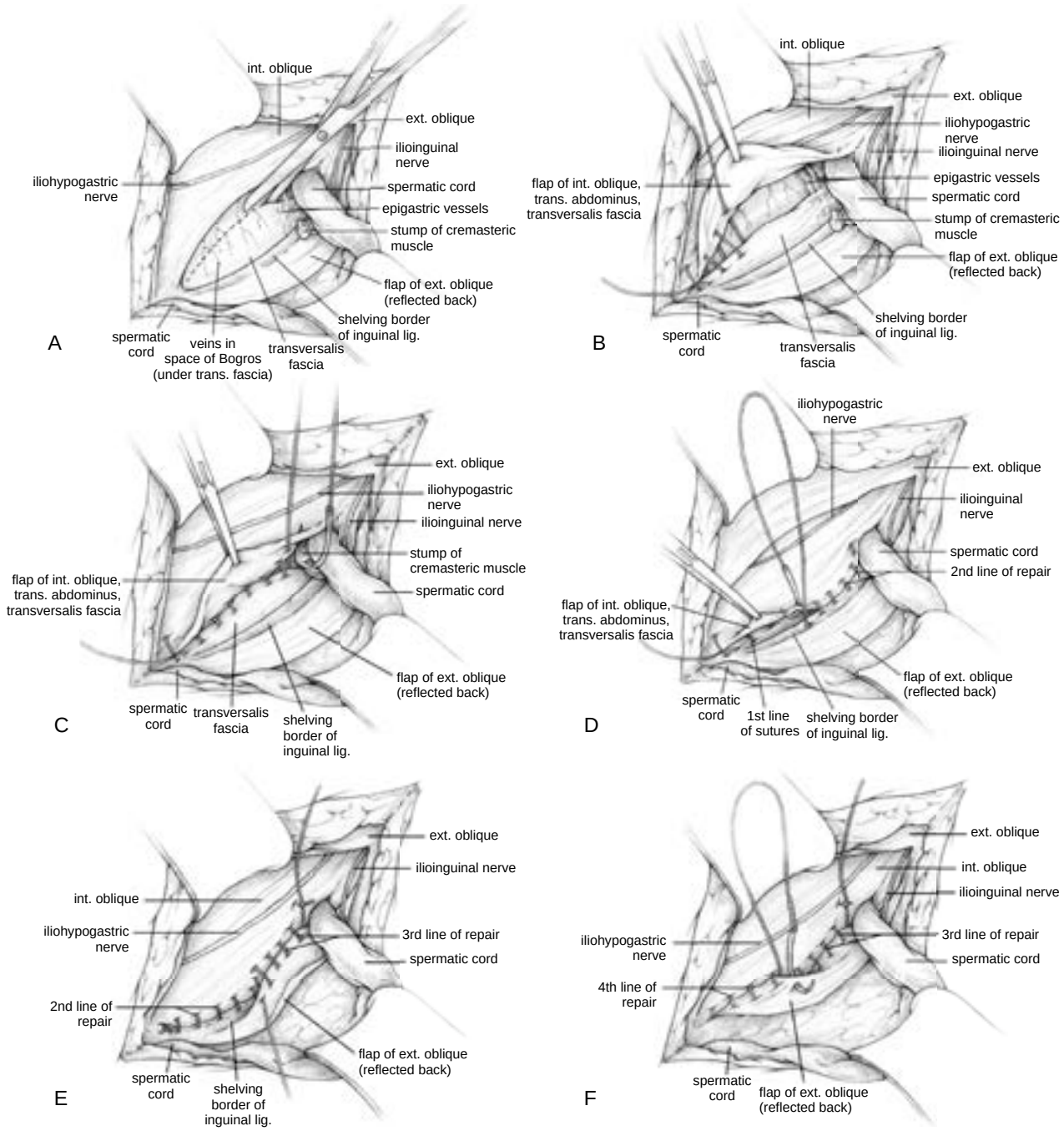


FIG. 5 Shouldice repair. *(From Shouldice EB. The Shouldice repair for groin hernias.* Surg Clin North Am. *2003;83:1163–1187.)*

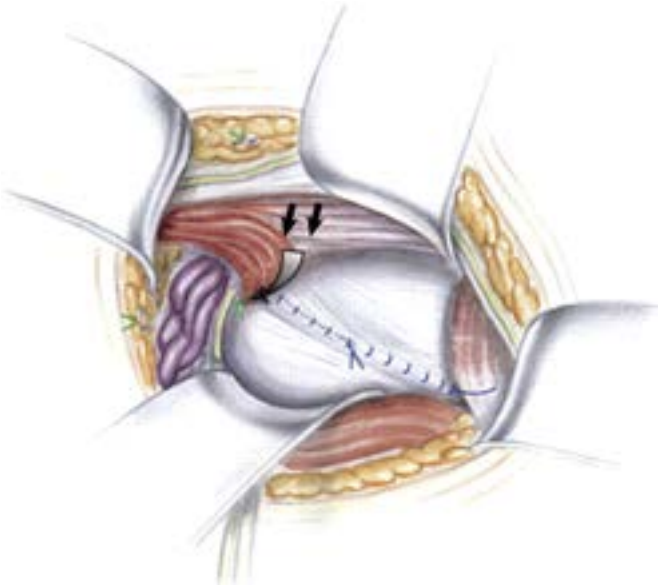


FIG. 6 Minimal repair technique. *(From Miller M, Thompson S.* DeLee, Drez and Miller's Orthopaedic Sports Medicine, *5th edition. Philadelphia: Elsevier, 2018.)*

the pubis to expose the rectus abdominis-adductor longus union to perform the tenotomy and then suture repair of the area using the Shouldice technique as the pelvic repair. The first suture will take the rectus abdominis laterally then the inguinal ligament, then as it comes back in the second line, it drifts past this starting point onto the pubic tubercle taking another two or three bites of the rectus abdominis sheath and the periosteum of the pubic tubercle, effectively reimplanting the rectus abdominis-adductor longus plate.

Isolated repair of a bulge in the direct space is also reported by Muschaweck et al. This can be combined with a pelvic repair and adductor tenotomy if indicated as previously discussed. The repair opens the weak area of the transversalis fascia, and a two-line repair using nonabsorbable suture is used (Fig. 6). The author reports return to unrestricted sports activities for this minimal repair technique in 83.7% of their athletes over a median of 14 days.

OUTCOME MEASURES

The use of validated outcomes tools is encouraged. The Copenhagen Hip and Groin Outcome Score (HAGOS) appears to be the closest patient-reported outcome tool focusing on young to middle-aged physically active people with hip and/or groin pain. It is unique as the questions relate to groin and hip problems.

SUMMARY

Athletic pubalgia is a complex surgical entity that can be managed by the general surgeon as the lead consultant as part of a multidisciplinary team. A thorough history, physical, and guided imaging such as an athletic pubalgia MRI are imperative in narrowing the differentials and directing the therapeutic options. This surgical entity is ever-developing, and progress over the past 20 years has allowed for a better and clearer understanding.

Suggested Readings

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Abdominal Wall Reconstruction

Dina Podolsky, MD, Kelly H. Tunder, DO, and Yuri W. Novitsky, MD

INTRODUCTION

The management of large abdominal wall defects remains a clinical challenge for general surgeons. For midline defects, the foundational principle of an abdominal wall reconstruction (AWR) implies restoration of the abdominal wall anatomy by medialization of the recti muscles. Such myofascial advancement is achieved via a set of "release(s)" of various muscle/fascial layers that, as a result of hernia-induced changes, resist easy linea alba restoration. In addition, another main goal of a typical AWR includes restoration of a dynamic/physiologic truncal muscle complex. Finally, to provide for a safe and durable AWR, adequate prosthetic reinforcement and soft tissue coverage of the repair are paramount. Since the original description of an open anterior component separation (ACS) technique by Ramirez in 1990, many modifications and additions to the AWR toolbox have been developed. Herein we will describe all

relevant anatomy, principles, technical details, and patient selection for various common AWR approaches.

ANATOMY

Muscle Groups

The abdomen consists of a midline muscle group composed primarily of the rectus abdominis (RA) and the variable pyramidalis, while the anterolateral muscle groups are composed of the external oblique muscle (EOM), internal oblique muscle (IOM), and transversus abdominis muscle (TAM). Importantly, the TAM extends medially underneath the lateral edge of the rectus and, especially in the upper half of the abdomen, is a major contributor to the posterior rectus sheath. In the subxiphoid region, the fibers of the TAM interdigitate with those of the anterior diaphragm.

Tendinous Structures

The *linea alba* connects both RA complexes in the midline, running from the xyphoid to the pubic symphysis, and has contributions from the aponeurosis of the EOM, IOM, and TAMs. The linea alba serves as a stabilizing force of the trunk and is considered to be an important anchor of both abdominal muscle groups. It is the more precise recent understanding of the importance of linea alba restoration that has fueled the evolution of abdominal wall surgery in the past 15 years. The linea semilunaris is another tendinous structure that connects the midline and anterolateral muscle groups. The essential function of the normal linea semilunaris has become apparent after evaluation of patients with linea semilunaris iatrogenic injuries. Those patients have discontinuity of lateral and central muscle groups, often associated with major hernia and overall abdominal wall morbidity. The linea semicircularis, also known as the *arcuate line of Douglas,* is the inferior border of the posterior rectus sheath; below this line, the posterior envelope of the rectus muscle is composed only of the transversalis fascia and peritoneum.

Vascular Supply

The vascular supply of the abdominal wall is divided into zones. Zone 1 (the RA complex around/above the umbilicus) is supplied by the superior and inferior epigastric arteries. Zone 2 (the area below the umbilicus) is supplied by branches of the iliac and femoral arteries as well as the inferior epigastric artery. Zone 3 (which is lateral to the semilunar line) is supplied by contributions from the lumbar and intercostal arteries.

Nerve Supply

The anterior abdominal wall is innervated by contributions from the thoracolumbar spinal cord at T6/7 to T11/L1 levels. These neurovascular bundles exit the spinal cord and run in the plane between the IOM and TAM and pierce the posterior sheath just medial to the semilunar line. This anatomic feature is important for two main reasons. First, the plane between the IOM and TAM is targeted for the transversus abdominis plane (TAP) blocks. Second, the neurovascular bundles are an important landmark to help identify the linea semilunaris during retrorectus dissection.

PATIENT SELECTION AND PREPARATION FOR AWR

Abdominal wall reconstruction should be considered in most patients with large defects, for whom restoration of the linea alba cannot be achieved via any other surgical technique. This tends to refer to patients with large/wide hernias (>8–10 cm), especially patients with previously failed hernia repairs. Preoperatively, patients undergo noncontrast computed tomography (CT) of the abdomen and pelvis to delineate the anatomy and help determine operative approach. We require a CT within 3 months of surgery to ensure an accurate representation of the abdominal wall. Preoperative optimization is an integral part of the process to improve postoperative outcomes. Optimization includes smoking cessation for a minimum of 4 weeks before surgery, adequate hyperglycemic control (HbA1c <7.5%) for diabetic patients, and weight control. Although the exact weight loss goals differ among patients/hernia problems, we typically require body mass index (BMI) to decrease to at least <35. For most morbidly obese patients, we offer a low-carbohydrate diet plan, consultation with a certified nutritionist, and/or a bariatric surgery evaluation. For morbidly obese patients with complex recurrent hernias, especially with a parastomal component, careful preoperative preparation and optimization are key and should not be overlooked. We view BMI of 45 an absolute contraindication for any elective AWR unless there are symptoms and signs of impending intestinal injuries. The approach to these patients is highly individualized.

SURGICAL TECHNIQUES

Anterior Component Separation

ACS has traditionally been shown to be a safe and effective option for patients with large midline defects, patients with hostile abdomens, or patients with prior posterior component separation (PCS). This technique should be avoided in patients with increased risk of wound infection, including morbidly obese patients and those with a history of soft tissue infection. This technique can be performed via either an open approach utilizing "perforator-sparing" strategies or minimally invasive/laparoscopic approaches. Mesh placement options for the open technique typically include the onlay (subcutaneous) position, the underlay (intraperitoneal) position, and, less frequently, the retrorectus plane. If periumbilical perforators are sparred, the onlay space is not available. Finally, laparoscopic anterior component separation typically allows for an intraperitoneal underlay mesh placement only. Frequent complications associated with the traditional open technique typically stem from the creation of large lipocutaneous flaps and include flap ischemia, major seromas, and wound infections.

Open ACS

Patient Positioning and Entry

The patient is placed supine on the operating table, and a Foley catheter is placed. In the hands of general surgeons, a midline incision encompassing all scars and attenuated tissue is performed. Plastic surgeons would most commonly begin with a low transverse incision, particularly if a panniculectomy is planned at the completion of the AWR.

The abdomen could be entered to address preoperative intestinal issues (like frequent bouts of obstructions), remove old intraperitoneal mesh, and access the posterior rectus sheath. Alternatively, the operation could be performed in a completely extraperitoneal fashion, staying outside the hernia sac.

Creation of Subcutaneous Flaps

This dissection is performed between the subcutaneous fat and the underlying fascial layers of anterior and lateral abdominal wall. This dissection is carried out laterally to the anterior mid-clavicular or anterior axillary lines. The cephalad extension is to, and at times above, the costal margin. Care should be taken to preserve the zone 3 perforators. Inferiorly, the dissection is extended to the inguinal ligament.

External Oblique Release

The external oblique aponeurosis is identified 1 to 2 cm lateral to the semilunar line and incised along the entire length of the dissection (Fig. 1). Obliquely oriented fibers of the internal oblique muscle



FIG. 1 External oblique (EO) muscle release. The EO aponeurosis is completely divided. The cephalad extent of the division is performed above the costal margin *(dashed line)*.

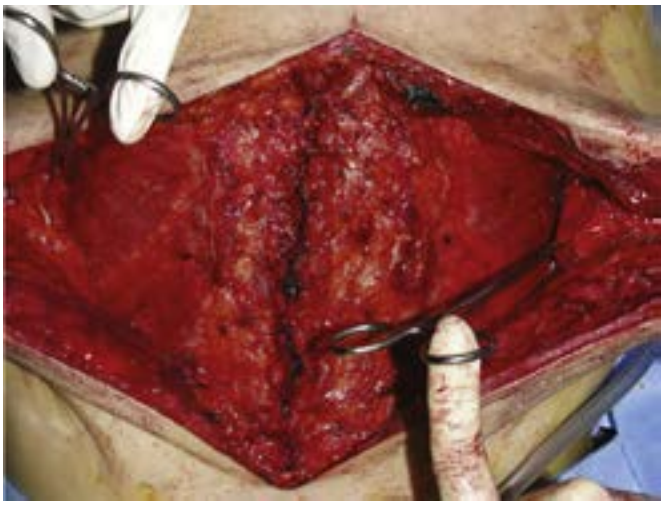


FIG. 2 Bilateral anterior component separation. Note that the lateral *(cut)* edge of the EOM is separated from the underlying IOM. Subsequent mesh placement will extend into the pocket, lateral to the edge of the divided EOM.

should be visible underneath. Alternatively, the muscular portion of the external oblique could be transected as well. This musculo-fascial division should be extended at least to, or even cephalad to, the costal margin, especially when medialization of the upper recti is important. Inferiorly, the vertical line of transection could include an inguinal ligament. Once the musculo-fascial division is completed, the actual separation of the layers of the abdominal wall must follow. The medial-to-lateral dissection proceeds in the avascular plane between the internal and external obliques to the mid-axillary line. The resultant space will allow placement of the mesh underneath divided lateral aspects of the EOM (Fig. 2) to allow for mesh coverage of the released area.

Posterior Rectus Sheath Release

This step was the key initial maneuver in the classic description of an open component separation by Ramirez. However, over time, this step evolved to become an adjunct to the EO release for select cases only. The release of the posterior rectus sheath could be performed by simply incising the center of the fascial layer from the arcuate line to the costal margin. Alternatively, a formal retrorectus dissection

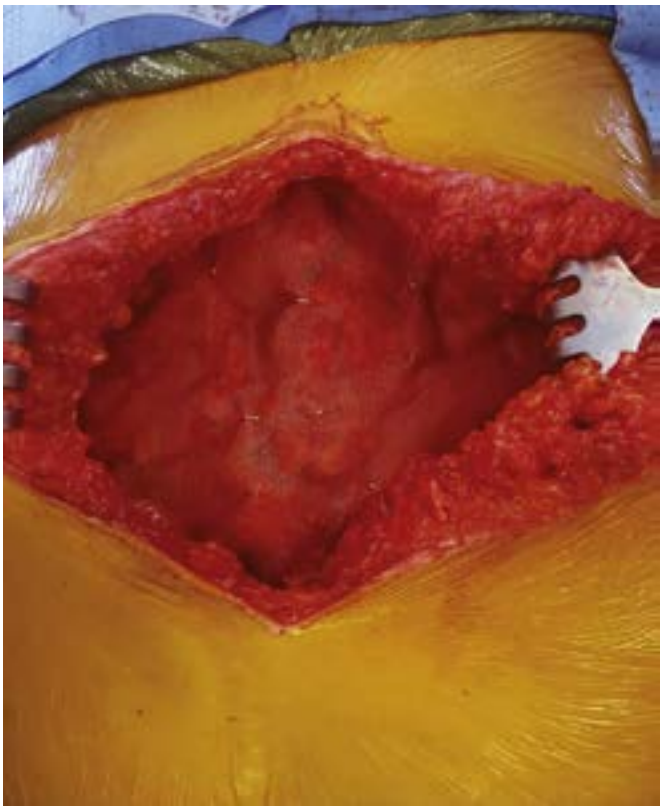


FIG. 3 The onlay mesh is fixated with staples and fibrin glue.

(see later) could be performed, especially if the retrorectus mesh placement is contemplated.

Restoration of the Linea Alba, Onlay Mesh Placement, and Closure

Any excess hernia sac is excised. The linea alba is recreated by using a running slowly absorbable suture. An onlay mesh is then positioned atop the closed fascia. The mesh extend should include the entirety of the developed flap. Laterally, the mesh edge should extend underneath the cut edge of the EOM. We often secure the edge of the EOM to the mesh, typically at least 5–6 cm from the mesh's edge. This allows for an adequate overlap of the defect as well as prosthetic coverage of the release itself. The mesh is further secured with either sutures, staplers, and/or a fibrin sealant (Fig. 3). Subcutaneous drains are placed, and the skin is closed in several layers.

Open ACS with Perforator Preservation

The concern with the traditional open ACS is blood flow compromise to the newly created skin flaps. A traditional ACS will sacrifice all blood vessels to the skin from the midline to approximately mid-clavicular or anterior axillary lines, and the flaps/wound closure will depend on collateral blood supply from the deep inferior epigastrics and lumbar (zone 3) arteries. The technique of perforator preservation attempts to address this issue by preserving the peri-umbilical perforators to the skin.

EO Aponeurosis Identification and Release

This step is the key difference between the traditional and perforator preserving ACS. Several variations of this approach have been described. One option is to develop subcutaneous pockets above and below the periumbilical area, creating access "tunnels" to the semilunar line (Fig. 4). After its identification, the external oblique just lateral to the semilunar line is incised. The transection is extended cephalad and caudally as described earlier. Finally, the incised areas

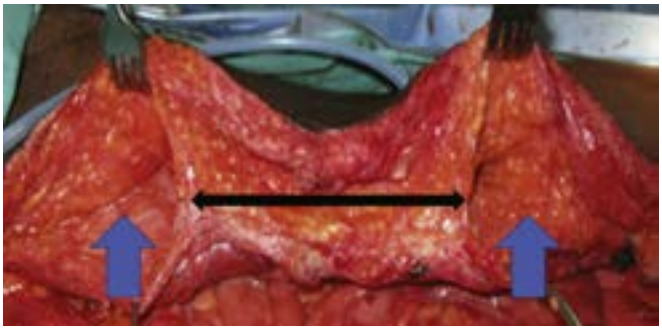


FIG. 4 Perforator-preserving anterior component separation. The lipocutaneous flaps *(blue arrows)* are raised above and below intact periumbilical perforator area *(black arrow)*.

of the EO are connected lateral to the preserved periumbilical bundle. Alternatively, the semilunar line and EO aponeurosis are identified via a separate, 6-cm transverse incision located at the inferior aspect of the ribcage. Via this incision the semilunar line and the EO aponeurosis just lateral to it are identified. As described earlier, both the EO aponeurosis and the EO muscle belly are transected. A long and narrow (and lighted) retractor can be used to create a subcutaneous tunnel along the length of the semilunar line toward the inguinal ligament and anterior superior iliac spine (ASIS). To complete transection of the inguinal ligament, a small subcutaneous tunnel is made from the midline to the semilunar line at about the level of the ASIS. The end of the divided EO muscle and fascia is identified and cautery is used to complete the transection. A finger is then used for blunt dissection of the EO away from the underlying IO, creating several centimeters in lateral overlap. (*Tip: In obese patients, it may be difficult to reach the inguinal ligament from a more cephalad incision. In these patients, make a counter 6-cm transverse incision by the ASIS to reach the lower half of the EO aponeurosis as well as the inguinal ligament.*)

Mesh Placement and Midline Closure

In a perforator-preserving ACS, the mesh can be placed either in the retrorectus or intra-abdominal position. The retrorectus position, which allows mesh integration from both sides, is preferred. Once the mesh is secured, the midline is closed with a running slowly absorbable suture. Any excise skin is trimmed via a vertical panniculectomy.

Robotic ACS

In the following sections, we outline the key differences for the minimally invasive surgical approach to ACS, which include patient positioning and trocar placement. The subcutaneous dissection, external oblique release, restoration of the linea alba, and onlay mesh placement are as described earlier.

Patient Positioning and Trocar Placement

The patient is placed supine, and the bed is flexed at the hip joint. This helps increase the space between the costal margin and ASIS. Both arms are tucked, and the abdomen is prepped in standard fashion. Pneumoperitoneum is established per surgeon preference. Three robotic trocars are inserted laterally under direct visualization, just lateral to the semilunar line. (*Tip: Care should be taken not to place the trocars too lateral, as that may make the subsequent dissection difficult.*) The 30-degree camera, grasping instrument, and monopolar robotic scissors are placed through the ports. A lysis of adhesions is performed as necessary.

Creation of Subcutaneous Flaps

The medial border of the contralateral rectus sheath is identified. The hernia sac is incised just above it to reveal the subcutaneous tissue, and the subcutaneous plane is developed similarly to the open technique described earlier.

Contralateral Port Placement

Once one side is complete, three more robotic ports are placed on the contralateral side. These ports are placed in the newly created subcutaneous pocket (and not intraperitoneal). The robot is redocked, and a similar dissection is carried out on the contralateral side.

Fascia Closure and Mesh Placement

Once both sides are released, the rectus complexes are medialized, and the linea alba is restored using running barbed sutures. The mesh (typically a macroporous polypropylene) is positioned and secured with sutures and glue. The lateral aspect of the mesh is extended underneath the divided lateral edge of the EO. The edge of the EO could then be sutured to the mesh to minimize the risks of lateral hernias. Several drains are placed.

Endoscopic ACS

Patient Positioning and Trocar Placement

The patient is positioned supine with both arms tucked and the bed flexed at the hip joint. A 2- to 4-cm incision is made near the tip of the 11th rib. Using retractors, the external oblique muscle fibers are identified and bluntly separated until the most posterior fibers are sliding free from the underlying internal oblique. The retractor is placed under the external oblique to lift it off the internal oblique. A balloon dissector is introduced and pushed toward the ipsilateral groin, approximately 2 to 3 cm medial of the anterior superior iliac spine, and the balloon is inflated (Fig. 5). When doing this, the tip of the dissector should be angled anteriorly to avoid going through the internal oblique. This is repeated directing the balloon port above the costal margin. Then a 12-mm port is inserted at the balloon dissector entry, and the space is insufflated. Two 5-mm ports are placed (one medial and inferior to the ASIS and the other in between at the same lateral margin as the 12-mm port).

External Oblique Fascial Division

The scope is placed in the upper 12 mm port, and the scissors are placed in the middle 5-mm port. A small incision is made perpendicular to the port and lateral to the semilunar line. Subcutaneous fat will be seen. Then one blade of the scissors is inserted above the

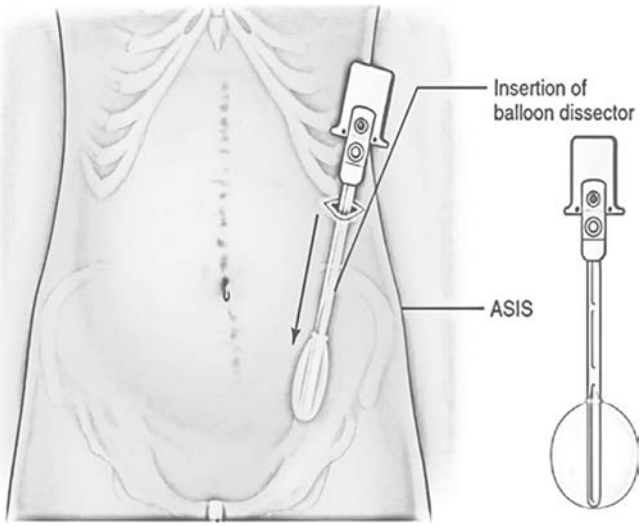


FIG. 5 Balloon placement during endoscopic anterior component separation. *(From Earle D. Endoscopic anterior component separation. In: Novitsky Y, ed.* Hernia Surgery. *Chan: Springer; 2016.)*

fascia and one below, and the fascia is cut down to just above the inguinal ligament, staying lateral to the semilunar line. Then the superior portion of the fascia is cut in the same way. Near the costal margin, the external oblique insertion will become more muscular and is better cut with an energy device. The midline hernia can then be repaired without the need for large subcutaneous flaps.

Alternatively, the EO aponeurosis could be accessed inferiorly through the groin incision similar to an open inguinal hernia repair. If that route is chosen, the balloon is placed in the cephalad dissection, additional ports are placed, and the ACS is completed as described earlier.

Posterior Component Separation

PCS via transversus abdominis release (TAR) was described by Novitsky as an alternative to ACS and as a natural extension of the traditional Rives-Stoppa (retrorectus) repair. The major advantage of TAR is avoidance of risks associated with lipocutaneous flaps. It not only allows for reliable means of linea alba restoration, but also affords wide mesh overlap of the visceral sac in the retromuscular (sublay) plane. We consider TAR for all patients with large hernias (typically >10–12 cm), including those who have previously had an ACS. Once again, this technique can be accomplished via the open, laparoscopic, and robotic approaches. Although the laparoscopic approach is feasible, we have abandoned it in favor of the robotic technique. Absolute contraindications to the robotic approach include inability to tolerate pneumoperitoneum or a hostile abdomen. For patients who require significant soft tissue reconstruction, including scar revision and/or concomitant panniculectomy, consideration should be given to an open approach or a hybrid robotic/open approach.

Open TAR

The patient is placed supine on the operating table, and a urinary catheter is placed. The patient is prepped and draped in sterile fashion. A midline incision is performed, and the abdomen is entered safely. All adhesions to the abdominal wall are taken down. In patients with history of obstructive symptoms, the interloop adhesions are lysed as well. All efforts are made to remove old mesh. A countable white towel is then placed to protect the viscera.

Retrorectus Dissection

The first step of TAR is a retrorectus dissection. The medial edge of the rectus muscle/posterior sheath is identified and incised 1 to 2 cm lateral to the linea alba. Upon incision of the posterior rectus sheath, it is critical to visualize the muscle fibers of the RA to confirm the correct plane of dissection (Fig. 6). The incision is extended along the length of the posterior fascia. The retrorectus space is then typically dissected along its entirety from the costal margin cephalad to the space of Retzius caudally and the semilunar line laterally. (*Tip: Use Allis clamps on the posterior sheath to medially retract the posterior sheath and aid in dissection.*) Great care must be taken to identify and preserve the neurovascular bundles that enter the posterior sheath 1 to 2 cm medial to the semilunar line (Fig. 7); injury to these bundles may lead to denervation injuries and atrophy of the rectus muscle. Furthermore, misidentification of the semilunar line and its injury may result in catastrophic iatrogenic injuries to the abdominal wall where lateral muscles are disconnected from the rectus complex (Fig. 8). The resultant iatrogenic "Spigelian" hernias contribute to destabilization of the abdominal wall that is a source of significant morbidity and is extremely challenging to fix. As such, both the neurovascular bundles and the semilunar line must identified throughout the entire dissection in this area, and any detected injuries to the semilunar line should be repaired immediately.

Transversus Abdominis Muscle Division

The next step is exposure and division of the transversus abdominis muscle. First, the posterior lamella of the internal oblique is incised 1 to 2 cm medial to the semilunar line (see Fig. 7), taking care to identify and protect any neurovascular bundles. It is easiest to start this dissection as cephalad as possible, where the muscular extension of the TAM is most medial and easily identifiable. Once the posterior lamella is incised in its entirety, the underlying TA muscle is

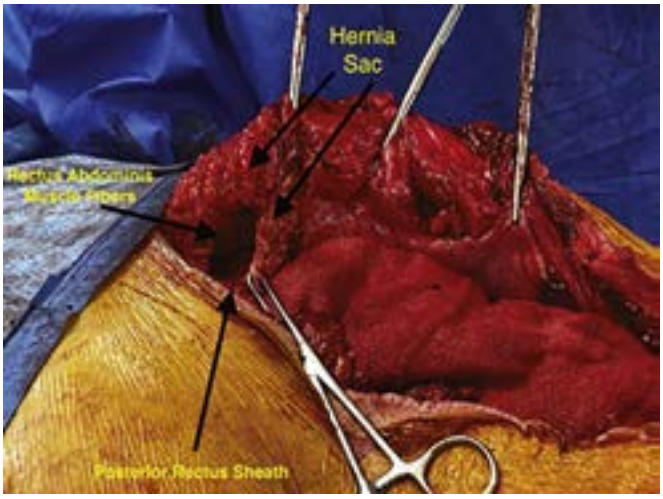


FIG. 6 Initial step of the TAR procedure. Proper incision of the posterior rectus sheath should reveal the fibers of the rectus abdominus muscle. If this incision is made too medially, an unintended subcutaneous dissection will take place.

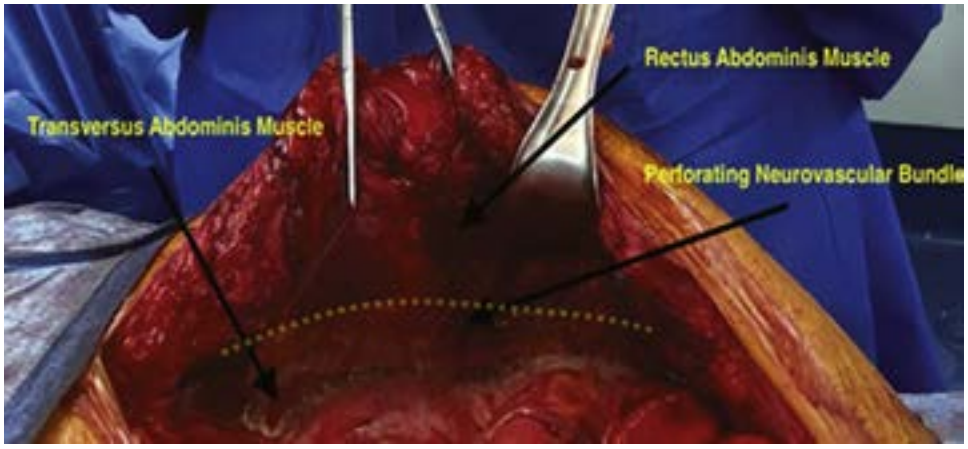


FIG. 7 Retrorectus dissection during TAM release. This step mimics the Rives-Stoppa procedure. Neurovascular bundles should be noted to avoid their injury and to facilitate identification of the linea semilunaris *(dotted line)*. Posterior lamella of the internal obliques is incised just medial to the perforators to reveal underlying fibers of the TAM.



FIG. 8 Iatrogenic bilateral semilunar line injuries during TAR. Note that the lateral muscle group is disconnected from the rectus abdominus complex. As a result, the obliques no longer have an insertion and will continue to contract/foreshorten over time. Furthermore, the rectus muscles are atrophic, likely resulting from the erroneous division of the neurovascular bundles.

identified. With firm medial retraction on the posterior sheath, the TA muscle and aponeurosis are transected (Fig. 9) using a right-angle dissector and Bovey cautery. (*Tip: Near the level of the umbilicus, the muscular aspect of the TAM is replaced with its aponeurotic aspect; make sure not to confuse that aponeurosis for posterior lamella of IO.*) This incision is extended caudally until the arcuate line is reached. Once transected, a peanut is used to sweep the cut muscle edge anteriorly off the underlying transversalis fascia and create the pre-transversalis plane. It is critical to complete this retromuscular dissection as posterolateral as possible to facilitate posterior fascial closure and enhance anterior fascial medialization. The best way to ensure that the dissection is completed is to either visualize the lateral aspect of the psoas or to ensure that the posterior layers are lying on the viscera detached from the TAM (Fig. 10). Superiorly, this plane is extended up to the seventh costal cartilage and can be taken to the central tendon of the diaphragm if necessary. Inferiorly, the space of Retzius and Bogros are dissected in the preperitoneal plane. At the 6 o'clock position, Cooper's ligaments and the pubis are exposed, and the dissection is extended laterally across the entire myopectineal orifice. The round ligament is transected as proximal as possible in women, and the spermatic vessels are identified and preserved in men. Hemostasis must be ensured, and hemostatic agents can be used on the bleeding raw muscle edges.

Posterior Sheath Closure

Once the dissection is completed bilaterally, the posterior sheaths are reapproximated with a running Vicryl suture to recreate an intact visceral sac (Fig. 11). All fenestrations in the posterior layer must be closed to prevent herniation of the viscera, and either omentum, biologic, or absorbable mesh can be used to inlay large posterior layer gaps. It is important to visualize the medial (cut) edge of the TAM on each side of the closure. If one notices other muscle attachment(s)

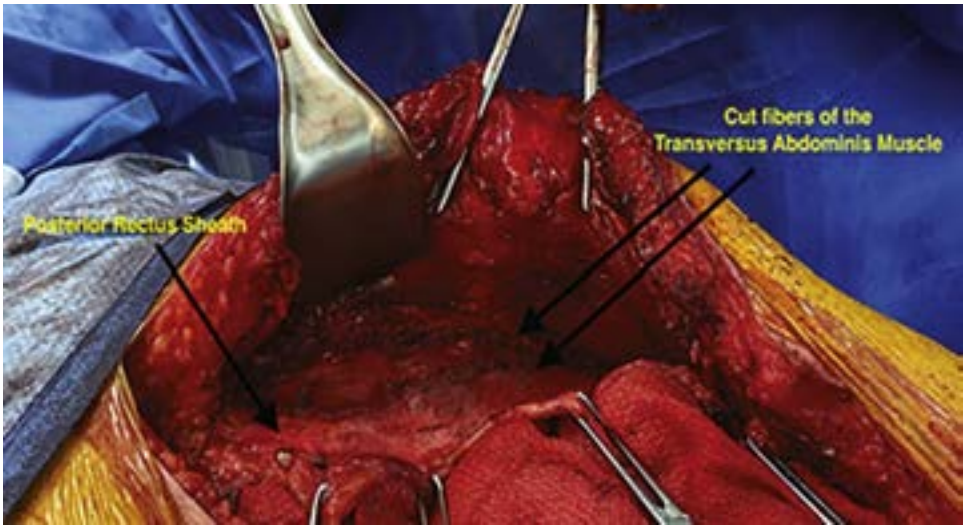


FIG. 9 Division of the TAM. Underlying transversalis fascia is exposed.

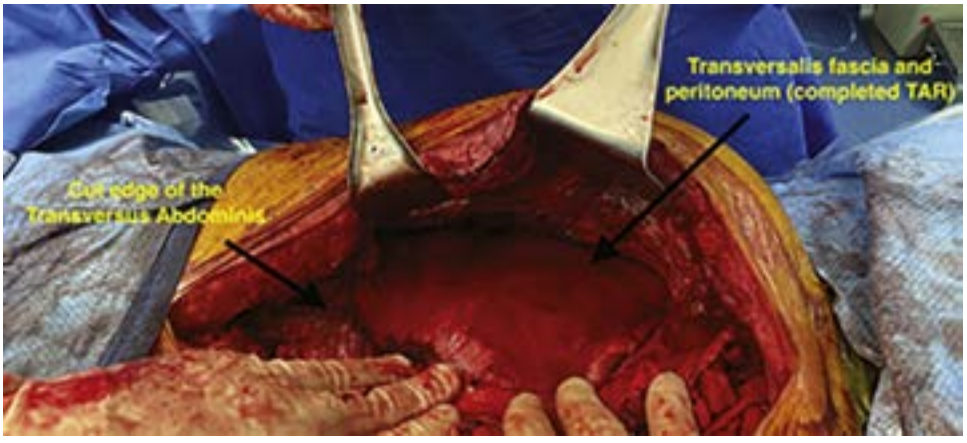


FIG. 10 Completed retromuscular dissection during TAR. Note that posterior layers are completely dissected away from the overlying (divided edge) of the TAM. This ensures maximal mobilization of the posterior layers as well as subsequent medialization of the rectus abdominis complex.

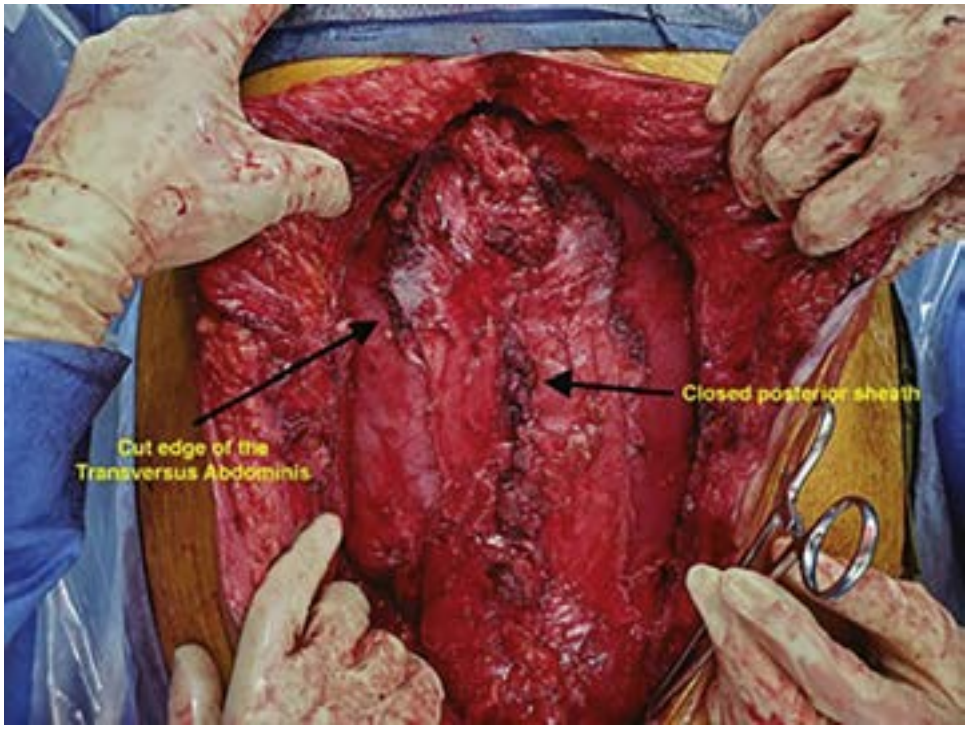


FIG. 11 Restored visceral sac.

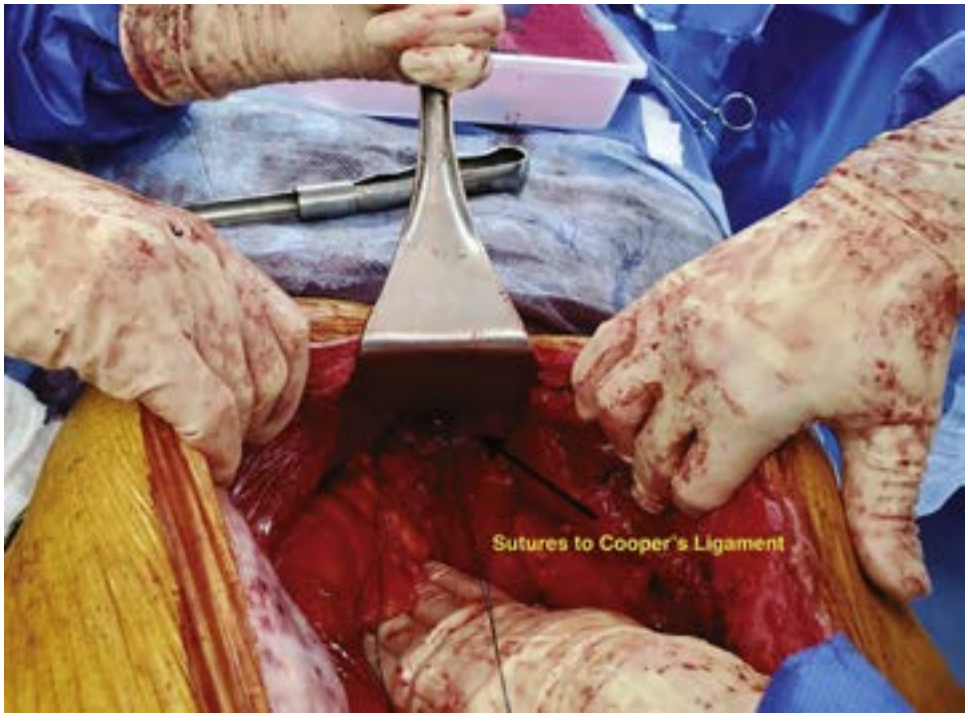


FIG. 12 Fixating sutures are placed through each of Cooper's ligaments.

on the posterior layers, it is likely that incorrect muscle layer(s) were divided, and thorough investigation and repair of a likely iatrogenic injury of the abdomen wall should be done.

Mesh Placement, Restoration of Linea Alba, and Soft Tissue Closure

Once the visceral sac is restored, the mesh is placed in the large retromuscular pocket. When possible, the mesh is secured bilaterally to Cooper's ligament with a slowly absorbable suture. We typically pre-place the sutures first and then pass the tails through the mesh to allow for the knots to be tied on the dorsal surface of the mesh (Figs. 12 and 13). Additional lateral fixation is utilized extremely rarely. We typically place the bottom mesh in a "diamond" configuration and then add an additional 30 cm by 30 cm macroporous polypropylene mesh as a square to cover the upper aspect of the visceral sac. We call such overlapping mesh configuration a *home plate*. Two drains are placed atop the mesh. Any hernia sac is excised, and the anterior fascia is trimmed to healthy fascia. The midline is closed

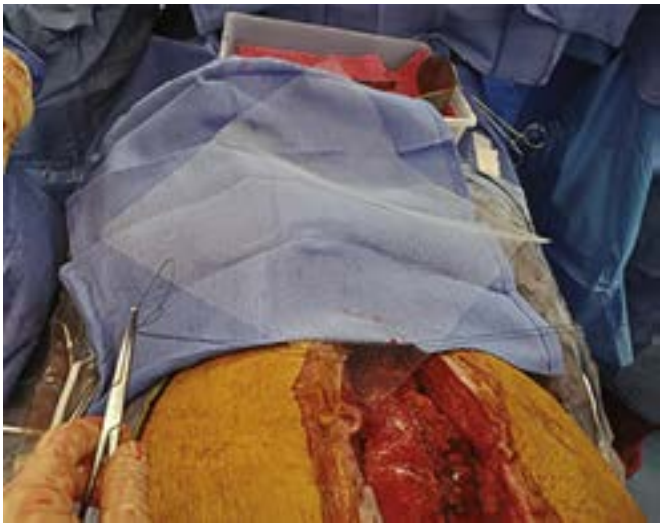


FIG. 13 The tails of the sutures are passed through the mesh to ensure that the knots are tied on the dorsal surface of the mesh.



FIG. 14 Patient positioning for robotic TAR.

with a running slowly absorbable suture. The redundant soft tissue is excised, a 15F subcutaneous drain is placed, and the skin is closed in layers. Then an abdominal binder is placed.

MIS TAR

Robotic TAR has been gaining popularity. As mentioned earlier, we no longer perform TAR laparoscopically. If a minimally invasive surgical approach is chosen, we prefer to utilize robotics. The principles of the robotic approach follow those of the open technique described earlier.

Patient Positioning and Trocar Placement

The patient is placed supine on the table with both arms tucked at the side (Fig. 14). Flexion of the operating table at the hips can increase the length between the costal margin and the ASIS in patients with short torsos. A Foley and orogastric tube are placed. The patient is prepped and draped in a sterile fashion. A half drape is attached to the cephalad aspect to create more three-dimensional sterile space for the robotic arms and to minimize chances of accidental breaks in sterility during instrument exchanges. The abdomen is entered, and pneumoperitoneum is established per surgeon preference. We typically use an optical trocar in the left upper quadrant, just lateral to the Palmer point.

Trocar Placement

Three robotic trocars are inserted under direct visualization at approximately the anterior axillary line (Fig. 15). The most important



FIG. 15 Trocar strategy for robotic TAR.

trocar is inferior as it should be about 2 cm medially and cephalad from the ASIS. Placing the port too low or too medially will result in significant instrument collisions that might be difficult to overcome. A 30-degree camera is placed in the middle trocar. We typically use monopolar scissors in the right hand and a fenestrated bipolar grasper in the left. Once the retrorectus dissection, identification/division of the TAM, and the retromuscular dissection are completed (as described earlier), three additional ports are placed on the contralateral side under direct visualization. The location of those trocars is essentially a mirror image of the first set. The contralateral dissection/TAR is then performed. The medialized posterior layers are reapproximated using a running absorbable 2-0 barbed suture. In contrast with the open TAR, we then proceed with an anterior fascia closure/linea alba restoration using permanent No. 1 barbed sutures. *(Tip: Reducing pneumoperitoneum helps facilitate closure of large midline defects.)* The robot is then undocked, and a large retromuscular mesh is placed. It is typically fixated with fibrin glue. Drains are not used routinely.

POSTOPERATIVE CARE AND OUTCOMES

Our typical postoperative care involves judicial fluid administration, a multimodal pain regimen, an early feeding strategy, and early ambulation with aggressive physical therapy. All patients are given abdominal binders to wear postoperatively for the first 2 weeks to provide core support and to reduce seroma formation. Retromuscular drains are removed once the output is less than 30 to 50 mL/day, typically 7 to 10 days postoperatively. The subcutaneous drains are kept until the output is less than 15 mL/day. It is critical to maintain subcutaneous drains for at least 2 weeks in all ACS patients. Our typical duration of hospitalization for open cases is 4 to 5 days and 1 to 2 days for robotic TARs.

Patients are seen in clinic at several weeks, 3 to 6 months, 12 months, and 24 months postoperatively. We typically obtain a CT scan at 12 months to ensure integrity of the repair and detect an occult recurrence. Alternatively, a validated screening survey is used to detect problems. According to our recent analysis, at a mean follow-up of almost 3 years, the recurrence rate after TAR was 3.4%, with the majority of recurrences resulting from central mesh failures.

PROCEDURE SELECTION STRATEGIES

The world of abdominal wall surgery has seen an explosion of surgical techniques in the past several decades. As a result of such rapid growth, the appetite to implement novel techniques has often

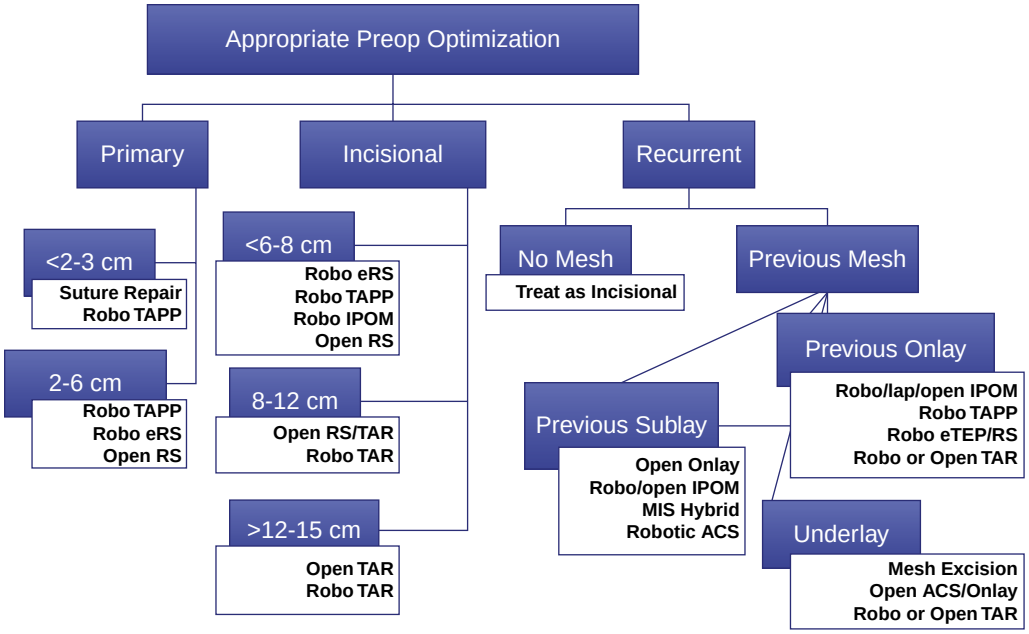


FIG. 16 Our algorithm for procedure selection for most ventral hernias. *eRS,* Extraperitoneal Rives-Stoppa; *IPOM,* intraperitoneal mesh repair; *RS,* Rives-Stoppa.

outpaced the necessary training and understanding of the nuances of various surgical approaches. However, we strongly believe that preoperative planning should be a comprehensive and stepwise process to choose the most appropriate surgical option. This process remains a challenge, even for experienced hernia and abdominal wall surgeons. As seen in our algorithm (Fig. 16), we utilize hernia characteristics, width, and previous repairs as main guiding principles of procedure selection.

The process of procedure selection begins with a thorough review of the patient's history, previous procedures, and recent imaging. A joint discussion of the goals, benefits, and limitations of various surgical strategies should then follow. Next, a comprehensive prehabilitation process and optimization strategies should be discussed and implemented. As mentioned earlier, these should include improvements in general physical conditioning/frailty, control of diabetes, smoking cessation, and weight management. Elective AWRs should be deferred until these comorbidities are addressed, unless there is evidence of impending intestinal obstruction/compromise. Often, those issues are best addressed in a multidisciplinary fashion. The ability of the physician and patient to address and overcome the aforementioned modifiable risk factors may ultimately influence procedure selection.

The first consideration in our process is whether a mesh reinforcement is going to be utilized. Although we use mesh reinforcement in most definitive repairs in our practice, we are acutely aware of the potential morbidity of synthetic mesh. In patients with small, primary hernias, a suture repair is often chosen, despite a small chance of increased recurrence. The benefit of mesh avoidance and yet durable repair in the vast majority of patients is presented to the patient. In patients with soft tissue or mesh infections, primary or staged repairs are often undertaken. Those patients with larger hernias are usually treated with repairs reinforced with mesh. Once the mesh repair is contemplated, consideration should be given to which location within the abdominal wall a mesh reinforcement will be placed. Subcutaneous onlay, retromuscular/pre-peritoneal sublay, or intraperitoneal underlay are all viable options with both benefits and drawbacks. The surgeon's preference for a particular mesh position will influence his or her choice of the technique. In our experience, sublay mesh has become the most preferred location, and as a result we often choose preperitoneal, retrorectus, or retromuscular repairs.

The next important question is whether a given patient is best suited for a reconstructive versus bridged repair. Patients in poor health or performance index might be better served by a less involved bridged hernia repair. In most of our elective repairs, however, we aim at defect closure and linea alba restoration. We believe this strategy results in a more physiologic repair, provides for a solid tissue substrate for mesh implant, reduces mesh eventration, and carries superior long-term durability.

Most patients with small to medium hernias do not require any advanced reconstructive options to achieve linea alba restoration. In addition, preoperative administration of BOTOX into the lateral musculature, albeit controversial, may result in chemical denervation and improved ability to medialize rectus muscles without additional reconstructive steps. Precise indications for BOTOX injections and their influence on improved long-term durability of hernia repairs are yet to be elucidated. We have been utilizing BOTOX in our most challenging patients with large defects but remain unconvinced about its utility in most patients. Reserving component separations to those patients whose linea alba cannot be otherwise restored allows to minimize unnecessary musculofascial divisions and the associated risks of donor site morbidity.

The introduction of robotics to the field of hernia and abdominal wall surgery has added another layer to the decision-making process. Although the role of robotics is being actively investigated, we have discovered that it has completely eliminated the laparoscopic approach to hernia repairs from our practice. Furthermore, it allows for a reliable and reproducible preperitoneal and extraperitoneal repair in most small to medium defects. Moreover, robotic AWRs have allowed us to offer minimally invasive repairs and reconstructions to patients with large abdominal wall defects. With the introduction and development of new and improved robotic platforms, the role of robotic surgery on AWRs, we believe, will continue to expand.

Finally, once a reconstructive repair is contemplated, the most appropriate AWR technique must be chosen. The most important determinant of that choice should be a surgeon's familiarity and expertise in a given AWR procedure. It is best to develop a "go-to" technique that allows for a durable reconstruction and preferred mesh positioning. It is certainly critical for a reconstructive abdominal surgeon to be familiar with the entire spectrum of options to allow for tailored preoperative planning and necessary intraoperative strategy shifts. One should not let the desire to embark on a particular AWR technique supersede his or her ability and expertise to perform a particular procedure. Incorrectly performed advanced

techniques do not simply lead to recurrences but may lead to catastrophic iatrogenic injuries to the abdominal wall with potential lifelong core dysfunction, chronic pain, and disability. Proper preparation and understanding of the physiologic/anatomic principles of complex AWRs, understanding of mesh science, and ability to deal with potential complications of a given technique should be mandatory for all surgeons embarking on a complex AWR. Understanding the main differences between various reconstructive options and associated mesh positioning should facilitate one's ability for a tailored approach. We continue to favor retrorectus and retromuscular mesh repairs using robotic techniques for most of our patients with both simple and complex abdominal wall defects. Future studies may provide more objective guidance for procedure selection.

Suggested Readings

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Loss of Domain in Abdominal Wall Reconstruction

Yewande Alimi, MD, David Hindin, MD, and Carla M. Pugh, MD, PhD

DEFINITION

Loss of domain (LOD) has been found in hernia literature since the mid-1900s. The term is commonly used to describe the distribution of abdominal wall contents between the hernia and the residual abdominoperitoneal cavity. Patients who have a large hernia with much of the abdominal viscera outside the abdominal compartment and undergo subsequent repair can have serious physiologic implications after repair. Notably, the increase in intraabdominal pressure adds significant force on the diaphragm and can cause respiratory failure and pneumonia. Although prior reports often use vague definitions for LOD to imply herniated organs that have lost the right of domain inside the abdominal cavity, a number of more recent articles have attempted to more clearly define features of LOD. However, in a systematic review reported by Parker and Alan in 2019, the quantity and variety of definitions for LOD were vast.

When reviewing the literature, LOD was most consistently defined by the principle of *lateral contraction of the abdominal wall muscles,* leading to reduced volume of the intraabdominal wall cavity and progressive visceral protrusion. Similarly, five articles utilized the concept of a *hernia sac being a so-called second abdomen,* leading to the concern that restoring this second abdomen into the primary abdominal cavity would create physiologic disturbances and complications. Parker et al. also compiled a series of definitions of LOD based on volumetric measurements. In these 20 studies utilizing volumetric definitions, LOD was defined with preoperative cross-sectional imaging combined with volumetric analysis. The measurements used to classify LOD, however, were found to be inconsistent across the literature. Notably, the ratio of hernia sac volume (HSV) to the abdominal cavity volume (ACV), or Tanaka's method, was documented in eight studies. Five other studies, however, instead reported a ratio of HSV to the total peritoneal volume, defined as the summation of the HSV and the ACV, or Sabbagh's method.

A fairly consistent concept in abdominal wall reconstruction literature regarding LOD hinges on the concept of the cylinder. Mancini et al. describe this concept as follows: the top of the cylinder is the diaphragm, and the bottom of the cylinder is the pelvic floor. These are fairly simple boundaries. The core of the cylinder is composed of the posterior abdominal wall muscles (this includes the spine and the fairly rigid erector spinae muscles) and the anterior abdominal wall muscles. The lateral abdominal wall is composed of the transversus abdominis, the internal oblique muscles, and the external oblique muscles—all of which converge at the semilunar line where their aponeuroses fuse. These lateral muscles all pull in different vector forces, culminating in summative forces that serve to functionally rotate and laterally flex the abdominal wall. The anterior abdominal wall is comprised of the rectus abdominus, which connects in the midline at the linea alba, and laterally as described earlier.

When the sum total of these aforementioned muscles all work together as a cylinder, they create the physiologic forces of the abdominal wall to allow for functions such as efficient expiration, inspiration, and defecation, among others. However, when the cylinder is broken, these abdominal wall forces no longer work together in concert. For instance, the linea alba loses its integrity when a midline abdominal hernia forms. In the case of LOD, the abdominal viscera are no longer held within the abdominal cavity, the lateral abdominal wall forces are not synchronized in their movement to create a unified abdominal force, and the cylinder forces are misaligned (Fig. 1). As the abdominal wall contents are not confined in the intact cylinder, the lateral wall musculature subsequently becomes foreshortened because of increasing fibrosis and thickening. In turn, this foreshortening leads to additional retraction of the rectus abdominus muscles, rendering them unable to generate sufficient abdominal wall pressures. The pressures that are generated are decompressed into the hernia sac, further rendering the abdominal wall musculature ineffective.

The broken cylinder phenomena results in the overall disruption of the normal mechanical forces required to complete efficient respiratory mechanics as well as gastrointestinal and genitourinary functions. As a consequence, the anterior and posterior portions of the cylinder no longer work in synchrony, in part caused by disruption of the rectus abdominis muscles, which themselves are no longer

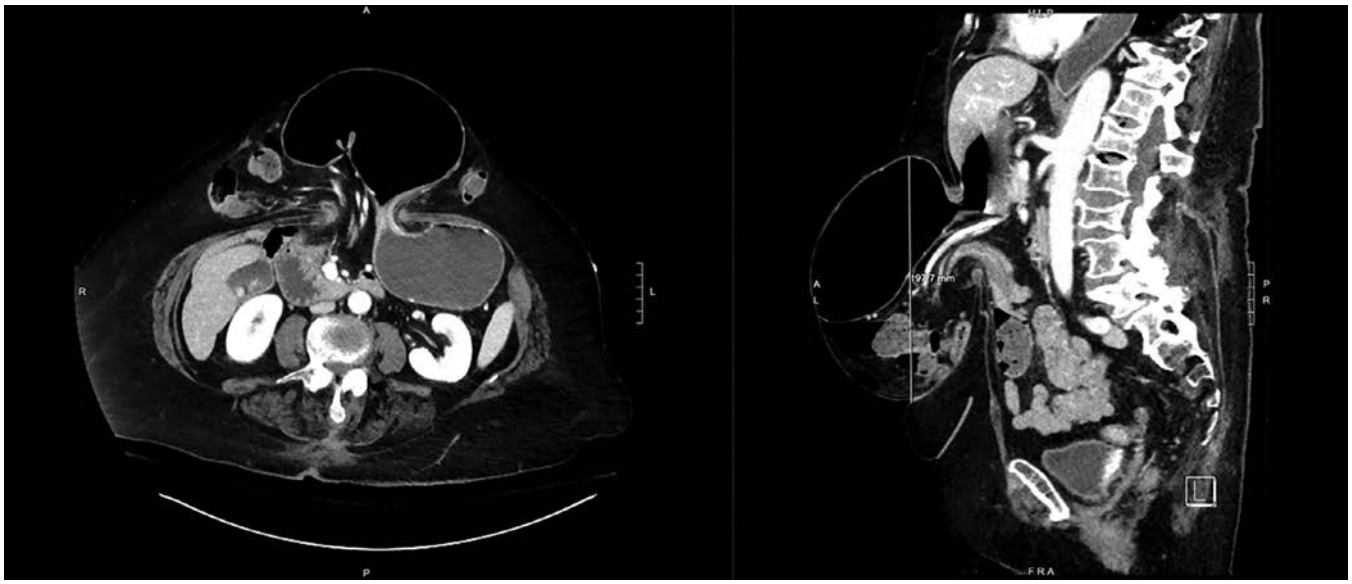


FIG. 1 Loss of domain. Demonstration of the broken cylinder.

coupled with the forces generated by the spinae muscles. This results in chronic forces on the erector and spine spinae muscles, which results in chronic back pain in some patients.

The inability to generate proper intraabdominal forces also results in abnormal intra-abdominal functions, leading to difficulty with defecation, urination, and expiration. With further deterioration, overflow urinary incontinence and constipation may develop. Similarly, given the abdominal wall's integral role in forced expiration with utilization of the lateral abdominal wall muscles, the inability to create these pressures in patients with LOD results in decreased forced expiration. This results in decreased exercise tolerance and impaired coughing and clearance of secretions.

Despite the variability seen in the literature, through an international Delphi consensus of expert surgeons, the Sabbagh volumetric method of defining LOD has been adopted [HSV/(ACV+HSV) (or TPV)] along with a verbal description of "a ventral hernia large enough such that simple reduction in its contents and primary fascial closure either cannot be achieved without additional reconstructive techniques or cannot be achieved without significant risk of complications due to the raised intra-abdominal pressure." No consensus was reached on the ultimate volumetric threshold to qualify as LOD, though in a majority of the literature this lands somewhere between 20% and 40%.

ETIOLOGY

LOD is a diagnosis that continues to be on the rise. This is in part because of the life-saving techniques employed in trauma and emergency general surgery that result in increased lives saved—but often at the cost of associated morbidity secondary to open abdomens and complex abdominal surgical wounds. The inability of achieving primary midline fascial closure following massive resuscitation, third spacing, and the general mismatch of abdominal content volume to abdominal wall circumference necessitates an eventual closure typically carried out using absorbable mesh with subsequent skin grafting. In addition to these planned closures, the emergency general surgery population also carries an increased risk of midline fascial dehiscence, a higher likelihood of requiring major abdominal wall debridement (e.g., ballistic injuries), and higher rates of surgical site infections following massive contamination or simply poor patient protoplasm at presentation (e.g., obesity, diabetes, smokers).

Finally, obesity itself is an independent cause of LOD, but it can also be an effect of LOD. The physical restrictions posed by massive LOD result in decreased activity in patients. This in turn may be compounded by further weight gain, resulting in even more profound obesity. Of note, patients with central obesity in particular have increased tensile forces in the central abdomen that place further stress on the abdominal wall musculature.

OPERATIVE PLANNING

The details of ventral hernia repair are developed in prior chapters within this text. The focus of this chapter is on the unique considerations in patients with LOD. As such, we will not expand on the surgical approach of open and minimally invasive ventral hernia.

The key to successful repair in patients with LOD is thorough preoperative planning. Although routine ventral wall hernias and inguinal hernias may proceed to the operative room without preoperative imaging with consistent signs and symptoms of the respective hernias, it is imperative for patients with LOD to undergo appropriate preoperative imaging. The modality of choice for most hernias is an abdominal computed tomography (CT) scan. Preoperative CT allows for the surgeon to identify the location of the abdominal wall musculature and its relative location to the hernia and the hernia sac. This imaging also serves as a tool to assess abdominal wall volumes and hernia sac volumes.

Volumetrics can be evaluated via sagittal and axial views on CT imaging. Sagittal views are helpful to obtain the length of the abdominal cavity (measured from the top of the diaphragm to the inferior aspect of the pubis symphysis) and the length of the hernia sac (measured from the top of the hernia sac to its bottom). On axial views, the width and height of the hernia sac and abdominal cavity can be measured. Volumes can be approximated using the equation $0.52 \times \text{length} \times \text{width} \times \text{height}$ measured from axial imaging approximating the volume of an ellipsoid (Fig. 2). The ratios of these two values (HSV/ HSV + ACV) can be used to determine evidence of LOD. There remains no consensus on the clinical value of this number, but a value greater than or equal to 20% has been previously used to suggest LOD by many hernia experts.

Patient Preparation

After establishing a diagnosis of LOD, it is important to adequately prepare the patient for the operating room. This entails minimizing any patient factors that increase the risk of hernia recurrence or wound complications. The major contributors to hernia recurrence

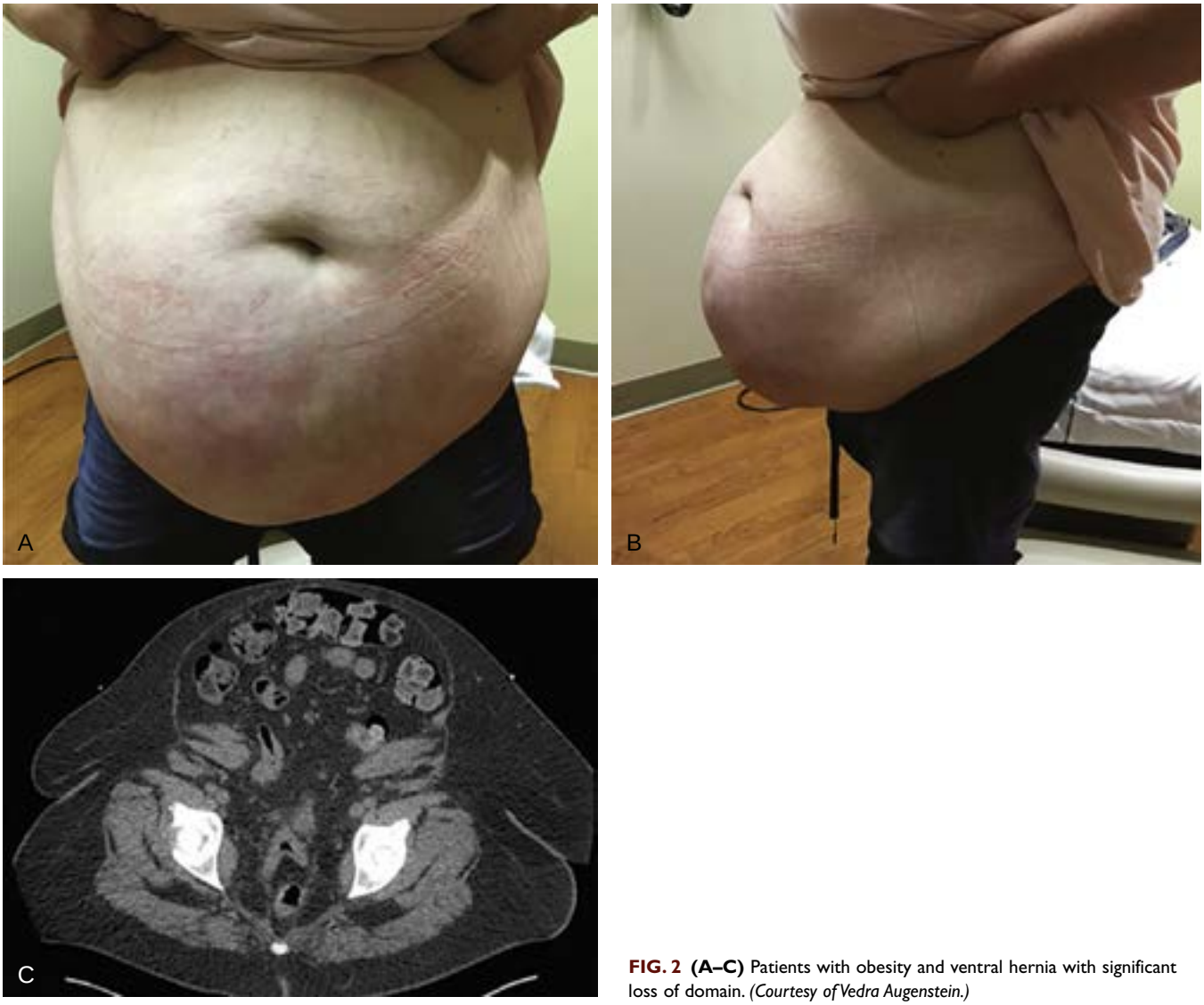


FIG. 2 **(A–C)** Patients with obesity and ventral hernia with significant loss of domain. *(Courtesy of Vedra Augenstein.)*

include nutritional status, diabetes status, smoking, and obesity. In patients with hypoalbuminemia, this should be corrected before surgical intervention, as low albumin is well-documented to correlate to higher mortality as well as poorer surgical outcomes. Patients who are active smokers should be advised on cessation of smoking for at least 1 month before surgical intervention. These patients are also advised to remain nicotine-free for at least 2 months following surgical intervention as any form of nicotine increases the risk of both wound complications and pulmonary complications.

Many surgeons advocate for optimization of hyperglycemia with a goal of A1c less than 8. Additionally, in patients with obesity, hernia experts advocate for preoperative weight loss depending on the severity of the symptoms of the hernia. In large hernias with significant LOD, the risk of strangulation is low, and there is a benefit of time. Although many surgeons encourage lifestyle changes, referral to medical weight-loss clinics, and surgical weight-loss evaluation when appropriate, these referrals are often ignored or not followed through. Some centers report that even in patients who are able to lose a substantial amount of weight preoperatively, a majority of these patients will ultimately regain the weight within 18 months of surgery. Nonetheless, the benefits of optimizing weight before repair of hernias with LOD include decreasing wound morbidity, allowing for a more technically feasible operation for the surgeon, and decreasing the rate of perioperative complications. We recommend a body mass index (BMI) lower than 40 kg/m^2 before proceeding to the operating room, and preferably below 35 kg/m^2. Utilizing a clinician-observed 4- to 8-week low-calorie, high-protein meal replacement program may be beneficial to obtain these goals as has been demonstrated in the bariatrics literature. Among patients who are unable to achieve these goals, we encourage referral to a bariatric surgical program for surgical weight loss followed by abdominal wall reconstruction in a staged fashion.

Surgical Approach

Many advocate that LOD is a relative contraindication for the use of minimally invasive techniques. Often, this reluctance is due to a desire to manage these hernias in an open fashion given the frequent need for component separation, additional maneuvers to mind the gap, and the necessity for wound excision. At specialized hernia centers, however, a growing mastery of robot-assisted transversus abdominis release procedures has opened the door for the management of more complex hernias in a minimally invasive fashion. Before approaching these complex hernias robotically or laparoscopically, however, adequate experience with the tool (laparoscope vs. robot) is paramount as well as achieving mastery of this procedure in the open plane.

STRATEGIES TO MIND THE GAP

Given the significant changes to the abdominal wall in patients with LOD, techniques to ultimately bring the fascia midline are integral to the management of these defects. We will explore a few of these reported modalities here. The most reliable and reported management strategy to mind the gap is the component separation. These techniques allow for adequate advancement of fascial edges toward the midline, providing for a tension-free closure.

Anterior Component Separation

The anterior component separation, first described by Ramirez et al. in the 1990s, calls for a release of the posterior rectus sheath that allows for a 1- to 2-cm advancement. This is followed by a release of the external oblique muscle about 1 to 2 cm lateral to the linea semilunaris. This is extended caudally and cephalad to the inguinal ligament and the costal margin, respectively. This can be done unilaterally or bilaterally, depending on the distance required to reapproximate the midline fascia. Of note, this method requires the formation of large subcutaneous flaps that add to the morbidity of this procedure. However, this release affords for up to 10 cm additional mobility at the waistline, 1 to 3 cm in the lower abdomen, and 3 to 5 cm in the upper abdomen. Following component release, mesh is typically placed in an onlay fashion, reinforcing the midline fascial closure as well as covering the area of the external oblique release. This can be fixated with suture, fibrin glue, or a combination of the two. Drains are placed in the subcutaneous layer (bilaterally if flaps were developed on both sides), and the skin is closed. This approach can be beneficial in patients having concurrent panniculectomy because of the generation of adipocutaneous muscle flaps. In other patients, however, these flaps represent a major drawback of the anterior component separation and can be associated with a large wound complication rate of between 26% to 42%. Of note, the anterior component separation is less reliable in patients with suprapubic or subxiphoid defects. Figure 2 depicts a case of a patient with obesity and significant LOD preoperatively with associated axial imaging. Given the concern for abdominal wall laxity, this patient underwent a staged repair with preoperative botulinum toxin A injections (detailed later in this chapter) followed by an anterior component separation (Fig. 3).

Posterior Component Separation

The posterior component separation is a technique most popularized by Yuri Novitzky in 2012. This technique proceeds similarly to the anterior component separation, with complete adhesiolysis and entrance of the posterior rectus sheath about 1 cm from its edge (Fig. 4A). The retromuscular plane is developed to the linea semilunaris, while protecting the rectus muscle neurovascular bundle (Fig. 4B). The posterior rectus sheath is then incised, exposing the transversus abdominis muscle. In the upper third of the abdomen, the muscle fibers of the transversus abdominis are easy to recognize and separate from the underlying transversalis fascia, so this dissection is initiated here. The muscle is divided along its medial edge, and the dissection can be carried cephalad toward the diaphragm and caudad toward the space of Retzius to the level of Cooper's ligament (Fig. 5). The posterior rectus sheath is subsequently reapproximated. In the original technique, mesh is now placed in the sublay fascia using full-thickness transabdominal sutures secured with a Reverdin needle. In usual practice, this can be done using the Carter-Thomason suture passer device (Fig. 6). The inferior edge of the mesh is adhered to Cooper's ligament using interrupted monofilament suture. Superiorly, the mesh is fixated to the xyphoid process and below the ribs to avoid lung injury. Drains are placed along the mesh in a retrorectus fascia exiting the skin on the abdomen away from the groin creases. The anterior rectus sheath is reapproximated, re-establishing the linea alba. No subcutaneous drains are required. The key benefits of this technique include its natural extension of the Rives-Stoppa, which is associated with low recurrence rates (3%–6%), whereas the anterior component separation can be as high as 30%. Additionally, this technique avoids the creation of subcutaneous skin flaps, decreasing overall wound morbidity and affording the placement of mesh in a large, well-vascularized submuscular plane.



FIG. 3 Patient with obesity and loss of domain following botulinum toxin A injection and anterior component separation. *(Courtesy Vedra Augenstein.)*

Tissue Expanders

An additional maneuver described to expand the abdominal wall to provide for midline closure includes the use of tissue expanders. This technique is based on tissue's ability to respond to stretch, or creep. Additionally, this is based on stress relaxation, which describes the phenomena by which the force required to maintain tissue elongation decreases over time. Although a discussion on the types of tissue expanders is outside the scope of this chapter, we will review their concept and benefit in LOD patients here. The tissue expanders are placed adjacent to the abdominal wall defect and may be placed in the subcutaneous plane or in the subfascial plane, utilizing a no-touch technique. This is dependent on the dimension that requires increased pliability. Expanders are utilized either immediately postoperatively, or they are delayed by 2 to 3 weeks and then sequentially expanded, usually on a weekly basis. Following expansion, the hernia is subsequently repaired as a second stage.

In addition to the use of tissue expanders, reports of progressive preoperative pneumoperitoneum (PPP) have been used in the management of patients with LOD. This technique is predicated on the fact that immediate reintroduction of abdominal wall contents into the abdominal cavity can result in significant increase in intrabdominal pressure, potentially precipitating the development of abdominal compartment syndrome (ACS). By preoperatively insufflating the abdominal cavity, this serves as an intraperitoneal pneumatic tissue expander lengthening the oblique musculatures, increasing the diameter of the abdomen, and resulting in an increased overall volume of the abdominal cavity. Physiologically, PPP creates a chronic abdominal compartment syndrome, reducing the impacts of the adverse cardiovascular effects of acute abdominal compartment syndrome because of the slow introduction of intraperitoneal air. This technique is accomplished by introducing a cuffed intraperitoneal catheter, similar to that of peritoneal dialysis catheter placement. Care should be taken to gain access to the abdominal cavity. A cuffed peritoneal dialysis catheter is then placed with a sheath introducer. After catheter placement, patients are transferred to a step-down unit. Because of the increased intra-abdominal pressure and decreased venous return, these patients are at high risk of developing deep venous thromboses and are maintained on a heparin drip

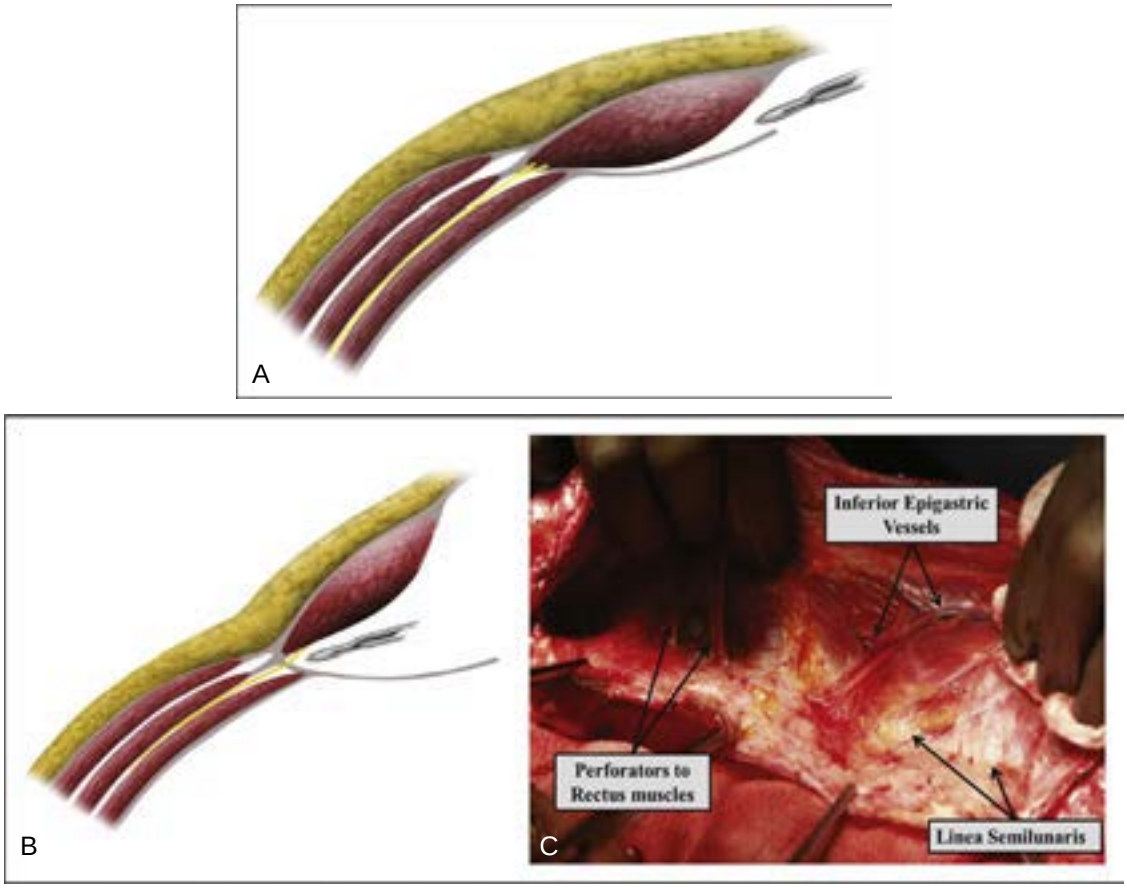


FIG. 4 Demonstration of posterior component separation. **(A)** Incising the posterior rectus sheath. **(B, C)** Development of the retromuscular plane while protecting the rectus muscle and the neurovascular bundle. *(From Novitsky YW, Elliott HL, Orenstein SB, Rosen MJ. Transversus abdominis muscle release: a novel approach to posterior component separation during complex abdominal wall reconstruction.* Am J Surg. *2012;204[5]:709–716).*

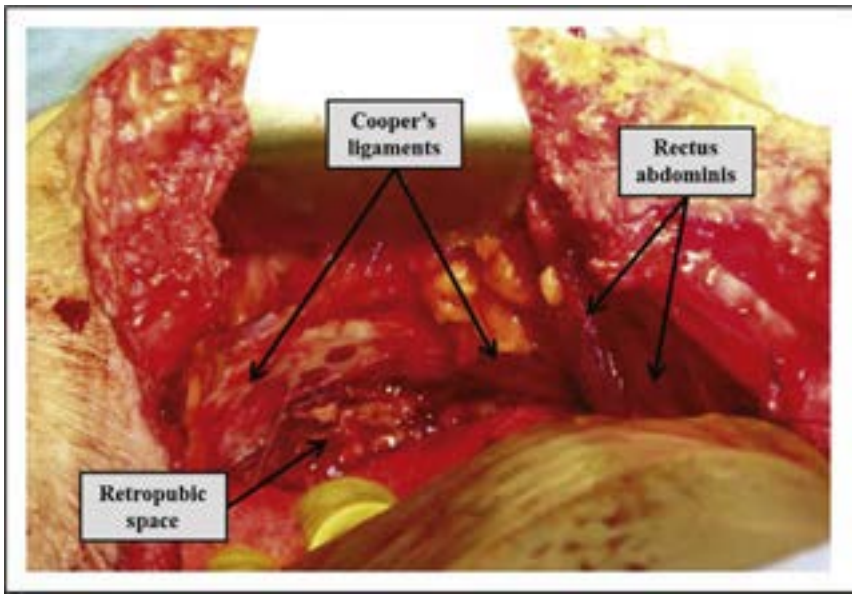


FIG. 5 Development of the space of Retzius to the level of Cooper's ligament. *(From Novitsky YW, Elliott HL, Orenstein SB, Rosen MJ. Transversus abdominis muscle release: a novel approach to posterior component separation during complex abdominal wall reconstruction.* Am J Surg. *2012;204[5]:709–716).*

during the duration of their PPP. Peritoneal insufflation begins on postoperative day 1 and is completed daily. Air is insufflated slowly (1–2 L/min) until the patient begins to feel mild discomfort. There is no target volume, but this is titrated clinically. Once the patient begins to feel some shortness of breath and anxiety, the insufflation is stopped. A CT scan is performed at day 7 to evaluate the hernia, evaluate expansion of the abdominal wall, and assess whether the abdominal viscera have returned to the native cavity. If this has not

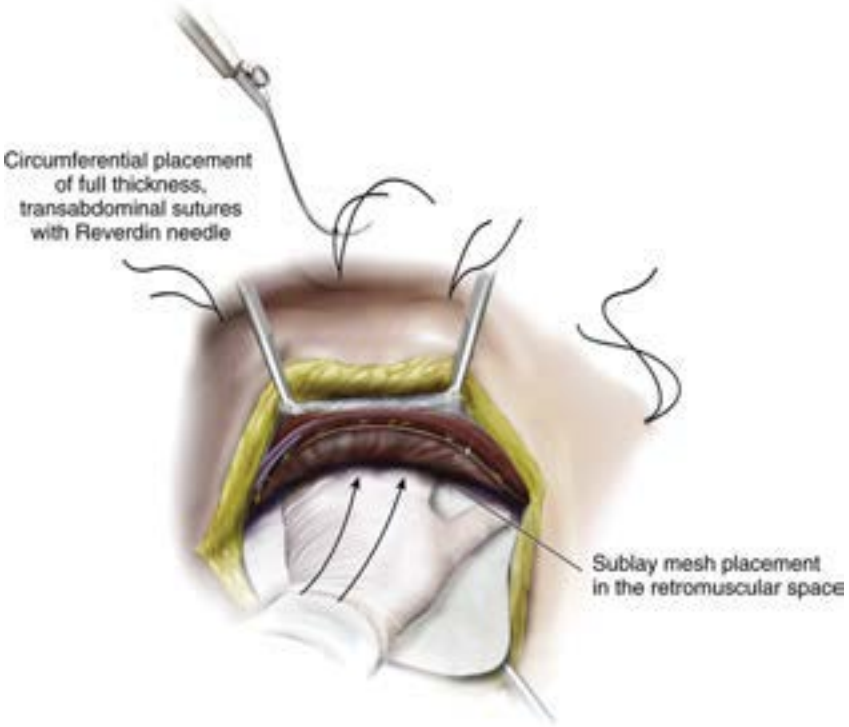


FIG. 6 Mesh fixation using full-thickness transabdominal sutures. *(From Rosen MJ. Atlas of Abdominal Wall Reconstruction. WB Saunders, 2012.)*

occurred, an additional 4 days of PPP are carried out, and a repeat CT scan is completed. If there remains no change, it is unlikely that PPP will be successful in expansion of the abdominal wall, and other techniques should be considered. Additional side effects associated with PPP include anorexia associated with an early satiety sensation. As a result, enteral nutrition should be actively encouraged throughout this process to promote postoperative wound healing. Subcutaneous emphysema is a common self-limiting sequala of this procedure. Of note, hemodynamic collapse as a consequence of PPP has also been described; it is for this reason that patients should only undergo PPP in a monitored step-down unit.

Botulinum Toxin A

A recent technique used in the field of abdominal wall reconstruction for abdominal wall expansion before repair includes botulinum toxin A. In 2021, Deerenberg et al. reported their off-label use of preoperative botulinum toxin A injection. This neurotoxin produced by *Clostridium botulinum* has an inhibitory effect on the presynaptic cholinergic nerve terminal. It is through this pathway that functional denervation of the muscle occurs within 2 days of use, with maximal effect occurring in the 2- to 4-week range. This effect then wears off after 3 to 6 months. Because of these intrinsic characteristics, its use is thought to cause relaxation of the lateral muscles of the abdomen, increasing the compliance of the abdominal wall and elongating the musculature. In their assessment of 108 patients, with an average of 2 failed prior repairs, fascial closure was obtained in 91% of patients, with 43% having adequate relaxation to not require component separation. In this cohort of patients receiving botulinum toxin A, 5 patients were categorized as severe LOD; 3 of these 5 patients developed recurrences and underwent surgery for their recurrent hernias. When comparing those with toxin alone to those undergoing an associated component separation, there was a significant reduction in overall postoperative complications, particularly surgical site recurrences and respiratory failure requiring intubation. They conclude that although this is an off-label use of botulinum toxin A, in well-selected patients a chemical component separation and preperitoneal placement of mesh may provide for a conservative and effective approach for complex ventral hernias. This again is another tool in the armamentarium of the hernia surgeon to mind the proverbial gap.

Perioperative Management

Respiratory complications following abdominal wall reconstruction can be very serious and are associated with morbidity and mortality as well as prolonged hospitalizations. Patients who develop changes in peak plateau pressures of 6 mm Hg experience an associated 8.6 × risk of developing respiratory complications. In patients with LOD, it is of utmost importance to monitor respiratory mechanics intraoperatively as well as in the postoperative period. Particularly in ventilated patients, peak airway pressures should be monitored. If there is evidence of elevated pulmonary plateau pressures during closure, notably values above 6 mm Hg from baseline after closure, one should consider ongoing ventilation for at least 24 hours with muscle relaxation and monitoring in the ICU. Documented preoperative predictors of respiratory failure include hernia size and hernia volume. This information may be used to counsel patients preoperatively regarding the need for postoperative ICU management.

Additional complications associated with repair of hernias in patients with LOD include wound complications. Although preoperative patient optimization is the best prevention for surgical site occurrences, including blood glucose control and cessation of smoking, surgical technique also contributes to development of surgical site occurrences. Attention to perforator sparing techniques, mesh placement in the sublay versus the onlay position, and avoidance of dead space and large adipocutaneous flaps can help decrease surgical site occurrences such as seromas, hematomas, and surgical site infections.

SUMMARY

Although the cylinder concept helps to better understand LOD from a mechanical force perspective, the Sabbagh method helps to better

understand this phenomenon from a volumetric perspective. The key to successful repair is preoperative planning with CT imaging and reduction of comorbidities. Although several techniques, approaches, and therapies are available to address LOD, the key to success is tailoring the approach based on the patient's anatomy and body habitus.

Suggested Readings

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Use of Various Meshes in Hernia Repair

Adrienne N. Christopher, MD, and John P. Fischer, MD, MPH

INTRODUCTION

Ventral hernias (VH) are among the most common abdominal wall pathologies encountered by general and plastic surgeons, with nearly 350,000 repaired annually in the United States alone. VH is a broad term referring to anterior defects of the abdominal wall that are classified by anatomic location and mechanism. Although repairs can be performed open or laparoscopically, here we focus on mesh most often used for open repairs. Despite some unique considerations related to surgical approach, there is generalizability in regard to understanding mesh properties and leveraging this knowledge to optimize any hernia repair, whether open, laparoscopic, or robotic. The fundamental goals of all VH repairs are similar—to prevent morbidity and improve functional status and quality of life. Patients presenting with symptomatic VHs (pain, alteration in bowel habits), significant protrusion that limits their ability to partake in activities of daily living, or VHs with risk of bowel obstruction/incarceration (i.e., large hernias with narrow necks) should be considered for repair to reestablish the integrity of the abdominal wall.

In 2000 and 2004, Luijendijk et al. and Burger et al. published two landmark trials that changed the way surgeons approach VH repair (VHR). In this multicenter randomized control trial comparing outcomes in patients undergoing primary suture versus mesh reinforced VHR, recurrence rates were halved in short- and long-term follow-up with the use of a reinforcing mesh material (23% vs. 46%; $P = 0.005$, and 32% vs, 63%; $P < 0.001$, respectively). Level 1a evidence provided by this work set the stage for defining the benefit of reenforcing any clean, ≤6-cm VH with mesh, including primary umbilical hernias. Furthermore, there is high-quality data that support mesh use in complex or large defects, and as a preventive measure in high-risk patients undergoing abdominal surgery. Current research has been dedicated to the development of various mesh scaffolds and biomaterials, with over 100 different commercially available mesh products. Mesh technology advancements coupled with advances in tissue based abdominal wall reconstruction have revolutionized the options available in the current surgical armamentarium. The hernia surgeon should be familiar with the various mesh classes available and indicated for use in VHR. Moreover, mesh selection and anatomic surgical plane should be considered collectively as the intrinsic properties and design of specific mesh products may make them more appropriately suited for specific anatomic locations.

The US Food and Drug Administration (FDA) defines mesh as a "medical device made of synthetic or animal derived materials used to provide additional support to weakened or damaged tissue." More specifically, the addition of mesh to a fascial closure helps to load-share the tension in the early stages of healing, thereby mitigating the risk of closure failure and re-herniation.

The ideal implantable mesh for VHR is biocompatible, nonadhesive, infection resistant, experiences minimal shrinkage, has tensile strength to withstand mechanical and physiologic forces placed on the abdominal wall, and is cost-effective and easy to use (Table 1).

Given that over 100 different mesh products exist, it is clear that no one product best meets all of these criteria. In fact, the characteristics and types of prosthesis vary greatly, complicating the appropriate selection for each clinical scenario.

MESH PROPERTIES

Biocompatibility

Any foreign material implanted into the body has the potential to elicit a host response. The biocompatibility of mesh products is

TABLE 1 Mesh Properties: Pros and Cons

Pros	Cons
Biocompatible, antiinflammatory macrophages (M2)	Significant host response, inflammatory macrophages (M2)
Facilitates neovascularization and tissue integration	Promotes scar tissue and chronic inflammation
High tensile strength	Low tensile strength
Elastic/flexible	Stiff, unable to return to original form after stretching
Cost-effective	Expensive
Minimal prosthetic footprint	Chronic foreign-body reaction, pain/stiffness
User-friendly	Difficult to manipulate

dictated by the degree of foreign body reaction that occurs at the biomaterial/host-tissue interface. Inflammatory (M1) and antiinflammatory (M2) macrophages play major roles in this reaction, with literature supporting that the M2 phenotype promotes tissue remodeling instead of scar tissue formation and fibrosis. The foreign body reaction can therefore be quantified by measuring the volume and type of inflammatory cells that migrate to the mesh after placement as well as the degree of collagen, scar tissue, and granuloma formation. Overall, these factors depend heavily on the intrinsic properties of the mesh including porosity, weight, constitution, and others.

Porosity

Mesh porosity refers to the ratio of open to solid space, or the percentage of mesh not occupied by mesh material. The open spaces, or pores, are defined by their relative sizes. Microporous meshes have pores <0.1 mm, small pore meshes 0.1 to 0.6 mm, medium-pore meshes 0.6 to 1.0 mm, large pore meshes 1.0 to 2.0 mm, and very-large-pore meshes >2.0 mm. Larger pores tend to facilitate the infiltration of macrophages, blood vessels, collagen, and antimicrobial agents, which increases soft tissue ingrowth and the ability of the mesh to resist bacterial colonization and infection. Conversely, in microporous meshes, scar tissue rapidly bridges the small pores, thereby minimizing integration capabilities and increasing the risk of chronic inflammation and rejection. However, large-pore mesh designs are generally created with less material and theoretically are less strong. In short, there is a delicate balance between mesh porosity and tensile strength.

Weight

The weight of a mesh is a measure of its mass per unit area and depends on the amount of material used (porosity) and the weight of the polymer itself. Meshes are typically classified as heavyweight (>80 g/m^2), medium-weight (50–80 g/m^2), lightweight (35–50 g/m^2), and ultra-lightweight (<35 g/m^2). Heavyweight meshes are made with thicker materials and have smaller pore sizes that result in a dense product with high tensile strength. However, they elicit larger foreign-body reactions resulting in greater degrees of fibrosis, adhesions, and chronic pain. Alternatively, lightweight mesh products are thinner with larger pore sizes. This construct facilitates less of an inflammatory response, which encourages incorporation of the mesh into surrounding tissues.

Tensile Strength

Tensile strength is defined as the maximum force that a mesh can withstand before breaking/failing. Mesh must be strong enough to withstand the maximum intraabdominal pressure generated by the average adult, which is typically about 170 mm Hg. Most mesh products easily accomplish this, as even lightweight mesh products can achieve twice this pressure before bursting. Most hernia repair failures occur from separation at the mesh-fascia interface, not from mesh failure due to lack of tensile strength.

Elasticity

Elasticity is the ability of a mesh to return to its original shape after being stretched or deformed. Meshes that cannot return to their original form after being stretched are less able to withstand the typical pressures applied to the abdominal wall in the postoperative period. In turn, a deformed mesh will not appropriately load-share tension across a fascial closure and will make the closure more prone to failure. Heavyweight meshes tend to be less elastic, whereas lightweight meshes are more elastic.

Constitution

The constitution of a mesh product refers to the various structural forms of the mesh, including monofilament, multifilament, or foil structures. In multifilament mesh products, multiple fiber strands are twisted together, which makes the product softer and more pliable when compared with the monofilament meshes. However, the small spaces between the strands are prone to infection as bacteria can get trapped in these areas.

MESH CLASSES

Mesh can generally be divided into three broad classes: synthetic, biologic, and composite/hybrid. Synthetic meshes are further classified as either nondegradable (permanent) or degradable, while all biologic mesh products are degradable. Early synthetic meshes were all uncoated to facilitate a prompt fibroblastic response through the open interstices of the mesh. However, this response was particularly problematic when mesh was placed in proximity to the bowel and other vascularized tissue as it caused unacceptably high rates of erosion and fistula. Coated synthetic products and composite/hybrid mesh products met some of these challenges and are so named because they contain more than one material. These prosthetics are typically composed of a synthetic mesh and a "barrier" on one or both sides of the mesh that is constructed from a variety of biofriendly materials to protect vascularized tissue from the synthetic implant. Meshes within all three of these classes have been created with variations of the aforementioned characteristics to optimize performance as adjuncts to VHR. Although there is consensus on the use of a reinforcement material to manage VH, the type of mesh to use is still widely debated, in part because of the diversity of defects, clinical situations, and mesh products available. Commercially available meshes are summarized here; however, meshes approved for hernia repair and those removed from the market because of poor performance change constantly. Having an open and honest conversation with patients before abdominal surgery with mesh placement is critical to facilitate shared decision making and set expectations about the potential complications and the recovery process.

Synthetic Meshes

Synthetic, nondegradable/permanent meshes are the original or traditional mesh products. These meshes tend to be the least expensive and are the most commonly used materials in current clinical practice. Typically, synthetic mesh products are composed of one of three materials: polypropylene (PP), polyethylene terephthalate polyester (POL), or expanded polytetrafluoroethylene (ePTFE).

PP products are the most commonly used of the synthetic products and are carbon-based monofilament or multifilament prosthetics that are completely resistant to biologic degradation (hence, permanent). Initial PP meshes were all heavyweight, dense, and microporous, while several newer PP products are lighter weight with larger pore sizes and lower densities. The high tensile strength and microporosity of many of the available PP meshes promote the formation of a fibrous scar tissue that surrounds the fibers, which facilitates incorporation of the mesh into the abdominal wall. However, these characteristics also can induce scarring and adhesions. Uncoated PP products are therefore unsuitable for cases in which they would be in contact with the abdominal viscera at the risk of bowel adhesions, obstructions, and fistulas. They should generally be avoided in combination with all vascularized tissue, including the greater omentum and hernia sacs. PP mesh is also vulnerable to bacterial inoculation. Infection is one of the most common reasons for mesh explantation, and PP should be used with caution in the setting of intraabdominal contamination. POL products are similar to PP; however, they tend to have greater pliability and reduced adhesiogenic properties. Nevertheless, it is still not recommended to place

these products in direct contact with the viscera as there have been unacceptable rates of erosion.

In addition to PP and POL, surgeons may encounter ePTFE, a fluorocarbon-based polymer. It has a macroporous ventral side that is constructed with ridges and depressions that promote tissue ingrowth, and it has the characteristic high tensile strength associated with synthetic products. Its microporous visceral side is smooth and nonerosive and therefore can be placed safely in contact with the intestine. However, the micoporosity reduces the accessibility of antimicrobials and immune cells; therefore, VHs repaired with ePTFE may be more prone to colonization and infection. In conclusion, permanent mesh products are reliable options for abdominal wall reinforcement in clean operative fields; however, intraperitoneal placement of uncoated synthetic products should generally be avoided as should placement when contamination is present or suspected.

Synthetic, degradable products (biosynthetics) have evolved to combine the tensile strength of synthetic mesh with the biocompatibility of biologic mesh. Specifically, they offer a safer side-effect profile in a contaminated field. The degradation profiles of these products vary from quick degradation (1–2 months) to complete degradation taking place over the course of years. In general, products formulated with slower degradation profiles have generated the most use, as those with quick degradation resulted in unacceptably high recurrence rates. The slow degradation allows for maximal wound healing and tissue regeneration before loss of integrity of the mesh occurs. Preclinical evidence has demonstrated that even after resorption, the associated tissues retain mechanical strength over time. These products therefore limit the inflammatory response and promote tissue integration but minimize the prosthetic footprint. Although promising for use in settings of contamination, robust long-term data on these newer products are sparse (Table 2).

Biologic Meshes

Biologic mesh constructs were developed to address a clinical need for mesh that could safely be used in settings of contamination or infection as it is currently "off-label" to use mesh in clean-contaminated, contaminated, and infected wounds according to the FDA. However, biologic materials are expensive and unfortunately have not performed as well as expected in these challenging scenarios. Biologics are designed from human, bovine, or porcine tissue to provide a scaffold for native tissue growth while harboring an ability to resist infection. The bio-scaffold encourages tissue integration, neovascularization, and collagen regeneration while biodegrading over time. However, reports of the use of biologics in the setting of contamination have seen recurrence rates of nearly 30% at 2 years. It is thought that the neovascularization promotes M2 macrophage delivery and activation, which in turn increases cytokine expression and inflammatory responses and promotes an intense foreign-body reaction. This leads to poor tissue integration and may be responsible for the high recurrence rates and expedient degradation rates in the setting of contamination (Tables 3 and 4).

In 2012, the Ventral Hernia Working Group (VHWG) published their recommendations for mesh use based on patient risk factors. They recommended the use of biologic mesh in VHs that are VHWG grade 4, which describes a wound that has septic dehiscence or an infected mesh. In VHWG grade 3, a potentially contaminated field, they caution using synthetic material and suggest there may be a role for biologic prosthesis in these settings. Although there may be a role for biologics in settings of severe contamination, this has not been substantiated with randomized clinical trials, and the use of biologic meshes in contaminated fields does not carry FDA clearance because of the disproportionately high number of adverse events. Certainly, with concerns regarding cost and outcomes, there is no strong evidence to support the routine use of biologic products, and many experts reserve its use as a last resort in settings of grossly contaminated fields (Table 5).

Composite/Hybrid Meshes

Composite, or barrier-coated, meshes are the basis of the newest mesh designs. These products are dual-sided prosthetics that often require a specific orientation in the abdominal cavity. The parietal side of the mesh is generally a synthetic material such as PP or POL that promotes integration and affords the tensile strength of the repair. The visceral side, however, is formulated from a variety of materials that act as a barrier between the mesh and the

TABLE 2 Synthetic/Biosynthetic Meshes

Product	Composition	Absorbable (Time)	Filament
Bard (Bard)	PP	No	Mono
Bard Soft (Bard)	PP	No	Mono
Phasix (Bard)	P4HB	Yes (12–18 months)	Mono
Ultapro (Ethicon)	PP + Poliglecaprone-25	Partial (2–3 months)	Mono
Vicryl (Ethicon)	Polyglactin	Yes (2–3 months)	Multi
Prolene (Ethicon)	PP	No	Mono
Prolene Soft (Ethicon)	PP	No	Mono
Gore-tex (Gore)	ePTFE	No	Multi
Enform (Gore)	PGA/TMA	Yes (6–7 months)	Mono
Gore BIOA (Gore)	PGA/TMA	Yes (6–7 months)	Mono
Versatex (Covidien)	POL	No	Mono
Prolite (Atrium)	PP	No	Mono
Prolite Ultra (Atrium)	PP	No	Mono
TIGR Matrix (Novus Scientific)	Glycolide/Lactide/TMC + Lactide/TMC	Yes (4 months to 3 years)	Multi

ePTFE, Expanded polytetrafluoroethylene; *P4HB*, poly-4-hydroxybutyrate; *PGA/TMC*, polyglycolic acid and trimethylene carbonate; *POL*, polyester; *PP*, polypropylene.

TABLE 3 Biologic Meshes

Product	Composition	Type	Absorbable
Alloderm (Allergan)	Dermis	Human	Yes
Strattice (Allergan)	Dermis	Porcine	Yes
XenMatrix (Bard)	Dermis	Porcine	Yes
Permacol (Covidien)	Dermis	Porcine	Yes
Veritas (Synovis)	Pericardium	Bovine	Yes
Periguard (Synovis)	Pericardium	Bovine	Yes
Surgisis (Cook)	Intestinal submucosa	Porcine	Yes
Gentrix (Acell)	Urinary bladder	Porcine	Yes
Surgimend (Integra)	Dermis	Bovine	Yes

TABLE 4 Intraoperative Predictors of Recurrence Based on Systematic Review and Meta-Analysis of 66 Studies

	Odds Ratio	95% Confidence Interval
Mesh Type		
Human ADM vs. porcine ADM	1.59	0.7–3.6
All biologic vs. synthetic	*1.98*	*1.22–3.22*
Human ADM vs. synthetic	0.9	.36–2.25
Porcine ADM vs. synthetic	0.28	0.07–1.12
Mesh Weight		
Lightweight vs. heavyweight	1.46	0.67–3.19
Lightweight vs. medium weight	1.62	0.91–2.87
Bridged Repairs		
Bridged repair vs. primary fascial closure	*2.62*	*1.72–3.97*
Mesh/Mesh Location		
Mesh vs. suture	*0.66*	*0.52–0.84*
Onlay vs. retrorectus	*1.96*	*1.41–2.72*
Onlay vs. preperitoneal	1.46	0.73–2.94
Onlay vs. intraperitoneal	2.15	0.87–5.34
Inlay vs. onlay	1.25	0.44–3.57
Inlay vs. preperitoneal	1.6	0.77–3.33
Inlay vs. intraperitoneal	3.64	0.87–15.14
Retrorectus vs. intraperitoneal	*0.42*	*0.2–0.91*
Preperitoneal vs. intraperitoneal	*2.94*	*1.0–8.62*

Data from Parker S, Mallett S, Quinn L, et al. Identifying predictors of ventral hernia recurrence: systematic review and meta-analysis. *BJS Open*. 2021;5(2).

intraabdominal contents to prevent adhesions and erosion (e.g., collagen, polyglactin, cellulose, titanium, omega 3, monocryl, polyvinylidene fluoride, hyaluronate). The barrier component can be absorbable or permanent. The two components are bound by an acrylic adhesive or heat sealant. A major benefit of composite mesh is that the "barrier" on the visceral undersurface allows for use in the intraperitoneal space (Table 6).

MESH LOCATION

Mesh can be placed in various configurations within the abdominal wall, including the space below the rectus abdominis muscles (sublay; retrorectus, preperitoneal, or intraperitoneal), the space above the rectus abdominis muscles and anterior fascia (onlay), or between the edges of the fascia (inlay) (Fig. 1). There are several important considerations to keep in mind. First, regardless of mesh location, a minimum of 4 to 5 cm of overlap between mesh and fascia on every side is recommended to account for mesh shrinkage, distribute tensile force, and help prevent recurrence. Additionally, ideal mesh placement is within a plane where the mesh is protected from superficial cutaneous infection and the intraabdominal contents, with enough space to accommodate adequate overlap. Lastly, placing the mesh within an area that encourages integration with the host tissue will reduce rates of mesh migration, failure, infection,

TABLE 5 Ventral Hernia Working Group (VHWG) Hernia Grading System: Assessment of Risk for Surgical Site Occurrences*

Grade	1 Low Risk	2 Comorbid	3 Potentially Contaminated	4 Infected
Patient/wound characteristics	Low risk of complications No history of wound infection	Smoker Obese Diabetic Immunosuppressed Chronic obstructive pulmonary disorder	Previous wound infection Stoma present Violation of the gastrointestinal tract	Infected mesh Septic dehiscence

*Wound infection defined as being contained within the skin or subcutaneous tissue (superficial) or involving the muscle and/or fascia (deep).

TABLE 6 Composite Meshes

Product	Composition	Absorbable (Time)	Filament
Sepramesh (Bard)	PP + Hydrogel Barrier*	Partial (1 month)	Mono
Ventralex (Bard)	PP + PDO + ePTFE	Partial (6–8 months)	Mono
Ventralex ST (Bard)	Ventralex + Hydrogel Barrier	Partial (6–8 months)	Mono
Ventrio (Bard)	PP + PDO + ePTFE	Partial (6–8 months)	Mono
Ventrio ST (Bard)	Ventrio + Hydrogel Barrier	Partial (6–8 months)	Mono
Ventralight (Bard)	PP + Hydrogel Barrier	Partial (1 month)	Mono
Ethicon Physiomesh (Ethicon)	PP + Polyglecaprone 25	Partial (1 month)	Mono
Proceed (Ethicon)	PP + Cellulose	Partial (1 month)	Mono
Synecor (Gore)	PTFE + PGA/TMC	Partial (6 months)	Mono
Parietene DS (Covidien)	PP + Collagen	Partial (1 month)	Mono
Symbotex (Covidien)	POL + Collagen	Partial (1 month)	Mono
Parietex (Covidien)	POL + Collagen	Partial (1 month)	Multi
C-Qur (Atrium)	PP + Omega 3	Partial (4 months)	Mono

*Hydrogel barrier: sodium hyaluronate and carboxymethylcellulose
ePTFE, Expanded polytetrafluoroethylene; *PDO*, polydioxanone; *PGA/TMC*, polyglycolic acid and trimethylene carbonate; *POL*, polyester.

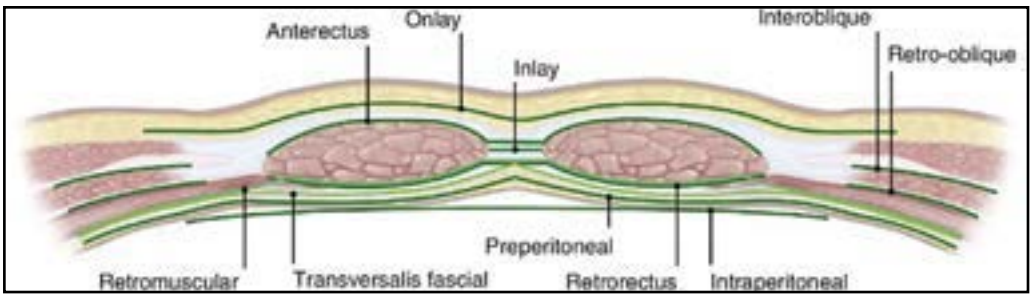


FIG. 1 Classification of abdominal wall planes. *(From Parker SG, Halligan S, Liang MK, et al. International classification of abdominal wall planes (ICAP) to describe mesh insertion for ventral hernia repair.* Br J Surg. *2020;107[3]: 209–217.)*

and recurrence. It is important to consider mesh type and plane collectively as some meshes are more suited for certain configurations.

SUBLAY

Sublay mesh refers to any mesh placed below the rectus muscle. More specifically, options for sublay mesh placement include: retrorectus—between the rectus abdominis and the posterior rectus sheath, preperitoneal—between the posterior rectus sheath and preperitoneal fat, or intraperitoneal—in the abdominal cavity secured to the undersurface of the peritoneum.

Retrorectus

For most hernia repairs, retrorectus mesh placement should be considered the gold standard. VHs repaired with retrorectus mesh have been found to have lower rates of recurrence and surgical site events than any other mesh configuration (Tables 7 and 8; see

TABLE 7 Outcomes by Mesh Location of 6277 Ventral Hernia Repairs

Outcome	Sublay: Retrorectus	Sublay: Intraperitoneal	Onlay	Inlay	*P*
Complication (%)	32.6	37.8	38.6	39.1	0.738
Infection (%)	10.2	17.7	14	12	0.276
Hematoma/seroma (%)	11	11.5	17.4	12.2	0.288
Mesh removal (%)	0.5	1.1	0.3	0.3	0.346
Recurrence (%)	5.8	10.9	12.9	21.6	*0.023*
Mortality (%)	0.5	0.5	0.3	0.3	0.929

Data from Sosin M, Nahabedian MY, Bhanot P. The perfect plane: A systematic review of mesh location and outcomes, Update 2018. Plast Reconstr Surg. 2018;142(3S):107S–116S.

TABLE 8 Multiple Treatment Meta-Analysis to Determine Best Treatment by Recurrence and Surgical Site Infection Rates

	Rank	Odds Ratio	95% Credible Interval	Probability of Being Best Among Four Treatments
Recurrence				
Onlay (reference)	3,4			<0.001
Inlay	3,4	3.946	0.49–13.26	<0.001
Sublay (retrorectus)	*1*	0.218	0.06–0.47	0.942
Underlay (intraperitoneal)	2	0.59	0.07–1.50	0.058
Surgical Site Infection				
Onlay (reference)	4			<0.001
Inlay	3	1.113	0.09–3.83	0.113
Sublay (retrorectus)	*1*	0.449	0.12–1.16	0.773
Underlay (intraperitoneal)	2	0.878	0.29–1.99	0.114

Data from Holihan JL, Nguyen DH, Nguyen MT, et al. Mesh location in open ventral hernia repair: a systematic review and network meta-analysis. *World J Surg*. 2016;40(1):89–99.

Table 4). The plane itself is relatively easy to develop, assuming there have been no prior surgeries or disruptions to the plane. It provides a broad muscle-mesh interface that facilitates revascularization, and it well-insulates the mesh from the intraperitoneal contents where adhesions may form. Given that the mesh is well protected on either side, surgeons can feel safer placing more permanent materials (e.g., synthetic mesh) in this space. However, lateral dissection in this plane is restricted by the innervation to the rectus muscle at the level of the semilunaris, making mesh placement and overlap in larger more complex defects suboptimal.

Technique

The posterior sheath is incised below the linea alba and separated from the rectus abdominis dissecting from medial to lateral. The deep inferior epigastric vasculature should be preserved. The retrorectus plane can then be developed laterally to the semilunar lines. The linea semilunaris is identified by the presence of the intercostal nerves perforating the lateral border of the rectus muscle as well as the lateral reflection of the posterior sheath as it transitions to the anterior sheath. The intercostal neurovascular bundles must be maintained as they provide segmental innervation to the rectus complex. Once the retrorectus plane has been developed, the posterior sheath can be reapproximated in the midline, and the mesh can be placed within the space. The mesh should be fixated to the lateral rectus sheath and semilunar line. Closed-suction drains are placed in this space to help minimize fluid collection around the mesh. The anterior rectus sheath, subcutaneous tissue, and skin are closed over the mesh in the midline.

Preperitoneal

In patients where the retrorectus space is not suitable for access or not large enough to accommodate a mesh with appropriate overlap for the defect, the preperitoneal space may be considered. In this configuration, the mesh is placed in direct contact with the undersurface of the posterior sheath above the peritoneum and is a good option for patients with a large preperitoneal fat pad to bolster mesh placement.

Technique

The development of the pre-peritoneal flaps involves entering the space of Retzius, an artificial cavity between the transversalis fascia and peritoneum. This space is best accessed at the lower midline level. After incision, the anterior rectus sheath should be incised and the rectus muscle reflected medially. The space can subsequently be developed with blunt dissection inferiorly to the pubis and Cooper's

ligaments, laterally to the psoas muscles, and caudally to the xyphoid process. The peritoneum should be reapproximated to completely cover any exposed abdominal viscera. Any defects in the peritoneum should be patched with tongues of omentum or primarily repaired with suture. Mesh can then be placed safely within the space and fixated using full-thickness, transabdominal, permanent sutures. When the mesh is sizable, it should be secured superiorly on either side of the xyphoid, at the pubis, at Cooper's ligament, and laterally along the costal margin.

In both retrorectus and preperitoneal mesh configurations, the mesh is protected from the subcutaneous space and the intraabdominal contents. In these cases, the placement of synthetic or biosynthetic mesh products is safe, and we recommend lightweight or medium-weight synthetic or biosynthetic implants. They have adequate tensile strength for a durable repair, yet they tend to elicit less chronic pain and foreign-body sensation, and they better resist infection because of their larger porosity. There is little role for the use of biologic implants in these scenarios.

Intraperitoneal

Intraperitoneal mesh placement requires less tissue dissection than accessing the retrorectus or preperitoneal planes. It avoids injury to the posterior sheath and the rectus muscle, and it can be considered for use when concomitant procedures are being performed in the same space (e.g., ostomy take-down or fistula resection). Because of mesh exposure to the intraabdominal viscera, mesh in this plane must have an anti-adhesive barrier coating to prevent bowel adhesions and erosion. Newer composite mesh products are specifically designed for these unique situations, with permanent polypropylene or polyester on one side, allowing mesh adhesion to the parietal peritoneum and antiadhesive materials on the other. Surgeons should avoid placing uncoated synthetic materials alone in these spaces, as the risk for adhesion and fistula formation is unacceptably high.

Technique

Care should be taken to thoroughly inspect the abdominal cavity for any residual adhesions or bowel injury. Mesh in this space should be placed in settings without frank contamination. Careful attention to mesh fixation in these cases is paramount as a poorly situated mesh is at risk of migrating into the abdominal cavity or allowing intraabdominal contents to herniate between the mesh and the peritoneum. At least four anchoring stitches should be placed in the corners, followed by systematic placement of interrupted sutures at a distance of 1 to 1.5 cm to complete the fixation.

ONLAY

Onlay is a technique whereby mesh is placed between the subcutaneous tissue and the anterior rectus sheath. Benefits of utilizing the onlay configuration are that (1) it is technically easier than sublay mesh placement as it does not require a significant myofascial dissection; (2) it allows placement of a larger piece of mesh than retrorectus techniques; (3) it does not risk devascularizing the rectus muscle, and (4) it prevents contact between the repair material and underlying viscera. However, large subcutaneous skin flaps must be created to accommodate mesh placement. This creates dead space and puts patients at an increased risk for superficial surgical site events. Moreover, because of the anterior location of the mesh, it is at higher risk of contamination if the incision becomes infected. Nonetheless, it can be considered in several instances including patients with larger defects in which the retrorectus space would be unable to accommodate a sufficient size mesh, patients with a history of extensive abdominal surgery without a useable posterior rectus sheath, or patients undergoing concurrent complex intraabdominal surgery with contamination to avoid mesh in proximity to the viscera.

Technique

Skin flaps should be developed carefully and only so far as to accommodate mesh placement. Following closure of the anterior fascia, mesh is placed either in the subcutaneous plane, representing the classic onlay, or in a hybrid plane inferior to released external oblique muscles, representing the modified onlay. Mesh fixation is achieved with the systematic placement of transfascial "U-stitches" utilizing slow-resorbing sutures. 12 o'clock and 6 o'clock stitches establish vertical tension across the mesh, followed by 3 o'clock and 9 o'clock stitches to establish horizontal tension. Several additional sutures can be placed in between for further fascial fixation. To make the mesh taut and wrinkle-free, same-size bites should be taken throughout the mesh and fascia. A running continuous suture is occasionally placed around the mesh edge to prevent irregular contouring of the mesh surface. If dead space is significant, surgeons may consider the placement of progressive tension sutures, whereby synthetic absorbable sutures are placed in a lateral to medial fashion through the abdominal wall fascia and the undersurface of the skin flap (incorporating a small bite of the Scarpa fascia). Closed-suction drains should be placed in the subcutaneous space to help drain fluid and prevent adverse wound events.

INLAY

In the inlay plane, also sometimes referred to as placement of a bridging or interpositional mesh, the mesh is connected directly to the edges of the fascia without complete fascial closure. This plane should be used only if no other mesh planes are available and is typically reserved for situations in which the fascial defect is too large to close primarily because of high rates of recurrence due to excess tension (see Table 4). Further, depending on surgeon comfort, the viability of fascial closure with tissue releases should be assessed before utilizing the inlay technique. However, in cases in which midline fascial approximation is not feasible, inlay mesh placement is preferred over failure to close. Inlay mesh repairs are associated with higher recurrence and surgical site events than sublay or onlay meshes. The mesh is exposed to the intraperitoneal contents and is also vulnerable to superficial wound complications. Additionally, the lack of overlap precludes mesh-tissue integration, thereby increasing the risk of recurrence in this population. Because of the location of the mesh, uncoated permanent mesh is not recommended in this setting because of a high risk of bowel adhesions, mesh erosion, and infection. Instead, surgeons should prioritize using slowly resorbable materials or materials with adhesive barriers on either side.

Technique

After dissecting the edge of the defect, opening the hernia sac, and reducing the contents into the intraabdominal space, excess peritoneum should be excised and the peritoneum closed, if possible, using running absorbable suture. The mesh may be anchored to the lateral aspect of the rectus abdominis musculofascial sheath at the semilunar line. The theoretic advantage of anchoring the mesh here, rather than at the edge of the defect, is that the semilunar line or lateral rectus sheath is a strong aponeurotic buttress and may reduce the risk of suture pull-through. Additionally, this provides a greater amount of mesh surface area peripheral to the defect. The mesh should be fixated using transabdominal, interrupted permanent sutures spaced about 1 cm apart. If the semilunar line is not accessible, the mesh should be fixated to the edge of the defect. In cases in which the fascia may be too attenuated to support the mesh, it can be fixated directly to the iliac or pubic bone for additional support. Drains are placed over the mesh and in the subcutaneous tissue, and the skin is meticulously closed.

IMPORTANT TENETS OF SKIN AND SOFT TISSUE MANAGEMENT

In addition to mesh implant and anatomic plane, special attention must be paid to the skin and soft tissue during VHR with mesh. This is critical to mitigate wound-healing problems that place patients at higher risk for mesh infection, explantation, and hernia recurrence. An otherwise successful reconstruction can be lost as a result of skin necrosis, wound dehiscence, or an infected fluid collection around the mesh. Several important tenets, established by Janis et al., are reviewed here.

Preservation of Blood Supply to the Abdominal Wall

The main blood supply to the abdominal wall is in close proximity to the umbilicus via perforators from the deep inferior and superior epigastric systems (Fig. 2). As most VHRs involve an incision through the midline and the umbilicus, these vessels are often sacrificed. Moreover, to achieve adequate visualization of a fascial defect, develop the necessary planes for fascial closure and mesh placement, and achieve adequate mesh overlap, lateral undermining of skin flaps may be necessary, further sacrificing the more laterally oriented perforating blood supply to the superficial abdominal wall. Risks for significant disruption are generally thought to be greater with mesh placed in the onlay plane as the lateral dissection to accommodate mesh placement is more significant with this repair technique. However, when certain component separations or transfascial suture fixations are required, even VHs with retrorectus or intraperitoneal repairs can require the development of significant lipocutaneous flaps. Careful attention to identifying and preserving vasculature when possible during skin flap elevation is crucial to optimize the remaining blood supply to the abdominal wall and minimize wound-healing complications. Flaps should be raised judiciously, and only so far as is absolutely necessary. As the medialmost skin edges are most at risk for vascular compromise, clinical assessment of the skin edges should be done before closure. A pale dermis without robust punctate bleeding is concerning for vascular insufficiency, and the skin should be resected to pink, bleeding tissue.

Skin and Soft Tissue Excess

In patients with large, chronic hernias, often the overlying skin and soft tissue can become attenuated over time. This skin usually has poor blood supply post-repair and creates excessive dead space that places patients at risk for fluid accumulation and subsequent infection. Additionally, obesity is a risk factor for hernia development, and many VH patients may be obese. Weight loss before surgery should be recommended in the case of elective repair. When delaying surgery for weight loss is not feasible, addressing the excess skin will prevent distracting forces on the incision that increase the risk for wound breakdown, skin necrosis, and surgical site infection. Consultation with a plastic surgeon for consideration of skin contouring and/or concurrent panniculectomy at the time of hernia repair is appropriate in these situations.

Dead Space

The accumulation of fluid within a surgical plane can be detrimental as it is at risk of becoming infected and can inhibit incorporation and revascularization of mesh. Fluid generally accumulates within dead space, and efforts to minimize these spaces must be made. Placement of closed-suction drains should be done for all patients who have had skin flaps raised and within the retrorectus space if a retrorectus dissection has been performed. Patients should be educated on frequent drain stripping to prevent clogging. Drain removal should be conservative, with sequential removal only when the output is serosanguinous and less than 30 cc daily over several days. The placement of progressive tension sutures, as described earlier, is another technique employed to minimize dead space in cases in which large flaps have been raised.

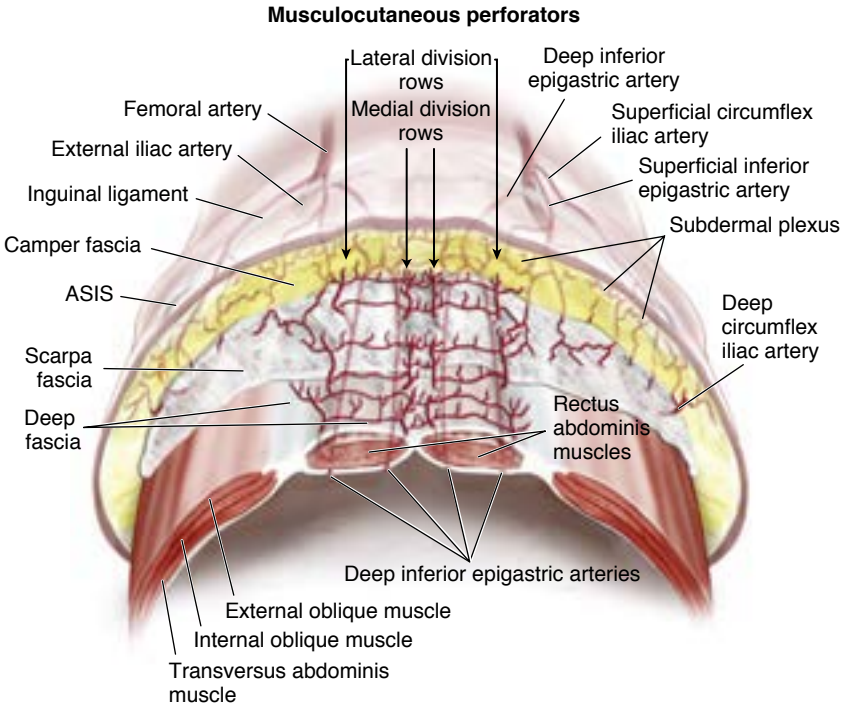


FIG. 2 Blood supply to the abdominal wall. *(From Rosen M. Atlas of Abdominal Wall Reconstruction. Philadelphia: Elsevier; 2017.)*

CONCLUSION

Advances in prosthetic materials and surgical techniques have changed the way we approach VHR. The hernia surgeon should take into consideration mesh properties, patient characteristics, and the unique clinical scenario before selecting a mesh type and anatomic plane for placement. In most situations, surgeons should favor using a lightweight mesh with large pores and less overall surface area. When feasible, use of the retrorectus plane will best protect the mesh both from the intraabdominal contents and the subcutaneous space. If mesh needs to be placed in contact with the intraabdominal viscera, a hybrid or coated product with an absorbable undersurface should be considered. VHR in the setting of contamination proposes unique challenges that may be met with newer biosynthetic products. In all cases, close attention to skin and soft tissue is paramount to minimize wound events and facilitate a successful reconstruction.

Suggested Readings

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Benign Breast Disease

Halley Vora, MD, and Tawakalitu O. Oseni, MD

GENERAL CONSIDERATIONS

Most women will experience a benign breast concern in their lifetime. These patients are often referred to general surgeons for evaluation and management.

Evaluation of any breast complaint begins with a focused history and physical examination. The history should include an assessment of the patient's presenting problem including onset, symptoms, quality, duration, presence of aggravating/alleviating factors, and any new changes in health. Additionally, personal and familial risk factors should be noted and if available, input into risk prediction models. Patients who are identified as increased risk either by history or diagnosis should be offered enrollment in high-risk screening programs and may benefit from risk-reducing lifestyle modifications or chemoprevention with tamoxifen or raloxifene.

Focused physical examination begins with visual inspection for any asymmetry, retraction, nipple abnormalities, or skin changes such as erythema or peau d'orange. Palpation should systematically cover all areas of both breasts including the axillary tail and should include examination of the axillary, supraclavicular, and cervical nodal basins. If the patient presents with a complaint of nipple discharge, then it is appropriate to attempt to elicit the discharge with palpation. Any nipple discharge should be characterized in terms of color and location as well as whether it arises from a single duct or multiple ducts, and if a trigger point can be identified.

Physical examination should be followed with the appropriate diagnostic imaging. In patients younger than age 30 years, diagnostic ultrasound is the initial study of choice; mammography is not usually helpful because of increased breast density and low likelihood of breast cancer in this patient population. For patients aged 30 to 39 years, diagnostic mammogram is indicated in addition to ultrasound because they often have reasonably interpretable mammograms despite dense breast tissue, and it may be possible to see microcalcifications or other abnormalities not detected by ultrasound. At age 40 years and older, patients should have up-to-date bilateral mammograms annually. Evaluation of any concerns should include diagnostic mammography and targeted ultrasound as needed. In general, for average-risk patients, mammography and ultrasound are sufficient imaging for evaluation of most breast complaints. More costly imaging such as magnetic resonance imaging should be reserved for suspicious clinical or imaging findings that remain indeterminate despite complete mammographic and sonographic evaluation. When a biopsy is indicated, an image-guided core needle biopsy is preferred, and a clip should be left marking the area biopsied.

COMMON BREAST COMPLAINTS

Breast Pain

Breast pain (mastalgia) is one of the most common benign breast complaints. It can be cyclic in nature, often related to fibrocystic and hormonal changes. Fibrocystic change presents with bilateral, menstrual-related cyclic pain, with tender, nodular and lumpy breasts often most prominent in the upper outer quadrants. Mastalgia is more common during the reproductive years; however, it can be experienced throughout life. Although breast pain is not commonly associated with cancer, obtaining a thorough history of the pain, completion of physical examination, and age-appropriate imaging is necessary. If there are irregular findings on initial workup such as a palpable mass or noncyclic pain, further diagnostic evaluation may be required.

Benign breast pain may self-resolve without intervention. Conservative lifestyle modifications can be recommended for management and relief. These include soft but supportive bras, reduction of caffeine and fatty foods, use of hot or cold compresses, and use of nonsteroidal antiinflammatory drugs (NSAIDs). Additional agents that may reduce breast pain include vitamin E, evening primrose oil, topical NSAIDs, and in resistant cases, danazol.

Nipple Discharge

Nipple discharge in the nonlactating breast can be caused by a variety of factors, most of which are benign. The character of the discharge as well as the history are important in determining possible causes. Most women who have lactated can induce, with palpation and pressure, a small amount of milky/clear discharge from one or both nipples; this type of induced discharge may not require further evaluation beyond age-appropriate screening. Spontaneous bilateral milky nipple discharge arising from multiple ducts in a nonlactating woman consistent with true galactorrhea is rare, and evaluation should include age-appropriate breast imaging, review of potential causative medications, and a serum prolactin level. Patients with an elevated prolactin level should be referred to an endocrinologist for further management.

The most common causes of spontaneous unilateral nipple discharge include duct ectasia and intraductal papilloma. The discharge can be serous or sanguineous in nature. Bloody discharge may be caused by a benign intraductal papilloma; however, the concern for cancer should be raised. Workup should include physical examination and diagnostic imaging including mammogram and ultrasound. Additional imaging may include ductogram, to identify ductal filling defects, although it is not commonly performed at many centers and may be uncomfortable for patients. Breast MRI with contrast has rapidly replaced ductograms as the diagnostic tool of choice for pathologic and persistent nipple discharge. It may also be utilized if suspicion remains high and other imaging is negative.

When a suspicious lesion is found on imaging, image-guided core needle biopsy should be performed. If the results are benign and concordant, no further intervention may be necessary. In some cases, no lesions are noted on imaging or patients continue to experience symptoms; thus, excision of the offending duct may be necessary. Surgical duct excision can be performed by intraoperatively eliciting discharge with pressure, placing a small lacrimal duct probe into the identified duct, and excising the duct through a periareolar incision. If a single duct cannot be identified or multiple ducts are producing the discharge, a central duct excision may be warranted. Women in their reproductive years should be made aware of the potential difficulty with breastfeeding in the future.

Mastitis/Abscess

Nonlactational breast infections are less common and can be painful and difficult to clear. Periductal mastitis is more common in women who are smokers, have large breasts, are overweight, or have had previous surgery or radiation to the breast. As with lactational mastitis, *Staphylococcus* and *Streptococcus* are the most common pathogens, and treatment should involve symptom relief, antibiotics, warm compresses, and NSAIDs. Complete resolution of uncomplicated mastitis may take a few weeks; however, mastitis that fails to resolve on antibiotics or worsens requires further evaluation, including diagnostic imaging to rule out an undrained abscess or underlying carcinoma and inflammatory breast cancer.

If an abscess is present in the nonlactating breast, drainage is indicated in addition to antibiotics. Ultrasound-guided aspiration of a breast abscess is ideally the first intervention. It is important to document sonographic resolution of the abscess after aspiration because undrained collections can lead to recurrent infections. Recurrent or deep-seated loculated collections may require open incision and drainage, often with general anesthesia or deep sedation because of the painful nature of the procedure. Subareolar abscesses in young smokers may be secondary to squamous metaplasia of lactiferous ducts. These patients may develop recurrent infections and a subsequent peri-areolar fistula requiring excision of the tract.

Mastitis and breast abscesses can usually be managed on an outpatient basis. One occasional exception is in patients with diabetes in whom severe breast infection can be accompanied by systemic sepsis requiring hospitalization and intravenous antibiotics.

MANAGEMENT OF BENIGN BREAST MASSES AND LESIONS

A palpable breast mass is one of the most common complaints leading women to present to a surgeon. In premenopausal women, most palpable breast masses are caused by benign lesions, with a minority representing cancer. Ruling out cancer is an essential part of the evaluation of a breast mass. In postmenopausal women, a new breast mass should be assumed to be cancer until proven otherwise. Diagnostic imaging can show distinct characteristics of benign masses helpful in distinguishing from a cancer. In most cases, solid masses are definitively diagnosed with image-guided core needle biopsy.

Fibroadenoma

Fibroadenoma is the most common benign solid breast mass. It is composed of benign proliferation of glandular epithelial and stromal components. They occur most commonly in younger women during the reproductive years, may grow during pregnancy, and often involute after menopause. On examination they are rubbery, mobile, and well-circumscribed. Ultrasound characteristics include a solid appearance, usually with uniform hypoechogenicity, smoothly marginated borders, and a round or ovoid shape that is typically wider than tall. Pathologic confirmation can often be made with image-guided core needle biopsy. The majority of fibroadenomas do not require surgical intervention and can be followed with serial imaging. Surgical excision of a fibroadenoma should be planned if it is large (>3 cm), has rapid growth (usually >20% in 6 months), is symptomatic, has unclear pathology or atypia on core biopsy, or causes significant anxiety in the patient.

Benign Phyllodes Tumor

Benign phyllodes tumors often present similarly to fibroadenomas. When compared with fibroadenomas, phyllodes tumors may grow more rapidly, are usually larger, and may present more commonly in later reproductive years. Even with these small clinical differences and imaging, it can be difficult to distinguish phyllodes tumors from fibroadenomas. A core needle biopsy is required to confirm the diagnosis. Unlike some fibroadenomas, all benign phyllodes tumors should be surgically excised with clear margins. Core biopsy reported as cellular fibroepithelial lesion could represent either a fibroadenoma or a phyllodes tumor and should be excised for diagnosis and local control.

Cysts

Cysts occur most commonly in the middle and late reproductive years. Most macroscopic cysts are asymptomatic; however, they can present as a cause of breast pain and focal mass. They result from dilation of the terminal ductal lobular unit and irregularity of normal lobular involution. Cysts are generally smooth, tense, mobile structures on physical examination. On ultrasound examination they can be simple or complex. Simple cysts appear anechoic, well-circumscribed, round, or ovoid; may have a thin wall; and have posterior acoustic enhancement. In addition to the characteristics of a simple cyst, complex cysts may have septae, intracystic echoes from internal debris, and a solid/hypoechoic component. In line with the *Choosing Wisely* recommendations of the American Society of Breast Surgeons, routine aspiration of small, asymptomatic simple cysts is not needed. Simple cysts that are symptomatic or concerning to the patient may undergo ultrasound- or palpation-guided aspiration. Cyst fluid that is bloody should be sent for cytopathology, while nonbloody cyst fluid can be discarded. Complex cysts, particularly those with thick septations, debris, or a solid component should undergo biopsy. Ultrasound-guided core needle biopsy should be performed with a clip left in place to mark the location if excisional biopsy is subsequently required.

Granulomatous Mastitis

Idiopathic granulomatous mastitis (IGM) is a rare benign inflammatory breast disease. The pathogenesis is poorly understood. Patients most often present with a painful mass and may have symptoms similar to abscess or infection. If an infection is present, it should be controlled. Patients can also present with symptoms mimicking breast carcinoma; therefore, an appropriate diagnostic workup with imaging and core needle biopsy is necessary. Management remains controversial and is usually multimodal. Medical management includes use of steroids, methotrexate, and/or antibiotics. Surgical excision may be warranted for complicated or refractory cases.

Fat Necrosis

Fat necrosis is caused by inflammation and disruption of oxygen supply to fat cells, ultimately leading to cell death. In addition to surgery and procedural causes of fat necrosis, other sources include trauma, radiation, anticoagulation, and infection. Fat necrosis can commonly present as a hard palpable mass, causing concern in patients and healthcare providers, especially in postsurgical patients. A mammogram may show an encapsulated fat density mass with associated coarse calcifications. Ultrasound characteristics include a mixed solid and cystic mass, a poorly defined hypoechoic mass with shadowing caused by calcifications, oil cysts, and no internal vascularity. Fat necrosis sometimes cannot be distinguished from cancer radiographically, making core needle biopsy necessary. Although

fat necrosis is benign, it can lead to abnormal physical examination findings, increased imaging, and multiple biopsies. Patients whose quality of life is severely affected may benefit from surgical excision.

Lipoma

Breast lipomas, similar to lipomas elsewhere in the body, are benign tumors originating from fatty tissue. They are well-circumscribed, encapsulated, soft, mobile masses that can be identified on ultrasound. Lipomas of the breast do not require surgical intervention unless symptomatic, large, or rapidly growing.

Proliferative Lesions without Atypia

Although many proliferative lesions without atypia may be observed, some require surgical consultation. These include complex sclerosing lesions, radial scars, and papillary lesions. The upgrade rate for these lesions averages approximately 5% to 10% in modern data sets. In the setting of complex sclerosing lesions, including radial scar, the majority should undergo excisional biopsy. For small lesions felt to be adequately sampled, with concordant imaging, observation can be considered. Intraductal papillomas or papillary lesions without atypia similarly are excised. Some criteria that can help determine the need for excision include size, presence of a palpable mass, associated symptoms such as nipple discharge, or if the individual is at elevated breast cancer risk. Lesions that are not excised should have close follow-up with imaging and examination.

Proliferative Lesions with Atypia

Atypical lesions should all be referred for surgical consultation as many require excisional biopsy. Atypical ductal hyperplasia (ADH) not only identifies if a patient is at increased risk of breast cancer diagnosis, especially if there is a relevant family history, but also has an upgrade rate ranging from 5% to 25% in the literature. When ADH is diagnosed on core needle biopsy, an excisional biopsy should be performed. Atypical lobular hyperplasia (ALH) is also a marker of increased risk and has a variable literature upgrade risk, notably less than that of ADH. Therefore, patients diagnosed with pure ALH on core biopsy may not require excision if the imaging and pathology are concordant. If a decision is made to forego excision, the patient should return for close follow-up with diagnostic imaging to assess for stability. Similarly, classic lobular carcinoma in situ (LCIS) may also be observed. Nonclassical variants of LCIS including pleomorphic and florid LCIS should undergo excisional biopsy. Papillary lesions with atypia also have a high upgrade rate and are recommended to undergo excisional biopsy.

SPECIAL POPULATIONS

Pregnancy and Lactation

Hormone-related changes occur frequently in the pregnant and lactating breast. Although the majority of changes are benign, a workup is necessary for any new or concerning lesions. Ultrasound is the preferred imaging method during pregnancy and lactation; however, mammogram should not be withheld if indicated. Many benign lesions during pregnancy and lactation have specific imaging findings and do not require further workup. Any suspicious mass or lesion on imaging should undergo image-guided core needle biopsy. If a biopsy must be performed during the months a woman is lactating, there is a low risk of milk fistula formation, regardless of whether the biopsy is an excisional biopsy or a core needle biopsy. Although milk fistulas are rare, the risk is higher for deep central lesions. Milk fistulas can be managed with conservative treatment and resolve with cessation of lactation.

Abscess

Infection in the lactating breast can be common. Lactational abscesses can develop from progressive mastitis or infected galactoceles. The most common causative organism is *Staphylococcus*. Breast ultrasound can confirm and evaluate the extent of the abscess. First-line management should include antibiotics with good gram-positive coverage such as dicloxacillin or trimethoprim/sulfamethoxazole, ultrasound-guided aspiration (may require serial aspirations) or catheter drainage, warm compresses, and continuation of breastfeeding. Although surgical drainage is no longer the first-line therapy, it may be necessary in large abscesses or refractory cases.

Galactocele

Galactoceles are lesions caused by the accumulation of milk resulting from a persistent plugged duct that leads to outflow obstruction. Initial management is conservative, with warm compresses, massage, and continued breastfeeding. However, if the galactocele continues to enlarge or becomes symptomatic, then intervention should be considered for symptom control and risk of infection from stasis. Cessation of breastfeeding and serial aspirations or catheter drainage may be required.

Lactating Adenoma

These lesions arise only during pregnancy and the puerperium and present as a painless mass. Lactating adenomas regress spontaneously after pregnancy/lactation. Ultrasound characteristics of lactating adenomas are similar to fibroadenomas, such as oval mass and posterior acoustic enhancement, and they may have a microlobulated margin indicative of distended acini. Infarction of these lesions may occur causing pain. Lactating adenomas do not typically require surgical intervention. Core biopsy may be necessary to confirm diagnosis in the absence of specific distinguishing features on imaging.

Male Gynecomastia

Gynecomastia is a benign enlargement of breast tissue in men. It can present as a unilateral or bilateral, painful firm or rubbery subareolar mass. Gynecomastia tends to have a bimodal distribution commonly occurring in puberty or in older age resulting from hormone-related changes. It has been associated with estrogen excess or testosterone deficiency. It may be associated with cirrhosis of the liver, primary hypogonadism, testicular tumors, obesity, and numerous medications and drugs including: steroids, estrogens, ketoconazole, digoxin, spironolactone, phenothiazines, efavirenz, and marijuana. If evaluation and the medical history implicates a specific drug, discontinuation of that drug (if medically acceptable) with reevaluation in 3 to 6 months may be reasonable. Gynecomastia can also be a side effect of prostate cancer treatment with anti-androgen medication; use of tamoxifen should be considered in these patients to reduce symptoms of mastalgia and the progression of gynecomastia during treatment. Radiologic evaluation includes diagnostic mammography to confirm diagnosis. Although gynecomastia is physically benign, it can cause emotional or psychological distress, particularly in adolescent and young adult males, in which case surgical management should be considered.

COVID-19 Vaccination–Associated Lymphadenopathy

In March 2020, the World Health Organization declared the coronavirus 2019 (COVID-19) a pandemic. Beginning in December 2020, COVID-19 vaccination programs began and subsequently continued to expand. As more patients receive the vaccine, a side effect of ipsilateral axillary swelling, tenderness, or lymphadenopathy has become notable. In patients who have up-to-date age-appropriate breast surveillance imaging, a thorough history and physical examination should be performed. If there are no significant findings beyond the unilateral lymphadenopathy in the ipsilateral arm with a recent history of vaccination, then close surveillance and follow-up may be performed. Most patients should have resolution of symptoms 6 weeks after the last dose of the vaccine. If symptoms persist or the history is

not appropriate, further diagnostic workup should be performed. It is important to note that screening breast imaging does not need to be delayed in the setting of the COVID-19 vaccine or vice versa.

Suggested Readings

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Screening for Breast Cancer

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INTRODUCTION

The American Cancer Society (ACS) estimates that in the United States in 2021 there will be about 284,200 new cases of invasive breast cancer and about 49,290 new cases of ductal carcinoma in situ. They estimate that approximately 44,130 deaths will be attributable to breast cancer in the United States. In the United States, breast cancer is the most commonly diagnosed cancer in women and the second most common cause of cancer death. Since the late 1980s, based on accumulated evidence from long-term follow-up of randomized controlled trials and observational studies of population-based screening, several organizations have published guidelines for breast cancer screening. Published guidelines have changed over time and have not always been in agreement across different organizations. In the past decade, there has been a greater emphasis on estimating harm from screening and recognizing the interplay between published recommendations and an individual woman's values, preferences, and informed decision making. This chapter considers screening modalities and guidelines used to identify early breast cancer in asymptomatic women, including women considered to be at average risk of breast cancer and in those considered to be at increased risk.

Potential improvement in outcomes with screening includes the possibility of improved breast cancer–related survival, but also lower morbidity of treatment. Early detection may be associated with the ability to provide disease control with a lumpectomy rather than a mastectomy, and with less toxic systemic treatments. Potential harms of screening must be considered. Potential harms include exposure to radiation and false-positive imaging findings, which can lead to additional imaging evaluation, potential biopsy, increased cost, and anxiety. As with all cancers, screening practices for breast cancer should be based on evidence regarding the prevalence of disease in the screened population, the effectiveness of the screening procedure, and any attendant harm, including the risks and costs associated with the screening test and any additional tests and procedures that follow a positive screening test. There have been debates about who should be screened, at what age, and with what method. As more data have emerged regarding the frequency and consequences of false-positive test results and overdiagnosis (i.e., diagnosis of low-grade, nonaggressive tumors that likely would not have an impact on a person's life) and as breast cancer treatment becomes more effective, the trade-off between benefits and harms of screening have evolved.

SCREENING MODALITIES

Breast Self-Examination

Breast self-examination (BSE) once was advocated as an integral part of screening for breast cancer, and women were instructed routinely in BSE technique. However, large randomized trials have failed to show a reduction in breast cancer–specific or all-cause mortality from regular BSE in populations at average risk. BSE is now deemphasized or absent in screening guidelines but still has some potential value. Some breast cancers are mammographically occult or develop between screening imaging. Many cancers are detected by patients themselves, independent of a clinical examination or radiologic screening. Teaching BSE and encouraging familiarity with self-examinations may encourage patients to bring changes to clinical attention. Although the value of BSE has not been demonstrated in trials, it must still be encouraged as it is low cost, widely available, and sometimes the first step in breast cancer detection.

Clinical Breast Examination

The contribution of clinical breast examination (CBE) to the early detection of breast cancer is unclear. About 10% to 20% of breast cancers are not visible on screening mammography, and CBE performed by trained personnel has been shown to increase breast cancer detection over mammography alone. One limitation of CBE is that effectiveness depends on technique and time spent on the examination, and it is difficult to standardize. Another limitation is the expense of clinician availability and time and of the high false-positive rate; there may be as many as 55 false-positive findings by CBE for each additional cancer detected by CBE. It remains an important screening tool globally, especially in places where screening imaging is not readily available. CBE has become less emphasized in US screening guidelines but still provides an important opportunity to discuss breast health, instruct patients on BSE technique, and educate patients on findings that should prompt a clinical visit and clinical breast examination.

Mammography

Mammography is the primary imaging screening modality for the early detection of breast cancer among asymptomatic women because it is the only method of breast imaging that has thus far been found to decrease breast cancer–related mortality. Standard screening mammograms provide two views of each breast: the mediolateral oblique projection images the breast from an oblique medial to lateral approach, and the craniocaudal projection images the breast from a superior to inferior view. The use of two views allows physicians to localize an abnormality to a particular quadrant within the breast and increases the sensitivity of mammography. The mammography interpretation is appended by an American College

TABLE 1 Breast Imaging Reporting and Data System Classification

Category		Management	Likelihood of Cancer in the Mammographic Finding
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	
1	Negative	Routine screening	
2	Benign	Routine screening	Essentially 0
3	Probably benign	Short interval follow-up (6 months)	>0 but <2%
4	Suspicious	Tissue diagnosis	4a. Low suspicion for malignancy (>2% to ≤10%) 4b. Moderate suspicion for malignancy (>10% to ≤50%) 4c. High suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known, biopsy-proven malignancy	Surgical excision when clinically appropriate	

of Radiology Breast Imaging Reporting and Data System (BIRADS) classification (Table 1). The BIRADS categories classify mammographic findings by level of suspicion that the finding represents cancer. Nine randomized-controlled trials including more than 650,000 asymptomatic, average-risk women have been conducted on screening mammography and have reported data on mortality. With long-term follow-up, pooled results from these studies found a 20% relative risk (RR) reduction for breast cancer mortality in women invited to screening as compared with controls, with the benefit most pronounced in older age groups (60–69 years). Pooled estimates from observational studies have demonstrated an even greater effect. The magnitude of these estimates is influenced by a number of factors, including whether they are based on invitation or exposure to screening and on the heterogeneity of the studied populations. Screening mammograms can be performed without a radiologist present, and suspicious findings prompt a call-back for a diagnostic mammogram, which is performed with a radiologist present, who can decide whether additional spot views or magnification views are necessary to interpret the positive finding on screening mammography.

Breast density has been well described as a factor associated with lower sensitivity of screening mammography. It is also established as an independent risk factor for breast cancer, but its importance as a risk factor can be overemphasized. Studies comparing women with the highest density to those with the lowest density resulted in an estimated 4-fold to 6-fold increase in risk. With use of average breast density as a reference point, the risk among women with heterogeneously dense breasts is 1.2 times as great as the average, and with extremely dense breasts it is 2.1 times as great. This is a modest increase in risk, similar to the increased risk of breast cancer associated with having a first-degree relative with unilateral, postmenopausal breast cancer. Breast density does not appear to be associated with increased mortality from breast cancer. It is not clear at this time whether screening recommendations should be altered for women with dense breasts or how women who have dense breasts should be counseled. Because breast density influences cancer risk and the performance of mammography as a screening tool, the American College of Radiology has included classification of breast density as a necessary component of mammographic interpretation.

Digital Mammography

The early randomized controlled trials addressing the effectiveness of screening used film mammography. Digital mammography has replaced film as the primary screening modality in most areas in the United States. In addition to facilitating remote reading and more efficient storage, the real advantage of digital image collection over film systems is higher contrast resolution and the ability to postprocess the image to enlarge it or change the contrast and brightness, helping radiologists more easily detect subtle abnormalities, particularly in a background of dense breast tissue. Most studies that have compared the performance of digital and film mammography have found little difference in cancer detection rates. There is suggestion of an increase in detection of invasive cancer in premenopausal and perimenopausal women and in women with dense breasts but also an increase in false-positive findings.

Mammography has limitations as a screening tool. Mammography uses radiation, which itself can be carcinogenic, although models indicate that the radiation risk from mammography is low enough to result in a net benefit from screening with respect to lives saved. Another limitation is the question of overdiagnosis, which refers to the detection of disease by screening that would not have become clinically important in a woman's lifetime. This could include ductal carcinoma in situ (which may or may not progress to invasive cancer) or a very indolent invasive cancer. Overdiagnosis may be reflected in results from randomized trials and cohort studies that demonstrate a higher incidence of cancer diagnosed in a population screened by mammography versus an unscreened population, despite a long follow-up. Another limitation is the risk of false-positive screening tests. This can result in additional imaging and procedures, potentially even surgical excision for a benign condition that would have never become symptomatic. False-positive screening tests are more common in younger women because mammography is less specific in this population and because cancer is less common.

Tomosynthesis

Tomosynthesis (or three-dimensional [3D] digital mammography) is a newer technology that involves the acquisition of multiple images of the breast recorded at different angles while the detector is held

stationary, providing the radiologist with a series of thin-slice (0.05-mm) images through the breast. Tomosynthesis can reduce call-back rates and may increase the cancer detection rates over two-dimensional (2D) digital mammography. It has not been shown to decrease disease-specific mortality. Efforts have been successful in limiting the amount of radiation used for this method, and digital 2D images can be produced from the tomosynthesis views, eliminating the need for separate 2D images. Tomosynthesis also can be costlier. The use of tomosynthesis mammography is increasing in the United States.

Whole-Breast Ultrasound

The role of whole-breast ultrasound screening was evaluated by the American College of Radiology Imaging Network National Breast Ultrasound Trial (ACRIN 6666). After screening 2809 women at very high risk, only 4 cancers per 1000 women were detected with an ultrasound scan alone. The difficulties of whole-breast ultrasound as a screening tool include: the length of time it takes to perform, low reproducibility from one ultrasonographer to another, and the number of false-positive findings. However, there is some evidence that breast ultrasound can increase detection of breast cancer as an adjunct to screening mammogram in women with dense breasts. Breast ultrasound as a screening tool is not routinely recommended, but it is sometimes considered in women with very dense mammograms and in high-risk patients for whom screening mammography or screening MRI are insufficient or cannot be performed. The best current use of breast ultrasound is primarily in diagnostic evaluation of abnormal findings on mammography, clinical examination, or MRI. A focused breast ultrasound scan can further characterize palpable or screening detected lesions and is commonly used to perform an image-guided needle biopsy of sonographically visible lesions.

Magnetic Resonance Imaging

The reported sensitivity of contrast-enhanced breast MRI for detection of invasive breast cancer is between 88% and 100%. Many benign lesions can also enhance on MRI, and low specificity is a problem that limits MRI as a screening tool. The specificity of screening breast MRI may continue to improve as technology advances. The positive predictive value of any test is greater as the prevalence of disease rises, and MRI has a higher utility in patients at higher relative risk for breast cancer. The efficacy of MRI as a screening tool in patients at high risk of breast cancer has been validated in multiple studies. Annual screening MRI as a supplement to screening mammography is part of current screening guidelines for many women at high risk of breast cancer, such as those with a known deleterious *BRCA* mutation or those with a predicted lifetime risk of over 20% on risk modeling. The National Comprehensive Cancer Network (NCCN) also recommends annual MRI screening for individuals who received radiation to the chest between 10 and 30 years of age, those with Li Fraumeni syndrome, or those with Cowden's syndrome. There are many patient groups for whom the value of breast MRI is less clear. There is currently insufficient evidence either for or against the use of screening MRI for persons with a lifetime risk estimate of 15% to 20% or in those with dense breast tissue on mammography. Screening MRI is not recommended for persons with a lifetime risk of breast cancer less than 15%. The potential harms of breast MRI include the significant cost of the test, exposure to gadolinium, and patient discomfort or claustrophobia, which can be a limiting factor in a significant proportion of patients.

Newer Methods

There are numerous methods in development that could in the future be considered for breast screening in some patients, but they are not currently appropriate for use in general population screening. These newer methods include: contrast enhanced mammography; molecular breast imaging (sestamibi scan, positron emission mammography, breast-specific gamma imaging); and artificial intelligence deep learning algorithms.

SCREENING RECOMMENDATIONS

Screening guidelines have existed for decades and have been published by many organizations including the ACS, the NCCN, the United States Preventative Services Task Force (USPSTF), the American College of Radiology, the American College of Obstetrics and Gynecology, the Society for Breast Imaging, the Canadian Task Force on Preventative Health Care, and the American College of Physicians. Published guidelines have changed over the years as new data and viewpoints are considered, and the recommendations vary somewhat from one guideline set to another. Although many unanswered questions remain, it is clear that screening for breast cancer remains a valuable part of breast cancer detection.

Screening in Average-Risk Individuals

The recommendations from the ACS and the NCCN for asymptomatic women at average risk are summarized in Table 2. The ACS recommendations for breast cancer screening are maintained on the

TABLE 2 American Cancer Society and National Comprehensive Cancer Network Screening Recommendations for Persons at Average Risk of Breast Cancer

	ACS	NCCN
Clinical encounter		Every 1–3 years: age 25–40 years Annual: age 40 years and older
Age to begin screening mammogram	45 years	40 years
Interval for screening mammogram	Annual: 45–55 years Annual or biennial: >55 years	Annual
Age to stop screening	Continue while in good health and while life expectancy is >10 years	No age limit. Consider comorbidities and whether abnormal findings would be acted upon.
Other considerations	Individualized decision for ages 40–44 years	Consider tomosynthesis for screening mammograms. Breast awareness encouraged for all.

ACS website (http://www.cancer.org/healthy/informationforhealthcareprofessionals/acsguidelines/breastcancerscreeningguidelines/index). The recommended age to start screening mammography for women at average risk was stated by the ACS at 45 years. This was based on an analysis of the risks of false positives in women younger than 45 years versus the small incremental benefits with respect to preventing breast cancer deaths in a relatively low-prevalence age group. Whereas previous recommendations suggested annual screening mammography start at 40 years of age, current recommendations describe the use of mammography between 40 and 45 years as a decision that should be made with consideration of risks and benefits of screening. The recommendation for annual screening mammography at 45 years of age and older was based on (1) clear data regarding the benefits of screening mammography in women between 50 and 75 years of age and (2) the observation that the incidence of breast cancer and proportion of incident breast cancers in women 45 to 49 years of age more closely resembled the 50- to 54-year age group than did the 40- to 44-year age group. Annual screening mammography should continue while a woman's life expectancy is at least 10 years, with the consideration to transition to biennial screening at 55 years of age. There is no ACS recommendation for the upper age limit to stop screening for breast cancer.

The recommendations of the ACS focus primarily on the outcome of lives saved after breast cancer screening. Other outcomes

TABLE 3 National Comprehensive Cancer Network Screening Recommendations for Persons at High Risk of Breast Cancer

	Clinical Encounter/Examination	Screening Mammography	Screening Breast MRI
Lifetime risk >20% (as defined by models that are largely dependent on family history)	Every 6–12 months over age 21 Consider referral to a genetic counselor	Annual Consider tomography Start 10 years before the age at which the youngest family member was diagnosed, but not before age 30	Annual Start 10 years before the age at which the youngest family member was diagnosed, but not before age 25 If not able to have MRI, consider whole-breast US or contrast-enhanced mammography
Thoracic radiation therapy between 10 and 30 years	Every year before age 25 (starting 8 years after RT) Every 6–12 months over age 25 (beginning 8 years after RT)	Annual starting 8 years after RT but not age 30 Consider tomography	Annual Start 8 years after RT but not before age 25 If not able to have MRI, consider whole-breast US or contrast-enhanced mammography
5-year risk of invasive breast cancer ≥1.7% in persons over age 35 years	Every 6–12 months	Annual Consider tomography	Not included in recommendations
LCIS/ALH or ADH and ≥20% lifetime risk	Every 6–12 months	Annual Not before age 30 Consider tomography	Consider annual MRI Not before age 25 If not able to have MRI, consider whole-breast US or contrast-enhanced mammography
Deleterious *BRCA* mutation	Every 6–12 months starting at age 25	Annual between age 30 and 75 Consider tomography Consider on an individual basis over age 75	Annual, beginning at age 25 Consider on individual basis over age 75
Li Fraumeni syndrome	Every 6–12 months starting at age 20	Annual between age 30 and 75 Consider tomography Consider on an individual basis over age 75	Annual between age 20 and 75. Consider on an individual basis over age 75
Cowden's syndrome	Every 6–12 months starting at age 25 or 5–10 years before earliest known breast cancer in the family	Annual beginning at age 35 years (or 10 years before earliest known breast cancer in the family). Consider tomosynthesis Consider on an individual basis over age 75	Consider annual MRI beginning at age 35 (or 10 years before earliest known breast cancer in the family). Consider on an individual basis over age 75

ADH, Atypical ductal hyperplasia; *ALH,* atypical lobular hyperplasia; *LCIS,* lobular carcinoma in situ. *NCCN,* National Comprehensive Cancer Network; *RT,* radiation therapy; *US,* ultrasound.

that may be important to patients were not vigorously addressed, and may have been undervalued. Such outcomes can include quality of life. The ACS found the quality of evidence regarding the effect of screening on quality-adjusted life years to be too low to incorporate this outcome into their screening recommendations. The stage at which a breast cancer is diagnosed may influence a woman's option for breast-conserving therapy. Early diagnosis may also allow for simpler and less toxic treatment.

As of 2021, NCCN screening guidelines recommend that women have a breast cancer risk assessment by 25 years of age and have guidance regarding potential risks and benefits of breast screening according to their risk level. The NCCN recommends CBE every 1 to 3 years and states that women of all ages should be familiar with their breasts and promptly report changes to their healthcare provider. An annual screening mammogram is recommended to begin at the age of 40 and is accompanied by annual CBE. The NCCN does not support an upper age limit for screening but does note that comorbidity, life expectancy, and the expectation that a positive examination finding would be followed by treatment should be incorporated into decision making in older women.

Screening in High-Risk Individuals

Several national medical organizations have developed guidelines and recommendations for enhanced screening in women at high risk of breast cancer. The group for which there is the best developed evidence-based recommendations includes women with deleterious *BRCA1* or *BRCA2* mutations. In 2017, a prospective cohort of 9856 women revealed the estimated cumulative risk for developing breast cancer by 80 years of age with *BRCA1* and *BRCA2* mutations was 72% and 69%, respectively. Many other findings can define an individual as being at high risk of breast cancer. Women who have had a prior diagnosis of breast cancer, atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ are also considered higher than average risk, as are women with a family history suggestive of familial breast and/or ovarian cancer, or a first-degree relative who has tested positive for a breast cancer–associated genetic mutation. Women who received mantle or chest wall irradiation between 10 and 30 years of age are at high risk of breast cancer. Enhanced screening schedules can also be used for women who are calculated to have an elevated lifetime risk of being diagnosed with invasive cancer according to a prediction model. A variety of models are available to predict risk, of which the most widely used is the Gail model, or modifications of the Gail model. This predication algorithm assesses breast cancer risk based on age, number of first-degree relatives with breast cancer, age of menarche, age of first live birth, number of previous biopsies (including presence of atypia), and race or ethnicity. The Tyrer-Cuzick model is commonly used and incorporates family history and gynecologic history.

Table 3 contains a summary of screening recommendations from the NCCN for persons at high risk of breast cancer based on risk category. NCCN guidelines are specific with respect to the age and modality of screening recommended. In general, annual screening mammography is recommended for women of significantly high risk beginning at 30 years of age, supplemental screening with breast MRI is recommended for a subset with very high risk, and screening ultrasound scan is recommended for women in whom MRI is unavailable. The results of a recent study with computer-simulated modeling concluded that annual MRI at age 25 years later alternating every 6 months with digital mammography beginning at age 30 years may be the most effective screening strategy for deleterious mutation carriers.

SUMMARY

Breast cancer remains a common cancer for which early detection can improve outcomes, including both lower morbidity of treatment and improved survival. Mammography remains the dominant screening strategy for most women. Enhanced screening with annual MRI can be appropriate and valuable for women who are at very high risk of breast cancer. The majority of breast cancers in the United States are diagnosed as a result of an abnormal screening study, and death rates from breast cancer in the United States have decreased 30% since the 1990s. It is estimated that approximately one-third of this effect is a result of screening, with the rest attributable to treatment advances. Challenges remain in providing appropriate screening for all who may benefit. There is great interest in developing newer screening methods that may provide screening at lower cost, with greater accuracy, and in areas currently without screening.

Suggested Readings

Gilbert FJ, Hickman SE, Baxter GC, et al. Opportunities in cancer imaging: risk-adapted breast imaging in screening. *Clin Radiol*. 2021;76(10):763–773.

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Role of Stereotactic Biopsy in Management of Breast Disease

Jessica M. Pastoriza, MD, William C. Mallon, MD, and Lisa K. Jacobs, MD, MSPH

Stereotactic breast biopsy is the sampling of nonpalpable or indistinct breast lesions through spatial localization of the lesion within the breast using radiographic imaging. The word *stereotactic* is derived from Greek and Latin roots meaning "touching in space." In the late 1980s, Dowlat introduced stereotactic breast biopsy technology to the United States. As breast biopsy tools became more advanced and spring-loaded and later vacuum-assisted core devices were developed, an image-guided biopsy approach has become predominant for initial tissue diagnosis. It is an important tool in the diagnosis of breast lesions as part of the triple assessment, which includes clinical, radiologic, and cytohistopathologic studies. In the past, nonpalpable breast lesions would have been surgically excised after needle localization, resulting in a vast number of surgeries for nonmalignant mammographic abnormalities. In the United States, it is estimated that more than 1 million surgical breast biopsies are performed, and only 15% to 30% are found to be malignant. More than one-half of all breast biopsies are performed stereotactically. It is endorsed by the American Society of Breast Surgeons and a quality

measure for the National Accreditation Program for Breast Centers. The sensitivity of core needle biopsies performed stereotactically or with ultrasound is 97% to 99%. The accuracy of stereotactic biopsy can be increased with a larger needle size.

Core needle biopsy devices are 8 to 14 gauge, and vacuum-assisted devices are 7 to 11 gauge with rotating cutters. The choice of percutaneous device depends on the target lesion (mass vs. microcalcifications), target location (mid-depth breast vs. adjacent to skin or implant vs. axilla), intent to remove the entire lesion, and the training and experience of the clinician. A core-needle biopsy or vacuum-assisted technique is usually preferable to fine-needle aspiration (FNA) cytology for all breast lesions because of the increased sensitivity and preservation of architecture for improved characterization of the lesion with marker analysis, and immunohistochemistry.

The stereotactic platform can be used for several image-guided breast interventions including but not limited to breast biopsy, needle localization for excision, and percutaneous therapy. For lesions <1 cm, percutaneous excision is performed using a vacuum-assisted or other enhanced tissue-acquisition device along with placement of a marking device (e.g., clip). For lesions >1 cm, 14-gauge core needle biopsy is often sufficient. In general, a clip or other marking device should be placed at the time of percutaneous biopsy of all suspicious lesions to improve the accuracy of future localization of the lesion, especially if there is concern that the lesion may be completely removed in the biopsy or if the patient is anticipated to undergo neoadjuvant chemotherapy. Neoadjuvant chemotherapy causes significant tumor regression and may result in loss of the target for eventual surgical excision.

According to the American Society of Breast Surgeons, image guidance for breast biopsies is recommended for both palpable and nonpalpable lesions to increase the accuracy of sampling. A percutaneous breast biopsy of a palpable mass without the use of image guidance may lead to a false-negative result because the biopsy device cannot be confirmed to be within the lesion of interest, as some palpable lesions have a surrounding inflammatory reaction that may be palpable but does not contain malignant cells. In most instances, ultrasound is preferred for image guidance in patients with palpable masses. Imaging modalities available for targeting of nonpalpable breast lesions include breast ultrasound, mammogram (stereotactic), and magnetic resonance imaging (MRI). If the lesion is visible sonographically, ultrasound guidance is preferred as it optimizes patient positioning and comfort.

TECHNIQUES

Ultrasound-guided biopsy is usually the most straightforward approach, but lesions better seen on mammography images, particularly microcalcifications, require stereotactic localization. The principles of localization involve mapping the distance between the geometric center of the breast with the target lesion in two different planes and then projecting the coordinates onto the patient's breast (Fig. 1).

Earlier techniques in stereotactic biopsy used mammographic projections to localize the target lesion within the breast and manual localization through the use of grids and two-dimensional (2D) images from two views (central with compression from superior/inferior and medial/lateral oblique compression of the breast). Advances in digital mammography have since superseded manual computations. Localization are performed with dedicated stereotactic equipment that fixes the breast in place. Stereotactic techniques have also been developed within other imaging modalities, including ultrasonography and MRI. These techniques offer more options and greater flexibility in performing stereotactic biopsy. Digital tomosynthesis creates a three-dimensional (3D) image of the breast using x-rays. It has been approved by the US Food and Drug Administration (FDA), but it is not available in all hospitals. This technique is called *mammography with tomosynthesis* and involves taking multiple x-ray images at 1-mm slices of each breast from many angles

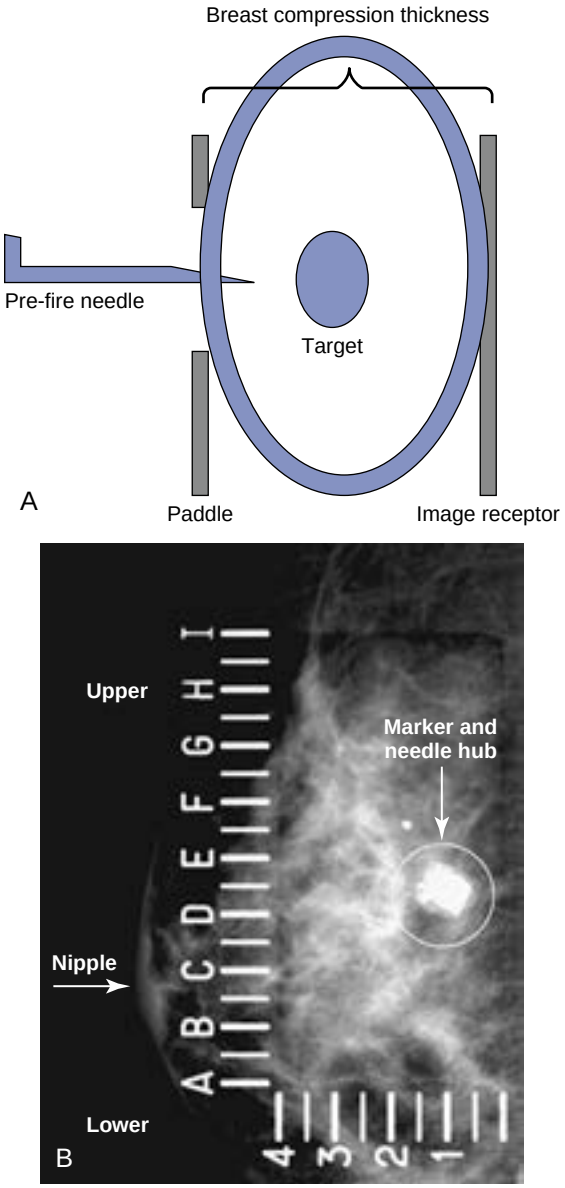


FIG. 1 Successful pre-fire positioning to target the lesion, with the needle near the lesion. (***B*** *from Ikeda DM:* Breast imaging: The Requisites. *2nd ed. Elsevier; 2011.)*

(Fig. 2). The breast is positioned in the same way as conventional mammography but with limited pressure. The x-ray tube moves in an arc around the breast while numerous images are taken within a few seconds. The information is then relayed to a computer that generates a highly focused 3D image throughout the breast. Performing a biopsy using 3D images can be beneficial when the mass is not easily seen on 2D imaging, and it is especially helpful in dense breast tissue, where 3D images can differentiate a true distortion or asymmetry seen on mammography from overlapping breast tissue.

INDICATIONS

There are six Breast Imaging-Reporting and Data System (BI-RADS) categories: (1) negative, (2) benign finding, (3) probably benign finding, (4) suspicious, (5) highly suggestive of malignancy, and (6) known biopsy proven malignancy. Indications for stereotactic biopsy include the following (Box 1):

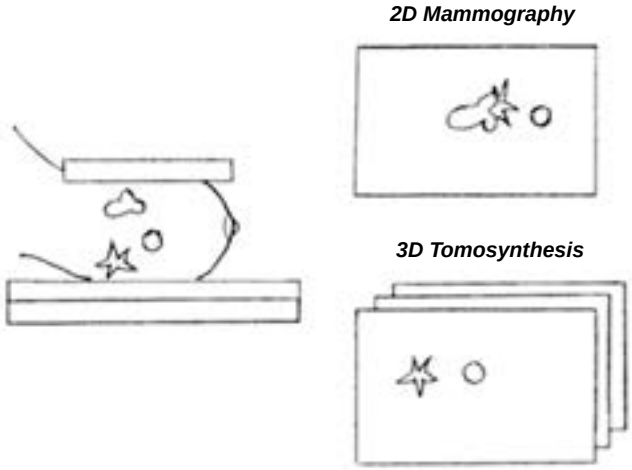


FIG. 2 Two-dimensional mammography and tomosynthesis image acquisition modalities. *(From Catelli A, Santoro A, Antignani E, et al. Safety and efficacy of tomosynthesis-guided breast biopsies in the prone position: monocentric study and review of the literature.* J Cancer Res Clin Oncol. *2022;148:967–974.)*

BOX 1 Indications for Stereotactic Core Biopsy

- Certain probably benign lesions, BI-RADS 3, depending on clinical suspicion, patient or physician preference, or when short-term follow-up is not practical
- BI-RADS 4, suspicious lesions
- BI-RADS 5, highly suspicious lesions
- BI-RADS 6, known biopsy-proven malignancy
- New suspicious microcalcifications, developing asymmetries, or architectural distortions
- Nonpalpable asymmetry, focal asymmetry, or density on mammogram not seen on ultrasound
- Mammographic lesions corresponding to suspicious areas of enhancement on magnetic resonance imaging
- New mass or area of a previous surgery site
- Area of abnormal tissue change

BI-RADS, Breast Imaging-Reporting and Data System.

- Highly suspicious microcalcifications or densities (BI-RADS 5) to confirm the diagnosis and facilitate treatment planning
- Suspicious microcalcifications or densities (BI-RADS 4)
- Probably benign microcalcifications or densities (BI-RADS 3) when there are valid clinical indications
- Multifocal or multicentric lesions to facilitate treatment planning
- Repeat biopsy in the setting of discordant imaging assessment with initial biopsy

CONTRAINDICATIONS

Lesion location can affect accurate targeting by image guidance. Contraindications include lesions immediately juxtaposed to an implant, lesions that are too posterior to the chest wall, or those that are too superficial to the skin or nipple (Box 2).

Multiple patient factors can preclude a stereotactic biopsy, such as inability to lay prone for stereotactic or MRI guided biopsy, mental disability that limits patient cooperation, body habitus (obesity, pregnancy, or kyphosis). Weight >300 lb exceeds the weight limit on a prone biopsy table. If a patient has thin or small breasts, adequate

BOX 2 Contraindications for Stereotactic Core Biopsy

- Patient unable to lie prone or cooperate
- Patient's excess weight
- Lesion location near nipple, too superficial to skin, too posterior to chest wall, or too close to implant
- Lesion mammographically occult
- Patient has severe kyphosis or movement disorders
- Lack of breast tissue thickness for adequate compression
- Pregnancy

breast tissue thickness may not be available while in compression to allow access for the computerized biopsy equipment. There may not be enough breast tissue to compress to safely biopsy without the needle penetrating through to the other side of the breast. Further, if the breast is too large and the lesion is deep, stereotactic biopsy may not be technically feasible. Stereotactic core biopsy is also not indicated in pregnant women. Patients who are unable to undergo stereotactic biopsy should be referred for surgical excisional biopsy. It is unclear how to manage patients who receive antiplatelets and anticoagulants, and the risk of bleeding must be balanced against the risk of stopping the anticoagulant.

EQUIPMENT

The first choice for diagnosis of most breast lesions is through core biopsy under ultrasound guidance. The potential for sampling error has led to more invasive and larger-volume percutaneous biopsy devices such as vacuum-assisted biopsy devices. The vacuum-assisted devices have the ability to sample larger tissue volumes. These devices consist of an outer shell with an aperture at its end for collecting tissue. It is a single-insertion device that uses vacuum suction to pull the target tissue into the collecting aperture. The tissue is then excised by a rotating cutter. Multiple harvests can be performed in 360 degrees around the lesion while the probe remains in the lesion during the whole procedure, allowing for up to 12 biopsies with a single insertion of the device. The vacuum device can be used under ultrasound guidance or stereotactic guidance, particularly for microcalcifications; the patient is prone or upright with the use of certain units, with adequate room to accommodate the device. The vacuum devices are available 7- to 12-gauge sizes; the 9-gauge device is most popular as it can remove up to 1 cm of tissue. The vacuum-assisted device has been demonstrated to be superior in the diagnosis of ductal carcinoma in situ (DCIS) compared with a 14-gauge core biopsy, with 6% found to be invasive carcinoma after vacuum-assisted biopsy at surgery compared with 21% with 14-gauge core biopsy. Repeat biopsy rates for inadequate sampling of microcalcifications is also significantly lower when using vacuum-assisted biopsy (11.6% vs. 23.7% for core biopsy), although an equal proportion of malignancy is diagnosed following re-biopsy. Although vacuum-assisted biopsy appears to be nearly three times more accurate than core biopsy in the diagnosis of atypical ductal hyperplasia (ADH), underestimation still occurs in 18% to 25% of cases. Vacuum-assisted biopsy removes more tissue than core biopsy, and it is possible to remove the entire lesion through this technique. For patients with microcalcifications, stereotactic vacuum-assisted biopsy is the standard approach; however, if calcifications are associated with a solid mass, then ultrasound-guided biopsy may be used.

PROCEDURE

Before performing a stereotactic biopsy on the breast, a complete mammographic examination should be performed and reviewed before the procedure, to confirm the location to be sampled. There

should also be documentation of a clinical breast examination and radioopaque markers placed on the skin over areas of palpable concern and pain. The possibility of a nondiagnostic result along with the risks, benefits, and alternatives to the procedure should be discussed with the patient. The procedure can be performed with a traditional prone stereotactic biopsy table or upright with an add-on stereotactic biopsy unit that attaches to the standard mammography equipment. The breast is compressed and held in position throughout the procedure between the image receptor and the compression plate. Imaging is performed to confirm that the targeted lesion lies within the area of accessibility. The computer-generated coordinates are then transferred to the stereotactic targeting device. Using sterile technique, local anesthetic is injected into the breast, and accurate needle positioning is determined through scout films. The ideal approach is the shortest distance from the skin to a targeted lesion. A scout view is obtained, and after the target is identified, two additional images are obtained 30 degrees apart, at +15 degrees and −15 degrees. The basis of stereotactic localization is the principle of parallax, which is used to locate the lesion in the 3D breast from a pair of 2D images. Scout view provides the x (horizontal) and y (vertical) coordinates of the lesion to be targeted in the breast. Two additional images are then used to determine depth (z coordinate). A small nick is made in the skin, and the vacuum-assisted device is inserted into the breast under image guidance and placed either in the suspicious lesion or adjacent to it. The device is typically rotated, and multiple biopsies are taken from the suspicious lesion. The distance from post-fire needle tip to image receptor plate should be 5 mm or more to avoid penetration of the opposite side of the patient's skin and penetration of the image receptor plate. Once the needle device is introduced into the breast and preimages are obtained to confirm the position, the needle is fixed and then post-fire images are obtained to confirm position. When the vacuum-assisted biopsy device is used, tissue sampling is performed in a 360-degree fashion. Typically, 6 to 12 samples are obtained. After the procedure, a radiopaque tissue marker (clip) is placed at the biopsy site. Sonographically visible markers are preferable. Specimen radiographs must be obtained to document appropriate sampling in all cases in which microcalcifications were targeted. Effort should be made to select an approach that will avoid puncturing blood vessels adjacent to the target and minimize hematoma by compressing the breast and skin entry site at the conclusion of the procedure. Post-procedure two-view mammography or stereotactic views should be performed to document clip position in relation to the biopsy site.

COMPLICATIONS

Complications include vasovagal reaction (less common prone), pneumothorax, hemorrhage, infection, or other wound complications. The overall incidence of severe complications from core or vacuum-assisted biopsy is less than 0.2%.

CONCORDANCE

For any combination of guidance methods and needle types, concordance between the cytologic or pathologic result and the radiologic appearance of the targeted lesion must be verified. This mandatory task must be performed by the professional who performed the image-guided sampling, usually a breast radiologist, in collaboration with the reporting pathologist. In most cases, the radiologist will consider the cytology or pathology result as concordant with imaging findings, especially when core needle or vacuum-assisted biopsy has been performed. However, in the case of inadequate sampling (more frequent in the case of FNA) or discordance between cytology/pathology and imaging findings, a repeat biopsy using the same or a different biopsy method can be considered. This is done after discussion in a multidisciplinary meeting. In the case of findings highly suspicious for malignancy on ultrasound, mammography/tomosynthesis, or MRI with discordant benign findings on FNA, core needle biopsy, and/or vacuum-assisted biopsy, surgical removal is indicated after preoperative image-guided localization if the lesion is nonpalpable (Box 3).

BOX 3 Indications for Surgical Excision After Stereotactic Core Biopsy

- Imaging findings and pathologic findings do not correlate (discordance)
- Atypical ductal hyperplasia
- Atypical lobular hyperplasia
- Radial scar, complex sclerosing lesion
- Papillary lesions
- Cellular fibroepithelial lesions and phyllodes tumors
- Lobular carcinoma in situ
- Mucocele-like lesions

FOLLOW-UP

For most patients with concordant radiologic-pathologic findings after biopsy, a follow-up mammogram is suggested at approximately 6 to 12 months. Following excision of DCIS associated with larger areas of malignant calcifications, a postoperative mammogram is suggested to ensure completeness of resection beyond specimen radiography and pathologic margin assessment. A shorter imaging period may be indicated in certain situations. If the patient is older than 35 years of age, a unilateral diagnostic mammogram is generally obtained as a new baseline study within 4 to 6 months of the procedure.

SUGGESTED READINGS

American Society of Breast Surgeons Official Statement on Performance and Practice Guidelines for Stereotactic Breast Procedures 2020.

Bick U, Trimboli RM, Athanasiou A, Catelli A, Santoro A, Antignani E, et al. Safety and efficacy of tomosynthesisguided breast biopsies in the prone position: monocentric study and review of the literature. *J Cancer Res Clin Oncol.* 2022;148:967–974.

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Molecular Targets in Breast Cancer

Reva K. Basho, MD, and Armando E. Giuliano, MD

INTRODUCTION

Breast cancer is the most frequently diagnosed non-skin cancer in women and the second leading cause of cancer-related death. Breast cancer is a heterogenous disease composed of distinct subtypes with varied molecular pathogenesis. Better understanding of tumor biology is critical to improving breast cancer therapies and survival. This chapter focuses on molecular targets and available therapies within breast cancer subtypes.

BREAST CANCER SUBTYPES

In 2000, Perou and colleagues first identified the five intrinsic subtypes of breast cancer based on gene expression analysis: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, basal-like, and normal-like. Each of these intrinsic subtypes reflects fundamental differences of the tumors at the molecular level. However, because of the limited applicability of gene expression profiling in the clinic, classification of breast cancer subtypes through use of immunohistochemistry (IHC) remains the cornerstone of breast cancer clinical management. Table 1 broadly maps the IHC profile and clinical classification of each of the intrinsic subtypes. Classification of IHC subtype guides clinical therapy, and the development of distinct molecularly targeted therapies for each of these subtypes has cumulatively improved breast cancer outcomes dramatically. Here, we review the currently approved molecularly targeted therapies across each of these breast cancer subtypes (Table 2).

HORMONE RECEPTOR–POSITIVE BREAST CANCER

The estrogen receptor (ER) was the first recognized molecular marker for therapy in breast cancer. ER expression has been shown to have significant predictive value on tumor response to hormone therapy in curative and metastatic disease. The role of progesterone receptor (PR) expression in predicting tumor response to therapy is less clear, although tumors that are positive for both ER and PR expression have improved response to hormonal therapy. The prognostic value of ER/PR expression in addition to predictive value remains controversial. HR-positive (ER and/or PR-positive) tumors, defined technically by expression level of either or both receptors ≥1%, comprise approximately 70% of all breast cancers.

Endocrine Therapy

Endocrine therapy is the backbone of hormone receptor (HR)-positive breast cancer treatment. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis including 10,645 patients with ER-positive breast cancer reported that 5 years of adjuvant endocrine therapy with tamoxifen reduced the 15-year probability of breast cancer recurrence and mortality compared with placebo, resulting in the established role of 5 years of adjuvant endocrine therapy in all patients with HR-positive breast cancer. Benefit was seen in both premenopausal and postmenopausal patients.

The two classes of endocrine agents available in the adjuvant setting are selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). SERMs are competitive ER antagonists in breast tissue but act as partial agonists in other tissues. The most widely used SERM for breast cancer treatment is tamoxifen. Common side effects include hot flashes and vaginal dryness/discharge. Tamoxifen acts as an estrogen agonist in endometrial tissue and is therefore associated with endometrial cancer. In the EBCTCG meta-analysis of adjuvant tamoxifen versus placebo, the risk of endometrial cancer was greater in postmenopausal women, with an absolute incidence of 3.8% in women who were 55 to 69 years of age upon entry into the clinical trial. Therefore, women on tamoxifen should be closely monitored for early signs of endometrial cancer including vaginal bleeding. Tamoxifen is also associated with a small risk of thromboembolic events, with an overall incidence of pulmonary embolism or cerebrovascular accident estimated to be <1%.

In contrast with SERMs, AIs block the conversion of adrenally synthesized androgens to estrogen. AIs do not alter ovarian estrogen

TABLE 1 Classification of Breast Cancer Subtypes

Intrinsic Subtype	IHC Profile	Clinical Classification
Luminal A	ER+, PR+, HER2–, Ki-67 low	HR-positive*
Luminal B	ER+, PR+/–, HER2–, Ki-67 high ER+, PR+/–, HER2+	HR-positive* HR-positive, HER2-positive
HER2-enriched	ER–, PR–, HER2+	HER2-positive
Basal-like	ER–, PR–, HER2–	Triple-negative*
Normal-like	ER+, PR+, HER2–	HR-positive*

ER, Estrogen receptor; *HER2,* human epidermal growth factor receptor 2; *HR,* hormone receptor; *PR,* progesterone receptor.
*Includes patients with HER2-low disease.

TABLE 2 Currently Approved Molecularly Targeted Therapies for Each Breast Cancer Subtype

Subtype	Targeted Therapies Currently Approved
HR-positive	SERMs AIs SERDs CDK 4/6 inhibition PI3K alpha specific inhibition in patients with *PIK3CA*-mutated tumors mTOR inhibition PARP inhibition in patients with germline *BRCA1/2* mutation
HER2-positive	HER2 monoclonal antibodies HER2 antibody-drug conjugates HER2 tyrosine kinase inhibitors
TNBC	Immune checkpoint inhibition PARP inhibition in patients with germline *BRCA1/2* mutation Trop2 antibody-drug conjugate
HER2-low	HER2 antibody-drug conjugate

AIs, Aromatase inhibitors; *CDK,* cyclin-dependent kinase; *HER2,* human epidermal growth factor receptor 2; *mTOR,* mechanistic target of rapamycin; *PARP,* poly(adenosine diphosphate-ribose) polymerase; *PI3K,* phosphoinositide 3-kinase; *SERDs,* selective estrogen receptor degraders; *SERMs,* selective estrogen receptor modulators.

production and therefore are not indicated as monotherapy in premenopausal women, but they can be administered to premenopausal women in conjunction with ovarian function suppression (OFS) therapy. Currently approved AIs for the management of breast cancer include anastrozole, letrozole, and exemestane. Common side effects include hot flashes, arthralgias, and vaginal dryness/discharge. AI therapy is not associated with an increased risk of endometrial cancer or thromboembolic events. However, AI therapy has been associated with an increased risk of osteoporosis and osteoporotic fractures. Use of adjuvant bisphosphonate therapy, particularly in patients with osteopenia/osteoporosis, has been shown to decrease the risk of osteoporotic fractures.

Several landmark studies have demonstrated superiority of AI over tamoxifen in postmenopausal patients. The EBCTCG meta-analysis comparing 5 years of adjuvant AI versus tamoxifen in 9885 postmenopausal patients with ER-positive breast cancer reported a reduction in 10-year breast cancer recurrence and mortality with AI therapy. As such, AIs are the adjuvant endocrine therapy of choice for postmenopausal patients with ER-positive breast cancer. Similarly, for patients with metastatic disease, they are preferred earlier-line agents over tamoxifen.

Given the superiority of AI therapy over tamoxifen in postmenopausal patients, comparative studies have also been conducted in premenopausal women. The Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) studies evaluated the addition of OFS to adjuvant endocrine therapy in premenopausal women, either with adjuvant tamoxifen or AI. In a combined analysis, the studies demonstrated statistically significant reduction in 8-year disease-free survival (DFS) with the addition of ovarian function suppression to either adjuvant tamoxifen or AI compared with tamoxifen monotherapy. Comparison of the two OFS-containing treatment arms demonstrated a reduction in 8-year DFS with OFS in combination with AI versus OFS in combination with tamoxifen; however, 8-year overall survival (OS) in the two arms was similar. It should be noted that the benefit of OFS was limited in patients with low-risk disease (older age, node-negative disease, T1 disease, low-grade disease). The long-term consequences of OFS in combination with AI therapy are not well understood at this time, but they may include increased cardiovascular events and osteoporotic fractures. As such, although OFS in combination with AI therapy is considered optimal adjuvant therapy for patients with high-risk disease, the decision to administer this combination in premenopausal patients should involve risk-benefit analysis specific to each patient case.

For patients with metastatic disease, selective estrogen receptor degraders (SERDs) are a third class of currently approved endocrine agents. SERDs bind to the estrogen receptor and result in degradation. The intramuscularly administered SERD fulvestrant is the only approved agent in this class at this time, but several oral SERDs are currently under investigation. The side effect profile of fulvestrant is similar to AI therapy. AI therapy and fulvestrant are both considered first-line options for patients with metastatic disease (in combination with OFS in premenopausal patients), with the alternative agent most frequently used as second-line therapy. It is important to note that up to 50% of patients with HR-positive breast cancer will acquire an estrogen receptor 1 *(ESR1)* mutation resulting in endocrine resistance. Patients with *ESR1* mutations remain sensitive to SERDs but are resistant to AI therapy.

Cyclin-Dependent Kinase Inhibitors

Cyclin-dependent kinases (CDKs) 4 and 6 are required for the cell cycle G1 to S phase progression. Cyclin D1 is a regulator of CDK 4/6 and is also a direct transcriptional target of ER, indicating that these pathways are linked. As such, CDK 4/6 inhibitors have been evaluated for the treatment of HR-positive breast cancer, as monotherapy and in combination with endocrine therapy. The single-arm phase 2 MONARCH-1 study evaluated single-agent activity of the CDK 4/6 inhibitor abemaciclib in 132 patients with HR-positive metastatic breast cancer that had previously progressed on endocrine therapy and chemotherapy. The study reported an objective response rate of approximately 20% in patients with median 3 lines of prior therapy for metastatic disease despite the majority of patients having visceral disease at the time of study entry. The randomized phase 2 PALOMA-1 study evaluated letrozole with or without the CDK 4/6 inhibitor palbociclib in 666 patients with HR-positive metastatic breast cancer who had received no prior therapy for advanced disease. The study reported a statistically significant improvement in median progression-free survival (PFS) in the palbociclib-treated patients, which resulted in accelerated approval by the US Food and Drug Administration (FDA) of letrozole and palbociclib as combination first-line treatment for postmenopausal patients with HR-positive metastatic breast cancer. Since that time, multiple phase 3 studies have demonstrated statistically significant improvement in median PFS with the addition of CDK 4/6 inhibition to AI or fulvestrant endocrine therapy, in both the first- and second-line setting for metastatic breast cancer. Many of these studies have also reported improvement in OS. The randomized phase 3 MONALEESA-7 study evaluated OFS and endocrine therapy with and without the CDK 4/6 inhibitor ribociclib in 672 specifically peri/premenopausal patients with HR-positive metastatic breast cancer with no prior endocrine therapy for metastatic disease and reported a statistically significant improvement in median PFS and OS. Subgroup analyses across studies of CDK 4/6 inhibitors have demonstrated consistent benefit in all subgroups, including patients with bone-only disease and elderly patients.

Based on these studies, the addition of CDK 4/6 inhibition to first-line endocrine therapy for HR-positive metastatic breast cancer is considered standard practice. There are currently three approved CDK 4/6 inhibitors available for treatment of metastatic disease: palbociclib, ribociclib, and abemaciclib. The three CDK 4/6 inhibitors show similar side effects with some exceptions. Abemaciclib is structurally distinct from the other two CDK4/6 inhibitors with greater selectivity for CDK 4 compared with CDK 6. CDK 6 plays a critical role in hematopoietic stem cell differentiation. As such, palbociclib and ribociclib are associated with higher rates of hematologic adverse events, particularly neutropenia, while abemaciclib is associated with a higher rate of diarrhea and fatigue. One question that remains unresolved is whether CDK 4/6 inhibition should be continued beyond progression in combination with an alternative endocrine agent. The phase 2 MAINTAIN study demonstrated an improvement in median PFS when ribociclib was administered in combination with alternate endocrine therapy after progression on endocrine therapy and CDK 4/6 inhibition. Ongoing clinical trials will help resolve this clinically relevant question.

Because of the success of these agents for patients with metastatic disease, CDK 4/6 inhibition has also been evaluated as adjuvant treatment in combination with adjuvant endocrine therapy. Results have been conflicting, however. PALLAS is a randomized phase 3 study that evaluated adjuvant endocrine therapy with and without 2 years of adjuvant palbociclib therapy in 5760 patients with HR-positive early breast cancer. The trial was terminated early because of lack of efficacy. Approximately half of the patients enrolled in the study had stage II disease with no or limited nodal involvement and generally favorable prognosis with standard adjuvant endocrine therapy alone, and >40% of patients discontinued adjuvant palbociclib before planned 2 years of therapy. It is unclear if these factors contributed to the overall negative study outcome. In contrast, the randomized phase 3 MonarchE study, which evaluated adjuvant endocrine therapy with and without 2 years of adjuvant abemaciclib in 5637 patients with HR-positive early breast cancer, reported a statistically significant improvement in 3-year invasive DFS and distant relapse-free survival (DRFS) in patients treated with abemaciclib, resulting in the FDA approval of adjuvant abemaciclib. The current approval is limited to patients with tumors expressing Ki-67 of at least 20% based on analysis conducted in the MonarchE study demonstrating the prognostic value of Ki-67.

In contrast with the PALLAS study, the MonarchE study limited enrollment to patients with clinically high-risk disease; approximately 75% had stage III disease, and the majority of patients received neoadjuvant or adjuvant chemotherapy. It is unclear if

the benefit of adjuvant CDK 4/6 inhibition is limited to patients with high-risk disease. It is interesting to note, however, that the randomized phase 3 PENELOPE-B study, which evaluated adjuvant endocrine therapy with and without 1 year of adjuvant palbociclib therapy in 1250 patients with HR-positive early breast cancer who had residual disease after neoadjuvant chemotherapy (a clinically high-risk group of patients), did not report improvement in invasive DFS in patients treated with palbociclib after a median 43-month follow-up. Data from the ongoing randomized phase 3 NATALEE study evaluating adjuvant ribociclib therapy is awaited.

Phosphoinositide 3-Kinase Inhibitors

Alterations in the phosphoinositide 3-kinase (PI3K)-AKT pathway are common in HR-positive breast cancer, with up to 40% of tumors harboring mutation in *PIK3CA*. Activation of this pathway results in cellular proliferation and tumor growth. Thus, agents that target this pathway have been explored in the treatment of HR-positive breast cancer. The randomized phase 3 SOLAR-1 study evaluated fulvestrant with and without the PI3K-alpha inhibitor alpelisib in 572 patients with HR-positive breast cancer who had progressed on prior endocrine therapy. In patients with *PIK3CA* mutation (N = 341), the study reported a statistically significant improvement in median PFS. This resulted in the FDA approval of the combination of fulvestrant and alpelisib in *PIK3CA*-mutated, HR-positive metastatic breast cancer patients who have progressed on prior endocrine therapy. Similarly, the randomized phase 2 FAKTION trial reported a statistically significant improvement in median PFS with the addition of the AKT-inhibitor capivasertib to fulvestrant in patients who had progressive metastatic disease on prior AI therapy. A confirmatory phase 3 study is underway (CAPItello-291). Common side effects of agents that target the PI3K pathway include diarrhea, hyperglycemia, and rash.

Neither the SOLAR-1 nor the FAKTION studies allowed for prior PI3K-AKT pathway targeting agents, so the potential role of sequencing PI3K inhibitors and AKT inhibitors remains unclear. Similarly, the mTOR inhibitor everolimus is also an approved agent available for HR-positive metastatic breast cancer patients in combination with endocrine therapy, but studies evaluating this agent predated the recent studies of PI3K and AKT inhibition, and the role for sequencing these agents remains unclear. There is also rationale for combining agents targeting the PI3K-AKT pathway with endocrine therapy in combination with CDK 4/6 inhibition, and clinical trials evaluating triplet therapy are currently underway.

Poly(Adenosine Diphosphate-Ribose) Polymerase Inhibitors

Approximately 5% of patients with breast cancer carry pathogenic germline mutations in *BRCA1* or *BRCA2*. These mutations are more likely in patients with a strong family history of breast and/or ovarian cancer. Patients with *BRCA1* tumors are more likely to develop TNBC than patients with *BRCA2* mutations who often develop HR-positive breast cancer. Tumors in patients with BRCA-mediated cancers have deficiency in homologous recombination repair. Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors target cancers with deficiency in homologous recombination repair by inhibiting single-strand DNA repair and induction of synthetic lethality.

The phase 3 OlympiAD and EMBRACA studies evaluated the PARP inhibitors olaparib and talazoparib, respectively, compared with physician's choice chemotherapy in metastatic HER2-negative patients with germline *BRCA1/2* mutations. Both studies reported a statistically significant improvement in median PFS and favorable toxicity profile with PARP inhibition compared with chemotherapy. OS benefit was not seen in either study. Based on these studies, both olaparib and talazoparib are FDA approved for both HR-positive and triple-negative metastatic breast cancer patients with a germline *BRCA1/2* mutation. These PARP inhibitors have slightly different toxicity profiles. Olaparib is associated with a higher incidence of nausea, while talazoparib is associated with a higher incidence of cytopenias and alopecia.

The OlympiA study evaluated 1 year of adjuvant PARP inhibition with olaparib in 1836 patients with high-risk breast cancer and a known germline *BRCA1/2* mutation. The study reported a statistically significant reduction in 3-year DFS with adjuvant olaparib versus placebo. Survival data are not mature at this time. Based on this study, 1 year of adjuvant olaparib therapy is recommended in patients with a germline *BRCA1/2* mutation and high-risk disease for both HR-positive and TNBC subtypes.

HER2-POSITIVE BREAST CANCER

Approximately 20% of breast cancers are HER2-positive. Assessment of HER2 status is conducted by evaluating samples of either the primary tumor or metastatic tissue with immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). HER2-positive disease is defined as: (1) IHC score of 3+ characterized by strong staining of the entire membrane circumference of more than 10% of cells or (2) IHC score of 2+ defined as weak to moderate complete membrane staining in more than 10% of cells with subsequent FISH testing resulting positive. HER2-directed therapy has dramatically altered the natural history of HER2-positive breast cancer. Before HER2-targeted therapy, HER2-positive breast cancer was associated with a poor prognosis with a short time to relapse and decreased OS. However, with the successful development of HER2-directed therapies—first for palliation and then for cure—breast cancer–specific outcomes are now dramatically improved. Central nervous system (CNS) metastases remain a challenge in the management of HER2-positive metastatic breast cancer, however. Approximately 50% of patients with metastatic disease develop CNS metastases in the course of their disease. Although significant progress has been made in the management of CNS metastases, this remains an area of unmet need.

HER2 Monoclonal Antibodies

HER2 is a transmembrane protein with tyrosine kinase activity encoded by the *ERBB2* gene. Ligand-dependent and independent signaling through HER2 results in cell proliferation and tumor growth. Humanized recombinant monoclonal antibodies bind to the extracellular domain of HER2 and inhibit downstream signaling. Trastuzumab was the first HER2-directed monoclonal antibody evaluated in large clinical trials and remains the backbone of HER2-directed therapy. Trastuzumab was first approved for treatment of metastatic HER2-positive breast cancer in conjunction with chemotherapy in 1998. Slamon and colleagues demonstrated that the addition of trastuzumab to chemotherapy for patients with HER2-overexpressing metastatic breast cancer resulted in statistically significant improvement in median PFS and OS. The randomized phase 3 German Breast Group 26/Breast International Group 03-05 study also demonstrated median PFS progression benefit with continuation of trastuzumab beyond progression in combination with alternative chemotherapy.

Trastuzumab was approved for adjuvant therapy in 2006 after several randomized pivotal trials demonstrated improved DFS and OS benefit with the concurrent addition of trastuzumab to adjuvant chemotherapy followed by adjuvant trastuzumab therapy to complete 1 year (HERA, BCIRG 006, NCCTG N9831/NSABP B-31). Several studies have evaluated shorter durations of adjuvant trastuzumab therapy, but they have largely demonstrated inferior outcomes with shorter durations. Therefore, 1 year of adjuvant HER2-directed therapy remains standard for patients with HER2-positive early breast cancer. Trastuzumab is well tolerated with minimal toxicity. Cardiac monitoring is required with trastuzumab administration as it does result in left ventricular ejection fraction decline in up to 10% of patients, though generally mild and asymptomatic.

Pertuzumab is a monoclonal antibody that targets an alternative extracellular site of HER2 than trastuzumab and inhibits dimerization. Pertuzumab has been evaluated in combination with chemotherapy and trastuzumab, first for metastatic disease and then for treatment

of patients with early disease. The phase 3 randomized CLEOPATRA study demonstrated statistically significant improvement in median PFS and OS with the addition of pertuzumab to docetaxel and trastuzumab in patients with previously untreated HER2-positive metastatic breast cancer. On the basis of this study, the combination of docetaxel, trastuzumab, and pertuzumab is the recommended initial therapy for HER2-positive metastatic breast cancer.

The addition of pertuzumab to taxane-based chemotherapy and trastuzumab was also evaluated for neoadjuvant therapy in two phase 2 clinical trials (NeoSphere and TRYPHAENA) and resulted in statistically significant improvement in pathologic complete response (pCR) rates. An exploratory event-free survival analysis of the NeoSphere study at 5-year follow-up showed a numerical trend in favor of pertuzumab. The OS benefit in the metastatic setting together with the pCR improvements in the neoadjuvant setting ultimately led to FDA approval in 2013 for neoadjuvant administration of pertuzumab in combination with taxane chemotherapy and trastuzumab-containing regimens for patients with tumors greater than 2 cm in size or node-positive disease.

The randomized phase 3 APHINITY study subsequently evaluated the combination of chemotherapy and trastuzumab with or without pertuzumab as adjuvant treatment. After 6 years of follow-up, the study reported a statistically significant benefit in invasive DFS but not OS with the addition of adjuvant pertuzumab. Upon subgroup analysis, the benefit of adjuvant pertuzumab was limited to patients with node-positive disease. On the basis of this study, dual HER2-targeting with trastuzumab and pertuzumab should be continued adjuvantly after neoadjuvant administration of pertuzumab in patients who derive benefit (have pCR after neoadjuvant therapy) or patients who undergo up-front surgery and are found to have node-positive disease. Studies of dual HER2-targeted therapy with trastuzumab and pertuzumab have not resulted in a significant increase in the incidence of cardiotoxicity relative to trastuzumab monotherapy. Pertuzumab therapy is associated with diarrhea, with grade 3 diarrhea seen in up to approximately 10% of patients when pertuzumab is administered in combination with taxane chemotherapy.

Margetuximab is a third HER2 monoclonal antibody that is FDA approved for HER2-positive metastatic breast cancer. It is an Fc-engineered HER2 monoclonal antibody that shares epitope specificity with trastuzumab. A key feature of margetuximab's engineered Fc domain is increased binding to the low affinity Fcγ receptor, resulting in increased activation of the innate and adaptive anti-HER2 immune response, relative to trastuzumab. The randomized phase 3 SOPHIA study evaluated margetuximab plus chemotherapy versus trastuzumab plus chemotherapy in 536 trastuzumab-refractory HER2-positive metastatic breast cancer patients. Margetuximab resulted in moderate improvement in median PFS. A prespecified analysis demonstrated greater magnitude of benefit in patients with low affinity Fcγ receptors, though receptor genotyping in not routinely performed. As such, the role of margetuximab in the management of HER2-positive metastatic breast cancer remains unclear.

HER2 Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) consist of a recombinant monoclonal antibody molecularly bound to a cytotoxic drug (known as the *payload*). HER2-targeted ADCs bind to HER2 on the cancer cell surface and are internalized by the cell, after which the cytotoxic drug component is released intracellularly and exerts its antitumor effect. There are currently two approved ADCS for HER2-positive breast cancer, but many additional agents are in development.

Trastuzumab emtansine (T-DM1) was the first ADC approved for HER2-positive metastatic breast cancer in 2013. The randomized phase 3 EMILIA study evaluated T-DM1 versus lapatinib and capecitabine in 991 patients with HER2-positive metastatic breast cancer previously treated with taxane and trastuzumab. The study reported a statistically significant improvement in median PFS and OS. On the basis of this study, T-DM1 is the preferred second-line therapy for patients with HER2-positive metastatic breast cancer who have progressed on docetaxel, trastuzumab, and pertuzumab. Common side effects seen with T-DM1 include thrombocytopenia and transaminitis.

Trastuzumab deruxtecan (T-DXd) is a ADC that differs from T-DM1 in that it has a higher drug-to-antibody ratio and a membrane permeable payload resulting in bystander effect. The single-arm phase 2 DESTINY-Breast01 study evaluated T-DXd in 184 patients with HER2-positive metastatic breast cancer who had been pretreated with T-DM1. Despite a heavily pretreated patient population with a median of six prior lines of therapy, the agent resulted in a response rate greater than 60%. The study also demonstrated a CNS response rate of approximately 60% in 24 patients with baseline CNS metastases. Drug-induced pulmonary toxicity is a concern with T-DXd, with interstitial lung disease seen in 13.6% of patients enrolled on study, including 4 patients (2.2%) experiencing fatal grade 5 events. The DESTINY-Breast03 study evaluated T-DXd versus T-DM1 in the second-line setting for HER2-positive metastatic breast cancer, and reported an improvement in median PFS (7.2 versus 25.1 months) with hazard ratio of 0.26. No grade 4 or 5 drug-related interstitial lung disease was seen on this study. Based on the DESTINY-Breast03 study, T-DXd is now considered standard second-line therapy for HER2-positive metastatic breast cancer. The ongoing DESTINY-Breast09 study is evaluating T-DXd in the first-line setting.

Trastuzumab duocarmazine is a third ADC that is on the horizon for HER2-positive metastatic breast cancer. The randomized phase 3 TULIP study evaluated trastuzumab-duocarmazine versus treatment of physician's choice in patients who had progressed on two or more prior lines of therapy including T-DM1 and reported a modest improvement in median PFS. Ocular adverse events were common, resulting in study treatment discontinuation in more than 20% of patients treated with trastuzumab-duocarmazine. FDA review is pending.

Driven by the success in treatment of metastatic disease, T-DM1 has also been evaluated for adjuvant therapy. The randomized phase 3 KATHERINE study evaluated adjuvant T-DM1 versus trastuzumab in 1486 patients with residual disease after neoadjuvant chemotherapy and HER2-directed therapy. The study reported a statistically significant improvement in 3-year invasive DFS with T-DM1 resulting in the FDA approval of T-DM1 in this setting. On the basis of this study, adjuvant T-DM1 is the recommended adjuvant therapy for HER2-positive breast cancer patients with residual disease after neoadjuvant therapy. The ongoing DESTINY-Breast05 study is comparing adjuvant T-DXd versus T-DM1 in HER2-positive breast cancer patients with residual disease after neoadjuvant therapy. Additional ongoing studies are evaluating T-DXd in the neoadjuvant setting.

HER2 Tyrosine Kinase Inhibitors

HER2 tyrosine kinase inhibitors (TKIs) competitively bind the intracellular adenosine triphosphate (ATP) domain of HER2, resulting in inhibition of downstream signaling. The HER2 TKIs may also bind and inhibit other members of the epidermal growth factor receptor (EGFR/HER) family, resulting in their unique toxicity profiles. HER2 TKIs are small, orally bioavailable agents with CNS penetration, and they have been studied in the management of CNS metastases. The first commercially available HER2 TKI was lapatinib. However, because it is a pan-HER inhibitor, it is associated with significant skin toxicity and diarrhea. As a result, other agents in the family are more widely used. Recent studies of HER2 TKIs in treatment of patients with metastatic disease have focused on patients who have progressed on second-line T-DM1 therapy.

Neratinib, a pan-HER TKI, was evaluated in combination with capecitabine versus lapatinib and capecitabine in 621 patients with pretreated HER2-positive metastatic breast cancer in the phase 3 randomized NALA study. Patients with asymptomatic, stable CNS disease were allowed on study. The combination of neratinib and capecitabine resulted in statistically significant improvement in median PFS and reduction in interventions for CNS disease. This resulted in FDA approval of the combination of neratinib and capecitabine. The combination is associated with significant diarrhea, with grade 3 diarrhea

seen in approximately 25% of patients. Grade 3 diarrhea is most prevalent during the first cycle, and the CONTROL study demonstrated that initiating neratinib at a lower dose with subsequent dose escalation to the full dose results in decreased incidence of diarrhea.

The pivotal HER2CLIMB study evaluated the HER2 TKI tucatinib versus placebo in combination with capecitabine and trastuzumab in 612 patients with pretreated HER2-positive metastatic breast cancer. Compared with other HER2 TKIs, tucatinib is more specific for HER2 inhibition, resulting in a more favorable toxicity profile. The HER2CLIMB study was unique in that it allowed patients with progressive CNS disease to enroll as long as urgent CNS-directed therapy was not indicated. In the overall study population, the study reported a significant improvement in median PFS and OS, resulting in the FDA approval of the combination of tucatinib with capecitabine and trastuzumab. In patients with progressive CNS disease (N = 174), there was a statistically significant improvement in CNS-PFS and OS. For the first time, efficacy of systemic therapy in the management of active CNS disease in HER2-positive metastatic breast cancer was demonstrated in a randomized phase 3 trial. Ongoing phase 3 studies are evaluating tucatinib in combination with T-DM1 for patients with residual disease after neoadjuvant therapy and for second-line therapy for metastatic disease.

One year of neratinib therapy has also been evaluated for extended adjuvant treatment (after completion of adjuvant trastuzumab-based therapy) in 2840 patients with HER2-positive early breast cancer in the randomized phase 3 ExteNET study. The study was largely limited to patients with stage II to III disease. In the overall study population, the 1 year of extended adjuvant therapy with neratinib resulted in a modest but statistically significant benefit in invasive DFS at 5 years, resulting in FDA approval in this setting. In an exploratory analysis, the benefit was greater in patients with HR-positive disease with residual disease after neoadjuvant therapy. The ExteNET study was conducted before approval of pertuzumab and T-DM1 for early breast cancer, however, and the overall benefit in patients who have previously received these agents for curative disease remains unclear.

TRIPLE-NEGATIVE BREAST CANCER

Approximately 10% of breast cancers are classified as triple-negative breast cancer (TNBC), defined by the lack of expression of ER/PR and HER2. As a result, TNBC comprises a heterogenous group of tumors with significant variability in disease response to therapy and clinical outcomes. Because of the lack of clinically identifiable targets, chemotherapy has historically been the backbone of therapy for patients with TNBC. However, recent gene expression analysis studies have helped identify subtypes of TNBC with increasing roles of targeted approaches. For example, PARP inhibitors are an available targeted therapy for patients with TNBC with germline *BRCA1/2* mutation (see earlier). Ongoing studies are evaluating PARP inhibition beyond germline *BRCA1/2* mutation in patients with other abnormalities of the DNA damage response pathway. Other agents that target the DNA damage repair pathway are also in development. In addition to PARP inhibition, several other targeted approaches have a role in the management of TNBC.

Immune Checkpoint Inhibitors

Harnessing the immune system against cancer cells has resulted in durable and sometimes complete antitumor response. Treatment with immune checkpoint inhibitors (ICIs) releases the immune system from inhibitory signals and reactivates an antitumor immune response. The success of an ICI depends on the immunogenic nature of the tumor. Studies have demonstrated higher density of tumor infiltrating lymphocytes in HER2-positive and TNBCs compared with HR-positive breast cancers, suggesting a role for an ICI. Early studies of ICI monotherapy resulted in only modest benefit in TNBC, however. The magnitude of response was greater in patients with metastatic disease who had no prior systemic therapy and patients with tumors harboring programmed death-ligand 1 (PD-L1) expression, which has emerged as the most reproducible biomarker for predicting ICI response. Subsequent studies have focused on the combination of ICI with chemotherapy, which results in neoantigen release and resultant augmentation of the immune response. Studies have also focused on evaluation of ICIs in earlier lines of therapy and in patients with tumors positive for PD-L1 expression.

The randomized phase 3 KEYNOTE-355 study evaluated chemotherapy with and without the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab in 1372 patients with metastatic TNBC who had received no prior therapy. The study demonstrated that in patients with PD-L1 expression, there was a statistically significant improvement in median PFS and OS, resulting in FDA approval. Benefit was not seen in patients with PD-L1–negative tumors. Overall, ICI therapy is well tolerated and is associated with a relatively mild toxicity profile. However, immune-related adverse events may develop, and patients must be closely monitored. Potential immune-related adverse events include the development of skin rash, thyroid dysfunction, inflammatory arthritis, colitis, pneumonitis, and hypophysitis.

ICI has also been evaluated as neoadjuvant treatment for TNBC. The randomized phase 3 KEYNOTE-522 study evaluated the addition of neoadjuvant and adjuvant pembrolizumab to neoadjuvant chemotherapy consisting of anthracycline, taxane, and platinum in 1174 patients with stage II to III TNBC. The study reported a statistically significant improvement in rates of pCR and event-free survival, resulting in FDA approval. Neoadjuvant treatment demonstrated a similar magnitude of benefit for patients with both PD-L1–negative and PD-L1–positive tumors. Therefore, PD-L1 testing is not a requirement for therapy. Adverse events in the pembrolizumab-chemotherapy treated patients were consistent with known safety profiles of chemotherapy and pembrolizumab monotherapy. Clinically, ICI therapy should be considered in patients with locally advanced TNBC. It is important to note that approximately 40% of patients will achieve pCR with chemotherapy alone, however. Therefore, addition of an ICI is not indicated in all patients with operable TNBC.

There are numerous ongoing studies of ICIs and other immune strategies in TNBC. Many novel combination approaches with ICIs are being investigated. Continuation of ICI therapy beyond progression is also being investigated. The landscape of immune therapy use in TNBC is likely to evolve significantly in the coming years.

Antibody-Drug Conjugates

Similar to HER2-positive breast cancer, ADCs have had an impact on the management of TNBC. Administration of chemotherapy as a payload incorporated into an ADC allows for administration of more potent therapy. Unlike HER2-positive disease, however, there is no clearly identified antibody target in TNBC. Sacituzumab govitecan is an ADC that is currently approved for metastatic TNBC. Sactizumab govitecan targets Trop-2, a transmembrane glycoprotein that functions in a variety of cell-signaling pathways and is upregulated in cancer. The ASCENT study is a randomized phase 3 study that compared sacituzumab govitecan versus single-agent chemotherapy in 468 patients with previously treated metastatic TNBC. The study reported a statistically significant improvement in median PFS and OS with sacituzumab govitecan compared with chemotherapy. Sacituzumab govitecan is associated with an adverse event profile similar to standard chemotherapy with cytopenias, nausea, fatigue, and alopecia being common. Several novel ADCs are currently in development for TNBC.

HER2-LOW BREAST CANCER

Approximately 50% of patients with breast cancer who are classified as HER2-negative still express HER2 at low levels (IHC 1+ or 2+ and FISH negative). These HER2-low patients are initially treated as HR+ or TNBC disease as above. Recent studies, however, have explored HER2 ADCs in these patients on relapse. The DESTINY-Breast04 study evaluated T-DXd versus physician's choice chemotherapy in

patients with HER2-low disease after prior endocrine therapy, if indicated, and at least one prior line of chemotherapy in the metastatic setting. The majority of patients enrolled (89%) had HR+ disease. The primary endpoint was PFS in the HR+ cohort. The study reported significant improvement in median PFS and OS in both the HR+ cohort and overall study population, resulting in FDA approval of T-DXd for HER2-low disease. Drug-related interstitial lung disease was seen in 12.1% of patients treated with T-DXd. Although the majority of these events were grade 1/2, three patients did experience grade 5 events. Other novel ADCs including disitamab vendotin and ARX788 are also being explored in the management of HER2-low disease. The efficacy of sequencing ADCS, either with a change in antibody target or change in payload, remains unclear at this time.

CONCLUSION

Significant advances have been made in breast cancer management. Through the identification of clinically relevant breast cancer subtypes, targeted approaches have been identified that provide benefit for many patients with breast cancer. However, with continued understanding of tumor pathogenesis and molecular targets, there is a growing need to better define the biology of each individual cancer in order to realize the potential of personalized cancer therapy.

SUGGESTED READINGS

ASCO: Endocrine treatment and targeted therapy for HR-positive, HER2-negative metastatic breast cancer. https://www.asco.org/practice-patients/guidelines/breast-cancer#/9326.

ASCO: Chemo- and targeted therapy for patients with HER2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor-negative. https://www.asco.org/practice-patients/guidelines/breast-cancer#/9781.

ASCO: Systemic therapy for patients with advanced human epidermal growth factor receptor 2–positive breast cancer. https://www.asco.org/practice-patients/guidelines/breast-cancer#/9786.

Breast Cancer: Surgical Therapy

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Surgery is a highly effective tool in the multidisciplinary treatment of breast cancer. The goals of breast surgery are to achieve locoregional control of the existing disease, reduce the risk of recurrence, and help determine the pathologic stage, which guides adjuvant systemic and radiation therapy recommendations. Since the introduction of the Halsted radical mastectomy in 1882, the surgical management of breast cancer has changed dramatically over time. In an effort to minimize surgical morbidity and provide a cosmetically acceptable breast, breast-conserving surgery has become an option for patients when used in conjunction with radiation therapy. The trend toward less-invasive breast and axillary surgery has had no detrimental effect on survival. This is caused in large part by significant advances in systemic and radiation therapies, both of which contribute to decreased rates of locoregional recurrence and increased breast cancer–specific survival. The breast surgeon is uniquely positioned to help navigate the array of surgical options and is an integral member of a multidisciplinary team that helps determine a treatment plan suitable for the patient's health and well-being.

SCREENING FOR BREAST CANCER

A woman in the United States has a 12.3% risk of developing breast cancer in her lifetime (i.e., 1 in 8 women). The majority of new breast cancers are diagnosed after an abnormal screening mammography. Imaging abnormalities, such as suspicious calcifications or a spiculated mass, warrant further characterization with supplemental mammographic views and/or sonography. The American College of Radiology uses the BI-RADS *(Breast Imaging Reporting and Data System)* assessment categories to designate the relative likelihood of a normal, benign, or malignant diagnosis, and standardize recommendations for further management. Breast cancer screening has led to a greater detection of breast cancer at an earlier stage, facilitating the use of early treatment.

The National Comprehensive Cancer Network (NCCN) guidelines recommend annual screening mammogram in asymptomatic women 40 years of age and older who have an average risk of breast cancer (less than 15% lifetime risk). Tomosynthesis—a 3D-mammogram constructed by a moving x-ray and digital detector—has an improved cancer detection rate and decreased call-back rate, and can be used as an alternative screening modality. Women with an increased risk for developing breast cancer are candidates for supplemental screening. In women with ≥ 20% lifetime risk as determined by risk models that are largely influenced by family history, annual breast MRI and mammogram should begin 10 years before the youngest family member's historical diagnosis with breast cancer. In women who received thoracic radiotherapy between the ages of 10 and 30 years, annual breast MRI and mammogram should begin 8 years after radiotherapy. Breast MRI screening as an adjunct to mammography may also be used in women with lobular neoplasia (lobular carcinoma in situ/atypical lobular hyperplasia) or atypical ductal hyperplasia and ≥ 20% lifetime risk. Contrast-enhanced mammography or whole-breast ultrasound should be considered for those who qualify but cannot undergo breast MRI. MRI screening is not recommended in women with an average-to-moderate risk of breast cancer. There is no clear age to stop screening in elderly women, and this should be individualized based on the individual's overall health and estimated longevity.

DIAGNOSIS OF BREAST CANCER

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in women. For 2021, the American Cancer Society estimated there will be 284,200 new invasive breast cancers (male and female) diagnosed in the United States, and approximately 44,130 deaths. Breast cancer mortality has decreased in the past two decades, largely attributed to mammographic screening and treatment advances.

For women who present with a palpable mass, imaging is warranted. Those with suspicious radiologic or clinical findings should undergo core needle biopsy for tissue diagnosis. Additionally, if clinically suspicious without imaging correlate, a biopsy should also be performed. The breast tissue biopsy allows histopathologic examination and provides information regarding in situ versus invasive cancer, histologic variant (e.g., ductal, lobular, mixed), hormone receptor status (estrogen, progesterone, and human epidermal growth factor receptor 2 [HER2]), and grade of the cancer. These findings guide therapeutic decisions.

In women with a new breast cancer diagnosis, further imaging may be necessary to evaluate the extent of disease. Axillary ultrasound can be used to evaluate for nodal involvement in women with a suspicious clinical examination. Routine breast MRI is not recommended but can be considered when disease extent is difficult to define by mammography and ultrasound.

A clinical stage is assigned based on the size of the largest tumor in the breast and the clinical axillary nodal status. Extent of disease evaluation may include positron emission tomography (PET) or computed tomography (CT) of the chest, abdomen, and pelvis, plus a bone scan; these are usually reserved for patients who have a high risk for distant disease, usually clinical stage III at presentation. However, NCCN guidelines (Breast Cancer Version 8.2021) state that the use of PET or PET/CT is not indicated in the staging of clinical stage I or II breast cancer, or for those with operable stage IIIA (T3 N1) breast cancer. Further imaging can also be used for patients who present with signs/symptoms concerning for metastatic disease (i.e., bone scan for patients with localized bone pain or elevated alkaline phosphatase, CT of the abdomen and pelvis for patients with abdominal pain or abnormal liver function tests, and CT of the chest for patients with pulmonary complaints).

DISCUSSION OF SURGICAL OPTIONS

The majority of women who are diagnosed with a new breast cancer in developed countries have no evidence of metastatic disease. Broadly, non-metastatic breast cancer is defined in two categories: (1) early-stage or (2) locally advanced. Women with early-stage breast cancer (stage I or II) are usually treated with primary surgery (breast-conserving surgery or mastectomy). Neoadjuvant therapy has become increasingly accepted in women with HER2-positive or triple-negative operable breast cancer and in situations in which downstaging of disease in the breast and/or axilla is desired. Women with estrogen receptor–positive tumors undergo primary surgery unless contraindicated because of comorbidities or unless categorized as those who desire downstaging to breast-conservation surgery, for whom primary endocrine therapy may be considered.

During initial evaluation, the patient's clinical prognostic stage, fitness for general anesthesia and surgery, contraindications to radiotherapy, life goals, including fertility and quality-of-life concerns, and estimation of contralateral breast cancer must be carefully assessed to accurately weigh surgical options. A personal history of breast cancer or high-risk pathologic factors (i.e., lobular carcinoma in situ, atypical lobular hyperplasia, atypical ductal hyperplasia), a history of irradiation to the chest, and a strong family history of breast cancer may affect surgical decision making. A thorough family history dating back three generations on both the maternal and paternal sides should be obtained to determine eligibility for genetic testing. Approximately 10% of newly diagnosed breast cancers are caused by a strong family history or genetic predisposition. Genetic counseling and panel testing to include breast cancer susceptibility genes such as *BRCA1, BRCA2, p53, PALB2, CHEK2,* and *RAD51C* may help in counseling women on surgical options that include risk-reducing surgical approaches, such as bilateral mastectomy. The decision between lumpectomy and mastectomy is often a very difficult choice for women. Previous randomized prospective trials have demonstrated similar breast cancer–specific and overall survival when comparing lumpectomy plus radiation versus mastectomy. Several studies in more recent years have found that women treated with lumpectomy plus radiation have better outcomes than those treated with mastectomy, as this is thought to be secondary to advancements in systemic and radiation treatment. For women with estrogen receptor–positive and HER2-positive breast cancer undergoing lumpectomy plus radiation, the 10-year rates of locoregional recurrence are approximately 2% to 3%, and 5% for those with triple-negative tumors, and do not significantly differ compared with mastectomy. The decisions regarding systemic therapy, including chemotherapy, HER2-targeted therapy, and endocrine therapy, are based on the characteristics of the tumor and are independent of the type of surgery performed. Conversely, adjuvant radiotherapy is recommended following lumpectomy for the majority of patients, but factors such as older age may play a role in decision making. Based on evidence from the Cancer and Leukemia Group B (CALGB) 9343 trial showing no survival benefit with the addition of radiotherapy in women ≥ 70 years of age with early-stage, hormone receptor–positive breast cancers, undergoing lumpectomy now allows for omission of radiotherapy in this subset of women. Decisions for postmastectomy radiation therapy are more complex and are based on clinical and tumor characteristics, including the presence of axillary nodal involvement.

The rate of contralateral prophylactic mastectomy in women with unilateral breast cancer has been steadily increasing in the United States, especially among young women. The majority of women opting for contralateral prophylactic mastectomy will derive no survival benefit, and many are even candidates for breast-conserving therapy. Most women overestimate their risk for contralateral second primary breast cancer, and education to address the possible misconceptions surrounding it is crucial to the shared decision-making process.

LUMPECTOMY

Breast-conserving surgery (i.e., lumpectomy) preserves the cosmetic outcome of the breast and minimizes the extent of surgery without sacrificing oncologic outcomes. Whole-breast radiation therapy, an essential component of breast-conserving therapy, has been shown to decrease the risk of breast cancer recurrence. Contraindications and relative contraindications to breast-conservation therapy (lumpectomy plus radiation) include current pregnancy, prior radiation therapy including chest radiation, multicentric or widespread disease that cannot be incorporated by local excision, large tumor size in relation to the breast that compromises cosmetic results (although the emergence of advanced oncoplastic techniques may allow for breast conservation), diffuse malignant-appearing calcifications on imaging, or persistently positive pathologic margins despite reexcision attempts.

An intraoperative radiograph of the lumpectomy specimen can be used to assess successful retrieval of the lesion with radiographically negative margins. For nonpalpable lesions, image-guided localization utilizing wire localization, radioactive seed localization, and other alternatives are now available (Fig. 1). Each method has its own advantages and disadvantages, and studies have not been able to prove one method to be superior.

Incision placement can vary according to the location of the lesion, but incisions should generally be placed over the tumor to avoid excessive tunneling. Because some women who undergo lumpectomy may ultimately require a mastectomy, consideration for the lumpectomy incision should consider the possibility of needing a mastectomy incision. Excision of the skin or underlying fascia is not required with the specimen as long as the tumor is not close to or involving the skin or fascia. To improve cosmetic outcome and hide the scar, a periareolar incision may be placed in select patients. Otherwise, incisions should follow natural skin creases (Langer's lines) in the upper inner or upper outer quadrants of the breast in a curvilinear or horizontal fashion. In the lower inner or lower outer quadrants of the breast, a curvilinear or radial incision can be used following the contour of the breast.

Some surgeons routinely perform circumferential cavity shave margins after the lumpectomy, as there is evidence that this practice decreases the rate of positive margins and reexcision by one-half. Shave margins should include the superior, inferior, medial, and lateral aspect of the cavity along with the anterior and posterior margins if the resection did not extend to the dermis or pectoralis fascia. The new cut surface represents the final margins and should be marked for the pathologist. The Society of Surgical Oncology (SSO)/American Society for Radiation Oncology (ASTRO) consensus guidelines for appropriate margins in the setting of lumpectomy are no tumor at the inked surface of the lumpectomy specimen for invasive cancer and a 2 mm margin for ductal carcinoma in situ. Requirements for optimal margin evaluation include orientation of the surgical specimens, descriptions of the gross and microscopic margin status, and reporting of the distance, orientation, and type of tumor (invasive or ductal carcinoma in situ) in relation to the closest margin. The number of reexcisions that can be attempted for persistently positive margins depend on the volume of breast tissue already resected in relation to the size of the breast. Failure to

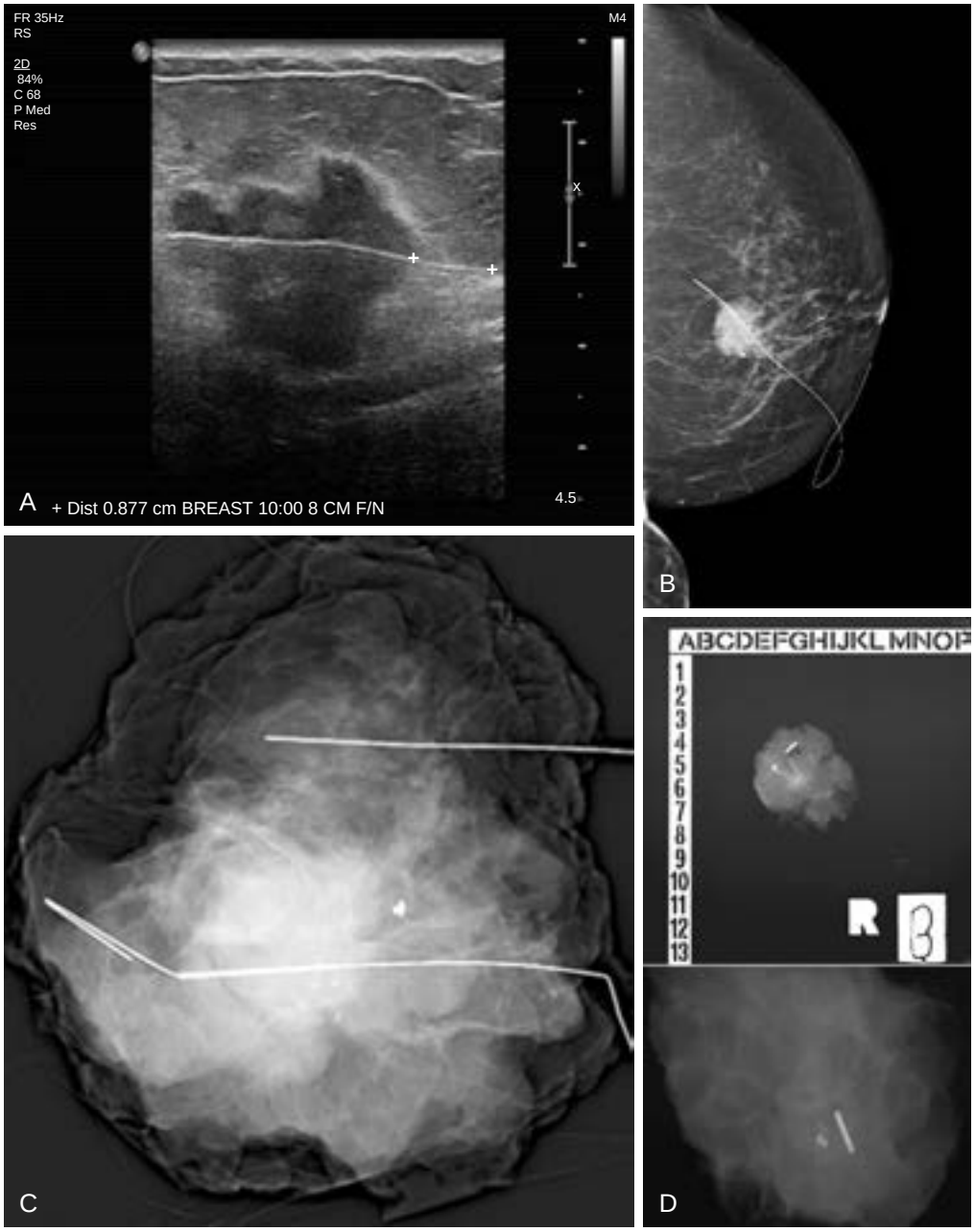


FIG. 1 Wire localized lumpectomy. **(A)** A localization wire is placed into a breast mass under ultrasound guidance. **(B)** The position of the localization wire is confirmed mammographically. **(C)** An intraoperative specimen radiograph of the lumpectomy specimen confirms successful excision of the mass and biopsy clip. **(D)** A specimen radiograph of a lumpectomy with radioactive seed localization (alternative to wire localization).

achieve clear or negative margins warrants a conversion to completion mastectomy. Wider margins have not been shown to reduce the risk of local recurrence, assuming appropriate adjuvant radiation and systemic therapies are delivered.

Oncoplastic surgery incorporates reconstructive surgery principles without compromising oncologic management to offer breast-conserving options in situations in which the resection itself would likely yield an unacceptable cosmetic outcome. Oncoplastic techniques are valuable for patients with a large tumor size relative to their breast size, when the nipple-areolar complex needs repositioning, or in women with preexisting aesthetic concerns (e.g., desire for contralateral breast reduction for macromastia). For boost cavity localization for radiotherapy treatment planning, close communication between the radiation oncologist and surgeon is necessary. Retrospective studies suggest that oncologic outcomes are similar in women undergoing surgery compared with those undergoing mastectomy. Additionally, patient-reported outcomes in women undergoing oncoplastic breast-conserving surgery were higher than those undergoing mastectomy with immediate reconstruction when comparatively measured using the BREAST-Q questionnaire and self-rated breast appearance scores.

MASTECTOMY

Removal of the totality of glandular breast tissue (mastectomy) is a surgical option for the treatment of breast cancer or for breast cancer risk reduction. Glandular breast tissue extends to the clavicle superiorly, to the inframammary fold inferiorly, to the sternum

medially, and to the latissimus dorsi muscle laterally. Mastectomy is performed in women with a contraindication for breast-conserving surgery, women with inflammatory breast cancer, and those who prefer mastectomy for various reasons, including patient preference. Bilateral prophylactic mastectomy reduces the risk of developing a breast cancer by over 90% in women with a *BRCA* mutation. The types of mastectomies used in modern breast surgery include simple mastectomy, modified radical mastectomy, skin-sparing mastectomy, and nipple-sparing mastectomy.

For a simple mastectomy performed without reconstruction, a large elliptical incision is made encompassing the nipple-areolar complex. When marking the incision preoperatively, the operating surgeon should take into account the vertical laxity of the breast to achieve a resection with minimal redundant skin. For example, a large ptotic breast will require a wider elliptical incision than a small, firm breast. Enough skin should be resected to achieve a resection so the skin lies flat against the chest; avoiding redundant skin in the axillary region deserves special attention, as it can be uncomfortable to patients otherwise. No axillary surgery is performed in a simple mastectomy. When a woman has clinically and biopsy-proven positive lymph node involvement, a modified radical mastectomy is performed, which includes a concurrent level I to II axillary lymph node dissection. A mastectomy dissection is performed along the plane defined by suspensory ligaments of Cooper, which serve as the connective tissue between the glandular breast tissue and subcutaneous fat. The thickness of the mastectomy flaps varies according to the thickness of the subcutaneous tissue in the individual woman.

For women planning for mastectomy with reconstruction, a skin-sparing mastectomy or nipple-sparing mastectomy can be performed. A skin-sparing mastectomy involves removal of the entire glandular breast tissue and nipple-areolar complex, but preserves as much of the skin envelope to allow for reconstruction. An elliptical incision is made incorporating the nipple-areolar complex and, if possible, any previous breast-conserving surgery scar. Incision planning with the plastic surgeon who will be performing the immediate reconstruction is ideal. Evidence suggests that the risk of locoregional recurrence in women undergoing skin-sparing mastectomy with immediate reconstruction is comparable to those undergoing a standard mastectomy without reconstruction.

Nipple-sparing mastectomy is appropriate in some patients and preserves the entire skin envelope of the breast, including the nipple and areola. Because of concern for occult tumor cells being harbored in the nipple-areolar complex, nipple-sparing mastectomy was historically reserved for prophylactic risk-reduction purposes. Growing evidence has demonstrated that nipple-sparing mastectomy provides safe oncologic outcomes, leading to its increasing use in recent years, particularly for therapeutic treatment for invasive breast cancer. However, appropriate selection of women for a nipple-sparing technique is controversial because of lack of level 1 evidence. Women ineligible for nipple-sparing mastectomy include those with locally advanced breast cancer, extensive disease in the periphery of the breast, direct invasion of the nipple with cancer, and tumors ≤ 1 cm from the nipple. The majority of nipple-sparing mastectomy incisions are placed along the inframammary fold. An inferolateral breast incision allows for access to the axillary tail if lymph node sampling or dissection is necessary. Alternative locations for incision placement include radially or as a periareolar incision (Fig. 2). Because nipple-sparing mastectomy results in long skin flaps, which confer an increased risk of flap and nipple necrosis, this technique is avoided in women with a prior history of radiation, smoking history, and larger or ptotic breasts. To minimize thermal damage to the nipple-areolar complex subdermal plexus, sharp dissection is of benefit. The retroareolar tissue margin is sent separately from the main mastectomy specimen for pathologic examination. If there is evidence of malignancy in the retroareolar margin, then resection of the nipple is indicated.

The complications of mastectomy include hematoma, seroma, wound infection, skin flap necrosis, chronic pain, phantom breast syndrome, and arm morbidity. Postmastectomy bleeding occurs approximately 3% of the time. It is standard practice to place closed suction drains beneath the mastectomy flaps and the axilla for

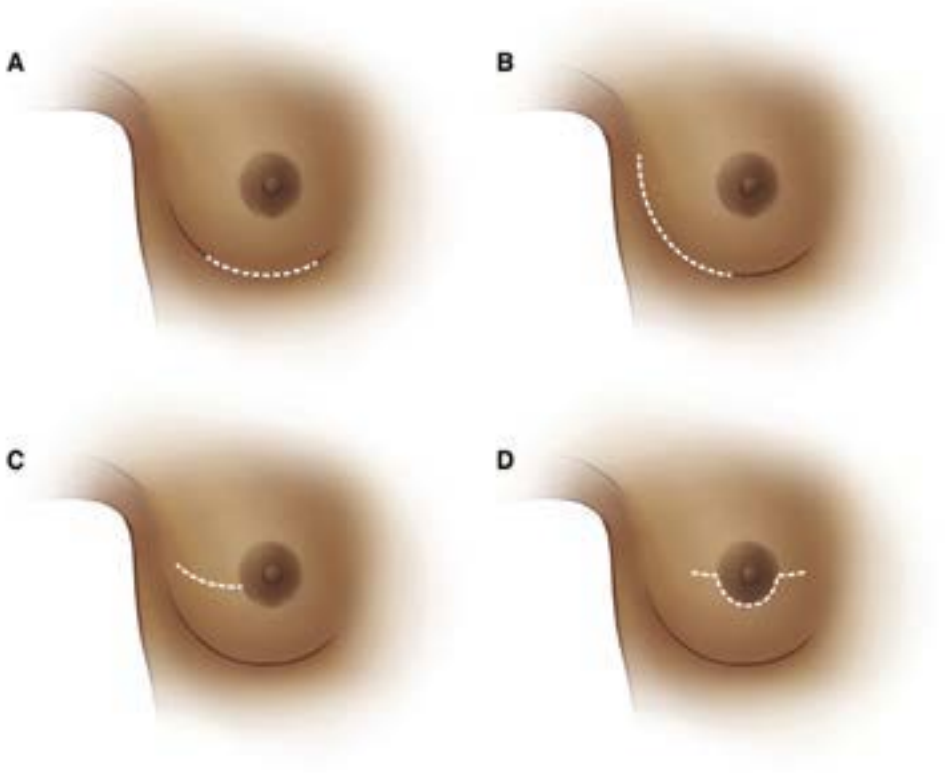


FIG. 2 Nipple-sparing mastectomy incisions. **(A)** Inframammary. **(B)** Inferolateral. **(C)** Radial. **(D)** Periareolar. *(Copyright 2021 Memorial Sloan Kettering Cancer Center.)*

seroma prevention. Women are encouraged to resume activities of daily living postoperatively, but they should be counseled to avoid rigorous shoulder exercises to reduce the risk of seroma formation. Clinically significant seromas should be aspirated to prevent wound infection, delayed wound healing, and poor cosmetic outcomes. Risk factors for a wound infection include obesity, smoking, diabetes, and older age. Most postmastectomy cellulitis can be managed with oral antibiotics. If skin flap or nipple necrosis is extensive or unable to be managed conservatively, surgical debridement or skin resection may be required.

MANAGEMENT OF THE AXILLA

The axillary lymph nodes receive 85% of the lymphatic drainage from the breast and are the regional nodal basin where metastatic breast cancer cells are most likely to be found. The remainder drain to the internal mammary, supraclavicular, and infraclavicular lymph nodes. Axillary lymph node dissection, which continues to be the standard of care for clinically node-positive disease, was historically the initial approach to breast cancer axillary staging and management. The development of sentinel lymph node biopsy in 1994 has been groundbreaking to the management of the axilla. It has allowed for safe omission of axillary lymph node dissection in most patients with clinically node-negative disease, saving them from unnecessary morbidity. Determining the axillary nodal status provides prognostic information and is used for decision making regarding adjuvant treatment. A sentinel lymph node biopsy can be performed in conjunction with a lumpectomy or mastectomy, and sentinel node mapping can be accomplished using blue dye, technetium sulfur colloid radiotracer, or both.

For women with clinically node-negative breast cancer, sentinel lymph node biopsy is the standard of care. Several landmark trials have shown that some women with positive sentinel lymph nodes may not need to undergo a completion axillary lymph node dissection. According to the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, patients with T1 to T2 tumors who are clinically node negative and undergoing lumpectomy with sentinel lymph node biopsy do not require a completion axillary lymph node dissection if they are found to have one or two positive sentinel lymph nodes. There is no difference in overall survival or locoregional recurrence in this subset of patients if they undergo a completion axillary dissection versus no further axillary surgery. This suggests that adjuvant radiation and systemic therapies have a significant effect on any potential remaining positive nodes and contribute to effective local control without a completion axillary lymph node dissection.

The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trial followed a similar design but included a subset of patients undergoing mastectomy and randomized patients with positive sentinel lymph nodes to axillary lymph node dissection or axillary radiation. There was no statistically significant difference in overall survival or axillary recurrence, but the patients who underwent completion axillary dissection had a 2-fold increased risk of lymphedema compared with those who underwent axillary radiation (40% vs. 22% at 1 year, and 28% vs. 14% at 5 years). The majority of patients in the AMAROS trial (82%) underwent lumpectomy, but 18% did undergo mastectomy; therefore, postmastectomy radiation can be considered in place of completion axillary dissection for patients undergoing mastectomy with a limited number of positive sentinel lymph nodes.

For women who present with clinically positive axillary lymph nodes confirmed by fine-needle aspiration or core needle biopsy, locally advanced breast cancer, or inflammatory breast cancer, axillary lymph node dissection may be performed. In general, level I and II anatomic lymph node dissection is preferred unless there are grossly positive axillary lymph nodes identified intraoperatively, in which case, level III lymph nodes should be removed as well. Women who present with clinically positive lymph nodes warrant consideration of neoadjuvant therapy for possible downstaging of the axilla. Subsequent surgical management of the axilla will then depend on the response to neoadjuvant therapy, which is dependent on molecular subtype, and greatest in triple-negative and HER2-positive tumors.

Lymphedema, caused by a disruption of the lymphatic system resulting in the accumulation of lymph fluid in the interstitial tissue, is a potential side effect of axillary surgery. The key to optimal management of lymphedema is early detection and diagnosis, as the early stages of lymphedema are reversible according to NCCN guidelines. Treatments for lymphedema include compression garments, physical therapy, and manual lymphatic drainage.

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer is an aggressive subtype and represents approximately 2% of breast cancers in the United States. Patients with this clinical syndrome present with acute onset of erythema and edema (peau d'orange) of a third or more of the skin of their breast. The differential diagnosis includes mastitis or cellulitis, especially for a pregnant or lactating woman. Failure to improve with antibiotics should prompt diagnostic breast imaging and a punch biopsy of the affected skin. Finding adenocarcinoma in the dermal lymphatics is diagnostic of inflammatory breast cancer in this setting, but a negative skin biopsy does not exclude the diagnosis. The workup of a newly diagnosed inflammatory breast cancer should include CT of the chest, abdomen, and pelvis along with a bone scan and/or PET scan. For women with non-metastatic inflammatory breast cancer, neoadjuvant chemotherapy is recommended followed by a modified radical mastectomy with axillary lymph node dissection. Because postmastectomy radiation is indicated, women who desire reconstruction should consider reconstruction in a delayed fashion.

LOCALLY ADVANCED BREAST CANCER

Women with locally advanced breast cancer include a subset of women with invasive breast cancer in whom clinical staging confines disease to the breast and regional lymph nodes (stage III). These patients have an increased risk of local recurrence and distant metastases, and thus are preferred to receive neoadjuvant chemotherapy. Women with stage IIIA locally advanced breast cancer who are eligible for primary surgery should receive postsurgical systemic treatment similar to that received by patients with stage II disease. Otherwise, among those for whom an initial surgical approach is unlikely to remove all disease or achieve long-term disease control, neoadjuvant chemotherapy is used to downstage the breast as well as the axilla. A woman's tumor response to neoadjuvant chemotherapy also provides foresight of escalation/de-escalation strategies if treatment is required in the adjuvant setting. Standard therapy for women in inoperable, noninflammatory, locally advanced breast cancer is anthracycline-based chemotherapy with or without taxanes. Women with HER2-positive tumors should include trastuzumab with possible use of pertuzumab in the chemotherapy regimen.

Repeating imaging with mammography, ultrasound, and breast MRI following neoadjuvant therapy can assess response to treatment and determine eligibility for certain surgical options. MRI is typically the most sensitive imaging modality for evaluating response to neoadjuvant therapy. All women should undergo surgery following their course of neoadjuvant chemotherapy, whether there was a complete clinical and/or radiologic response or if there was evidence of disease progression. The choice between lumpectomy or mastectomy should follow the same criteria used for the treatment of early-stage breast cancer.

Management of the axilla following neoadjuvant therapy is dependent on the nodal status at diagnosis and the response to treatment in the axilla (Fig. 3). Studies show equivalent sentinel lymph node identification and false-negative rates compared with those seen with initial sentinel lymph node surgery and a low risk of nodal recurrence after a negative sentinel lymph node biopsy result;



FIG. 3 Management of the axilla for patients receiving neoadjuvant therapy. *ALND,* Axillary lymph node dissection; *SLNB,* sentinel lymph node biopsy; *intraop*, intraoperative.

therefore, patients who are clinically node negative before and during neoadjuvant treatment should undergo sentinel lymph node biopsy post-systemic treatment. As demonstrated in the SENTINA (Sentinel Neoadjuvant) trial, the false-negative rate of a repeat sentinel lymph node biopsy (e.g., a sentinel lymph node biopsy performed before neoadjuvant therapy and then repeated again after neoadjuvant therapy) is unacceptably high. Thus, the preferred approach is to perform a sentinel lymph node biopsy following neoadjuvant therapy in patients who are clinically node negative at diagnosis.

For patients who present with clinically positive axillary lymph nodes at diagnosis (either identified by physical examination or axillary ultrasound), an image-guided tissue biopsy either by fine-needle aspiration or core needle biopsy is indicated. Marking of the biopsy-proven involved node with either a radiopaque clip or other marker is favored, as it enables identification of the metastatic node following neoadjuvant chemotherapy. Following neoadjuvant therapy, the axilla should be reassessed for treatment response. If the axilla has converted from clinical N1 to posttreatment clinical node-negative (ypcN0), then a sentinel lymph node biopsy may be appropriate in select patients. The surgical technique used during the sentinel lymph node biopsy procedure is also critical to minimize the false-negative rate to an acceptable level. As demonstrated by the ACOSOG Z1071 and SENTINA trials, using dual tracer (isosulfan blue dye and technetium sulfur colloid radiotracer), attempting to remove at least three sentinel lymph nodes, and successfully retrieving the previously biopsied clipped lymph node all contribute to a lower false-negative rate. The clipped lymph node is not one of the sentinel lymph nodes in 9% to 24% of cases. The term *targeted axillary dissection* has been coined to refer to retrieval of the clipped lymph node in addition to the sentinel lymph nodes. Techniques to aid in successful retrieval of the clipped lymph node include use of intraoperative ultrasound to identify a sonographically visible biopsy clip, preoperative wire or radioactive seed localization of the clipped lymph node, and injection of tattoo ink into the clipped lymph node to assist in intraoperative visualization. The breast and nodal specimens are pathologically examined to determine neoadjuvant treatment effect by assessing the presence and extent of residual disease. Achieving pathologic complete response (pCR) of the breast and axilla (ypT0 and ypN0) is associated with improved survival in triple-negative and HER2-positive breast cancers.

In the event of persistently clinically positive nodes (ypN+) or evidence of extensive nodal involvement (cN2 or cN3) before treatment, an axillary lymph node dissection is recommended. The possibility of omitting axillary lymph node dissection in women with residual nodal disease after neoadjuvant chemotherapy awaits results from the ALLIANCE A011202 trial that randomizes patients to axillary lymph node dissection or axillary radiation alone in patients with a positive sentinel node.

BREAST CANCER STAGING: AMERICAN JOINT COMMITTEE ON CANCER

The tumor, node, metastasis (TNM) staging system for breast cancer is an internationally accepted system used to assess disease prognosis and guide management. The eighth edition of the American Joint Committee on Cancer (AJCC) staging guidelines, released in

late 2017, is the most recent system approved. Prognosis can vary widely for cancers with the same T and N status; thus, the latest staging system incorporated underlying tumor biology to improve the prognostic value. The staging groups in the AJCC staging system are now divided into anatomic and prognostic staging groups. The anatomic staging groups are based purely on TNM criteria and are used when biomarker information is unavailable. The standard anatomic TNM staging system classified tumors based on the size of the tumor (T), the number of lymph nodes involved (N), and the presence or absence of distant metastatic disease (M). Women are staged clinically, using physical examination with or without imaging and data from biopsy results, and pathologically, incorporating all information from clinical stage and surgical resection. The TNM status combination defines the anatomic stage of the tumor (stages I–IV).

The prognostic staging groups are based on TNM criteria and biomarker information, including the grade of the tumor and the estrogen receptor, progesterone receptor, and HER2 receptor status. The Oncotype DX Breast Recurrence Score (Exact Sciences, Redwood City, CA), if applicable, is also included. Oncotype DX is currently the only multigene panel included in the staging system, but others may be added in the future. The assigned stage based on clinical/pathologic prognostic staging groups reflects the biology of the tumor and expected prognosis based on treatment with appropriate therapies.

ADJUVANT THERAPY

Adjuvant therapy can be provided in the form of systemic therapy and/or radiotherapy. Systemic therapy, which encompasses antihormonal therapy, chemotherapy, and biologic agents, has been associated with significant reductions in locoregional and distant recurrence risk. In women with estrogen receptor–positive tumors, antihormonal therapy with an aromatase inhibitor or selective estrogen receptor modulator for 5 to 10 years is standard treatment. Some estrogen receptor–positive tumors are higher risk than others and may benefit from adjuvant chemotherapy in addition. High-risk features include a high tumor grade, large tumor size, pathologically involved nodes, low expression of estrogen receptor and/or progesterone receptor, and presence of lymphovascular invasion. Multigene assays (i.e., Oncotype DX) can also be used to stratify patients with estrogen receptor–positive, HER2-negative disease at high risk for whom chemotherapy is beneficial. The RxPONDER trial found that postmenopausal women with early-stage estrogen receptor–positive, HER2-negative breast cancer and one to three positive nodes derive no invasive disease–free survival benefit with the addition of chemotherapy to adjuvant endocrine therapy if the Oncotype DX Recurrence Score was ≤ 25, allowing for the safe omission of adjuvant chemotherapy. In most patients with triple-negative breast cancers, chemotherapy is the mainstay of treatment. Anti-HER2 therapies with trastuzumab and the possible addition of pertuzumab have dramatically improved outcomes in women with HER2-positive tumors, and are recommended for early-stage and advanced breast cancers.

Radiation therapy can be delivered to a portion or to the whole breast postlumpectomy, the chest wall postmastectomy, and/or the regional lymph nodes, including the axillary and supraclavicular nodes. Whole-breast radiation therapy following lumpectomy reduces the risk of recurrence, with a subsequent reduction in mortality rates after 15 years of follow-up in women with both positive and negative axillary nodes. Postmastectomy radiation therapy provides a long-term survival benefit for women with node-positive disease, regardless of the number of nodes involved. Deescalation of radiotherapy has been of more interest recently, given the reductions in local recurrence rate that have been noted. Rather than conventional radiotherapy, radiation to an anatomically defined, volume-based target (partial-breast irradiation) is an option in women with low-risk breast cancer. Outcomes of partial breast irradiation are equal to whole-breast radiotherapy so long as the patients selected for this treatment are at low risk and an adequate tumoricidal dose is delivered to the target volume. Potential candidates for partial-breast irradiation include women ≥ 50 years of age with small (<2 cm), node-negative breast cancers that have been excised with negative surgical margins, and it should be cautioned in those with multicentric disease, lymphovascular invasion, extensive intraductal component, or close margins (<2 mm).

SURGERY FOR STAGE IV BREAST CANCER

For patients who present with stage IV breast cancer, a prompt referral to medical oncology to discuss systemic therapy is indicated. Primary tumor resection may or may not be performed, depending on the extent of metastatic disease and the response to systemic therapy. Recent randomized trials have not shown a consistent and clear benefit with surgery, and surgery's impact on survival remains controversial. In general, surgery to address the breast primary site is reserved for patients with stable oligometastatic disease and a reduction in breast tumor size in response to chemotherapy; locoregional lymph node surgery may be contemplated in the setting of a multidisciplinary discussion with surgery, medical oncology, and radiation oncology. For patients with widespread metastatic disease and/or a poor response to systemic therapy, surgery is considered for palliative purposes.

CONCLUSION

Surgery is a key facet in the multidisciplinary treatment of patients diagnosed with breast cancer. Over time, the integration of surgical techniques with advances in radiation and systemic therapies has allowed for less-invasive surgical procedures. This has resulted in decreased surgical morbidity for patients without a detrimental effect on outcomes and survival.

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Pregnancy and Breast Cancer Management

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EPIDEMIOLOGY OF BREAST CANCER IN PREGNANCY

Breast cancer is one of the most common cancers in pregnant and nonpregnant women. Gestational or pregnancy-associated breast cancer is defined as breast cancer that is diagnosed during pregnancy, in the first postpartum year, or any time during lactation.

Unfortunately, in recent years, we are faced with increasing numbers of pregnancy-associated breast cancers caused by both the decreasing age of breast cancer diagnosis and the globally increasing age of childbearing. The diagnosis and management of malignancy in the prenatal and postnatal settings is associated with several challenges.

Currently in the United States, 1 in 1000 pregnancies are complicated by breast cancer. Worldwide, there are 10,000 cases of breast cancer in pregnancy diagnosed per year. The incidence rate has been reported to range from 17.5 to 39.9 per 100,000 births, but the rate is substantially lower during pregnancy (ranging from 3.0 to 7.7) than during the postpartum period (ranging from 13.8 to 32.2).

Pregnancy has direct effects on the metabolism, gene expression profile, and proliferation of the mammary epithelial cells in response to hormones. These alterations can significantly affect a woman's risk of developing breast cancer. Women who become pregnant before 20 years of age have a 50% reduced risk of developing breast cancer compared with nulliparous women. This protective effect is extended to subsequent pregnancies, with a 10% reduction in risk for subsequent pregnancies. This protective effect is not present for women whose first pregnancy is between 30 and 34 years of age, and the risk of developing breast cancer is actually increased for those whose first pregnancy is after 35 years of age. The overall risk of developing breast cancer increases immediately after giving birth independent of race, age, or number of pregnancies. Interestingly, studies have shown a 2.8-fold increase in metastasis and a 2.7-fold increase in mortality in breast cancer patients diagnosed with breast cancer at age less than or equal to 40 years, within 5 years postpartum. Breast cancer in pregnancy tends to be more advanced at diagnosis, but when matched for tumor characteristics and stage, outcomes are similar to nonpregnant patients.

Studies have demonstrated that disease-free survival (DFS) and overall survival (OS) were the same when comparing breast cancer in pregnant patients versus nonpregnant patients when they receive standard-of-care therapy. It is important to note that management of the pregnant breast cancer patient involves a unique set of considerations that are important for surgeons to be familiar with in their practice as giving these patients the appropriate levels of care can ensure that their outcomes are similar to those of the general population.

PREGNANCY CHANGES TO THE BREAST

The mature breast is located on the anterior thoracic wall and lies on top of the pectoralis major muscle. When a woman undergoes puberty, this leads to changes in the breast that remain incomplete until pregnancy. The breast after puberty consists of adipose tissue and lactiferous units called *lobes*. These eventually drain into the lactiferous ducts and then into the lactiferous sinus to the nipple-areolar complex (Fig. 1). During pregnancy, the breast undergoes both anatomic and physiologic changes to prepare for lactation. During the first trimester, the ductal system expands and branches out into the adipose tissue in response to the increase of estrogen and progesterone produced by the corpus luteum, which occurs during the second week of pregnancy. At about 8 weeks after fertilization, trophoblasts, the cells that eventually become the placenta, produce the human chorionic gonadotropin (hCG) hormone. HCG works to prevent degradation of the corpus luteum and stimulate the corpus luteum to continue the production of progesterone and estrogen. HCG peaks and then declines at 9 weeks (Fig. 2). Elevated levels of estrogen cause an involution of adipose tissue as well as ductal proliferation and elongation, and progesterone stimulates the development of lobules. Mononuclear inflammatory cells also infiltrate the breast tissue. During this time, estrogen stimulates the pituitary gland producing elevated levels of prolactin. By the 20th week of gestation, the proliferative process is most pronounced and the mammary glands are sufficiently developed to produce components of milk as a result of prolactin stimulation. Lobule growth continues during the second and third trimesters via cellular proliferation and increased cell size. Myoepithelial cells become flattened and less prominent, whereas epithelial cells are enlarged. During the second trimester, secretory substances accumulate in the epithelial cells of lobule acini, and during the third trimester, increased levels of prolactin promote alveolar cell differentiation and initiate lactogenesis. Milk production is inhibited by high estrogen and progesterone levels, and colostrum is produced during this time. In the third trimester, and then rapidly after birth, these levels decrease, allowing for milk production and eventual let-down to allow for breastfeeding. Most pregnancies cause the areola to darken, the breast to increase in size, and the areolar glands to become more prominent. Postlactational involution occurs at the cessation of milk production caused by a decline in prolactin. Massive apoptosis and cell death occur in the mammary gland, and the tissue in the breast is remodeled. The connective tissue of the lobules goes from a loose to a dense structure. Acini lose lining cells, and the basement membrane of the acini becomes thickened. Preclinical studies have shown that postpartum mammary gland involution promotes tumor growth. Using xenograft and isogenic tumor transplant models, the normal tissue microenvironment of the actively involuting mammary gland has been demonstrated to increase breast cancer tumor take and metastasis compared with the mammary microenvironment of the nulliparous or parous host, which can explain the increased incidence in the postpartum period.

PRESENTATION AND DIAGNOSTIC WORKUP

Breast cancer diagnosis and staging are more difficult in the pregnant patient because of the physiologic changes in the breast. Physical examination may be more challenging as some masses detected on examination are physiologic and unique to this time, including galactoceles, lactating adenomas, or infarctions. Further on examination, the patient may have findings of bilateral edema and erythema in dependent portions of the engorged breast as well as swelling in the axilla if there is axillary breast tissue. Nipple discharge bilaterally is physiologic, and bloody nipple discharge bilaterally can occur in up to 15% of nursing mothers.

When obtaining imaging studies, limiting radiation exposure to the fetus is of utmost importance. Breast cancer in pregnancy most commonly presents as a painless mass. Ultrasound is the first imaging modality used to assess these patients. Breast ultrasonography can determine whether a breast mass is a simple or complex cyst or a solid tumor without the risk of fetal radiation exposure and may be used to guide the diagnostic biopsy. During pregnancy, duct ectasia

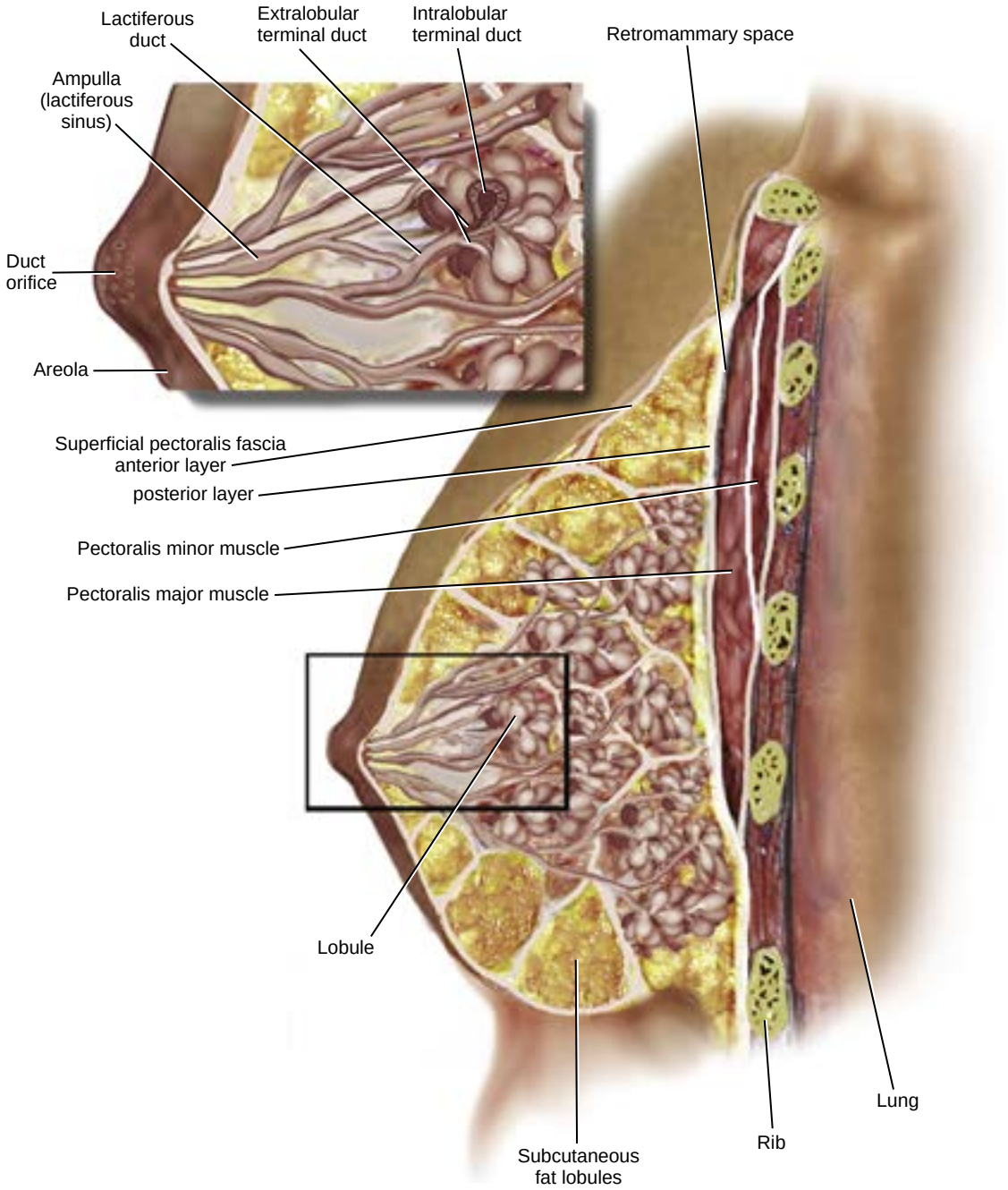


FIG. 1 **Anatomy of the mature breast before pregnancy.** *(From Stahl DL, Columbus KS, Baggish MS. Anatomy of the female breast. In:* Baggish and Karram Atlas of pelvic anatomy and gynecologic surgery. *4th ed. Philadelphia: Elsevier; 2016:1169–1180.)*

is frequent, and breasts are more hypoechoic on ultrasound imaging because of lobular hyperplasia and duct dilation. During lactation, there is diffuse hyperechogenicity, a prominent ductal system, and increased vascularity.

A bilateral mammogram with abdominal shielding is recommended and may help determine the extent of disease, especially by visualizing calcification, which would normally not be seen with ultrasound. Mammogram is also useful for evaluating the contralateral breast. The ionizing radiation to the fetus from the mammogram is <0.03 μGy, which is significantly lower than the threshold of acceptable fetal exposure of <50,000 μGy, and therefore is considered safe in pregnancy with shielding. Abdominal shielding is recommended, although there are no data regarding fetal outcomes when mammography has been performed with or without shielding. Mammographic sensitivity is altered by the increased water content, higher density, and loss of contrasting fat in the pregnant or lactating breast. Nevertheless, data suggest that mammography is sufficiently sensitive to diagnose breast cancer during pregnancy and lactation. It is recommended to perform mammography immediately after breastfeeding as breast density will be lower. Figure 3 shows the mammogram and sonogram of a 10-week-pregnant patient with inflammatory breast cancer. Multifocal lesions are noted in the left breast, but a hyperechoic background is also notable bilaterally.

Magnetic resonance imaging (MRI) with contrast is contraindicated throughout the entire pregnancy as gadolinium is considered

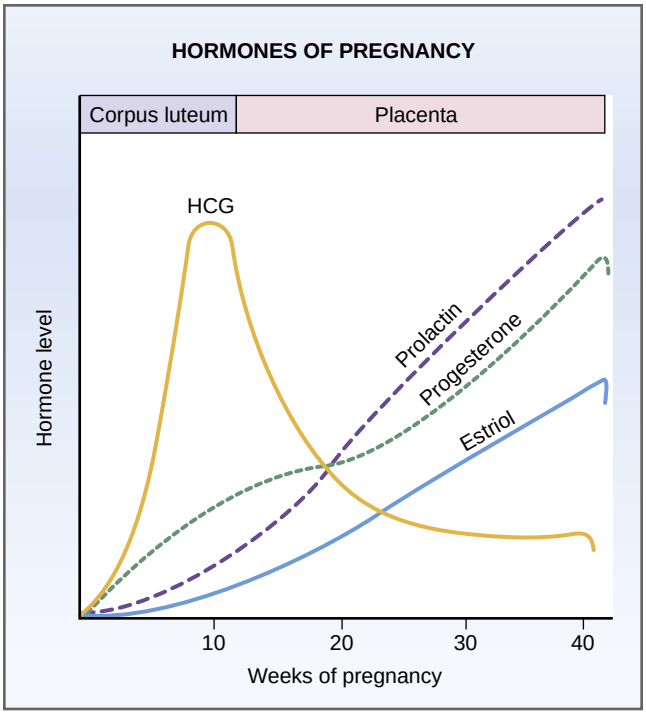


FIG. 2 The hormones of pregnancy. HCG, prolactin, progesterone, and estriol (primary form of estrogen) shown throughout the different stages of pregnancy. *(From Costanzo LS. Reproductive physiology. In:* Physiology. *6th ed.; Philadelphia: Elsevier 2018:461–482.)*

teratogenic. MRI without contrast can be considered but is unlikely to be helpful as MRI is a dynamic study assessing uptake and release of gadolinium over short time intervals.

Gadolinium-enhanced breast MRI may be considered in women who are postpartum and lactating at the time of diagnosis if the mammogram and/or ultrasound images are equivocal.

The American College of Radiology guidelines do not require that patients discontinue breastfeeding. MRI may be difficult to interpret in the lactating state because the increased enhancement from physiologic hypervascularity increases the background enhancement, where diffuse high-signal intensity on T2-weighted images can decrease efficacy. Prudence must be exercised in this setting to avoid unnecessary interventions to the lactating breast.

Biopsy

A clinically suspicious breast mass requires biopsy for definitive diagnosis, regardless of whether or not a woman is pregnant and despite negative mammographic or ultrasound findings. Core, vacuum-assisted, or excisional biopsies can be performed relatively safely during pregnancy, preferably under local anesthesia.

Ultrasound-guided core biopsy or vacuum-assisted biopsy is the preferred method and is a safe procedure regardless of gestational period. Either technique of biopsy can be used. Vacuum-assisted devices have a larger-gauge biopsy needle and lower false-negative rate. Reported complications from breast biopsy in the pregnant patient are similar to those in the nonpregnant patient and include infection, allergy to local anesthetic, hematoma, and milk fistula during pregnancy. In regard to formation of a milk fistula after core

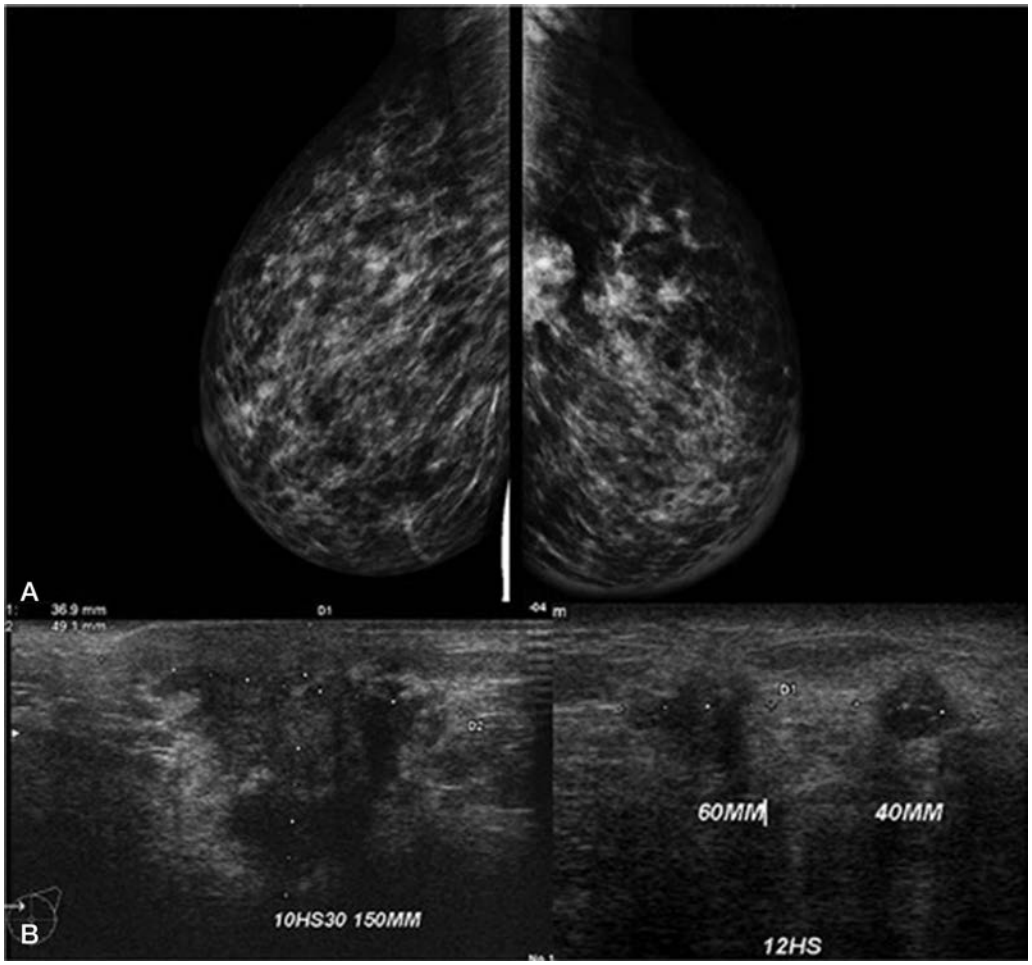


FIG. 3 Inflammatory breast cancer in a 32-year-old woman who is 1 month pregnant. Multifocal lesions in mammography **(A)** and ultrasound **(B)**. *(Courtesy Dr. Adriana Langer. From Alipour S, Omranipour R, et al.,* Diseases of the breast during pregnancy and lactation. Advances in Experimental Medicine and Biology, vol 1252. Springer; 2020.)

needle biopsy, the literature contains only sporadic case reports, which makes this a low to nonexistent risk. The risk may be higher in more centrally located lesions and in the setting of excisional biopsies, but it is a process that will resolve spontaneously.

After performing the biopsy, it is important to alert the pathologist that the biopsy is from a pregnant patient as histologic changes occur as a result of hormonal influences, such as epithelial proliferation in the lobular unit and an increased glandular vascularity as described. If there is radiographic and pathologic discordance, an excisional biopsy is then performed.

It is important to note that fine-needle aspiration (FNA) biopsy can also be considered, but it is suboptimal compared with core needle biopsy. Given the physiologic changes of the breast secondary to pregnancy, the cytologic analysis is challenging and will demonstrate increased cellularity and frequent mitosis, which can be physiologic from pregnancy and not secondary to an underlying malignancy.

Staging

It is important to limit the exposure to ionizing radiation in the pregnant patient. The most sensitive period for radiation-associated malformations is during organogenesis, at 8 weeks of gestation. CT scan, scintigraphy (bone scan), and PET scans are contraindicated throughout the pregnancy because of the high radiation exposure.

Staging workup is performed on those patients with clinical stage III (cT3N1 or any ≥ N2) or stage IV disease or symptoms suggestive of distant metastases. Workup consists of a chest x-ray with abdominal shielding, liver ultrasonography or noncontrast MRI for visceral organ evaluation, and noncontrast skeletal MRI if bone metastases are suspected. Bone is the most common metastatic site in breast cancer, and it is important to note that alkaline phosphatase increases in pregnancy so cannot be used as a marker for bony metastases. Diffusion-weighted whole-body MRI without gadolinium can be considered after the first trimester if metastatic disease is suspected. If brain metastasis is suspected, MRI is the most sensitive imaging technique.

The use of PET in pregnancy is very limited. Estimates of fetal radiation dose from ^{18}F fluorodeoxyglucose (^{18}F-FDG) are 6.29×10^{-3} to 2.46×10^{-2} mGy/MBq, where earlier bladder voiding reduced these doses by 25% to 45%; however, there is no evidence to support its use. The amounts of ^{18}F-FDG excreted in breast milk after a PET scan are low, and guidelines would suggest the only adjustments that a nursing mother should make after a PET scan are to avoid close contact with the infant for up to 12 hours.

HISTOLOGY OF BREAST CANCER IN PREGNANCY

There are no obvious differences in histologic types of breast cancer among those associated and not associated with pregnancy. Invasive ductal carcinoma, not otherwise specified (NOS) is the most prevalent type of tumor in pregnancy; representing 78% to 88% of cases. Invasive lobular carcinoma is reported with a very low frequency in some studies. Mucinous, medullary, and other types of carcinoma are also reported. Ductal carcinoma in pregnancy has a higher histologic grade, a more aggressive profile, and a more advanced stage at diagnosis: a larger tumor size, a higher frequency of nodal involvement, less frequent expression of estrogen receptors (ERs) and progesterone receptors (PRs), and a higher proportion of inflammatory breast cancer.

TREATMENT: BREAST CANCER IN PREGNANCY

There are still certain cultures and countries that recommend abortion when a woman is diagnosed with breast cancer during her pregnancy. Termination of pregnancy does not improve maternal prognosis or outcome. The conversation with these patients should focus on balancing the risks to the fetus from the cancer treatment with the risks to the mother from the cancer, which leads to alterations to standard treatment options and sequences that have not been shown to change the prognosis of these women.

The treatment of their cancer should adhere as much as possible to standard treatments for breast cancer in the nonpregnant patient. Surgery and chemotherapy are possible and safe during pregnancy and should be tailored based on anatomic stage, tumor biology, and the gestational age of the fetus to guide choices of treatment and sequence of treatment.

Managing the pregnant breast cancer patient should involve a multidisciplinary team including the breast surgeon, medical oncologist, radiation oncologist, radiologist, maternal fetal medicine specialist, anesthesiologist, obstetrician, neonatologist, and genetic counselor.

Genetic testing is indicated when a pregnant patient is diagnosed with breast cancer. Special surveillance tests, chemoprevention, and risk-reducing surgery would not be recommended for pregnant women found to carry pathogenic variants. These interventions can be considered postpartum. The probability of detecting a pathogenic *BRCA* variant in a young patient with a triple-negative breast cancer is approximately 20%.

SURGICAL CONSIDERATIONS

Surgery may be performed at any time during pregnancy in all trimesters, but the safest time to operate on a pregnant patient is in the second trimester (weeks 12–24). General anesthetics all cross the placenta but have not been reported to increase the risk of congenital anomalies. Spontaneous abortion has been reported in women undergoing surgery in the first and early second trimesters of pregnancy. Key tenets for a successful operation are avoiding maternal hypoxia or hypotension. The goal should be to maintain the mean arterial pressure (MAP) at 60 mm Hg, as this is the optimal MAP for uterine perfusion during surgery.

After 20 weeks' gestational age, the position of the patient should be in the left lateral tilt position for uterine displacement off the inferior vena cava. After 24 weeks, which is when the fetus is considered viable, intraoperative fetal monitoring is necessary. Maternal fetal medicine specialists should also be available and the neonatologist on standby should the patient start to labor during the operation. Figure 4 shows a pregnant patient positioned in the operating room with fetal monitoring after undergoing a mastectomy.

Mastectomy versus Breast Conservation

In the past, mastectomy was considered the standard surgical procedure for the local management of all pregnant patients with breast cancer. However, mastectomy is not mandatory at all stages of pregnancy. Breast conservation and mastectomy are options for these patients depending on the gestational age at diagnosis. Mastectomy can be performed in all trimesters. When considering breast-conserving surgery, timing for radiation therapy must be considered as radiation cannot be given during pregnancy. Therefore, mastectomy is the standard for local control in the first trimester. Suitability for breast-conserving surgery in the second and third trimesters is determined in the same way as for nonpregnant patients and considers tumor size, tumor location, and tumor–to–breast size ratio as well as adjuvant therapy.

Breast-conserving surgery is not recommended in the first trimester or early second trimester as this would cause a significant delay in the receipt of radiation and increase the risk of local recurrence. Breast conservation is an option in the second trimester if followed by adjuvant chemotherapy during the remainder of the pregnancy and then radiation therapy soon after delivery. In the third trimester, breast-conserving surgery can be performed and followed with postpartum radiation. Further, breast conservation can be performed preceding neoadjuvant chemotherapy, which



FIG. 4 Positioning and monitoring of the pregnant patient after mastectomy. *(From Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy.* Lancet. *2012;379:570–579.)*

would start during week 14. The patient can then receive adjuvant chemotherapy until the end of the pregnancy and postpartum radiation thereafter. This decision should be made in the context of a multidisciplinary team discussion. Figure 5 outlines the breast and axillary surgeries allowable by trimester of pregnancy.

Axillary Staging/Sentinel Lymph Node Biopsy

Historically, axillary lymph node dissection was recommended to all women diagnosed with breast cancer in pregnancy as data on the safety and efficacy of sentinel lymph node biopsy (SLNB) in the pregnant patient was lacking. Currently, there are sufficient data demonstrating that SLNB is safe and can be performed in all trimesters with the use of technetium-99. SLNB involves locoregional administration of relatively low injected radioactivity doses. There is rapid clearance of the negligible radioactivity in the body, with a substantial and stable uptake at the injection site, which is removed surgically shortly thereafter. Considering the radiopharmaceuticals and the amounts of activity typically used for SLNB in optimized protocols, the doses absorbed by the fetus are mostly less than 20 μGy. There is no need to perform an upfront axillary dissection for a clinically node-negative

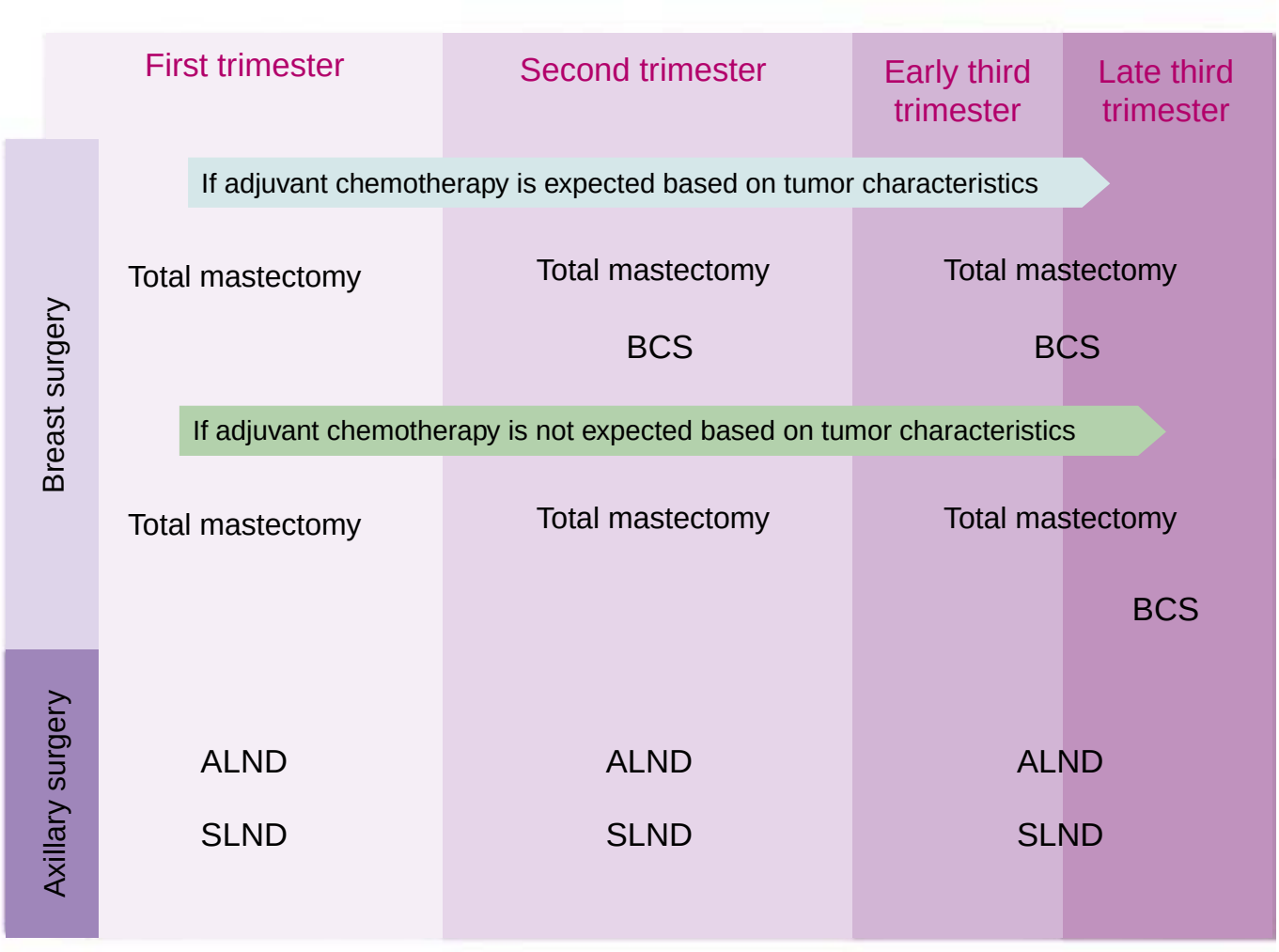


FIG. 5 Type of surgery of the breast and axilla for pregnancy-associated breast cancer in different trimesters; when two types of surgery are allowed, the choice depends on tumor characteristics and patient preference. Blue dye should not be used for sentinel lymph node dissection in pregnancy. ***ALND,*** Axillary lymph node dissection; ***BCS,*** breast-conserving surgery; ***SLND,*** sentinel lymph node dissection. *(From Omranipour R. Surgery for pregnancy-associated breast cancer. In Alipour S, Omranipour R, et al.,* Diseases of the breast during pregnancy and lactation. Advances in Experimental Medicine and Biology, vol 1252. Springer; 2020.)

axilla. Pregnant patients with breast cancer should be offered SLNB rather than axillary dissection whenever it is indicated according to general practice in the nonpregnant patient. Blue dye is currently contraindicated in pregnancy. Isosulfan blue causes anaphylaxis in 1% of patients, and methylene blue places the fetus at risk for methemoglobinemia. Further, the blue dyes have unknown teratogenicity.

Immediate Reconstruction

It is safe and feasible to reconstruct after mastectomy using tissue expanders. Studies have demonstrated an increase in operating room time and anesthesia, but no increase in maternal morbidity, obstetric complications, or adverse fetal outcome. Further, immediate reconstruction with tissue expanders may preserve reconstructive options for patients undergoing postmastectomy radiation (PMRT), especially in patients who would be poor candidates for an autologous flap in the future.

CHEMOTHERAPY IN PREGNANCY

The decision to administer chemotherapy to the pregnant breast cancer patient should follow the same guidelines as in nonpregnant patients, taking into account the gestational age and the overall treatment plan such as the timing of surgery and the need for radiotherapy. Chemotherapy can be administered in the adjuvant or neoadjuvant setting and should be administered after the first trimester. Chemotherapy is contraindicated in the first trimester because of the risk of fetal teratogenesis during weeks 4 to 12 but can be started as early as week 14. Chemotherapy has been shown to be safe in the second and third trimesters. Fluorouracil, cyclophosphamide, doxorubicin, and taxanes are all safe in pregnancy. Clinicians can use standard regimens used for nonpregnant patients. One of the most common regimens is doxorubicin-based (doxorubicin plus cyclophosphamide or doxorubicin plus cyclophosphamide and taxanes [paclitaxel weekly to every 3 weeks or docetaxel every 3 weeks]. There are other regimens described such as fluorouracil, epirubicin, and cyclophosphamide. Some investigators recommend weekly epirubicin treatment on the basis of fetal safety data, but this is not the standard treatment for breast cancer, and clinicians should not put maternal prognosis at risk to limit or reduce unproven fetal damage. The main advantage of weekly regimens during pregnancy is shorter nadir periods that might reduce the risk of complications when unexpected delivery occurs. Dose-dense regimens of doxorubicin with cyclophosphamide and taxane result in improved DFS and OS in hormone receptor–negative nonpregnant breast cancer patients. Hormone receptor–negative disease is more common in pregnancy, but the data on dose-dense chemotherapeutic regimens during pregnancy are scarce. Small studies have shown that there is no increased risk of maternal or fetal complications with the use of dose-dense regimens.

In regard to supporting the pregnant patient on chemotherapy, antiemetics (i.e., metoclopramide, ondansetron, granisetron, and prochlorperazine) are considered safe. Steroids are used before induction of chemotherapy and are safe in pregnancy, specifically methylprednisolone and hydrocortisone, which are extensively metabolized in the placenta and are therefore preferred. Further, growth factors used for white blood cells and red blood cells during chemotherapy are considered safe in pregnancy, specifically in the second and third trimesters.

Chemotherapy doses are similar to those in the nonpregnant patient and are based on body surface area and creatinine clearance. Doses should be adapted throughout the pregnancy, taking into account the weight changes. Gestational changes include an increase in heart rate and blood pressure, an increase in plasma volume and glomerular filtration rate, and hormonal changes in hepatic function. For doxorubicin, epirubicin, paclitaxel, and carboplatin, these changes result in a decrease in plasma drug exposure and peak plasma concentration. There is also an increase in distribution volume and drug clearance secondary to the physiologic changes during pregnancy. This raises doubt about the effectiveness of such regimens in this setting, but no direct relation exists between toxic tissue effects and prognosis. Further, studies have shown similar outcomes to nonpregnant women when controlling for stage and tumor characteristics and regimens received.

Chemotherapy is avoided after 35 weeks' gestational age or within 3 weeks of planned delivery. A 3-week interval should be left between the last cycle of chemotherapy and the delivery to avoid problems associated with myelosuppression (bleeding, infection, anemia) in the mother and baby and to avoid drug accumulation in the fetus. Further, the myelosuppression (i.e., pancytopenia, neutropenia) caused by the chemotherapeutic agents may increase the risk of sepsis complications at delivery. The placenta of these patients should be sent for evaluation as there are reports of placental metastasis, but none of fetal metastasis.

Treatments that are contraindicated during pregnancy are HER2-targeted therapy (risk of oligohydramnios resulting in pulmonary and renal insufficiency); methotrexate (teratogenic); tamoxifen (teratogenic causing craniofacial malformations, ambiguous genitalia, and fetal death); bisphosphonates (category C risk of maternal toxicity, fetal underdevelopment, embryolethality, hypocalcemia, and skeletal retardation); and radiation therapy.

If neoadjuvant chemotherapy is to be administered during pregnancy, the regimen is started at 14 weeks' gestation and is continued for a standard cycle as tolerated. At this point, the patient can decide between mastectomy or breast conservation, which is followed by postpartum radiation therapy.

Further, there have been several cases reporting radiation administered for breast cancer in pregnancy with low fetal doses and resulting in the delivery of healthy babies. Therefore, radiation might be considered in the first or early second trimester if the risk of delay or omission is believed to outweigh that of harming the fetus, but this is not the standard and should be discussed with the multidisciplinary team.

PEDIATRIC OUTCOMES AFTER MATERNAL CANCER DIAGNOSIS

The rate of congenital abnormalities in children exposed to chemotherapy is 3%, which is similar to the national average. Overall, the outcomes of the babies born to women with breast cancer during their pregnancy are favorable and comparable to those of women without breast cancer. But it is important to note that pregnant patients have a higher rate of preterm delivery (61.2% compared with 8% in the general population). Women treated for breast cancer during pregnancy also tend to have children of lower birth weight, but this normalizes over time. There have been no long-term health problems or cognitive developmental issues in children born to mothers that had breast cancer treatment during their pregnancy. If oncologically safe, the patient should be encouraged to carry the pregnancy to as close to term as possible.

Breastfeeding

Lactation from the treated breast is not contraindicated, but there may be reduced milk volume after breast-conserving surgery secondary to scar tissue. It is contraindicated for mothers to breastfeed while undergoing chemotherapy or radiotherapy.

KEY POINTS

- Ultrasound is the first-line imaging modality used.
- Surgery can safely be performed at any time during the pregnancy.
- The recommended method of sentinel node localization is with technetium-99 (99m-Tc sulfur colloid) alone.
- Radiation, trastuzumab, and tamoxifen are contraindicated and given only in the postpartum period.

- Chemotherapy is contraindicated in the first trimester. Anthracycline-based chemotherapy can be safely given in the second and third trimesters and should be stopped 3 to 4 weeks before delivery.
- Dosing of chemotherapy should be similar to that in the nonpregnant patient, based on body surface area.
- Prognosis in the pregnant breast cancer patient appears to be the same as in nonpregnant patients if standard therapy is given.

Suggested Readings

Alipour S, Omranipour R, et al., *Diseases of the breast during pregnancy and lactation. Advances in experimental medicine and biology;* 2020.

Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. *Lancet*. 2012;379(9815):570–579.

Loibl S, Schmidt A, Gentilini O, et al. Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncol*. 2015;1(8):1145–1153.

Ablative Techniques in the Treatment of Benign and Malignant Breast Disease

Marissa Vane, MD, MSc, and Armando E. Giuliano, MD, FACS, FRCSEd

Extending the trend toward less invasive treatment, ablative techniques for benign tumors and small breast cancers have continued to progress. Ablative treatments are all image-guided percutaneous techniques (using ultrasonography, mammography, magnetic resonance imaging [MRI], or computed tomography [CT]). Complete tumor ablation can be achieved using different types of energy instead of or in addition to immediate or delayed surgical excision. The goal of these ablative techniques is to reduce the complications, decrease morbidity, shorten hospitalization, and improve the cosmetic outcome and quality of life while not increasing recurrence rates. Ablation techniques include radiofrequency ablation (RFA), microwave, laser ablation, electromagnetic waves, cryoablation, and high-intensity focused ultrasound (HIFU).

RADIOFREQUENCY ABLATION

RFA is a widely used ablative technique for various solid tumors at different sites, including liver, lung, kidney, and bone. RFA uses low-frequency electromagnetic waves to generate heat and ablate these tumors. To perform RFA, a needle is inserted percutaneously within the tumor, usually with ultrasound guidance, but CT or MRI guidance may be used. A generator creates a high-frequency alternating current; in response, ions attempt to follow the changing direction, causing agitation and frictional heating. This results in destruction of the tumor tissue through thermal coagulation and protein denaturation (Fig. 1).

In most studies, RFA is followed by immediate or delayed surgical excision of the tumor. Izzo et al. performed one of the first feasibility studies that included 26 breast cancer patients with a mean tumor size of 1.8 cm (range, 0.7–3.0 cm). Complete tumor ablation was obtained in 96% (25 of 26) of the patients. Since then, multiple RFA studies have been performed with success rates varying from 77% to 100%. Only a few studies performed RFA without surgical excision. Oura et al. included 52 patients with a tumor size of 2 cm or less who underwent RFA alone. MRI after 1 to 3 months showed no evidence of residual disease. After a follow-up of 15 months, none of the patients developed locoregional or distant recurrences. Cosmetic outcome was reported excellent in 83%, good in 11%, and fair in 6% of the patients.

Excision RFA (eRFA) consists of surgical excision of the tumor followed by RFA. The aim is to decrease the rate of reexcisions after breast-conserving surgery, to improve locoregional recurrence rates by extending the margins, and ablating possible residual disease. Klimberg et al. performed a study in 100 patients undergoing breast-conserving surgery followed by eRFA in which biopsy showed at least 1 cm circumferential ablation around the resection cavity. Of these 100 patients, 78 had negative margins (>2 mm) and 22 had margins 2 mm or less, of which 3 were focally positive. Recurrence after 5 years of follow-up was seen in 3% of the patients treated with systemic hormonal therapy and in 10% without systemic hormonal therapy. Recently, results of the multicenter Radiofrequency Ablation After Breast Lumpectomy study were presented. A total of 267 T0 to T2 breast cancer patients treated with breast-conserving surgery followed by eRFA were included. Results showed a reexcision rate for positive margins of <5%. The rate of breast recurrence was 2.5% after 3 years of follow-up.

RFA appears to be limited to tumors with a maximum size of 2 cm. RFA treatment is not suitable for infiltrating lobular breast tumors, tumors with an extensive in situ component, and in patients treated with neoadjuvant systemic therapy. Complications from RFA are rare and generally mild, including skin or muscle burns and ecchymosis.

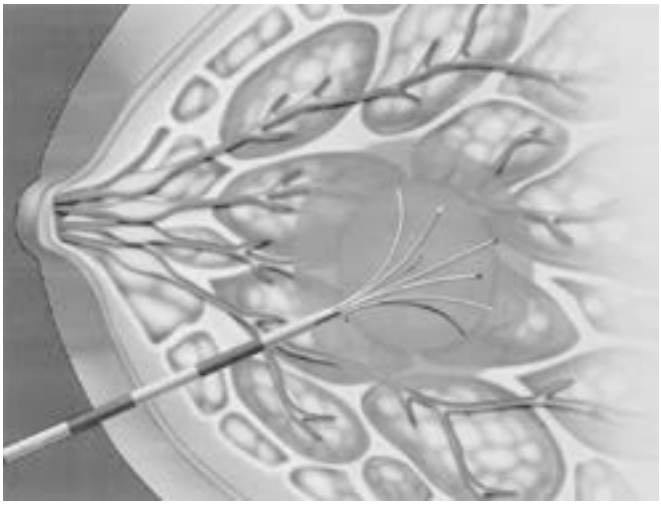


FIG. 1 Radiofrequency ablation showing star array probe with breast and surrounding frozen ablation zone. *(Courtesy RITA Medical Systems. From Simmons R. Ablative techniques in the treatment of benign and malignant breast disease.* J Am Coll Surg. *2003;197:334–338.)*

MICROWAVE ABLATION

Thermal ablation can also be performed with the use of microwaves. Microwave ablation (MWA) uses electromagnetic waves at frequencies of at least 900 mHz. Localized heat caused by water molecules moving within tissues results in tissue destruction. Tissues with high water content, such as breast tumors, are heated and damaged more rapidly compared with tissues with lower water content, such as normal breast tissue with surrounding fat, which may remain unharmed. To perform MWA, the breast must be compressed between two plates. The electric-field probe is inserted into the central portion of the tumor under ultrasound or CT guidance. A fiber-optic temperature probe is placed in the tumor to guide and adjust the temperature. Skin temperature probes are applied to the skin to monitor the temperature to avoid skin burns. A cooling system can be used to provide air cooling, decreasing the risk of thermal injury to the skin.

The first pilot study of MWA was performed by Gardner et al. to assess the feasibility and safety of this technique. MWA was performed in 10 breast cancer patients with a mean tumor size of 4.3 cm (range, 1.0–8.0 cm). A reduction in tumor size was seen in 60% (6 of 10) of the patients. Dooley et al. performed a small trial that randomized patients to breast-conserving surgery followed by MWA versus breast-conserving surgery alone. This study found that patients with early breast cancer treated with breast-conserving surgery and MWA had 0% (0 of 34) positive tumor margins compared with 9.8% (4 of 41) for those with breast-conserving surgery only. More recently, Zhou et al. showed that complete tumor ablation using contrasted enhanced ultrasound was seen in 90% (37 of 41) of patients treated with MWA.

CRYOABLATION

Cryoablation is the only ablative technique using cold instead of heat to create tissue necrosis. It is accomplished percutaneously guided by ultrasound, MRI, or CT. Cryoablation involves two phases: freezing and thawing. Liquid nitrogen is inserted into the probe and results in a local freezing reaction; thereafter, a second gas (i.e., helium) is released through the probe to arrest the freezing process, allowing thawing to occur (Fig. 2A). Tumor cells are destroyed through direct intracellular and indirect vasculature injury. Intracellular ice formation results in shearing and irreversible rupture of cell membranes. Extracellular formation occurs, creating a hypertonic environment. Water flows out of the cells resulting from osmosis, causing cellular dehydration and damage. When thawing occurs, water flows back into the cell, increasing intracellular volume and lysis occurs. Freezing and thawing is repeated. After at least two freeze-thaw cycles, an ice ball is created, which can be visualized with imaging. The tumor-ice ball remains in situ and is reabsorbed by the body (Fig. 2B).

Several studies have investigated the efficacy of cryotherapy in the treatment of fibroadenomas. The prospective Fibroadenoma Cryoablation Treatment Registry included 444 patients with fibroadenomas treated with cryotherapy. Two freeze-thaw cycles were used with a temperature of −160°C for the treatment of lesions with a median size of 1.8 cm. A reduction in size of 51% was seen after a follow-up of 6 months. Furthermore, palpability of the fibroadenomas reduced from 75% at pretreatment to 46% after 6 months and 35% after 12 months of follow-up. Recently, the role of cryoablation in the treatment for malignant breast tumors has been evaluated. The systematic review of Lanza et al. showed complete tumor ablation in 73% of included patients after a mean follow-up of 8 months. Cosmetic satisfaction was reached in 99% of the patients. In 2016, the American College of Surgeons Oncology Group undertook Z1072, a phase II trial exploring the effectiveness of cryoablation in the treatment of breast cancers, and published their results. Patients with a malignant tumor size less than 2 cm with less than 5% intraductal component were included. There was a complete tumor ablation in 76% (66/87) of patients. If multifocal tumors were excluded, the success rate increased up to 92% (80/87). The Freezing Instead of Resection of Small Breast Tumors trial is currently recruiting women with early-stage invasive breast cancer to investigate whether cryoablation can achieve complete tumor ablation and adequate local control without surgical excision.

Criteria for cryoablation include tumor size smaller than 2 cm, location at least 1 cm from the skin surface, and lack of an extensive in situ component (<25% of carcinoma in situ). Advantages of cryoablation are patients' comfort and treatment of larger lesions with sparing of normal breast tissue. Disadvantages are potential risk of thermal injury to the skin, losing staging information (e.g., tumor size and margin status), and timing of the sentinel lymph node biopsy.

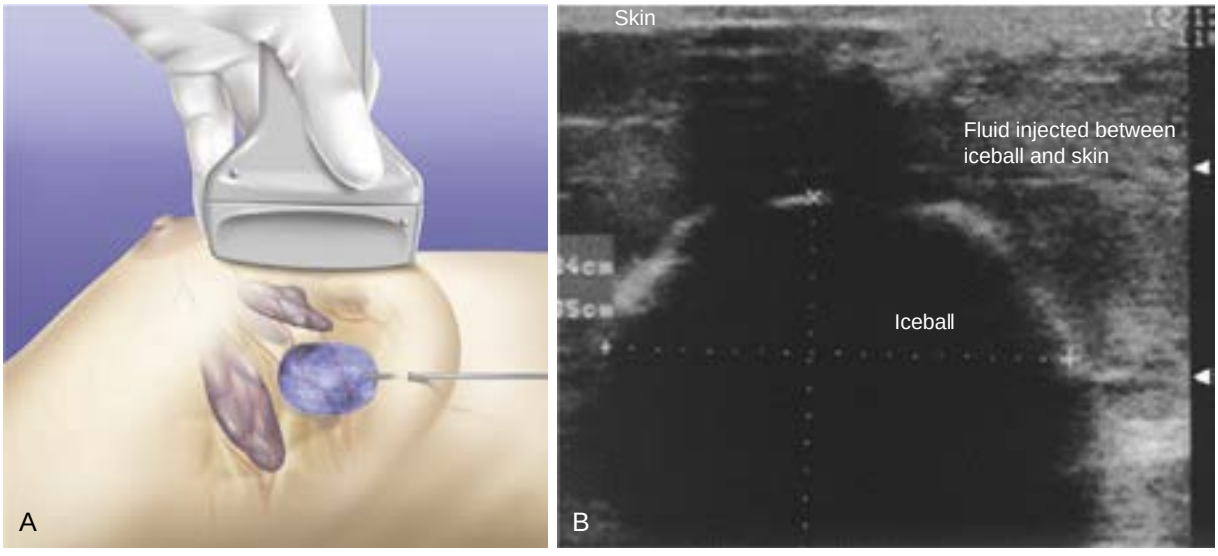


FIG. 2 **(A)** Ultrasonography is used to monitor the developing cryogenic zone created by the cryoprobe. **(B)** Ultrasound image of hypoechoic ice ball and protective saline injection. (***A*** *from Kaufman C, Littrup P, Freman-Gibb L, et al. Office-based cryoablation of breast fibroadenomas: 12 month follow-up.* J Am Coll Surg. 2004;198:914–923; ***B*** *from Kaufman C, Bachman B, Littrup P, et al. Office-based ultrasound-guided cryoablation of breast fibroadenomas.* Am J Surg. *2002;184:394–400.)*

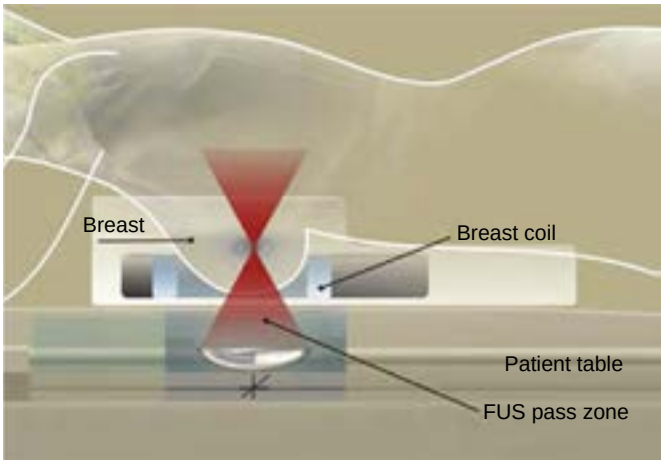


FIG. 3 MRI-guided high-intensity focused ultrasound (FUS) therapy for a breast cancer patient in prone position. *(From Zhou Y. Noninvasive treatment of breast cancer using high-intensity focused ultrasound.* J Med Imaging & Health Inform. *2013;3:141–156.)*

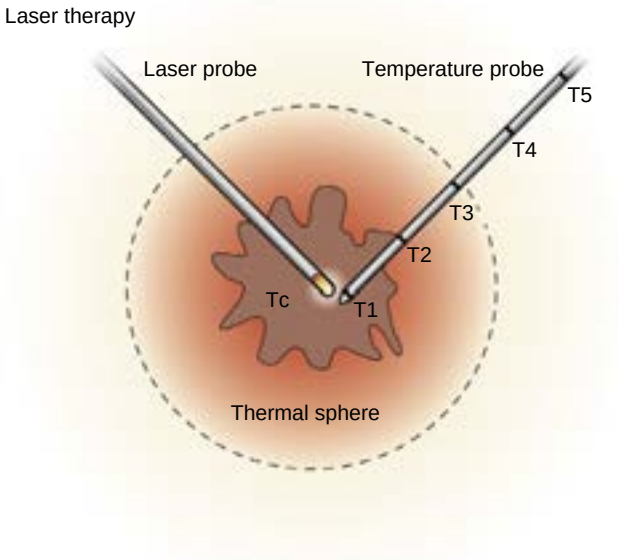


FIG. 4 Laser and temperature probes in and adjacent to a breast cancer. *(From Dowlatshahi K, Francescatti DS, Bloom KJ. Laser therapy for small breast cancers.* Am J Surg. *2002;184:359–363.)*

HIGH-INTENSITY FOCUSED ULTRASOUND

HIFU is a complete noninvasive thermal-based ablative technique using transcutaneously focused ultrasonic waves (Fig. 3). The focused ultrasound waves cause rapid (1–2 seconds) temperature elevation within the targeted tissue up to 50°C to 95°C. This causes melting of the lipid bilayer of the cellular membrane and protein denaturation, leading to tissue necrosis, whereas tissues outside the targeted area are spared. Because of the small ($0.8 \times 0.2 \times 0.2$ mm^3) ablation zone, multiple overlapping sonifications are required to treat an entire lesion. Complete ablation can take up to 2 to 3 hours.

Peek et al. published a systematic review, including 9 HIFU studies and 167 breast cancer patients. No residual tumor after HIFU treatment was found in 46.2% (55 of 119) of the patients. The most reported complication was pain (40.1%), followed by edema (16.8%), skin burn (4.2%), and pectoralis major injury (3.6%). Symptomatic palpable fibroadenoma patients were included in a separate HIFU-fibroadenoma trial. Twenty of the included patients were treated with HIFU, whereas the other 20 underwent an ultrasound after 6 months (control group). Primary outcome was reduction in treatment time; secondary outcomes were reduction in volume on ultrasound after 12 months and the complication rate. Treatment time was reduced with 29.4% in circumferential ablation compared with whole lesion ablation. Reduction in volume was reported in 43.2% of the patients after 12 months of follow-up.

HIFU is a completely noninvasive ablative technique. Cosmetic outcome is very good because there is no scarring at skin entry site. Disadvantages are patient discomfort, general or spinal anesthesia, and prolonged treatment times.

INTERSTITIAL LASER

Laser interstitial thermotherapy (LITT) is a hyperthermic ablative technique. Laser fibers are percutaneously inserted into the tumor, whereas a second probe is placed to measure the temperature (Fig. 4). A refraction of laser light is produced at the tumor, producing heat and causing coagulation necrosis and protein denaturation, resulting in irreversible tissue destruction. The level of necrosis depends on the temperature and ablation time. Three types of lasers are available: carbon-dioxide, argon, and neodymium-doped yttrium aluminum garnet laser. The two latter lasers have the benefit of being able to treat larger volumes. Only a few studies have evaluated LITT followed by surgical excision. Dowlatshahi et al. performed a study in 54 breast cancer patients and showed complete tumor ablation of 70% in tumors with a mean diameter of 12 mm (range, 5–23 mm). Incomplete tumor ablation was attributed to technical issues, such as inadequate laser energy, patient motion, malfunctioning thermal probes and fluid pump, and suboptimal target visualization. LITT under MRI guidance showed a complete ablation in 76% of the tumors ranging from 1.8 to 4.0 cm. LITT performed in patients with fibroadenomas (n = 24) showed a reduction of 60% after 6 months of follow-up.

The advantage of LITT is that it has a photocoagulation effect that reduces bleeding during the procedure. Disadvantage is that tumors larger than 2 cm or tumor with extensive in situ component are not good candidates for laser therapy.

IRREVERSIBLE ELECTROPORATION

Irreversible electroporation is a nonthermal ablative technique that uses electrical fields to create permeable cell membranes and cause cell death. Electroporation occurs when short electric pulses (1000 V/cm field) are passed across the cell membranes, resulting in membrane permeabilization. This ablative technique only affects the cell membrane while sparing the extracellular matrix and other tissues (i.e., blood vessels). Permeabilization can be reversible or irreversible, depending on the number, duration, and time between electric pulses and electric field strength. Irreversible electroporation has been investigated for a short period and much of in vivo research involves animal models only. Disadvantages of this technique are the potential occurrence of cardiac arrhythmias and general anesthesia because the electric pulses cause muscle contractions.

SUMMARY

A meta-analysis showed that complete ablation rates of ablative techniques such as RFA, MWA, cryoablation, LITT, and HIFU vary and have been highest in patients undergoing RFA (87.1%), followed by MWA (83.2%), cryoablation (74.1%), laser ablation (52.2%), and HIFU (47.6%). Other important but less investigated outcomes are recurrence and complication rates. No local recurrences have been reported using MWA (0%). Other ablative techniques have small but measurable recurrence rates: cryoablation (1.4%), HIFU (2.9%), RFA

(3.1%), and laser ablation (10.7%). Complications occur in about 10% of patients. Most commonly seen were skin burns followed by pectoralis major muscle damage. MWA is associated with the highest posttreatment complication rate of 14.6%, followed by cryoablation (10.9%), RFA (10.5%), HIFU (6.5%), and laser ablation (6.3%). Excellent cosmetic outcome has been reported in patients treated with ablation. Cryoablation results in greater than 90% excellent cosmesis compared with 85.3% in patients treated with RFA and 59.3% in patients treated with HIFU. HIFU may ultimately have the best cosmetic outcome because this technique is completely noninvasive.

All ablative techniques show several benefits compared with breast-conserving surgery; however, larger multicenter randomized controlled trials are required to confirm the efficacy of ablation compared with resection. Current problems are the lack of a predictive tool for assessing complete tumor ablation, determination of accurate tumor size, information on the timing of axillary surgery, and adequate patient and tumor inclusion criteria. Ablative treatment techniques may be most suitable for patients with contraindications to operation or patients with a preference to avoid breast-conserving therapy. Furthermore, ablative treatment can only be used for small (T1) breast tumors (≤2 cm) 1 cm from the skin and pectoralis major, less than 25% carcinoma in situ component, and, most important, tumors must be visible using imaging modalities. In addition, many techniques result in a palpable mass, disturbing to patient and surgeon. Intraoperative RFA after surgical excision may become a means to avoid radiation after breast-conserving surgery for patients with favorable tumors.

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Lymphatic Mapping and Sentinel Lymphadenectomy

Roi Weiser, MD, and V. Suzanne Klimberg, MD, PhD, MSHCT

INTRODUCTION

Axillary surgery has been a standard part of breast cancer treatment since the introduction of Halsted's radical mastectomy at the end of the nineteenth century. With it, for the first time, long-term survival and regional control were achieved for a growing number of patients. But this dramatic improvement in outcome came with the cost of significant side effects, including a lymphedema rate of up to 80%. Henceforth, reducing the rate of lymphedema, "the most dreaded complication of breast cancer treatment," has been a central motivation in the evolution of axillary surgery. In addition, screening has promoted early detection of breast cancer, producing a growing number of clinically node-negative patients, 60% of whom would have a pathologic negative axilla after excision. For them, axillary lymph node dissection (ALND) would come with the cost of side effects with no therapeutic advantage.

The concept of a reproducible pattern of tumor lymphatic spread has been utilized since the 1960s in parathyroid, penile, and testicular cancer as well as in melanoma surgery. With the use of blue dye and radiotracers for lymphatic mapping, the first node(s) in the chain of lymph nodes draining the anatomical location of a tumor, termed *sentinel lymph nodes* (SLNs), can be identified and examined. Negative findings would confirm with high probability the lack of further lymphatic and metastatic spread, obviating the need for further surgery or staging. These principles of sentinel lymph node biopsy (SLNB) have been utilized in breast cancer since the 1990s to identify clinically node-negative patients who have a high probability of a pathologically negative axilla and in whom a completion axillary lymph node dissection (cALND) would be redundant.

INDICATIONS FOR SENTINEL LYMPH NODE BIOPSY

Currently, SLNB is the standard of care for operable invasive breast cancer patients with T1–T2 (up to 5-cm) tumors with or without multicentricity and a clinically negative axilla (Box 1). This is true whether breast conservation or mastectomy are planned. Though data are more limited in these situations, many clinicians would extend these indications to tumors larger than 5 cm (T3), patients undergoing neoadjuvant chemotherapy with prechemotherapy-negative nodes, recurrent disease in the breast, and after ipsilateral breast surgery or radiation. However, ALND should be performed for T4 tumors and for patients with recurrent axillary disease or those who have had prior axillary surgery. Axillary surgery including SLNB can be forgone in a subset of ≥70-year-old patients with hormone receptor–positive, HER2-negative, clinically T1–T2, N0 disease who will be treated with endocrine therapy. Several studies have shown that omitting SLNB does not affect disease-free survival (DFS) or overall

BOX 1 Indications for SLNB in Operable Breast Cancer*

Indications for SLNB

T1/T2 (up to 5 cm) tumors, possibly T3 (>5 cm)
Clinically node-negative disease (cN0)
Female or male
Unicentric or multicentric disease
DCIS (Tis) when mastectomy is planned or when high-risk features exist
Possible after prior breast surgery
Possible after NACT
Limited clinically node-positive disease (cN1) after NACT with favorable response†

SLNB Not Recommended

T4 tumors and inflammatory breast cancer
Clinically positive axillary involvement without neoadjuvant chemotherapy or recurrent axillary disease
More than "limited" nodal involvement (several level I/II nodes, involvement beyond level I/II)
Prior axillary surgery
Pregnancy before week 30

*Based on ASCO Clinical Practice Guidelines. Lyman GH, Somerfield MR, Bosserman LD, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2017;35:561–564.

†The meaning of a limited positive axilla is controversial. We recommend performing targeted axillary dissection (see text) when no more than one suspicious lymph node is present before NACT or when all suspicious lymph nodes were marked and are excised during targeted axillary dissection for evaluation.

ASCO, American Society of Clinical Oncology; *DCIS,* ductal carcinoma in-situ; *NACT,* neoadjuvant chemotherapy; *SLNB,* Sentinel lymph node biopsy.

survival (OS) in these patients while improving quality of life, and it is endorsed by the Society of Surgical Oncology (SSO) through the Choosing Wisely campaign (https://www.choosingwisely.org/societies/society-of-surgical-oncology/).

Another subgroup of patients that qualifies for SLNB includes patients with ductal carcinoma in-situ (DCIS) with high-risk features who have higher chances of invasive cancer on final pathology, including high-grade tumors, estrogen or progesterone receptor (ER/PR)-negative tumors, large-size tumors, and mass-forming tumors. SLNB would also be indicated for DCIS patients who are planned for a mastectomy, which would make a second-stage SLNB less feasible.

Patients with clinically node-negative disease with one to two positive SLNs who undergo breast conservation with postoperative whole-breast irradiation and systemic therapy can also be treated with SLNB alone, under ACOSOG Z0011 criteria. Similarly, patients with micrometastasis to their SLNs and those with one to three positive SLNs who will undergo nodal irradiation can have SLNB alone with equivalent oncologic results to patients who undergo cALND.

A more controversial group that could be considered eligible for SLNB and is being studied in an ongoing clinical trial are patients with palpable axillary involvement at presentation, who undergo neoadjuvant chemotherapy (NACT) with a complete clinical response. These patients would be considered eligible by most for a targeted axillary dissection (TAD) in which an SLNB is performed in addition to retrieval of the clipped positive node. This technique demonstrates very low false-negative (FN) rates. However, data as to the effect of TAD on local and systemic recurrence are not yet available, and an ongoing Alliance study is investigating whether it is safe to leave resistant disease behind.

Patients with T4 disease that ulcerates the skin or invades the chest wall, patients with inflammatory breast cancer, and those with more than limited axillary involvement would not be eligible for SLNB. Pregnancy is also a relative contraindication for SLNB. The use of blue dye has the risk of causing anaphylactic shock (<1% with isosulfan blue) and is discouraged during pregnancy because of fetal concerns. The injection of technetium (^{99m}Tc)-labeled sulfur colloid has been shown to cause minimal irradiation exposure to the fetus, though data are limited as to its safety and efficacy. Its use is not contraindicated during pregnancy, though it is discouraged by some before 30 weeks of gestation.

SLNB: TECHNIQUE

Before surgery begins, a tracer is injected into the breast that will allow identification of the SLN or nodes. The two main tracers used are a radiotracer and blue dye (isosulfan blue or methylene blue) or a combination of the two techniques. Several other tracers are available or under investigation, including indocyanine green (ICG) fluorescence mapping as well as magnetic tracers. The most commonly used radiotracer is ^{99m}Tc-labeled sulfur colloid. A 0.25 to 2.5 mCi dose in 0.4 to 4 mL is injected into the breast. During surgery, the radiotracer is identified in the SLN using an intraoperative gamma counter, such as the Neoprobe GDS. If injected a day before surgery, 2.5 mCi are injected. The blue dye most often used is 3 to 5 mL of isosulfan blue. Its main adverse reaction is a 2% rate of hypersensitivity with a <1% rate of anaphylaxis; therefore patients should be screened for makeup and tattoo allergies, which are associated with a higher risk of allergic reaction. When encountered, a hypersensitivity reaction should be treated with systemic antihistamines (e.g., Benadryl) and systemic steroids (e.g., hydrocortisone). Patent Blue V, an additional blue dye, can be similarly used. It also belongs to the triarylmethane dye group and has a strong cross-reactivity with isosulfan blue. Dilute methylene blue is a third option, but we personally prefer not to use it because of the danger of dermal necrosis on dermal injection as well as considerable drug interactions. It is also contraindicated in pregnancy and in patients with G6PD deficiency. Of note, with the use of blue dye, transient skin and urine discoloration are expected, and occasional skin tattooing occurs, especially when the dye is injected intradermally.

Several practical aspects of tracer injection have been raised since the advent of SLNB.

1. Preoperative versus intraoperative injection: The preoperative injection of a radiotracer at the nuclear medicine clinic is a painful procedure, with obvious scheduling and financial burden. Studies comparing preoperative to intraoperative injection have shown intraoperative injection to be as accurate, with a 96% to 99.8% detection rate. Costs have been shown to be over 7-fold lower. We therefore practice and advocate the use of intraoperative injection after induction of anesthesia and before prepping the patient. Nevertheless, preoperative injection with subsequent lymphoscintigraphy or SPECT-CT, which is useful in identifying the lymphatic basin in truncal melanoma, can prove advantageous in breast cancer patients who have had prior surgery that could have resulted in alternative lymphatic drainage.
2. Peritumoral, subareolar, dermal, or intratumoral injection: During the first multicenter trial involving 443 patients who underwent SLNB followed by ALND in which injection was done peritumorally, all 13 FN SLN cases were in patients with tumors located in the upper outer quadrant of the breast. Hypothesizing that the proximity of the injection site to the axilla caused the radiotracer's zone of diffusion to interfere with SLN identification led us to investigate the subareolar region as an alternative injection site. A multicenter prospective study including 3961 patients showed a 99.3% identification rate with subareolar injections versus 91.1% with peritumoral injections, with similar FN rates. Moreover, this technique can be safely used in cases with multifocal and multicentric tumors. Radiotracer can also be injected

dermally. In any case, one should avoid injection into the tumor or seroma/hematoma cavity.

3. Some surgeons massage the breast after injection of a tracer, especially after the injection of blue dye. Not much data exist on this subject. One study comparing 50 cases of 3 to 5 minutes of massage to no massage after peritumoral injection of Patent Blue V showed no difference in detection rate between techniques with higher rates of false negativity without massage. We do not practice routine massage after tracer injection.
4. Single or dual tracer: There have been conflicting reports as to the advantage of dual tracing, (blue dye in addition to a radioisotope) over the use of a radiotracer alone. Blue dye alone has been shown by some to have a comparable and by some an almost 10% poorer detection rate compared with a radiotracer alone. Some studies show no advantage to the addition of blue dye to a radioisotope, while others show an improvement in detection of 1.5% and an improvement in FN rate of <1%. Nevertheless, cases in which blue dye detected an SLN that the radiotracer did not are mostly cases in which no radioactivity was detected in the axilla by lymphoscintigraphy or during surgery. More experience with any technique results in a higher rate of detection and a lower FN rate. We recommend using only a radiotracer, injected intraoperatively to the subareolar region, and having the blue dye ready on the field. We consider dual tracing after neoadjuvant therapy, prior breast or axillary surgery, and in patients with a high BMI. If before the incision, no radioactivity is detected in the axilla, blue dye is injected to the breast for dual tracing. If we have a reading, we use the blue dye for axillary reverse mapping (ARM).
5. ARM is used during SLNB to identify the lymphatics draining the arm that cross the axilla. We inject 5 mL of isosulfan blue to subcutaneous tissue of the upper inner volar aspect of the ipsilateral arm and radioactivity and/or the tracer of your choice in the breast. This results in split mapping, differentiating lymph nodes draining the breast that should be excised as SNLs from those draining the extremity that should be preserved to prevent lymphedema. Blue arm lymphatics are detected in 29% to 47% of SLNB-only cases, with blue lymphatics juxtaposing the SLN in almost 8% of cases. This procedure allows to preserve these lymphatics and to identify transected arm lymphatics so they can be reapproximated or re-anastomosed. This procedure has been shown to reduce the rate of lymphedema in SLNB to less than 1%.
6. Dosages in bilateral cases: In bilateral cases, a double dose of Technetium can be injected. The dose of blue dye is divided between breasts.
7. Eventually the choice of technique, including location of injection, timing of injection, use of lymphoscintigraphy, and single or dual tracer use should be governed by the experience and level of comfort of the individual surgeon and the specifics of each case.

In the operating room, after induction of anesthesia, the patient is positioned supine with both arms extended to 90 degrees. We usually do not prep and drape the arm into the field for SLNB. Before incision, the gamma probe is used to evaluate the maximal reading around the injection site in the breast and then in the axilla, and the gamma probe is adjusted to separate the zone of diffusion from the SLN. Most often the point of maximal reading in the axilla is at the lateral aspect of the pectoralis muscle at an imaginary line connecting it with the inferior part of the hairline. The maximal point is marked. Then blue dye is injected in the volar aspect of the arm or the breast. At this time, we use the gamma probe to evaluate the internal mammary (IM) area, the neck, and the lower chest to detect possible extramammary SLNs. If one is detected, intraoperative ultrasonography is used for visualization, and if a node is visualized, it is excised (discussed later). If not visualized by ultrasound, it may be considered a false-positive read.

Before incision, for better visualization of the axilla and to reduce the interference of radioactivity from the injection site, the breast can be secured inferomedially with a 1050 adhesive drape. An incision is made close to the point of maximal reading, preferably inferior to the axillary hairline and in a natural skin crease. Care should be taken not to extend the incision anterior to the pectoralis muscle as it does not provide more exposure and gives a poor cosmetic result on the breast. One can create an incision that is parallel and posterior to the pectoralis muscle as well. In mastectomy cases, the SLNB can be performed through the mastectomy incision. Then dissection is carried down toward the two layers of axillary fascia, which are identified lateral to the pectoralis muscle and incised, "entering" the axillary space. As this point, axillary fat is apparent, and the gamma probe is used to redirect dissection in a line-of-sight technique, much like using a flashlight in a dark room to find a finite point. Retractors are placed in the direction of maximal reading and dissection continues. If blue dye has been used in the breast, attention is given to any blue lymphatics to be followed toward blue SLNs. Dissection should also follow these lymphatics proximally to ensure that a proximal SLN is not left behind. Some practice sharp dissection of axillary content, following or clipping apparent lymphatics in their way. Blunt dissection is best, separating the fat while preserving lymphatics, until the SLN is identified. It is held by Babcock forceps, while the surrounding fat is dissected free from the hilum, exposing the afferent and efferent lymphatics (Fig. 1). These are approximated by a clamp, and they are ligated together using an absorbable suture after removing the node, enabling lymphatic recanalization. The gamma probe is used at this point to detect further nodes, taking node(s) with 10% or more of the maximal SLN count. It is important to note that any suspicious node, by palpation or visualization, regardless of read or coloration, is regarded as an SLN and excised; replaced lymph nodes are less likely to take up the localizing agent. Ultrasound is a useful tool to evaluate indeterminate nodes, especially in obese patients as fatty nodes are often palpable. After no reads over 10% are identified, the cavity is irrigated, and hemostasis achieved. The axillary fascia is approximated using absorbable sutures, and the incision is closed.

In the majority of cases, ARM should be performed with SLNB. The technique of surgery does not change, apart from preserving the blue lymphatics and lymph nodes encountered during surgery. An exception to their preservation would be when an SLN by gamma probe reading is also a blue ARM node. In these cases, the blue SLN, called by some a *crossover node,* is resected as an SLN, and the lymphatics are reapproximated using an absorbable suture.



FIG. 1 Sentinel lymph node biopsy. The sentinel lymph node, identified with the gamma probe, can be seen held by Babcock forceps. Fat and a blue axillary reverse mapping node have been bluntly dissected away from it and preserved. Next, a clamp will be applied under the node to approximate its afferent and efferent lymphatics. It will be excised, and the lymphatics will be ligated.

The evaluation and excision of IM SLNs is not routinely recommended. Surgeons are usually unfamiliar with this procedure and fear its potential risks of bleeding and pneumothorax. Studies have shown IM nodes function as SLNs in 7% to 8% of cases, with higher rates of positive nodes, up to 40%, when axillary nodes have been found to be positive. It is rare for the IM node to contain metastasis without a positive axillary node. Nevertheless, in such cases of positive IM SLNs, staging as well as adjuvant treatment can be affected. We usually excise the IM SLN when it is detected by the gamma probe and visualized by intraoperative US. In these cases, an incision is made over the IM node, exposing the pectoralis. Then the muscle is bluntly divided along its fibers until the intercostal space is exposed. The intercostal muscles are further split along their fibers, exposing the intercostal space with the IM node, which is bluntly excised. Care should be taken not to use electrocautery, to avoid a pneumothorax.

TROUBLESHOOTING SLNB

We suggest a few troubleshooting algorithms for common problems one might encounter during SLNB. One of the more common problems, especially when starting to perform SLNBs, is not finding the SLN during surgery (Fig. 2). Preparing for such cases by identifying high-risk patients before surgery can be helpful, and one could consider preoperative lymphatic imaging or using dual tracing during surgery to better identify SLN location. During surgery either before or after incision, several techniques can be helpful in locating the SLN, including dermal instead of subcutaneous injection of the radiotracer and promoting tracer advancement by injection of sterile saline into the injection site and massaging the breast. One can also look for suspicious axillary nodes using ultrasound or palpation, and for extraaxillary SLNs using the gamma probe. If the SLN still cannot be found, the surgeon should assess the likelihood of lymphatic involvement and importance of axillary staging and decide whether performing axillary sampling or ALND is necessary at this point.

A second problem that can be encountered is continuous high reads in the axilla without being able to discern a specific SLN (Fig. 3). It is important that nuclear medicine use an unfiltered radioactive colloid as the filtered colloid advances easily beyond the SLN. Technical tips would be to make sure the probe is not pointed in the direction of the breast, fixing the breast away from the axilla and removing a superior-lateral tumor when peritumoral injections are performed. Dual tracing and removing palpable nodes or nodes that are suspicious on ultrasound examination can also help. Eventually, if five nodes have been removed, no further surgery is needed.

RESULTS OF SLNB AND LYMPHATIC MAPPING

SLNB in Node-Negative Patients

The largest multicenter randomized controlled trial (RCT), randomizing clinically node-negative patients to SLNB or ALND, was the NSABP B-32. It randomized 5611 women, 3989 of whom eventually

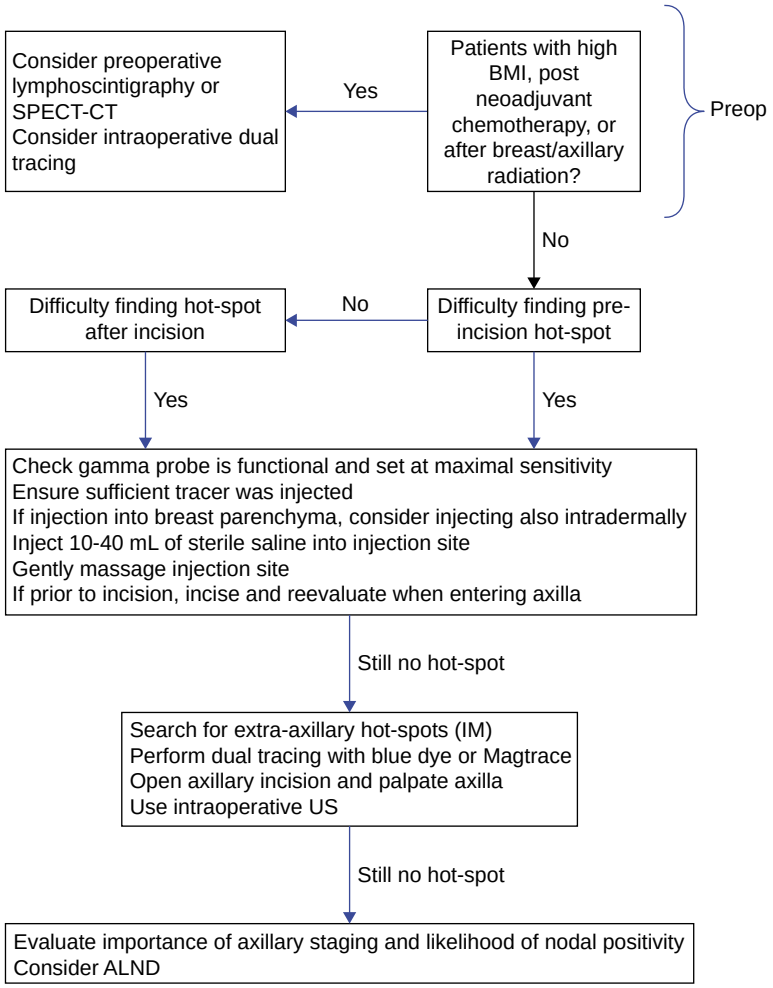


FIG. 2 Troubleshooting no uptake of radioactive tracer in axilla.

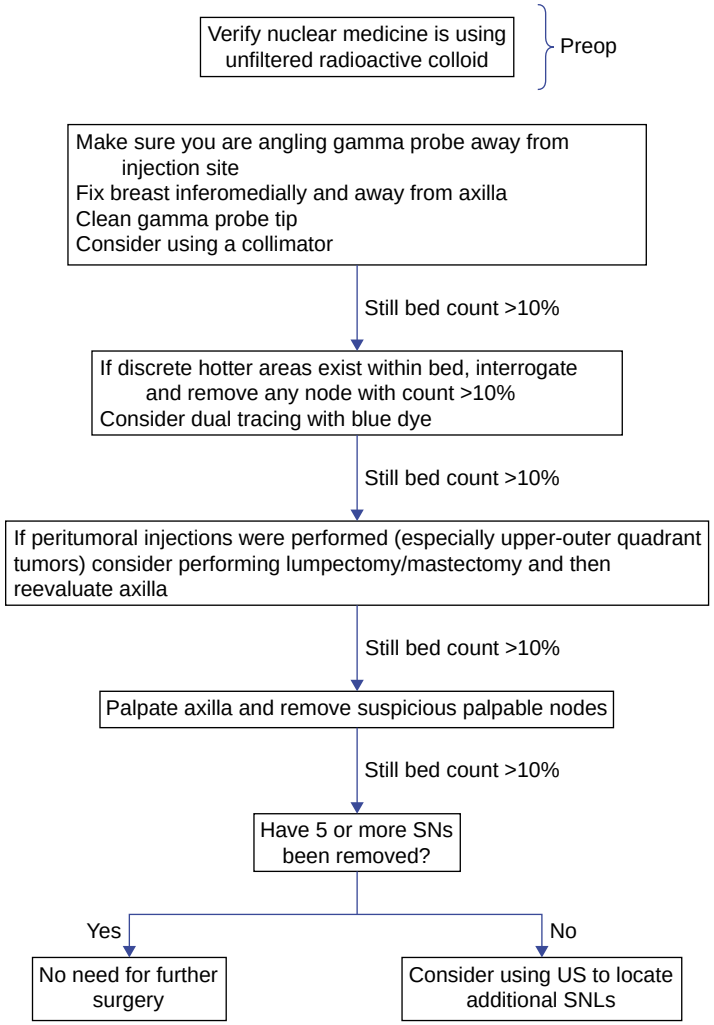


FIG. 3 Troubleshooting inability to achieve a <10% background or inability to identify sentinel lymph node resulting from high reads.

had negative SLNs, to cALND or no further surgery. The trial had a success rate of over 97% in identifying the SLN during SLNB, and it was able to show a reduction in lymphedema rate from 14% with ALND to 8% with SLNB. With these findings, it validated earlier findings from retrospective studies and smaller prospective studies that showed improvement in lymphedema rates from as high as 77% with ALND to single-digit rates with SLNB. Table 1 summarizes the findings of these studies.

Apart from the success in reducing the side effects of axillary surgery, SLNB was shown to be a good predictor of axillary status. The first multicenter trial, published in the *New England Journal of Medicine* in 1998, demonstrated an FN rate of 11.4%. Following studies have shown lower FN rates, with rates as low as 2.5%. Consequently, a detection rate of >95% and an FN rate of <5% are considered a good clinical result, and FN rates have been shown to decrease with surgeon experience. Regardless of the FN rate, this trial and others have demonstrated low or no axillary recurrence and similar survival rates with SLNB compared to ALND in these patients.

An additional advantage with SLNB is that a higher rate of positive lymph nodes is detected when SLNB is employed compared with ALND, with a 4-fold increase in the rate of detected micrometastasis or isolated tumor cells. This is made possible by the pathologists having to examine a limited amount of lymph nodes, allowing for 2-mm serial sectioning of each node, sometimes using immunohistochemistry as an adjunct. This proves the potential of SLNB, not only to safely reduce the rate of lymphedema, but to also more accurately stage the axilla.

Positive SLNs in Clinically Node-Negative Patients

After establishing the ability of SLNB to safely identify patients with both a clinically negative axilla and pathologically negative SLNs, additional subgroups of patients in whom SLNB alone would be sufficient were sought. Upon cALND of patients with a clinically negative axilla and a positive SLN, 40% to 50% of patients have no additional lymphatic involvement, exposing them to unnecessary morbidity. Several RCTs have been performed to identify such patients who could safely avoid cALND. They are summarized in Table 2.

The largest and practice-changing multicenter ACOSOG Z0011 randomized women with one or two positive SLNs and a T1 or T2 tumor, with cN0 disease, who underwent breast-conserving surgery and postoperative whole breast irradiation (WBR) and adjuvant

TABLE 1 Studies of ALND versus SLNB with Reduction in Lymphedema Rates and False-Negative Rates

Study	SLNB (n)	ALND (n)	Lymphedema SLNB (%)	Lymphedema ALND (%)	False-Negative Rate (%)
Schrenk, 2000	35	35	0	17	–
Haid, 2002	57	140	4	27	2.6
Swenson, 2002	169	78	4	14	–
Blanchard, 2003	683	91	6	34	2.8
Schijven, 2003	180	213	1	7	–
Veronesi, 2003	259	257	7	75	4.6
Ronka, 2005	43	40	13	77	–
Leidenius, 2005	92	47	5	28	–
Mansel, 2006 (ALMANAC)	515	516	5	13	5.9
McLaughlin, 2008	600	336	5	16	–
Krag, 2010 (NSABP B-32)	2008	1975	8	14	9.8

TABLE 2 Randomized Controlled Trials Investigating No cALND in Patients with Positive SLNs

Study	Year	*n*	Positive Node Criteria	Local Recurrence (%)		Regional Recurrence (%)		Overall Survival (%)		Non–sentinel-Positive Nodes
				ALND	SLNB	ALND	SLNB	ALND	SLNB	
ACOSOG Z0011	2011	891	pN1 ≤2 nodes	5.6	3.8	0.5	1.5	83.6	86.3	27%
AATRM	2013	233	pN1mi, pN0(i+)	0.9*	0	0	1.7†	99	100‡	13%
IBCSG 23-01	2014	934	PN1mi, pN0(i+)	3.0	2.8	0.6	1.9	87.5	90.4§	13%
AMAROS	2013	1425	pN1			0.43	1.19	90.5	88.8	33%
OTOASAR	2017	474	pN1 ≤2 nodes			2.0	1.7	77.9	84.8¶	38.5%

*Cutaneous axillary recurrence.
†Locoregional recurrence.
‡Disease-free survival (DFS) 99% of ALND and 97.5% of SLNB.
§DFS 74.8% of ALND and 78.4% of SLNB.
¶DFS 72.1% of ALND and 77.4% of SLNB + radiation.
ALND, Axillary lymph node dissection; *SLNB,* sentinel lymph node biopsy.

TABLE 3 Early Trials for SLNB in Node-Positive Patients after NACT

Trial	Eligibility	Biopsy Required	Number of Patients	SLN Identification Rate	False-Negative Rate (No IHC)
ACOSOG Z1071	cN1-2 (endpoints reported for cN1)	Yes	cN1 = 651 cN2 = 38	92.7%	12.6%
SENTINA (Arm C)	cN1-2	No	592	87.8%	14.2%
SN FNAC	cN1-2	Yes	153	87.6%	13.3%

IHC, Immunohistochemistry.

systemic therapy, to cALND (n = 445) or observation (n = 446). The study had low accrual, with only 47% of the targeted 1900 patients entered, as well as a low event rate. Nevertheless, it was able to show no significant difference between the groups in respect to 10-year locoregional recurrence (6.2% vs. 5.3%), DFS (78.2% vs. 80.2%) and OS (83.6 vs. 86.3%). In 27% of patients in the cALND group, additional positive lymph nodes were found, with nodal recurrence in either group being <1%. Many suggestions have been made to explain this result, the most probable one being the effect of tangential radiation. It is important to note that though survival and recurrence rates were comparable between the ALND and SLNB groups in the Z0011 trial, so were the 1-year objective lymphedema rates, with 11% of ALND patients versus 6% of SLNB patients having measurable lymphedema ($P = 0.0786$).

Other studies have examined replacing cALND with axillary radiation. These include the OTOSAR and AMAROS trials. Both included patients with T1 or T2 tumors (the OTOSAR limited tumor size to 3 cm). They both showed equivalent axillary recurrences of less than 2%, as well as equivalent DFS and OS. Most patients had one positive SLN (75%–78%), and in both trials over 80% of patients underwent breast conservation. Another subset of patients examined by RCTs was patients with micrometastases (≤2 mm) in their SLNs. The IBCSG 23-01 and AATRM trials examined patients with T1 or T2 tumors (the AATRM limited tumor size to 3.5 cm). Neither trial found a difference in DFS between patients who underwent cALND versus those who were only observed. Locoregional recurrence was also very low and similar between the groups, an interesting finding regarding that additional positive nodes upon cALND were found in 13% of patients in both trials. The IBCSG 23-01 reported an improvement in lymphedema rates in the radiation group of 4% versus 13% in the cALND group.

Population-based studies have shown that clinicians are extending Z0011 criteria as well as the criteria of the other RCTs and implementing them on patients who would not have qualified for the trials, including patients with T3 tumors, those with three or more positive SLNs or clinically positive nodes, and those who undergo mastectomy or do not undergo postoperative WBR or adjuvant systemic therapy. As far as mastectomy patients, who are not represented in the Z0011 and are poorly represented in the other RCTs, the omission of cALND is based mostly on extrapolation, rather than on direct data.

SLNB and TAD in Node-Positive Patients after Neoadjuvant Treatment

With the advent of modern chemotherapy regimens and HER2-directed therapy, the rate of pathologic complete response (pCR) of primary tumors and lymphatic metastases has increased considerably. This improvement in response prompted investigations into the use of SLNB to identify such patients who might not profit from an upfront ALND. Several such studies were conducted, including the ACOSOG Z1071, SENTINA, and SN FNAC, all of which showed SLNB to have FN rates well over 10% (Table 3). Of note, unlike SLNB in untreated patients, in these cases the residual positive lymph nodes left behind would contain potentially resistant disease, conceptually different than SLNB on untreated patients.

Upon subgroup analysis of the ACOSOG Z1071, when looking at patients in whom the clipped node was retrieved, the FN rate

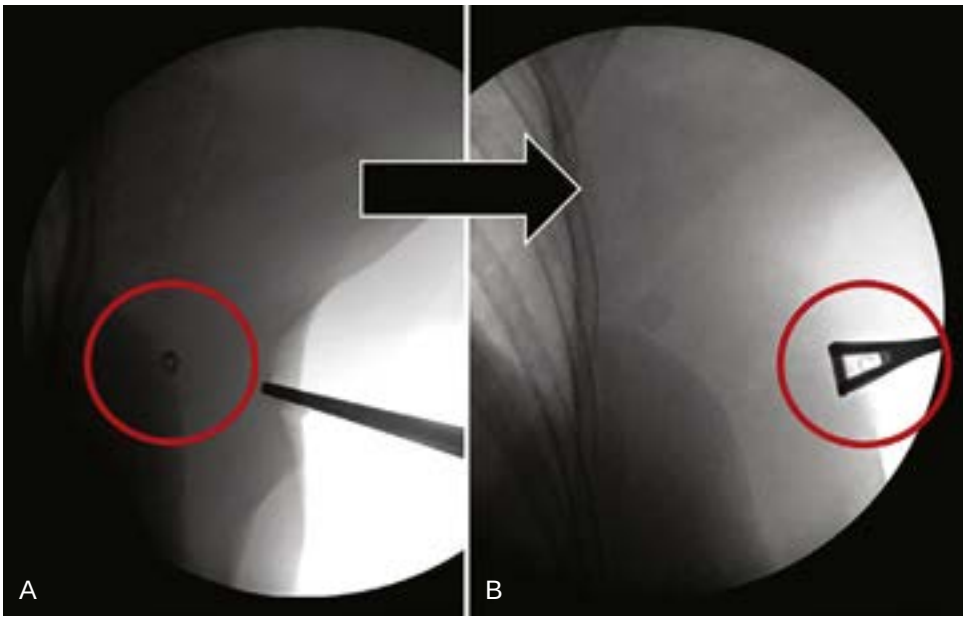


FIG. 4 Fluoroscopy-guided localization of a ring clip *(red circles)* in a left axillary lymph node. **(A)** Clamp pointing to and localizing the clip. **(B)** Babcock forceps grasping the clipped node.

decreased to 6.8%. Other trials have shown the proven positive clipped node to be other than the SLN in 24% of patients, with its retrieval lowering FN rates to 4.5%. This led to further investigation and the definition of TAD, as retrieval of the clipped node as well as performing SLNB, which showed an FN rate as low as 2.3% in the report by Caudle et al. Localizing the clipped node can be easily done using intraoperative fluoroscopy guidance (fluoroscopic intraoperative neoplasia and node detection [FIND]; Fig. 4). Other techniques for clip node localization that necessitate additional painful, time-consuming and costly procedures have been suggested, such as needle localizations, tattooing of the node, and placement of localization devices.

The Alliance 11202 is investigating the omission of cALND in patients with positive nodes upon TAD after NACT, randomizing them to cALND versus axillary radiation. Both arms will receive radiation to the infraclavicular, supraclavicular and IM nodes. The NSABP B-51 examines similar patients with negative nodes upon TAD after NACT. It omits cALND in all of these patients and randomizes them to adjuvant nodal basin radiation or no further treatment.

Axillary Reverse Mapping

Much like SLNB, mapping the lymphatic drainage of the breast, ARM maps the lymphatic drainage of the ipsilateral arm (Fig. 5). Both techniques have the same motivation of reducing lymphedema rate and other side effects of ALND, and both employ lymphatic mapping for more accurate and selective axillary surgery. In a large prospective phase II trial, ARM has been shown to reduce the lymphedema rate after ALND to 6.5% and after SLNB to 0.8%. Split mapping, with radioactivity in the breast and blue dye in the arm, allows for differentiation between lymphatics draining the breast and those draining the arm. It further allows to prioritize oncologic principles by excising crossover nodes—blue arm nodes that are found to be "hot." In addition, mapping the ARM lymphatics allows for identification and ligation of afferent and efferent transected lymphatics or for selective utilization of the LYMPHA (LYmphatic Microsurgical Preventive Healing Approach) procedure, both proven to reduce lymphedema rates.

There have been over 20 retrospective and prospective single-arm studies of the ARM procedure and 5 RCTs (Table 4). Patient

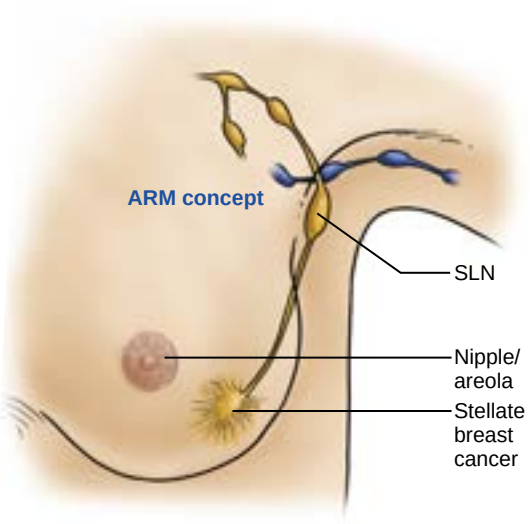


FIG. 5 Axillary reverse mapping (ARM) using split mapping, with lymphatics draining the breast and the sentinel lymph node in gold and the lymphatics and lymph nodes draining the arm in blue.

populations vary among trials in their burden of axillary disease (from N0 to N3 disease) and the surgery they undergo. The vast majority of trials show a significant reduction in lymphedema rate when utilizing ARM across all patient populations and surgical techniques. Moreover, the rate of positive ARM nodes is as low as 2.3%, with lower numbers seen with more limited axillary involvement. Furthermore, considering that many of the ARM trials did not follow protocol and did not inject a radiotracer into the breast, which would have allowed the identification of some of these nodes as crossover nodes to be resected, the actual rate of positive ARM nodes might be even lower. In addition, axillary recurrence rates with ARM are well below 1.5%, comparable with standard ALND. Currently recruiting is the Alliance A221702, a multicenter RCT examining the use of ARM.

TABLE 4 ARM Randomized Controlled Trials

Trial	*n*	Patients and Surgery	Blue Identified	Lymphedema		ARM Nodes with Metastasis	ARM Technique
				ALND	ALND + ARM		
Yue, 2015	265	Planned MRM, >50% N2/3	93.5%	33.1%	5.9%	8.5% (N1 3.6%, N2 8.2%, N3 20.8%)	Blue dye + radiotracer in arm. All ARM nodes underwent FNA
Faisal, 2019	48	Planned ALND	83.3%	16.7%	4.2%	0%	Only blue in the arm
Yuan, 2019	1656	ALND d/t cN+/+SLN with mastecto-my/>2+SLNB with BCS	83.2%	15.3%	3.3%	6.8%	Blue dye + ICG in arm + blue dye directly into blue node
Abdelhamid, 2020	98	cN0 with +SLN and delayed cALND	93.8%	20.9%	6.5%	2.3%	Only blue in the arm*
Beek, 2020 multicentric	94	cN0 with +SLN and delayed cALND	79.2%	Objective 32.3% Subjective 26.7%	Objective 23.5% Subjective 6.1%	2.9%	Only blue in the arm

*In ALND-only group, had blue dye injected with removal of the blue ALND nodes.
ALND, Axillary lymph node dissection; *ARM,* axillary reverse mapping; *BCS*, breast conserving surgery; *cALND,* completion axillary lymph node dissection; *FNA,* fine-needle aspiration; *ICG,* indocyanine green; *MRM,* modified radical mastectomy; *SLN,* sentinel lymph node; *SLNB*, sentinel lymph node biopsy.

CONCLUSION

Lymphatic mapping has made it possible to perform more accurate axillary surgery and reduce the side effects of ALND, mainly that of lymphedema. SLNB as well as the ARM procedure allow for patient-directed surgery, with more limited surgery for a growing number of indications and the identification and protection of the arm lymphatics. In addition, ligation of resected lymphatics and localization of clipped positive nodes after neoadjuvant treatment can help further reduce the rate of lymphedema. Clinical trials are ongoing to further advance axillary surgery and should be advocated among patients.

SUGGESTED READINGS

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SURGICAL MANAGEMENT OF THE AXILLA

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OVERVIEW

There are two main indications for axillary surgery in breast cancer patients today: for staging/risk stratification and for therapeutic management of regional disease. Before the 1990s, both of these goals were achieved with a standard, anatomically defined axillary lymph node dissection (ALND). Although ALND provides excellent and durable axillary control (with axillary recurrences typically occurring in no more than 2%–3% of patients), this is achieved at the expense of significant morbidity including risks of ipsilateral upper extremity lymphedema (occurring in 10%–40% of patients); sensory loss in the upper, inner arm skin and posterior shoulder; and occasional patients will also suffer from shoulder dysfunction/stiffness. Advances in systemic therapy and radiation therapy (both of which can effectively control microscopic/clinically occult nodal

metastases) have resulted in deescalation of axillary surgery. The majority of breast cancer patients treated in affluent, westernized populations can avoid the morbidity of ALND by undergoing targeted, minimally invasive surgery with lymphatic mapping/sentinel lymph node biopsy (SLNB), and selected low-risk patients can avoid axillary surgery completely. Patients who have access to surgery but reside in medically underresourced low- and middle-income countries continue to require ALND as a basic component of their management.

Ongoing clinical research in multidisciplinary management of breast cancer is expected to further reduce the number of patients requiring therapeutic ALND. Improvements in screening results in earlier detection of breast cancer, when the axillary burden of disease is likely to be low-volume or nonexistent. For patients who present with more advanced, documented node-positive disease, advances in systemic therapy and the neoadjuvant treatment sequence can successfully downstage many, thereby averting the need for ALND. Patients who continue to routinely require an anatomically based ALND include those with high-risk disease such as inflammatory breast cancer; cases of residual nodal disease despite delivery of optimal neoadjuvant systemic therapy; and patients with clinically evident axillary nodal disease undergoing primary surgery because of a medical contraindication to receiving appropriate neoadjuvant systemic therapy.

SURGICAL APPROACHES TO AXILLARY LYMPH NODE DISSECTION

Review of the axillary anatomy and familiarity with operative techniques for the ALND remain important in contemporary surgical oncology. Although fewer patients need to undergo this procedure, those who do require a therapeutic ALND typically have more challenging anatomy because of prior SLNB dissection or because of regional nodal disease that has either recurred or resisted systemic therapy.

The axilla is divided into three levels defined by the pectoralis minor muscle—level I is inferolateral to the pectoralis minor, level II is posterior to the pectoralis minor, and level III is superomedial to the pectoralis minor. A conventional ALND for breast cancer patients involves resection of levels I and II with sparing of level III. The rationale for this anatomic focus is based on the facts that although an axillary "sampling" procedure limited to resection of level I alone will reduce frequency of lymphedema, it risks missing "skip metastases" that have gone directly to level II or III in 20% to 25% of patients, thereby understaging and/or undertreating up to one-fourth of patients. In contrast, skip metastases that have gone directly to level III, leaving levels I and II negative, occur in only 2% to 3% of cases. The lymphatic mapping/SLNB experience has validated these concepts as the SLN will usually reside in the level I fat pad, but in approximately 25% of patients it is located in level II, and only 2% of patients will have SLN(s) limited to level III of the axilla.

A standard level I and II ALND will typically yield 10 to 30 lymph nodes in this fat pad. Patients who have received neoadjuvant chemotherapy often have relatively fewer nodes because chemotherapy response and fibrosis can obliterate the architecture of discrete nodes. Mastectomy patients undergoing elliptical incisions that include resection of the nipple-areolar skin can usually undergo ALND through the mastectomy wound. A separate transverse axillary incision is usually necessary in patients undergoing lumpectomy surgery or in nipple-sparing mastectomy cases in which an inframammary fold incision or limited periareolar incision precludes adequate exposure of the axillary contents. After the skin incision is deepened through the subcutaneous fat, key elements of exposure include entry into the clavipectoral fascia; medial retraction of the pectoralis major/minor muscles; and lateral retraction of the latissimus dorsi muscle. The axillary fat pad between these anatomic boundaries must be cleared while ensuring protection of the axillary vein, the thoracodorsal bundle (which includes the nerve innervating the latissimus dorsi), the long thoracic nerve (which innervates the serratus anterior), and the medial/lateral pectoralis bundles (which innervate the pectoralis major and minor muscles). Damage to the thoracodorsal nerve can cause arm/shoulder weakness and dysfunction; long thoracic nerve disruption causes winging of the scapula; and transection of the pectoralis nerves can result in denervation atrophy of the pectoralis musculature. Approaches to the intercostobrachial nerves vary by surgeon; these cutaneous nerves traverse through the axillary specimen and are often routinely sacrificed in the ALND, thereby resulting in a loss of sensation in the skin of the underarm and posterior shoulder. Some surgeons attempt to preserve these nerves by dissecting them out of the axillary fat pad, but this approach is potentially associated with traumatic damage and postoperative neuropathic pain. A surgical drain is left at the end of the procedure and removed postoperatively when drainage is minimal.

There are two basic operative techniques that can be followed to optimize the safe performance of an anatomically defined ALND. One approach involves attention to the superior aspect of the dissection first, with entry into the clavipectoral fascia, exposure of the axillary vein, and dissection proceeding in an inferior direction as the axillary contents are retracted in a downward direction. With this approach, prompt identification of the lateral thoracic vein can be a helpful anatomic cue as this vein can be readily seen branching directly and perpendicularly from the axillary vein, running vertically through the axilla. The proximal aspect of the thoracodorsal bundle can typically be found running just posterior (and usually lateral) to the lateral thoracic vein. Once the thoracodorsal bundle has been identified, every effort must be made to preserve it intact, whereas the lateral thoracic vein can be ligated and sacrificed. As the axillary tissue is retracted inferiorly, the serratus anterior muscle at the medial aspect of the surgical field is inspected to identify the long thoracic nerve running vertically, and adjacent to this muscle. Although the pectoralis minor and major muscles are retracted medially, their neurovascular bundles will be found curving around the lateral muscle edges. Venous branches of these bundles running into the axillary tissue can be sacrificed, but the main nerves should be preserved intact.

An alternative operative approach to ALND involves proceeding through the dissection with an initial lateral and inferior dissection. This approach can be particularly useful in patients who have had prior SLN dissection, and it can be useful to identify the critical neurovascular structures before dissecting around the fat necrosis and fibrotic mass of the SLN surgical site. This operative approach involves identification of the vertically running edge of the inferior aspect of the latissimus dorsi muscle as a first step in the procedure. The axillary fat is reflected medially from this muscle, exposing the vertically running thoracodorsal bundle lying posterior to the axillary fat and anterior to the belly of the latissimus dorsi muscle. One or two venous branches can generally be found running horizontally from the thoracodorsal vein to the serratus anterior muscle, and the long thoracic nerve can invariably be identified running vertically into this intersection. The axillary fat pad is then retracted further superiorly, while maintaining consistent exposure of the long thoracic and thoracodorsal neurovascular bundles. The thoracodorsal vein will be traced proximally to its entry into the axillary vein, and at this point the dissection can be completed from the anterior/superior approach as described earlier.

SENTINEL LYMPH NODE BIOPSY: HISTORY

Lymphatic mapping and SLNB was introduced in the mid-1990s and rapidly replaced the ALND as an accurate technique for identifying node-negative breast cancer patients. The goal is to replicate the pathway taken by metastatic cells from the primary tumor in the breast, through the intramammary lymphatics, and then to identify the first few nodes likely to have accepted these metastases. Blue

dyes and/or technetium-labeled sulfur colloid injections into the breast are effective mapping agents that are readily taken up by the lymphatic system of the breast. Visual inspection identifies the blue-stained nodes, and use of an intraoperative gamma detector identifies the radioactive nodes. Early studies of lymphatic mapping involved peritumoral injections of these mapping agents, with concomitant ALND so the accuracy of the procedure could be defined. Within a few years, the completion ALND was abandoned in favor of a stand-alone SLNB for patients found to have no evidence of sentinel node metastases. Lymphatic mapping and SLNB became even more easily incorporated into clinical practice following the demonstration that the mapping agents can be injected into the subareolar tissue with comparable and accurate identification of the SLNs; this approach allows for standardization of the mapping regardless of tumor location or tumor size and supports lymphatic mapping/SLNB in patients with multifocal/multicentric disease. The embryologic development of the breast lymphatic system results in the majority of intramammary lymphatics draining through the subareolar plexus before reaching the axillary nodes. A single set of SLNs can therefore be expected to represent the primary lymphatic drainage of the entire breast.

Data generated from multiple large prospective studies conducted internationally have confirmed the safety of relying on a negative SLN to stage the axilla without increasing rates of axillary recurrence. In 2003, the Milan trial demonstrated that SLNB is a safe and accurate staging method for the axilla, with reduced morbidity in comparison with ALND. Of 516 patients with tumors clinically T2 or smaller, the accuracy of SLNB was 96.9% with a sensitivity of 91.2% and specificity of 100%. Patients in the SLNB cohort demonstrated less arm pain and improved arm mobility. The NSABP B32 trial was another phase 3 clinical trial, and it demonstrated equivalent overall survival, disease-free survival, and regional control between stage-stratified patients randomized to either SLNB with ALND or SLNB with ALND only if the SLNB was positive. The American College of Surgeons Oncology Group (ACOSOG) Z0010 study was not randomized, but it also validated the use of SLNB in early-stage breast cancer. This was a prospective study of 5119 patients with T1/T2 tumors and SLNs that were negative by H&E staining, all of whom underwent lumpectomy followed by adjuvant whole-breast radiotherapy. At median follow-up of 8.4 years, axillary recurrences occurred in fewer than 0.5% of patients. Risk factors for locoregional recurrence included tumor characteristics such as hormone-receptor negativity and lymphovascular invasion. The ALMANAC trial compared quality-of-life outcomes between patients with clinically node-negative disease undergoing SLNB versus those undergoing ALND. This trial showed that the relative risk of lymphedema and sensory loss was significantly lower in SLNB group as well as drain use, length of stay, and time to resumption of normal activities.

AVOIDING AXILLARY LYMPH NODE DISSECTION IN PATIENTS WITH SENTINEL NODE METASTASES

Decisions regarding systemic therapy in breast cancer are increasingly made on the basis of primary tumor features including tumor phenotype (based on estrogen receptor, progesterone receptor, and HER2/neu evaluation). Nodal status continues to play a role in risk stratification, but documentation of the full extent of nodal metastatic burden based on a complete ALND has become less relevant compared with the simple distinction of absence versus presence of axillary nodal disease. This premise was the basis for the ACOSOG Z0011 trial, which randomized lumpectomy patients with T1/T2 breast cancer and metastases in one or two SLNs to undergo completion ALND or no ALND, but all patients received adjuvant breast radiation and systemic therapy. This trial randomized 891 patients between May 1999 and December 2004, at which point the study was closed early because of sluggish accrual rates and anticipated failure to meet the targeted 1900 accrual goal. These patients nonetheless provided practice-changing data, confirming the safety of omitting completion ALND in selected patients with SLN metastases. The 10-year cumulative incidence of nodal recurrence was 0.5% for the ALND patients compared with 1.5% for the patients undergoing SLNB alone ($P = 0.28$). Overall survival rates have also been reported as equivalent for the two randomization arms.

Of note, however, the Z0011 trial pertains to patients with early-stage breast cancer undergoing lumpectomy and breast radiation. Questions persist regarding the optimal axillary management of mastectomy patients found to have SLN metastatic disease, as the precise findings from a completion ALND in these patients will influence decisions regarding postmastectomy radiation (PMRT). PMRT is considered standard of care management in cases of at lease four metastatic axillary nodes and it is considered in patients with one to three metastatic nodes. Decisions regarding PMRT carry heightened significance in the setting of patients undergoing immediate reconstruction as the radiation can potentially compromise the reconstruction appearance and infectious risks.

The IBCSG 23-01 and AATRM trials also randomized patients with SLN metastases to ALND versus no ALND, but both studies were limited to patients with micrometastatic axillary disease (metastatic focus no larger than 2 mm). Unlike the Z0011 trial, both of these studies included mastectomy patients, but more than 90% of the participants from each trial underwent breast-conserving surgery. The 5-year median follow-up from both studies demonstrated excellent outcomes, with fewer than 1% rates of axillary recurrence and 98% overall survival rates. These data have therefore served to establish the safety of omitting the completion ALND (as well as PMRT) among mastectomy patients found to have SLN micrometastatic disease.

The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial provided high-level, phase 3 evidence that regional radiation can replace ALND in women with SLN macrometastatic disease, regardless of whether mastectomy or lumpectomy has been performed. This study randomized 1425 women with SLN metastases to undergo ALND versus axillary radiation. At more than 6 years median follow-up, there were no statistically significant differences in axillary recurrences (0.54% vs. 1.03%, respectively) or overall survival (93.3% vs. 92.5%, respectively). The 5-year rates of symptomatic lymphedema, however, were twice as high in the ALND patients (23%) compared with the axillary radiation patients (11%). This study therefore documented lower morbidity from axillary radiation compared with ALND with comparable regional control of disease. These results, however, must be interpreted in the context of other studies and issues. First, the ACOSOG Z0011 study demonstrated that SLN biopsy alone (without axillary radiation) is adequate in breast-conserving surgery patients. Second, for mastectomy patients with SLN metastases, the decision to commit to axillary radiation/PMRT to avoid ALND requires acceptance of the possibility that completion ALND may have confirmed minimal-volume axillary disease, indicating that PMRT was not necessary. Multidisciplinary discussion of these mastectomy/reconstruction cases is especially important, with consideration of possible focused axillary radiation to avoid radiating the mastectomy flaps overlying the reconstruction. Table 1 summarizes the prospective randomized clinical trials involving management of breast cancer patients with SLN metastatic disease.

MANAGEMENT OF THE AXILLA IN PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY

Early studies of lymphatic mapping and SLNB following the delivery of neoadjuvant chemotherapy began appearing in the literature by 2000. They usually involved patients undergoing completion ALND (similar to the early years evaluating SLNB in the setting of primary surgery) so identification as well as false-negative rates could be reported. Although many surgeons wanted their patients to reap the

TABLE 1 Prospective Randomized Clinical Trials of Axillary Management in Breast Cancer Patients with Node-Positive Disease

Trial Concept	ALND vs. SLND Alone in BCS Patients with SLN Micrometastases or Macrometastases	ALND vs. SLND Alone in BCS or Mastectomy Patients with SLN Micrometastases		ALND vs. Axillary XRT in BCS or Mastectomy Patients with SLN Micrometastases or Macrometastases	Regional XRT vs. No Regional XRT in BCS Patients with High-Risk Breast Cancer
Trial title	**ACOSOG Z11**	**IBSCG**	**AATRM**	**AMAROS**	**MA.20**
Stage eligibility	T1/T2 tumors ≤2 metastatic SLNs	T1/T2 tumors SLN N1mic	T < 3.5 cm SLN N1mic	T < 3 cm SLN N1	Any T with N+ T2/N0
Breast surgery eligibility	BCS only	BCS or mastectomy	BCS or mastectomy	BCS or mastectomy	BCS only
Median follow-up	6.3 yr	5.0 yr	5 yr	6.1 yr	62 mo
Randomization arms and sample sizes	ALND n = 445 SLN alone n = 446	ALND n = 464 SLND n = 467	ALND n = 112 SLND n = 121	ALND n = 744 AxXRT n = 681	ALND n = 916 ALND + RNI n = 916

Outcomes		Axillary recurrence	5-yr OS		Axillary recurrence	5-yr OS		Axillary recurrence	5-yr DFS**		Axillary recurrence	5-year OS		Regional recurrence	5-yr OS
	ALND	0.5%	91.5%	ALND	0.2%	97.6%	ALND	1/112	>95%	ALND	0.54%	93.3%	ALND	21/916	90.7%
	SLND	0.9%	92.5%	SLND	0.9%	97.5%	SLND	2/121	>95%	AxXRT	1.03%	92.5%	ALND/ RNI	4/916	92.3%

ALND, Axillary lymph node dissection; *BCS,* breast cancer surgery; *DFS,* disease-free survival; *OS,* overall survival; *RNI,* regional nodal irradiation; *SLN,* sentinel lymph node; *SLND,* sentinel lymph node dissection; *XRT,* radiation therapy.

benefits of neoadjuvant chemotherapy with regard to primary tumor downstaging and improved lumpectomy eligibility, several concerns remained regarding whether neoadjuvant chemotherapy would cause fibrosis of the intramammary lymphatics and compromise accuracy of the lymphatic mapping technology. Several meta-analyses evaluating this question demonstrated SLN identification rates of at least 90%. National Comprehensive Cancer Network (NCCN) guidelines ultimately included the recommendation that for patients presenting with clinically node-negative disease and receiving neoadjuvant chemotherapy, SLN biopsy can be performed at the time of breast surgery, and no additional axillary surgery is necessary if the SLN dissection is negative.

Many neoadjuvant chemotherapy patients are found to be node positive at the time of diagnosis by axillary staging with ultrasound- and sono-guided needle biopsy. Axillary management for these patients continues to evolve but is trending toward further deescalation of axillary surgery if the post-neoadjuvant chemotherapy SLN surgery indicates downstaging of the axilla.

The ACOSOG 1071 study was designed to specifically address the question of whether a post-neoadjuvant chemotherapy SLN biopsy is accurate in documenting axillary downstaging for women presenting with needle biopsy–proven node-positive disease. All 687 patients underwent SLN biopsy with completion ALND, and a disappointing 12.6% false-negative rate was reported, which exceeded the predefined 10% rate that would have been deemed acceptable. The Z1071 study as well as two other comparable prospective studies (the SENTINA and Canadian SN FNAC protocols) all demonstrated that the SLN false-negative rates could be reduced by using dual-agent (blue dye and isotope) mapping and by ensuring that at least two SLNs are identified/resected. The most convincing strategy for ensuring that the axilla is accurately staged following neoadjuvant chemotherapy involves performing a "targeted" SLN biopsy. This approach requires that the originally biopsied metastatic node have a clip inserted so this biopsied/clipped node is localized and resected along with the lymphatic mapping/SLN biopsy procedure following the delivery of the neoadjuvant chemotherapy. Data from the University of Texas MD Anderson Cancer Center as well as subset analysis from the Z1071 study demonstrated that this approach brought the SLN biopsy false-negative rate down to 1.4% and 6.7%, respectively.

Lymphatic Mapping and SLNB in Special Situations

Several scenarios require special consideration with regard to lymphatic mapping and SLN biopsy. These are discussed in the following sections.

Pregnancy

Phantom model studies have demonstrated negligible isotope exposure to the fetus following isotope injection into the breast for lymphatic mapping, but the NCCN continues to recommend counseling pregnant patients regarding the paucity of data regarding SLN biopsy in this setting. Blue dye injections are contraindicated during pregnancy.

Ductal Carcinoma in Situ

Patients with ductal carcinoma in situ (DCIS) undergoing mastectomy surgery should be offered a concomitant SLN biopsy for staging purposes in the event that an invasive cancer is identified in the mastectomy specimen. Once the breast has been removed, the opportunity to reliably perform lymphatic mapping via breast injection has been lost. For DCIS patients who are undergoing lumpectomy but the preoperative biopsy is thought to have understaged the extent of disease (e.g., DCIS associated with a spiculated mass on imaging), a concomitant SLN biopsy may be offered to reduce the chance of requiring a second surgical procedure for staging purposes.

Reoperative Axillary Surgery

Several studies have demonstrated that lymphatic mapping and SLN biopsy can be attempted in patients who have undergone prior axillary surgery either via ALND or SLN biopsy. However, these patients are more likely to have aberrant lymphatic drainage, and their SLNs may be located in the contralateral axilla or in the internal mammary nodal basin. Risk of this aberrant lymphatic drainage is higher after ipsilateral ALND and after ipsilateral locoregional radiation.

Situations in Which Axillary Staging Can Be Omitted

Older Patients with T1/HR-Positive/HER2-Negative Breast Cancer

The highest age-based incidence of breast cancer is in patients older than 70 years of age. Overall survival in this population is reduced because of comorbidities that limit life expectancy. Axillary staging guides systemic therapy but may provide limited benefit to older, frail patients who are unable to tolerate chemotherapy to comorbidities. Elderly patients are also more likely to have hormone receptor–positive disease for which endocrine therapy may be the only indicated adjuvant systemic therapy. These differences in clinical presentation and tumor biology, in addition to the desire to limit surgical extent in patients with comorbidities, underscore the rationale for questioning the utility of axillary staging in elderly women. The Society of Surgical Oncology therefore recommends not performing routine SLN biopsy for women older than 70 years of age with clinically node-negative, hormone receptor–positive breast cancer as SLNB does not affect locoregional control or mortality in this population. These recommendations are based on the IBCSG 10-93 trial that showed no differences in disease-free survival or overall survival in breast cancer patients 60 years of age and older with early-stage, clinically node-negative and hormone receptor–positive disease that were randomized to undergo lumpectomy with versus without axillary clearance.

DCIS Patients Undergoing Breast-Conserving Surgery

DCIS patients undergoing lumpectomy do not require routine axillary staging surgery with SLN biopsy. However, they must have meticulous evaluation of their surgical specimen. If invasive disease is identified, they should be advised to return to the operating room for lymphatic mapping/SLN biopsy to inform adjuvant systemic therapy recommendations.

THE NEXT FRONTIER IN DEESCALATION OF AXILLARY MANAGEMENT: ONGOING TRIALS OF AXILLARY MANAGEMENT AFTER NEOADJUVANT THERAPY

Ongoing clinical trials are now attempting to further clarify optimal management of node-positive breast cancer patients receiving neoadjuvant chemotherapy.

The Alliance Trial A11202 is a phase 3 randomized clinical trial designed to determine whether radiation is adequate for locoregional control of disease in patients who have residual axillary node involvement following neoadjuvant chemotherapy. This trial enrolls patients presenting clinical T1/T3 N1 disease. If the axilla is clinically negative after neoadjuvant chemotherapy is delivered, then a staging SLNB is performed. Patients with residual metastatic disease in the sentinel node(s) afterward are randomized to ether ALND with regional nodal irradiation or axillary radiotherapy with regional nodal irradiation. Patient accrual began in February 2014 and is expected to complete in January 2024. Survival and recurrence outcomes will be reported.

Additionally, the NSABP B-51/RTOG 1304 phase 3 randomized clinical trial is designed to investigate whether regional radiation can be omitted in patients whose axillary metastatic disease has been downstaged by neoadjuvant chemotherapy. This trial is therefore frequently referred to as the "Sister Study" to the Alliance 11202 trial. This trial is expected to complete patient accrual by August 2028.

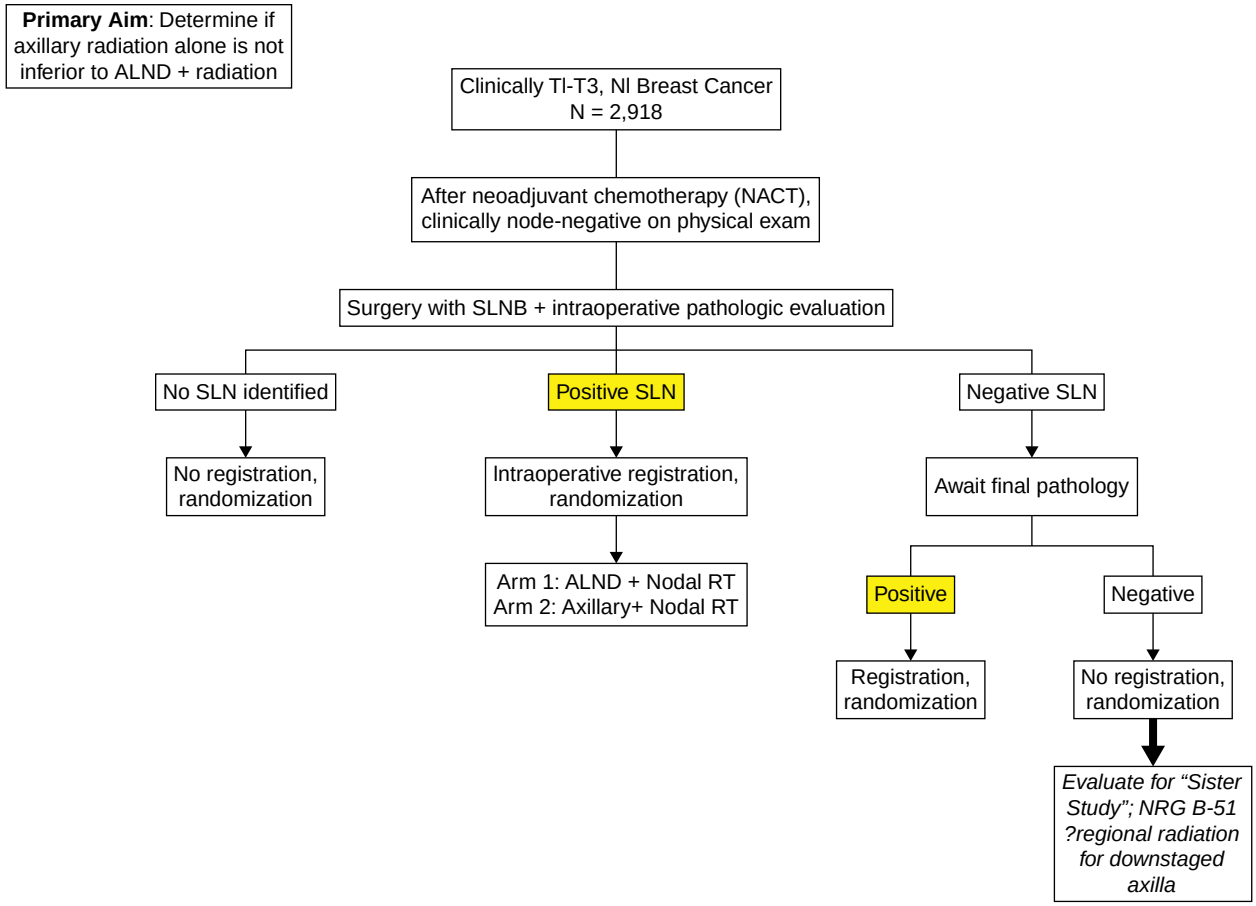


FIG. 1 Next frontier in deescalating axillary management: algorithm for the Alliance 11202 and NRG B-51 trials of patients presenting with node-positive breast cancer and receiving neoadjuvant chemotherapy.

Figure 1 demonstrates the management algorithm for these two studies exploring deescalation of axillary management in women presenting with node-positive disease following neoadjuvant chemotherapy.

SUMMARY

In summary, surgical management of the axilla remains a key element of adequate staging and subsequent guide to treatment decisions. Although management has changed significantly over the past few decades, the deescalation of axillary surgery to avoid ALND when possible has facilitated improved outcomes and reduced surgical morbidity of breast cancer surgery.

SUGGESTED READINGS

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Inflammatory Breast Cancer

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INTRODUCTION

Inflammatory breast cancer (IBC) is a rare presentation of locally advanced breast cancer. Although the incidence is 1% to 3%, IBC has a disproportionally dismal prognosis with a 5-year survival rate of 41% overall in the United States. IBC is a clinical diagnosis characterized by the hallmark presentation of skin edema, erythema, and peau d'orange. However, the diagnostic criteria includes erythema/edema that covers at least one-third of the breast and is acute in onset (within 6 months). It lacks unique histologic subtypes, molecular markers, and/or genetic signatures. Pathologically, IBC is defined by extensive tumor involvement and tumor emboli in dermal lymphatics, causing the quintessential skin findings. Radiologically, IBC lacks a central tumor in 50% of patients. At the time of diagnosis, 85% of patients have regional lymph node disease, and 30% have distant metastases. Even with the adjunct of chemotherapy and radiation, survival rates remain dismal.

WORKUP

For patients presenting with breast erythema (Figs. 1A and 2A), a standard history and physical examination should focus on duration of symptoms, exposures, and a bilateral breast and regional lymph node exam. Traditional risk factors for breast cancer, such



FIG. 1 A 59-year-old woman with inflammatory breast cancer, clinically T4d/N1/M0, ER+/PR+/HER2, who presented with erythema of the right breast **(A)**. Subsequent mammogram demonstrated skin thickening and developing global asymmetry with a prominent focal asymmetry at 9–10:00 measuring up to 6.1 × 6.1 cm **(B).** Follow-up ultrasound documented skin thickening measuring up to 0.8 cm and multiple hypoechoic irregular masses at 9:00 7 to 10 cm from the nipple, largest measuring 2.3 × 1.6 × 2.1 cm **(C).** Breast MRI demonstrated an irregular heterogeneously enhancing mass with microlobulated margins at 9–10:00 anterior depth measuring 2.7 × 2.1 × 2.2 cm; additional nonmass enhancement noted in the anterior upper outer quadrant measuring 9.2 × 9.4 cm; diffuse skin thickening; and multiple enlarged right axillary lymph nodes, largest measuring 5.7 × 3.6 × 3.0 cm **(D)**.

as family history, should also be assessed. The differential diagnosis for patients with erythema, edema, skin thickening, and/or peau d'orange (pitting or dimpling of skin) should include IBC as well as benign etiologies such as breast lymphedema, infectious sources causing mastitis, and inflammatory dermatologic conditions (e.g., dermatitis). The initial workup for patients with these clinical exam findings should include a bilateral diagnostic mammogram and targeted ultrasound of the affected breast. For patients with imaging findings suggestive of malignancy (BIRADS 4 or 5), core needle biopsy should be performed with or without a skin punch biopsy of the skin changes. Mammographic findings may include skin thickening, single or multiple breast masses, an asymmetry (see Fig. 1B–C), or it may be nonspecific (see Fig. 2B). For patients with negative, benign, or likely benign mammogram/ultrasound findings (BIRADS 1-3), additional workup may include a breast MRI and/or skin punch biopsy of the abnormal skin. Breast MRI is not routinely recommended if a diagnosis can be established by mammogram/ultrasound. However, breast MRI may also demonstrate skin thickening, single or multiple masses, nonmass enhancement, (see Fig. 1D) or it may be nonspecific.

When diagnosing IBC, it important to recognize that it is mainly a clinical diagnosis. Although a pathologic diagnosis of breast cancer is required, the remaining diagnostic criteria are clinical. The minimum criteria required for diagnosing IBC include: (1) rapid onset of breast erythema, edema, peau d'orange, and/or breast warmth with or without underlying mass; (2) duration of symptoms for no more than 6 months; and (3) erythema involving at least one-third of the breast. Once cancer has been confirmed histologically (typically by core needle biopsy of the breast), tumor grade and biomarkers (i.e., estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor 2 [HER2]) should also be assessed. If a skin punch biopsy is performed of the skin changes (typically at least two biopsies from separate areas), tumor emboli in the dermal lymphatics (Fig. 3), along with the previous skin changes, are confirmatory of an IBC diagnosis but not required. Of note, tumor emboli in dermal lymphatics without the aforementioned skin changes are not sufficient alone for a diagnosis of IBC.

Patients with IBC are categorized as having clinical T4d disease, and thus, they have a minimum of stage III breast cancer. However, many patients with IBC are metastatic at diagnosis, and thus, systemic staging is recommended for all patients with IBC. Staging should include a CT with contrast of the chest, abdomen, and pelvis, and a bone scan or FDG-PET/CT. For premenopausal women, fertility counseling is also recommended before initiation of

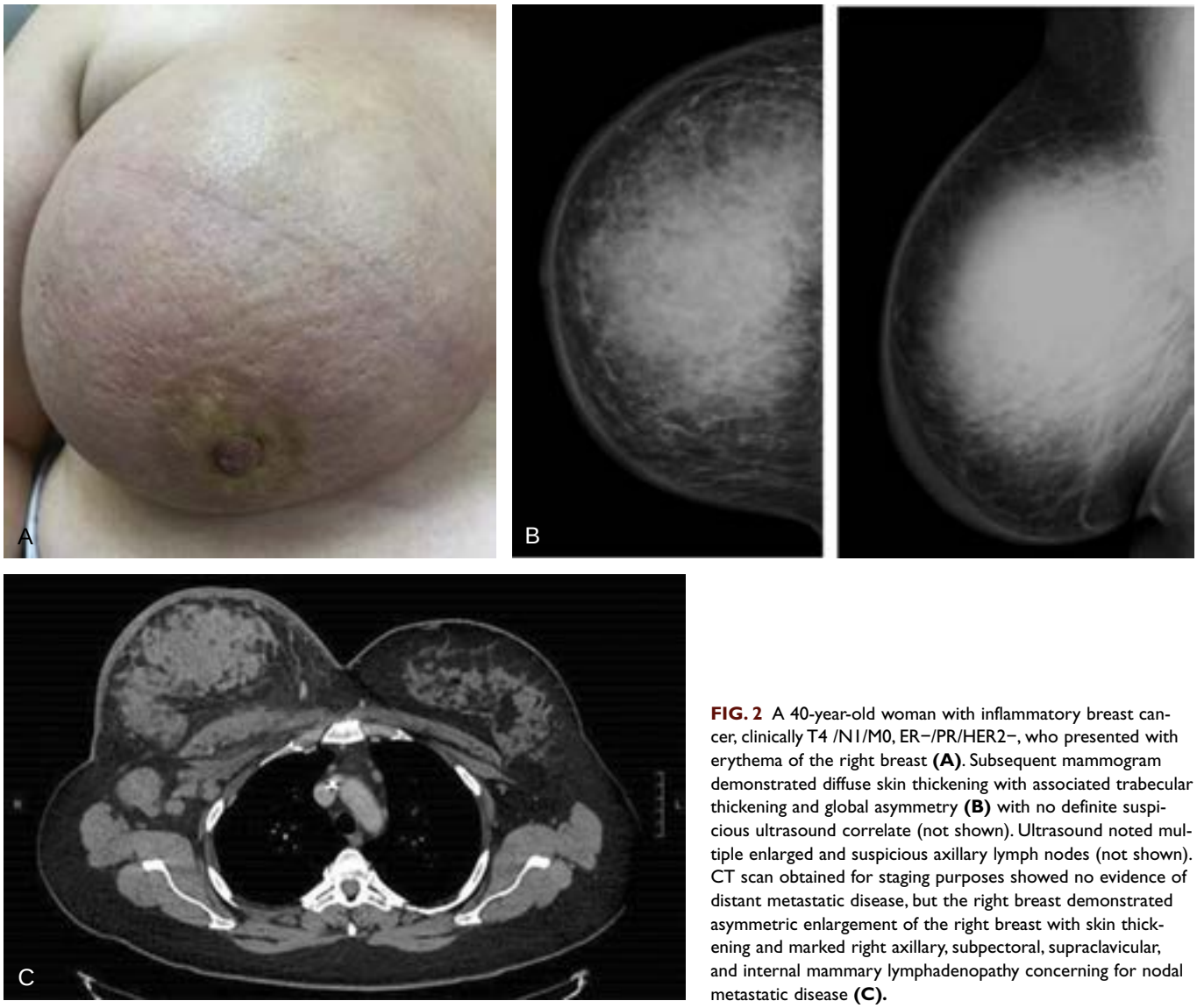


FIG. 2 A 40-year-old woman with inflammatory breast cancer, clinically T4 /N1/M0, ER−/PR/HER2−, who presented with erythema of the right breast **(A)**. Subsequent mammogram demonstrated diffuse skin thickening with associated trabecular thickening and global asymmetry **(B)** with no definite suspicious ultrasound correlate (not shown). Ultrasound noted multiple enlarged and suspicious axillary lymph nodes (not shown). CT scan obtained for staging purposes showed no evidence of distant metastatic disease, but the right breast demonstrated asymmetric enlargement of the right breast with skin thickening and marked right axillary, subpectoral, supraclavicular, and internal mammary lymphadenopathy concerning for nodal metastatic disease **(C).**

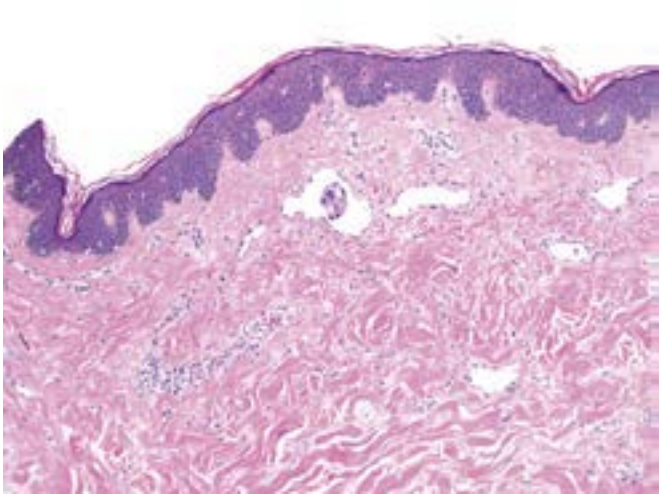


FIG. 3 Patient presented with breast erythema and edema, and skin punch biopsy of breast skin from this patient with inflammatory breast cancer demonstrated tumor emboli in the dermal lymphatics (original magnification, 40×; hematoxylin-eosin stain). *(Micrograph courtesy of Dr. Rex Bentley.)*

chemotherapy. Genetic testing should be considered for all appropriate patients at risk for hereditary breast cancer.

TREATMENT FOR NONMETASTATIC IBC

The standard treatment algorithm (Fig. 4) includes a combination of systemic therapy (chemotherapy, anti-HER2-targeted therapy, and/or endocrine therapy when appropriate) and local-regional management (surgery and radiation). Neoadjuvant chemotherapy with or without endocrine therapy improves overall survival. Patients who do not achieve meaningful clinical response or develop disease progression are typically offered additional systemic therapy and/or preoperative radiation therapy. The duration of the preoperative therapy varies based on the regimen given but may last up to 4 to 6 months. Following completion of neoadjuvant systemic therapy, repeat staging scans may be considered, particularly for those without a clear response. Those who have at least a partial response are offered a modified radical mastectomy (MRM) 4 weeks after completing systemic therapy. After allowing sufficient time to recover from surgery (typically 4–6 weeks), postmastectomy radiation is delivered to the chest wall and regional nodes (ipsilateral axilla, infraclavicular, supraclavicular, and internal mammary). A cumulative dose of 50 to 60 Gy is typically given over 4 to 6 weeks.

When selecting systemic therapies, neoadjuvant anthracycline and taxane-based chemotherapy regimens are preferred. For patients with HER2+ disease, HER2-targeted therapies are also recommended, including trastuzumab ± pertuzumab. Following surgery, the planned chemotherapy regimen should be completed (if not completed preoperatively), and endocrine therapy should be initiated, if ER+ and/or PR+. For patients with HER2+ disease, patients should complete up to 1 year of HER2-targeted therapy, which may be administered concurrently with radiation and endocrine therapy.

SURGICAL APPROACH TO IBC

Surgical management of the breast is intended to optimize local control in a clinical setting where there is extensive local disease in the form of lymphovascular invasion (cT4d). Standard surgical management of the breast in patients with IBC follows neoadjuvant chemotherapy and includes an obligatory MRM, which comprises a total mastectomy and ipsilateral level I/II axillary lymph node dissection (ALND; Box 1), regardless of response to neoadjuvant therapy. A level III dissection to the thoracic inlet may be pursued if there remains gross disease in the level II or level III space. Surgery is generally performed 4 weeks following completion of chemotherapy to allow immunologic recovery for optimal surgical healing. Although repeat systemic staging may be considered before surgery, it is not required. Repeat breast and/or axillary imaging is also not typically necessary.

Breast conserving surgery and sentinel lymph node biopsy are absolutely contraindicated for IBC due to the widespread local disease, most evident in the dermal lymphatics, which defines this unique disease entity. Although there are clinical scenarios in which a sentinel lymph node biopsy following neoadjuvant chemotherapy may adequately stage the axilla, IBC still requires a complete node dissection, even for those who were clinically node negative at the outset. Nipple-sparing and skin-sparing mastectomy, as well as immediate reconstruction, are relatively contraindicated as removal of the involved skin and radiation to the remaining skin are critical aspects of the treatment of the dermal involvement. Postsurgical complications or the added steps in the reconstruction process may cause a delay to radiation impacting local control and recurrence risk.

MODIFIED RADICAL MASTECTOMY

Total Mastectomy

Although most patients require general anesthesia for this procedure, a regional nerve block, such as a thoracic paravertebral nerve block, may be considered. Standard preoperative prophylactic antibiotics should be given, sequential compression devices should be placed on the bilateral lower extremities, and a urinary Foley catheter may be considered but is not required and should be removed at the end of the case, if placed. Once in the operating room, the patient is placed supine on the operating room table with ipsilateral arm extended and widely prepped. The planned skin incision includes a broad skin ellipse to encompass the nipple-areolar complex and as much of the remaining involved skin as possible. It is typically oriented in a transverse-oblique direction across the width of the breast to permit ease of axillary node dissection from within the mastectomy incision. Mastectomy flaps are raised in the avascular plane between breast parenchyma and subcutaneous fat, extending to the clavicle *superiorly*, the lateral border of the sternum *medially*, the rectus sheath/inframammary fold *inferiorly*, and to the anterior border of the latissimus muscle *laterally*. When dissecting in the superior-lateral aspect of the breast, care must be taken to include the axillary tail of Spence. Once all mastectomy planes have been carried down to the chest wall, attention is turned to the superior aspect of the breast, and the breast and underlying pectoralis fascia are excised from the pectoralis muscle. For the small bleeding vessels coming through the pectoralis muscle that are encountered during this aspect of the dissection, hemostasis may be achieved with electrocautery and/or clips. Medially, internal mammary perforators are identified in the intercostal spaces along the lateral edge of the sternum and controlled with clips or ties at their origin. At the lateral border of the pectoralis muscle, the breast may be completely dissected free from final attachments or the axillary tail left in continuity with the axillary tissue for progression to axillary node dissection, as described later. The breast should be oriented for pathologic assessment.

Axillary Lymph Node Dissection

Following excision of the breast from the chest wall, the ALND may be completed en bloc with the breast or performed separately following transection of the breast at the axillary tail. A standard axillary dissection for breast cancer includes levels I and II of the axilla, and it typically involves removal of at least 10 lymph nodes. The boundaries of this dissection include the axillary vein superiorly, the chest wall

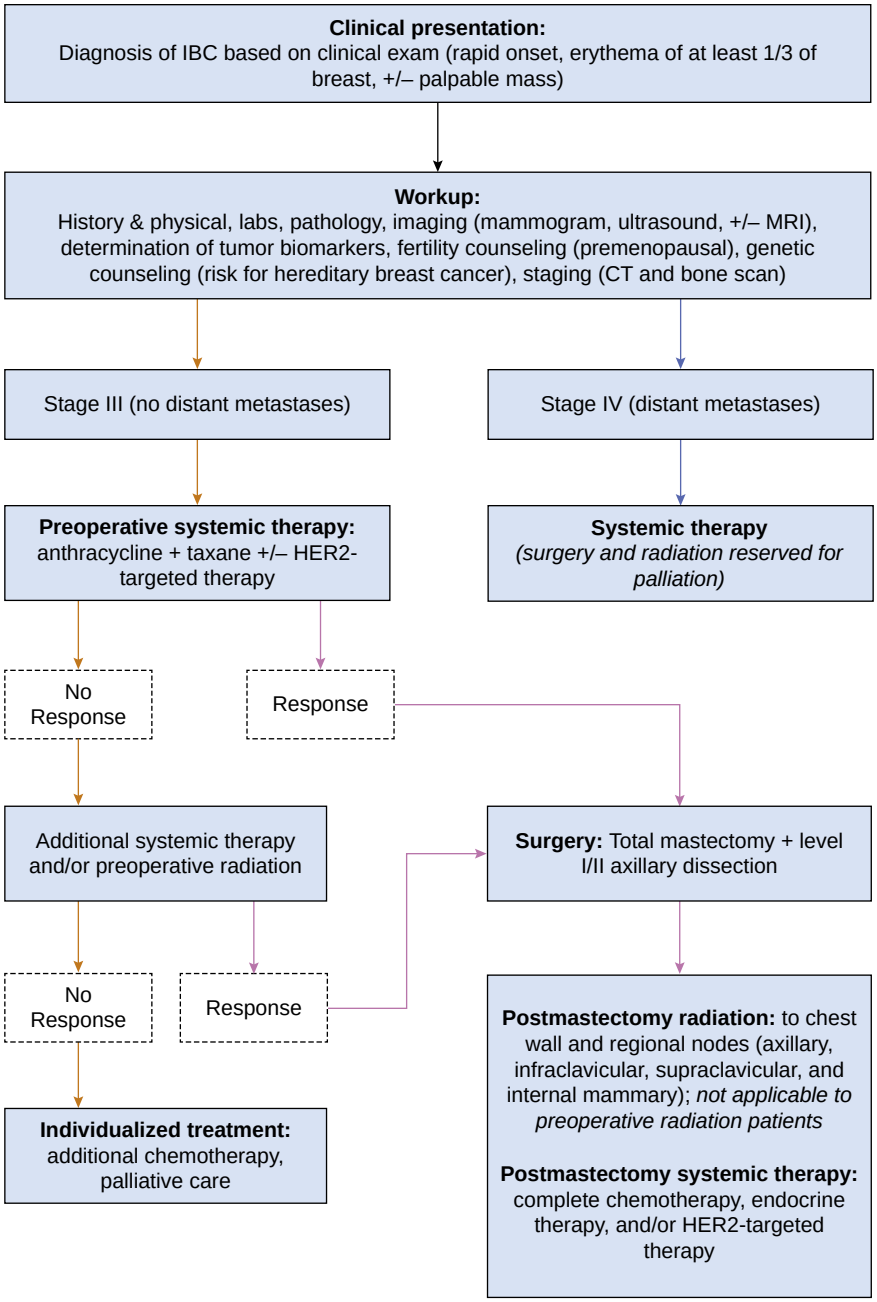


FIG. 4 The standard presentation, workup, and treatment algorithm for patients with inflammatory breast cancer *(IBC)*.

medially, the axillary skin laterally, the pectoralis muscle anteriorly, and the latissimus dorsi muscle posteriorly. Attention must also be given to identifying the thoracodorsal and long thoracic nerves (Fig. 5) to avoid injury.

To start the dissection, the clavipectoral fascia is incised at the lateral edge of the pectoralis major muscle inferiorly, and progression is made superiorly toward the apex of the axilla. The pectoralis muscles are progressively retracted superiorly and medially while mobilizing axillary fat and nodal tissue laterally. The medial pectoral neurovascular bundle may be identified at the entry to Rotter's space and either preserved or ligated based on palpable and/or suspected nodal involvement of Rotter's nodes. This approach may be continued superiorly along the pectoralis edge to identify the axillary vein *medially* in the apex of the axilla; however, *lateral* identification of the vein is preferred. The latissimus dorsi muscle is identified *inferiorly* and *laterally* in the axillary space, and the vertically oriented fibers are followed superiorly, progressing up the anterior surface of the latissimus. The axillary vein may be identified superiorly, as it crosses anterior to the latissimus muscle's tendinous band. This *lateral* approach to axillary vein identification is safest, with no critical structures laterally in the axilla, and permitting optimal control of the vein when encountered, as compared with the medial, apical aspect of the axilla.

The axillary vein is then dissected free of fatty and nodal tissue, anteriorly and inferiorly, with venous tributaries being clipped and divided as progression is made laterally to medially. The thoracodorsal neurovascular bundle is identified entering the axilla in a deep posterior position, usually in the center of the specimen, approximately halfway between chest wall and latissimus muscle. This is identified and protected, as injury causes weak arm/shoulder

BOX 1 Key Procedural Steps and Pitfalls for a Modified Radical Mastectomy

Key Operative Steps

Mastectomy

1. Plan the elliptical skin excision to encompass nipple-areolar complex, oriented transverse-obliquely to accommodate subsequent axillary node dissection
2. Raise avascular mastectomy flaps to the borders of the breast (clavicle *superiorly*, lateral sternal edge *medially*, rectus sheath/inframammary fold *inferiorly*, latissimus dorsi *laterally*)
3. Excise breast and underlying pectoralis fascia from the pectoralis major muscle

Axillary Lymph Node Dissection

1. Incise the clavipectoral fascia at the lateral border of the pectoralis muscles
2. Following the anterior surface of the latissimus muscle, identify the axillary vein as it crosses the tendinous portion superiorly
3. Dissect the fatty and nodal tissue from the inferior aspect of the axillary vein, managing small venous tributaries
4. Identify and protect the thoracodorsal neurovascular bundle in the center of the axillary space
5. Identify and protect the long thoracic nerve along the medial chest wall
6 Sweep axillary specimen inferiorly, dividing final attachments, including anterior thoracodorsal neurovascular branches

Potential Pitfalls

Mastectomy

1. Inadequate skin excision leaving excess tissue with residual dermal lymphatic disease
2. Excessive skin resection with tension on closure leading to dehiscence and delay to radiation
3. Failure to identify or control the internal mammary sternal perforators at sternal border

Axillary Lymph Node Dissection

1. Dissection around *medial* shelving edge of latissimus causing injury to thoracodorsal bundle at insertion site into latissimus muscle inferiorly in axilla
2. Dissection *superior* to axillary vein causing severe worsening of lymphedema risk
3. Dissection *medial* to long thoracic nerve, mobilizing nerve into axillary specimen
4. Failure to recognize a smaller caliber bifid axillary vein, and/or distinguish axillary vein, thoracodorsal vein, and anterior thoracoepigastric vein.

movements. A large anterior tributary to the axillary vein, often a large proximal vein, is the anterior thoracoepigastric vein that must be ligated, once certain distinction has been made from the thoracodorsal vein. The axillary specimen is then mobilized laterally, and the intercostobrachial nerve may be encountered as it runs medial to lateral across the surgical field to the upper inner aspect of the arm, as opposed to the vertically oriented thoracodorsal and long thoracic nerves. If possible, the intercostobrachial nerve should be preserved to limit some of the unavoidable sensory neuropathy that results from an ALND, although it is often sacrificed to allow for improved visualization of the axilla and easier mobilization of the axillary contents.

The long thoracic nerve is identified along the medial chest wall, coursing vertically along chest wall and entering inferiorly into the serratus anterior. This nerve is carefully protected against the chest wall, as injury may result in a winged scapula. When retracting laterally during this dissection, the long thoracic nerve may also be pulled laterally away from the chest wall, and thus, it may be occasionally identified by easing the lateral retractors when it is not readily visible.

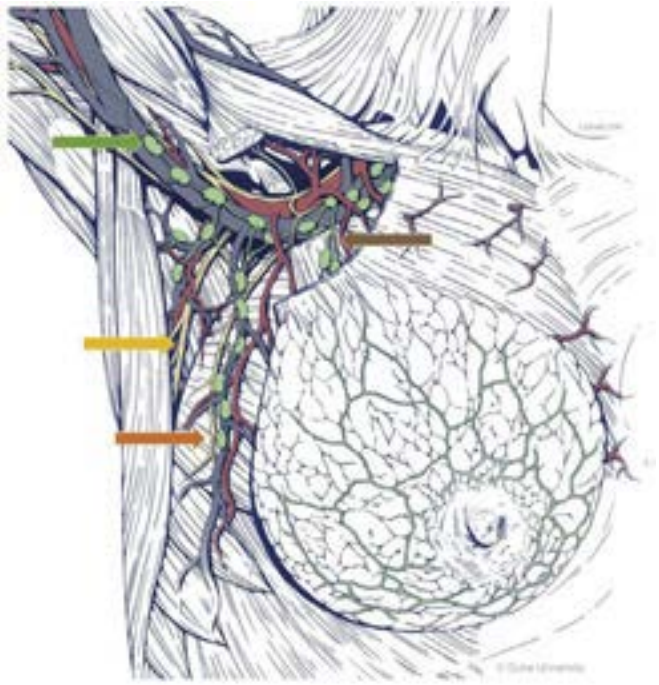


FIG. 5 Select key anatomic landmarks of the breast and axilla to consider when performing a modified radical mastectomy. *Green arrow* highlights the superior/anterior lymphatic chain overlying the axillary vein from the upper extremity. *Yellow arrow* highlights the thoracodorsal neurovascular bundle as it inserts into the medial aspect of the latissimus dorsi muscle. *Orange arrow* highlights the long thoracic nerve as it inserts into the serratus anterior muscle. *Brown arrow* highlights Rotter's nodes in Rotter's space between the pectoralis muscles. *(Illustrated by Megan Llewellyn, MSMI, CMI; copyright Duke University; with permission under a CC BY-ND 4.0 license.)*

The remaining axillary tissue is then dissected free in the apex of the axilla, connecting the cleared axillary vein to the chest wall, beneath the pectoralis minor muscle. The nodal specimen is mobilized inferiorly, and tissue between the thoracodorsal and long thoracic nerves are clamped, tied, and divided to be included within the specimen. A blunt sweep of this tissue clears the specimen from the latissimus and subscapularis floor of the axilla. The remaining anterior branches of the thoracodorsal neurovascular bundle are clipped and divided to free the specimen from its final attachments.

The specimen may be sent for intraoperative specimen radiograph to confirm any previously biopsied and clipped nodes are included within the specimen. The axilla should then be palpated for any residual adenopathy, paying particular attention to Rotter's space and level III of the axilla. If suspicious adenopathy is identified, attempt at resection should be undertaken. Once all specimens have been removed, it is prudent to verify that the thoracodorsal and long thoracic nerves remain intact by either visual verification and/or stimulation of the nerves. Following hemostasis, two closed suction drains are placed, one looped into the apex of the axilla and the other under the mastectomy flap. When reapproximating the wound edges, additional skin may need to be resected to allow for a tighter closure, and this skin should also be sent for pathologic evaluation. The mastectomy flaps are closed in layers with a deep interrupted dermal and a subcuticular skin closure. After dry dressings are placed, a binder or wrap may provide additional compression of the surgical site and help minimize drain output.

POSTOPERATIVE MANAGEMENT

Patients are generally admitted for 23-hour observation to monitor drain output and assess adequacy of pain control. Immediate normalization of the patient is recommended with early ambulation, oral fluid intake, regular diet, oral analgesia, and resuming all prior

medications. Intravenous antibiotics may be reasonably delivered during overnight observation but discontinued before discharge. The chest wall should be examined in the early postoperative period to ensure there is no hematoma, which is classically visible by sanguineous drain output, chest wall swelling, and/or mastectomy flap ecchymosis. Applying ice to the chest wall and/or axilla may improve pain control and help minimize residual oozing.

Drain output may be expectedly higher in volume as compared with a standard mastectomy, in light of breast edema, and surgical drains should remain in place until a threshold of volume has been reached and not a designated duration after surgery. The binder/wrap placed in the operating room should be continued until the drains are removed, even if the other surgical dressings are removed. Drains may be removed once the volume is below 30 mL per 24-hour period and are generally removed sequentially and not on the same day.

SPECIAL CONSIDERATIONS FOR SURGERY

Given the aggressive nature of the disease, few factors will alter the surgical approach for IBC—essentially all patients who undergo surgery should have a MRM. For patients with extensive skin involvement, attempts should be made to remove/treat as much of the involved skin as possible with surgery and/or radiation. For patients with extensive nodal involvement, surgical resection should include as many of the involved nodes as possible, including those in Rotter's space and level III, as applicable. For elderly patients, the surgical management should not be particularly altered based on age alone, but the patient's comorbidities may dictate additional preoperative and postoperative considerations, such as evaluation by other medical specialists for risk stratification and optimization before surgery or referring the patient for physical therapy after surgery. For pregnant patients, the surgical approach should also not be altered, but radiation therapy should be delayed until after delivery.

POTENTIAL SURGICAL COMPLICATIONS AND MANAGEMENT STRATEGIES

Early operative intervention is encouraged for a hematoma, as this is likely from an inadequately controlled internal mammary perforator, pectoralis muscle perforator, or axillary venous branches. Operative evacuation of a hematoma is beneficial to improve chest wall flap apposition and infection prevention from a retained hematoma. Postoperative cellulitis is often managed with oral antibiotics, while flap necrosis and incisional dehiscence may require additional surgical attention, although routine dressing changes (wet-to-dry) are often adequate. These fairly common complications should be identified and managed early to ensure timely initiation of adjuvant radiation.

If the drain output is unexpectedly high and white appearing shortly after surgery, the possibility of a chyle leak should be considered. Lymphatic fluid in the drain may appear more milklike than expected and sending the fluid for triglyceride assessment is diagnostic (often >110 mg/dL). Chyle leaks may be managed with continued drainage, a pressure dressing, and diet modification (low fat). If the chyle leak does not resolve, reexploration and ligation of the leak is recommended.

For patients with persistently elevated serous drain output after several weeks, it is often reasonable to remove the drains at 4 weeks if they are close to meeting the cutoff threshold. However, if the patient develops a seroma after drain removal, a percutaneous drain may be replaced by interventional radiology. Drain output should be strictly monitored, and a higher threshold may be used for drain removal. If a high drain output still persists or a chest wall seroma reaccumulates, sclerotherapy may be considered. This may be accomplished by instilling 95% to 99% ethanol into the drain (or seroma cavity after aspirating the seroma) and then reaspirating the ethanol after 10 to 20 minutes. Pressure dressings may also be helpful after sclerotherapy to help minimize the space for reaccumulation.

Unfortunately, chronic pain may develop in 20% to 30% of patients following MRM; this is termed *postmastectomy pain syndrome* (PMPS). This neuropathic pain may involve the chest wall, axilla, and/or upper arm, and it may be described as dull, burning, aching, numbness, and/or shooting or pricking pain. It may be exacerbated by movement, straining, overhead activity, and/or cold weather. Most women report that it is mild, but it may impact their quality of life. Risk factors for PMPS include ALND, radiation, younger age, minority race/ethnicity, and preexisting pain and/or psychologic disorders. Given that the etiology is unknown, treatment can be difficult, and collaborating with pain specialists may be considered.

The combination of ALND and radiation dramatically increases the risk of lymphedema, which may be as high as 40% in this population. The initial treatment strategy for lymphedema may include wearing a compression garment, exercise, physical therapy, massage, and/or decongestive therapy. Surgical treatments for lymphedema are still considered largely experimental.

Following axillary surgery, patients may also experience axillary web syndrome, which is also known as cording. This refers to a rope or cordlike texture that develops in the axilla just deep to the skin and may extend partially down the arm. The treatment for cording is exercise, physical therapy, massage therapy, hot compresses, and over-the-counter nonsteroidal antiinflammatory medications. Similarly, patients that develop shoulder stiffness following axillary surgery may also benefit from range of motion exercises and physical therapy.

OTHER CONSIDERATIONS

Once all therapies for IBC have been completed, ongoing surveillance should include a history and physical examination one to four times a year for 5 years, then annually, as well as annual mammography for the contralateral breast. However, systemic staging is not routinely recommended in the absence of clinical signs or symptoms of metastatic disease. Monitoring for lymphedema is prudent. All patients should be encouraged to maintain an active lifestyle, eat a healthy diet, limit alcohol intake, and maintain a healthy weight. Breast reconstruction may be considered after 2 to 5 years without signs of recurrence or distant disease, which often requires autologous tissue flap-based reconstruction.

For patients with a suspected recurrence, a biopsy is required for definitive diagnosis, and if confirmed, biomarkers should be repeated. Systemic staging is recommended, and goals of care should be discussed, particularly for those with distant disease. When an isolated chest wall or axillary recurrence is present, local therapy, including surgery, should be considered.

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Ductal and Lobular Carcinoma in situ of the Breast

Lauren M. DeStefano, MD, and Kristine E. Calhoun, MD

Breast cancer is one of the most common types of cancers and is the second leading cause of death in women. Due to advances in screening, there has been an increase in the incidence of high-risk lesions and preinvasive cancers over recent years, with approximately 48,000 new cases of ductal carcinoma in situ (DCIS) diagnosed annually. Although DCIS and lobular carcinoma in situ (LCIS) sound similar, they are distinct entities with different treatments and prognoses. DCIS is a noninvasive, nonobligate precursor to invasive carcinoma that originates in the ducts of the breast. LCIS originates in the lobules of the breast and has been described as both a nonobligate precursor of breast carcinoma and a high-risk marker of developing a breast carcinoma in either breast. Due to these differences, LCIS was removed from the 8th edition of the AJCC staging system and is now considered lobular neoplasia.

DUCTAL CARCINOMA IN SITU

Diagnosis

DCIS is most often diagnosed on mammography as new or changing suspicious-appearing calcifications. As mammography screening increased in the 1980s and 1990s, the incidence of DCIS increased more than 11-fold (7 per 100,000 to 83 per 100,000). Today, mammographically detected DCIS accounts for 25% of all breast cancers. Rarely, DCIS can present as a palpable or mammographically detected mass. DCIS associated with Paget's disease can present as nipple discharge or changes.

Once an abnormality is noted on screening mammography, additional diagnostic views may be completed to further characterize the abnormality. Stereotactic, or mammographic-guided, core needle biopsy is typically performed next to obtain a tissue diagnosis and help guide the next steps in the patient's treatment. If the lesion is not amenable to stereotactic core needle biopsy, for example, due to proximity to skin, chest wall, or mammary implant, a surgical excisional biopsy can be performed for tissue diagnosis.

After a diagnosis of DCIS is made, many surgeons elect to obtain a preoperative breast MRI to aid in surgical planning. This is controversial, as it has not been proven to decrease positive margin rates but has increased the incidence of additional biopsies as well as the rate of mastectomies. Genetic counseling and testing should be offered preoperatively, especially to those under 60 or with a strong family history in first-degree relatives. Although some guidelines such as from the National Comprehensive Cancer Network (NCCN) offer criteria for those who should be offered testing, other guidelines, such as from The American Society of Breast Surgeons (ASBrS), state testing should be available for all patients with a personal history or diagnosis of a breast cancer.

Treatment

It is well established that a diagnosis of DCIS has an excellent prognosis; with a multimodality approach to treatment, including surgery, radiation therapy and endocrine therapy, survival rates for DCIS at 15 years are greater than 95%. It is also well established that local control and survival are similar after mastectomy as well as after breast conservation. Multiple randomized clinical trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP) have examined outcomes of breast conservation. NSABP B-06 established equivalent long-term survival for breast conservation (lumpectomy plus radiation) compared with mastectomy for patients with invasive carcinoma. These results have been extrapolated for DCIS, although there was never a study specifically comparing mastectomy to breast conservation for DCIS. NSABP B-17 and B-24 focused on outcomes comparing treatment modalities within breast conservation. In B-17, breast tumor recurrences (IBTR) were compared among lumpectomy alone (LO) versus lumpectomy followed by radiation therapy (LRT). Long-term data demonstrated a 52% reduction in the risk of IBTR in the LRT group compared with the LO group.

Based on these data, the primary treatment of DCIS includes surgery: either breast conservation (lumpectomy plus/minus radiation) or mastectomy. Although there is no survival benefit for mastectomy, there are instances when mastectomy is recommended over breast conservation. Indications for mastectomy include extensive span of disease, multicentric disease, patients with contraindications to radiotherapy, or known pathogenic mutation. For those undergoing mastectomy, there are three types of mastectomies that one can offer their patient. A total mastectomy includes removal of the breast parenchyma, skin, and nipple-areolar complex. No reconstruction is typically offered with a total mastectomy; however, a flat aesthetic closure has gained popularity amongst these patients. A skin-spring mastectomy includes removal of the breast parenchyma along with the nipple-areolar complex, sparing enough skin to rebuild the breast mound. In a nipple-sparing mastectomy, only the breast parenchyma is removed, sparing the skin and nipple-areolar complex. For both a skin-sparing and nipple-sparing mastectomy, reconstruction can be immediate with placement of a tissue expander, mammary implant, or autologous tissue, or it can be delayed if there are concerns for flap integrity. There are no data suggesting one type of mastectomy is superior to another; however, it is important to evaluate the location of the lesion as well as proximity to the nipple-areolar complex when determining the type of mastectomy to offer one's patient.

For patients who opt for breast conservation, a lumpectomy, or segmental mastectomy, is the standard operation. Lumpectomies are often performed via preoperative localization, which can be with a wire placed preoperatively by breast imagers or with one of several newer wireless technologies to target the lesion for surgical excision, such as infrared reflectors (Scout devices), radioactive seeds, Mag seeds, or Tag devices. Large lumpectomies with preoperative bracketing utilizing multiple wires or devices can be performed by breast surgeons familiar with oncoplastic techniques or in conjunction with a plastic surgeon who performs oncoplastic techniques, allowing for breast conservation in patients previously deemed not candidates for breast conservation. These techniques employ volume rearrangement such as oncoplastic reduction mammoplasty or mastopexy, or involve volume replacement such as with a lateral intercostal perforator artery flap (LiCap).

In 2014, the Society of Surgical Oncology and the American Society for Radiation Oncology released updated consensus guidelines indicating that "no ink on tumor" is a safe margin for invasive carcinoma; however, since DCIS is typically not a mass but scattered calcifications, the margin guidelines for DCIS remain at 2 mm. Subsequent consensus guidelines reestablished the 2-mm margin as standard of care for DCIS. If a negative margin is unable to be achieved with a reexcision lumpectomy, a patient may be advised to proceed with a completion mastectomy with or without reconstruction.

Axillary lymph node sampling is not routinely performed during lumpectomy for DCIS; however, sampling in the form of axillary sentinel lymph node biopsy is recommended at time of mastectomy in the event of tumor upstaging to invasive carcinoma on final surgical pathology. Once the breast has been removed and breast lymphatics severed and destroyed, sentinel node mapping is not possible should invasive cancer be found, hence the need to do the mapping concurrent with the breast removal. Traditionally, a combination of radioactive sulfur along with a blue dye is used to identify the axillary sentinel lymph node at time of the mastectomy. Newer tracers have been developed to allow for a delayed sentinel lymph node procedure if final pathology yields an invasive carcinoma in the mastectomy specimen.

In NSABP B-24, the addition of tamoxifen (a selective estrogen receptor modulator) to breast conservation for estrogen receptor-positive (ER+) disease was examined. Long-term data demonstrated a 32% risk reduction of ipsilateral IBTR for breast conservation plus tamoxifen compared with placebo. Comparing across B-17 and B-24, ipsilateral IBTR were shown to have a 70% risk reduction for lumpectomy plus radiation and tamoxifen compared with LO. Furthermore, the addition of tamoxifen in B-24 demonstrated a 32% reduction in contralateral breast cancers. Although more than half of the IBTR were invasive, the use of radiotherapy or addition of tamoxifen was not associated with overall mortality reduction in either study. NSABP B-35 later examined the breast cancer-free interval of tamoxifen compared with anastrazole (an aromatase inhibitor) among postmenopausal women. Results demonstrated that anastrazole was superior to tamoxifen in postmenopausal women under age 60 and equivalent in women above the age of 60. These data lay the basis for endocrine therapy for patients with ER+ disease.

Although an operation is currently included in the standard of care in the treatment of DCIS, there are some who believe there is overtreatment for DCIS, particularly those that are low grade, small, and ER+. There are currently ongoing studies to evaluate the role of monitoring without surgical intervention. The COMET (US) and LORETTA (Japan) trials are phase III randomized trials currently underway to compare operative intervention versus monitoring and endocrine therapy for patients with low-risk DCIS. The LORIS (UK) and LORD (Europe) trials are examining the role of monitoring alone without endocrine therapy. These trials will be instrumental in determining if there are low-risk DCIS patients who can be safely treated without surgical intervention.

Surveillance

After completion of local control for DCIS (surgery plus/minus radiation), patients should begin surveillance. It is recommended that patients undergo interval history and physical examinations every 6 to 12 months for the first 5 years and then annually thereafter. Annual mammography should continue, with the first mammogram 6 to 12 months after completion of breast conservation therapy. Patients who were undergoing high-risk surveillance with annual MRIs in addition to their annual mammogram should continue their high-risk surveillance. Patients who have undergone mastectomy no longer require mammography or MRI and instead are monitored with a comprehensive chest wall examination every 6 to 12 months.

LOBULAR CARCINOMA IN SITU

Classifications

LCIS was first described in 1941 as a rare form of incidentally found noninvasive breast cancer. After much data looking at long-term outcomes, LCIS has been reclassified as lobular neoplasia to demonstrate the more indolent nature of this process. Histologically, LCIS is classified as classic (cLCIS), pleomorphic (pLCIS), and florid (fLCIS). cLCIS is more common in premenopausal women compared with pLCIS and fLCIS, which are more commonly diagnosed in postmenopausal women. pLCIS and fLCIS have been described as having behavior more similar to DCIS, so many treat these entities in a similar manner as DCIS. However, there is a paucity of data on long-term outcomes and recurrence risks after excision.

Diagnosis

Although DCIS is often mammographically detected and suspected during workup, LCIS is often incidentally found when a biopsy or procedure is performed for a different indication. The incidence of LCIS found in benign breast core needle biopsies is under 3.5%, and those found in reduction mammoplasty specimens is under 1.2%; however, the exact incidence is truly unknown given that most women are asymptomatic, and the lesions are mammographically occult. pLCIS and fLCIS can be associated with calcifications, and rarely a mass lesion, on mammography.

Treatment/Management

Recent studies have indicated that the upgrade rate of LCIS to an invasive carcinoma on surgical excision is less than 5% when there are no other lesions present that require excision and there is radiologic-pathologic concordance. Based on this, the American Society of Breast Surgeons (ASBrS) has released a consensus statement regarding the management of LCIS, wherein the society does not advocate for routine excision of LCIS in the previous scenario. However, since pLCIS and fLCIS have a higher upgrade rate (40%) compared with cLCIS (1%–4%), many advocate for excisional biopsy when these variants are seen on core needle biopsy. If cLCIS is found in a surgical specimen, margin status is irrelevant, unlike DCIS; however, the significance of margin status in pLCIS and fLCIS is relatively unknown and controversial. Because many believe these lesions behave more similarly to DCIS, these lesions are typically excised to negative margins, which can be challenging given their typically diffuse distribution within the breast.

Although the incidence of LCIS has increased over time while surgical intervention has decreased, survival has remained unchanged and is exceedingly high. Although the upstage rate of cLCIS is relatively low, the lifetime risk of developing an invasive carcinoma (either ipsilaterally or contralaterally) is upwards of 40% with an absolute risk of 1% to 2% per year. This is an increase compared with the general population of almost 10-fold. Due to this, many advocate for high-risk surveillance in this patient population. Management options for LCIS include annual breast MRIs in addition to annual mammography, chemoprevention, and even risk-reducing prophylactic bilateral mastectomies. Many trials have demonstrated a risk reduction in the development of breast carcinoma of greater than 50% with 5 years of endocrine therapy compared with placebo in patients with LCIS. The side effect profiles vary between SERMS, such as tamoxifen, and aromatase inhibitors, such as Anastrozole, and can range from postmenopausal-like symptoms and decreasing bone density to thromboembolism and endometrial carcinoma. The maximal risk reduction is seen with bilateral risk-reducing prophylactic mastectomies, which reduce the risk of a breast carcinoma by almost 95%. This is not routinely recommended but could be considered in those with additional risk factors or those who are unable to tolerate chemoprevention or high-risk surveillance.

Suggested Readings

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Advances in Neoadjuvant and Adjuvant Therapy for Early-Stage Breast Cancer

Julia Tchou, MD, PhD, and Seye Adekeye, MD, PhD

Over the past several decades, the treatment for early-stage breast cancer (clinical stage I and II) has almost always begun with surgery followed by adjuvant systemic therapy and adjuvant radiotherapy when indicated. Several landmark studies (listed in Suggested Readings) published in the past several years, primarily between 2017 and 2019, have changed this conventional approach. In this chapter, we review the key factors and rationale affecting the surgeon's recommendation of surgery first vs. neoadjuvant chemotherapy (NAC) in patients with clinical stage I or II breast cancer. Finally, we have provided a treatment decision algorithm (Fig. 1) used at our institution for the treatment of early-stage breast cancer according to receptor status.

ROLE OF RECEPTOR STATUS IN DETERMINING TIMING OF CHEMOTHERAPY (NEOADJUVANT VS. ADJUVANT)

Breast cancer is a heterogeneous disease. Gene expression profile analyses have stratified breast cancer into several molecular subtypes, which can be approximated by the expression of three receptors, namely estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor-2 or HER-2/neu (HER2). For practicing surgeons who care for breast cancer patients, the decision for systemic therapy in the adjuvant setting (after surgery) or in the neoadjuvant (before surgery) setting is significantly influenced by the composition of the expression pattern of the three receptor subtypes. Therefore, it is critical to confirm the expression status of ER, PR, and HER2 protein before proceeding with tumor resection.

For practical reasons, molecular subtype is generally determined using standard histopathology assessment, i.e., immunohistochemistry. The tumor is then classified into three subtypes defined by their receptor status as: (1) ER+ and/or PR+, which is also often referred to as hormone receptor positive (HR+) and HER2- (HR+/HER2-); (2) HR- and HER2- also known as triple negative breast cancer (TNBC); and (3) (HR+ or HR-) and HER2+, or simply HER2+. Following subtype classification, tumor size (T) and nodal status (N) further direct local (surgery ± radiotherapy) and systemic treatment planning.

HR+/HER2- BREAST CANCER

For patients with HR+/HER2- breast cancer, the decision for NAC at our institution is often reserved for those with bulky lymphadenopathy or those with large tumors, e.g., tumors ≥T2 (≥5 cm). The purpose of NAC is to downstage disease in the axilla and/or breast to ease the axilla staging procedure and improve breast conservation success rate, respectively. For patients with smaller HR+/HER2– breast cancer (e.g., tumors <5 cm), especially in those with low axilla disease burden (≤cN1), surgery is often recommended first to allow for accurate pathologic staging of the axilla. Surgical management includes breast conservation versus mastectomy with sentinel lymph node biopsy for cN0 or axillary dissection for cN1 disease.

For those with pathologic node negative (pN0) disease, the use of the 21-gene recurrence score assay (Oncotype Dx) is now standard of care to help guide the recommendation of adjuvant chemotherapy. The 21-gene recurrence score assay yields a recurrence score ranging from 0 to 100 and stratifies risk of recurrence into two risk groups: low or high risk. For women age 50 or above, recurrence score ≤25 is considered low risk, while recurrence score of 26 or higher is high risk. For women <50 years old, recurrence score of 15 or lower is considered low risk. For those with low-risk recurrence score, endocrine therapy (e.g., tamoxifen, anastrozole, or other aromatase inhibitors) will be recommended for systemic therapy based on menopausal status. For those with high-risk recurrence score, systemic chemotherapy will be recommended followed by endocrine therapy. The typical systemic chemotherapy in this setting is composed of four cycles of two drugs often abbreviated as TC: Cyclophosphamide (Cytoxan) and Paclitaxel (taxol) or Docetaxel (Taxotere).

For those with ≤3 positive axilla nodes (pN1) disease, systemic adjuvant chemotherapy followed by endocrine therapy is standard of care in premenopausal women. For postmenopausal women, preliminary results from an ongoing study (RxPONDER Trial, NCT01272037) showed that chemotherapy followed by endocrine therapy may not improve survival beyond the benefits of endocrine therapy alone if their tumor recurrence score is ≤25. Subgroup analysis showed that the invasive disease-free survival (iDFS) 5-year rates were similar in postmenopausal women who received

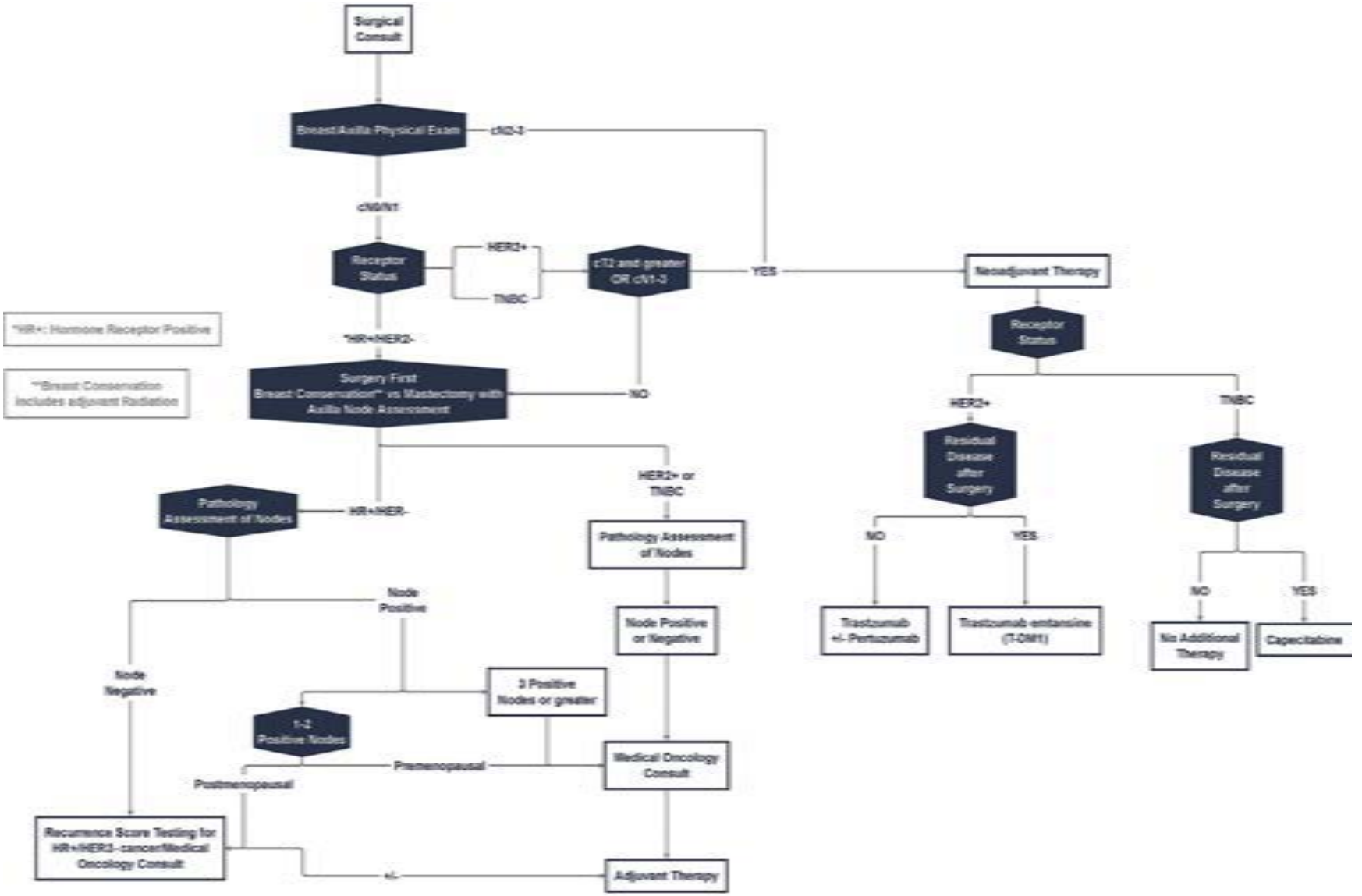


FIG. 1 Algorithm for the treatment of early-stage breast cancer according to receptor status.

chemotherapy plus endocrine therapy (91.9%) versus endocrine therapy alone (91.6%) ($P = 0.82$). In contrast, the iDFS 5-year rates in premenopausal who received chemotherapy plus endocrine therapy was 94.2% vs. 89% with endocrine therapy alone ($P = 0.0004$). The typical systemic chemotherapy regimen in women with node positive disease is generally comprised of three drugs: doxorubicin (Adriamycin), Cyclophosphamide (Cytoxan), and Paclitaxel (taxol) or Docetaxel (Taxotere).

Adjuvant radiation therapy is guided by the pathologic nodal staging information, which helps guide the decision for the inclusion of regional node (supraclavicular and internal mammary nodal basins) radiation field postlumpectomy or postmastectomy.

TRIPLE NEGATIVE BREAST CANCER

This breast cancer subtype comprises about 15% to 20% of all breast cancer subtypes. The aggressive tumor biology of TNBC renders this breast cancer subtype to be more sensitive to chemotherapy than the more common and indolent HR+/HER2- breast cancer subtype. The complete pathologic response (pCR) rate after NAC for TNBC is around 50%, whereas pCR rate in HR+/HER2− is only ∼15% to 20%. Therefore, NAC is often recommended to patients with larger tumors and axilla nodal involvement to improve the feasibility of breast conservation surgery.

The ability of NAC to downstage disease in the axilla may allow the patients to have a less invasive axilla staging procedure (e.g., targeted sentinel node axilla dissection), which involves the removal of the biopsy-proven clipped node along with 2 or 3 additional sentinel nodes rather than the conventional axilla node dissection. Removal of fewer axilla nodes may decrease the likelihood of lymphedema and other complications associated with axilla node dissection. The ability of NAC to downstage the extent of disease in the breast may improve the success rate of breast-conserving surgery by allowing the surgeon to excise a smaller volume of breast tissue, thus reducing the need for mastectomy.

The treatment paradigm of TNBC has changed in the past several years. NAC has become the standard of care in patients with early-stage TNBC with tumor size >2 cm regardless of axilla nodal status based on results of the CREATE-X study published in 2017. In this study, patients with either HR+/HER2− or TNBC were enrolled between 2007 and 2012 to receive NAC. Patients with residual tumor (n = 910; i.e., nonpathologic complete response) at the time of surgery were randomized to receive capecitabine plus standard postsurgical care therapy (n = 443) versus control (n = 444) who received standard postsurgical care therapy alone. Capecitabine is given daily orally twice a day on days 1 to 14 every 3 weeks for 6 or 8 cycles. Subgroup analysis showed that women with TNBC and tumor size >2, among other clinical variables, had significantly improved disease-free and overall survival with hazard ratio (HR) (95% CI) of 0.58 (0.39–0.87) and 0.52 (0.30–0.90), respectively. Of note, the HR for women with tumor size ≤2 cm was 0.65 (0.30–1.44), which was not statistically significant. Based on this study, NAC is recommended for women with tumor size ≥2 cm (cT2) regardless of nodal status. After NAC therapy and surgical management, the need for further adjuvant chemotherapy depends on the presence of residual disease in the surgical specimen. Adjuvant capecitabine comprising of 6 to 8 cycles is recommended for those with residual disease (nonpathologic complete response (non-pCR), while no additional systemic therapy is recommended for those with pathologic complete response (pCR). More recently, KEYNOTE-522 study demonstrated that immune checkpoint blockade therapy (pembrolizumab) in combination with chemotherapy in the neoadjuvant setting was shown to improve pCR rates and disease-free survival in women with ≥ T1c, node (+) or ≥ T2, any nodal status TNBC.

HER2+ BREAST CANCER SUBTYPE

The introduction of trastuzumab in the adjuvant setting has revolutionized the treatment of HER2+ breast cancer. Trastuzumab (Herceptin) binds to HER2 to elicit antibody-dependent cellular cytotoxicity (ADCC). Trastuzumab was approved for use in the adjuvant setting in the United States in 1998. The release of trial results of five major studies (Herceptin Adjuvant [HERA] Breast International Group [BIG] 01-01 trial, the Breast Cancer International Research Group [BCIRG] 006 trial, the National Surgical Adjuvant Breast and Bowel Project [NSABP] B-31 trial, the North Central Cancer Treatment Group [NCCTG] N9831 trial, and the Finnish FinHer trial in 2005) investigating the benefits of Trastuzumab in the adjuvant setting provided the basis for its use in clinical practice.

Since then, other HER2-directed monoclonal antibodies have been developed (e.g., pertuzumab), which inhibits the dimerization of the HER2 receptor. More recently, the NeoSphere trial, published in 2012, supported the use of dual HER2 blockade in the neoadjuvant setting, demonstrating that the addition of dual HER2-targeted NAC therapy (i.e., chemotherapy combined with pertuzumab and trastuzumab) significantly improved the rate of pCR for patients with nonmetastatic HER2+ invasive disease. Analysis of the cohort at 5 years revealed improved survival advantages for those who received dual HER2 blockade in the neoadjuvant setting. Therefore, based on the NeoSphere study, the combination of dual HER2-targeted therapy, trastuzumab and pertuzumab, is superior to single agent (trastuzumab alone) HER2-targeted therapy. This is not surprising as the combination of trastuzumab and pertuzumab are mechanistically synergistic in their tumor cell kill activities.

NAC is usually not recommended for patients who present with smaller breast tumors (<2 cm) and clinically negative axilla. For these patients with clinical stage I disease, surgery first is recommended followed by adjuvant systemic chemotherapy. The chemotherapy regimen is based on HER2-targeted therapy (comprising of either single [trastuzumab] or dual [trastuzumab and pertuzumab] HER2-targeting agent) plus various chemotherapy combinations that may include taxanes (docetaxel or paclitaxel), carboplatin, and/or doxorubicin.

NAC is generally recommended if tumor size is ≥2 cm (cT2) and/or axilla nodes are clinically positive. In the neoadjuvant setting, both the NOAH and TECHNO trials found that the pCR rate following addition of trastuzumab to NAC was improved. Patients with operable HER2+ breast cancer who had pCR were shown to have improved long-term outcomes (i.e., improved progression-free and overall survival). Similarly, results from the APT trial showed that early-stage, node-negative HER2+ patients had a 3-year DFS of 98% after treatment with weekly TH followed by 1 year of trastuzumab monotherapy. An updated report showed that DFS remained favorable at 93% after 7 years.

As in patients with TNBC or other subtypes, the presence of residual disease or non-pCR confers worse prognosis. In patients with pCR (i.e., no residual disease in the breast and axilla surgical specimens), adjuvant systemic therapy is composed of trastuzumab ± pertuzumab (the infusion is given every 21 days for a total of 1 year, up to 18 cycles). For those with residual disease, a recent phase III clinical trial, the KATHERINE study published in 2019, demonstrated that patients who received emtansine or DM-1, conjugated with trastuzumab, known as T-DM1, in the adjuvant setting, had significantly improved overall and disease-free survival compared with those who received standard of care adjuvant trastuzumab. Results from the KATHERINE study, much like those from the CREATE-X study, have been practice-changing for women with early-stage HER2+ breast cancer.

IMMUNOTHERAPY IN BREAST CANCER

Immune checkpoint blockade (ICB) therapy has revolutionized the treatment of a wide variety of malignancies, including melanoma and lung cancer. The success of ICB therapy has changed the treatment paradigm in oncology over the past several years; however, the idea to use the immune system to attack "invading" tumor cells isn't completely new. More than 100 years ago, surgeon William Coley boldly tested a new strategy for shrinking tumors: injecting a combination of pathogens and toxins directly into malignant masses. Clinicians and researchers now recognize Coley's eponymous "toxin" as an early

form of immunotherapy, a treatment that enhances the immune system's ability to recognize, attack, and kill tumor cells. In 2013, *Science* designated cancer immunotherapy as the breakthrough of the year. In 2018, James P. Allison and Tasuku Honjo received the Nobel Prize in Physiology and Medicine for their discovery of immune checkpoint receptors CTLA-4 and PD-1, respectively. This well-deserved recognition confirmed the pivotal role of immunotherapy as an effective cancer treatment strategy.

The objective response rate of ICB therapy as a single agent in patients with breast cancer has been poor. In patients with metastatic breast cancer who had been heavily treated before enrolling in a Phase 1b study (JAVELIN NCT01772004), the objective response rate (ORR) of avelumab (antiprogrammed death-ligand 1 [PD-L1]) was only 5.2% (confidence interval [CI], 1.1–14.4) in TNBC, 2.8% (CI 0.3, 9.7) in the hormone receptor-positive (HR+) subtype, and 0% (CI 0, 13.2) in HER2+ breast cancer. The response rate to pembrolizumab (antiprogrammed cell death protein 1 [PD-1]) was slightly better in patients who had tumors that expressed PD-L1. In the KEYNOTE-028 study, the ORR of pembrolizumab in patients with advanced or metastatic HR+ cancer was 12% (CI 2.5–31.2). Similarly, in the KEYNOTE-012 study, the ORR of pembrolizumab in patients with metastatic PD-L1+ TNBC was 18.5% (CI 6.3–38.1).

When combined with chemotherapy, the clinical benefit in patients with advanced or metastatic TNBC was significantly improved compared with chemotherapy alone in a recently published study in 2018 entitled "Impassion130 study: Atezolizumab (anti-PDL1) and Nab-paclitaxel in advanced TNBC". In this study, patients with advanced or metastatic TNBC were randomized to receive atezolizumab + protein-bound paclitaxel (nab-paclitaxel) or nab-paclitaxel alone (n = 451 per group) between June 2015 and May 2017. In the intention-to-treat analysis, the median overall survival was 21.3 months in the group that received atezolizumab plus nab-paclitaxel and 17.6 months in the group that received placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI, 0.69–1.02; $P = 0.08$). Among patients with PD-L1–positive tumors, the median overall survival was 25.0 months and 15.5 months in the two treatment groups, respectively (hazard ratio, 0.62; 95% CI, 0.45–0.86). These results paved the way for the approval of atezolizumab by the FDA in March 2019 to be used in combination with protein-bound paclitaxel, for adults with unresectable, locally advanced, or metastatic TNBC whose tumors express PD-L1 (defined as PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area), as determined by an FDA-approved test. The role of immunotherapy in women with early-stage TNBC is less clear and under investigation (KEYNOTE-522 clinical trial NCT03036488). Recently published findings from this study showed that the combination of pembrolizumab with a platinum-based chemotherapy regimen led to an increased rate of pCR in early-stage TNBC compared with chemotherapy treatment alone. The implication of this finding is significant; however, whether clinical practice will be changed remains to be determined.

In summary, the role of immunotherapy in breast cancer continues to be defined. There are several ongoing trials studying the use of immunotherapy as an adjunct for treatment in the different breast cancer subtypes, and more options are expected to be discovered in the coming years.

SUMMARY

The decision for neoadjuvant or adjuvant chemotherapy in the treatment of patients with nonmetastatic breast cancer is heavily influenced by the tumor receptor status. The ability of NAC to downstage disease may drive the decision for NAC, but results from several clinical trials have further confirmed the clinical benefit of NAC, as a stratification tool, in patients with early-stage HER2+ or TNBC. The presence of residual disease after NAC, or non-pCR, now serves as a biomarker to identify patients to receive additional adjuvant therapy such as capecitabine or T-DM1 for those with TNBC or HER2+ disease, respectively. As immunotherapy for breast cancer continues to evolve, the use of immunotherapy in the neoadjuvant and adjuvant setting may become standard of care for some patients in the future.

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Treatment Trends in Locally Recurrent and Metastatic Breast Cancer

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BACKGROUND AND EPIDEMIOLOGY

Globally, breast cancer is the most common cause of cancer in women. Although overall survival has improved significantly over the last several decades, up to 20% of breast cancer survivors will experience a recurrence during their lifetime. Over the past three decades, rates of locoregional recurrence have declined thanks to improvements in therapeutic interventions as well as widespread adoption of surveillance programs. It is worth mentioning that recurrence rates of ductal carcinoma in situ (DCIS), which do not represent invasive breast cancer, have also decreased due to improvements in detection, surgical technique to obtain negative margins, and use of adjuvant hormone therapy. Recurrences of true breast cancers, when they do occur, are most common within the first 3 to 5 years after resection. Recurrences can occur locally (in the ipsilateral breast or chest wall of the original tumor), regionally (in axillary, supraclavicular, or internal mammary nodal basins), or distally (in lungs, bones, brain, and other organs). Local recurrences are most common, but about 40% of patients with recurrent disease

have both local and regional nodal recurrence. Rarely is there an isolated regional nodal recurrence. The presence of metastatic foci defines stage IV of disease, where 5-year survival rates range between 11-42% depending on the specific phenotype of breast cancer, with a median survival of 18 to 24 months. Despite widespread screening efforts in developed countries, roughly 15-20% of patients will present with metastatic disease.

DEFINING A BREAST CANCER RECURRENCE

Biomarker testing of hormone receptor and HER2 receptor statis is used to differentiate between recurrent disease and a new, primary tumor. Generally, recurrent tumors carry the same receptor phenotype as the primary tumor. However, in a small study in the 1990s, authors hypothesized that a loss of hormone receptor expression in recurrent tumors may explain why the tumors did not respond to endocrine therapy and recurred.Likewise, tumors that were initially HER2- may present as HER2+ when they recur.

Recurrence risk varies by intrinsic breast cancer subtypes, which are often divided into luminal A (ER or PR+ and *HER2*−), luminal B (ER or PR+ and *HER2*+), and triple negative breast cancer (TNBC). Yu et al. (2019) retrospectively observed that luminal A tumors have low risk for distant metastatic disease that persists in the long term, and that luminal B tumors have higher initial risk of distant metastatic disease, which decreases after the first 5 years following treatment. TNBCs have high recurrence risk compared with receptor-positive breast cancers and generally are more locally aggressive with higher grade pathologic features. When TNBCs recur, they tend to do so earlier than their receptor-positive counterparts. Basal subtypes, which include TNBCs as well as EGFR+ and HER2-overexpressing breast cancers, have a higher risk of recurrence even after chemotherapy and radiation. Despite these generalizations, Groenendijk et al. (2019) demonstrated that when subjected to an 80-gene signature assay, 13% of luminal-type tumors were reclassified as basal-type, with behavior and response to therapy similar to that of TNBCs. A possible explanation is the inability of conventional immunohistochemistry or in-situ hybridization techniques to distinguish between functional and nonfunctional estrogen receptor variants in some patients.

Following treatment, younger patients have a higher risk of recurrence compared with older women. Those with *BRCA1/2* mutations also bear a higher risk of recurrence compared with their *BRCA1/2*-negative counterparts. Recurrence risk is largely determined by tumor biology but can also be influenced by initial treatment modality. Following lumpectomy, risk of recurrence is higher in those found to have positive margins, positive lymph nodes, as well as those of younger age at diagnosis. Lack of adjuvant radiation therapy also increases risk of recurrence following lumpectomy. For those who underwent breast conservation therapy (BCT) consisting of lumpectomy followed by radiation therapy, risk of recurrence is predominantly dictated by tumor biology (with larger, higher-grade, and hormone receptor-negative tumors independently contributing to higher risk of recurrence).

Historically, patients who underwent BCT were found to have higher rates of local recurrence compared with those who underwent mastectomy alone, although contemporary data suggest that improvements in modern breast cancer therapies have reduced the local recurrence risk following BCT. For patients who underwent mastectomy, the risk of recurrence increases with increasing number of positive axillary lymph nodes and larger tumor size. Recurrences tend to occur earlier and involve more regional nodes, which is associated with worse outcomes and a higher incidence of distal metastases.

GENOMIC ASSAYS USED TO STRATIFY RECURRENCE RISK

Gene expression profiling assays can use tumor features to prognosticate the risk of locoregional recurrence. The Oncotype Dx 21-Gene Breast Recurrence Score measures the expression of 21 genes in early-stage ER+/HER2− breast cancers to predict whether an individual will benefit significantly from adjuvant chemotherapy (in addition to hormonal therapy. TAILORx trial, a phase III clinical trial investigating the benefit of chemotherapy in hormone receptor-positive, HER2−, axillary node-negative breast cancers, used the Oncotype Dx Breast Recurrence Score to assign a cancer recurrence risk score between 0 and 100 to tumors based on the gene expression profile. Those with low-risk tumors (0–10) received hormone therapy only, whereas those with high-risk scores (greater or equal to 26) underwent treatment with hormone therapy and chemotherapy. Those with intermediate scores (between 11 and 25) were randomized to either hormone therapy alone or combination therapy, and the study found no difference in 5-year invasive disease-free survival between the two groups. 5-year overall survival was similar in both groups. Additionally, those with low-risk score (0–10) had very low recurrence rates with hormone therapy alone, and those with high-risk scores had high distance recurrence rates (13%) despite combination therapy. The findings of the trial thus suggest that chemotherapy may be avoided in patients with recurrence scores between 0 and 10, patients older than age 50 with a recurrence score between 11 and 25, and patients under age 50 with a recurrence score between 11 and 15.

Similarly, MammaPrint uses a 70-gene assay to assess risk of recurrence and is validated for early-stage tumors under 5 cm in size with 0 to 3 positive lymph nodes. MammaPrint is used in decisions regarding withholding chemotherapy. The MINDACT trial sought to provide prospective evidence for using a genomic assay in addition to clinical risk assessment to identify patients who would benefit from adjuvant chemotherapy. The study found that for patients with high clinical risk but low genomic risk based on the MammaPrint assay, the use of adjuvant chemotherapy increased 5-year distant metastasis-free survival by only 1.5%, thus concluding that approximately 46% of patients with breast cancer who are clinically high risk may be able to avoid chemotherapy based on a low genomic risk as determined by the MammaPrint assay. Further analysis at a median of 8.7 years of follow-up later revealed a small distant metastasis-free survival benefit (5%) among the subset of women under age 50 who had received chemotherapy and confirmed the lack of a clinically substantial benefit for women over age 50. The effect modification of age is thought to be related to the ability ovarian suppression in those who receive chemotherapy.

EVALUATION AND MANAGEMENT OF RECURRENT DISEASE IN BREAST CANCER

The presence of symptoms such as a palpable lump, pain, or skin changes in a patient with a history of breast cancer should prompt further workup for a recurrence of disease, beginning with a focused history and physical exam that includes inspection and palpation of the breast(s), chest wall, and regional nodal basins. Approximately half of ipsilateral breast cancer recurrences have detectable findings on clinical exam. Palpable masses can be evaluated with ultrasound, diagnostic mammogram, and MRI. Following the history and clinical exam, the evaluation of a suspected breast cancer recurrence begins with staging imaging with CT scans of the chest, abdomen, and pelvis, and bone scans to identify bony metastases. MRI of the breasts is highly sensitive in detecting breast cancer and have a high negative predictive value and thus is most useful in those with a high pretest probability of breast cancer. In practice, this commonly translates into those with at least a 20% lifetime risk of developing a second primary breast cancer based on risk models that take family history heavily into account. Otherwise, breast MRI is not routinely used to screen for asymptomatic recurrence. Brain MRI with contrast is obtained if there is concern for central nervous system involvement, and spine MRI with contrast can evaluate complaints of back pain or concerns for spinal cord involvement. PET CT is most useful in situations

when standard staging MRI or CT are equivocal and can also be helpful in identifying regional lymph node recurrence and occult distant metastases. Suspicious lesions can be biopsied, and once a recurrence has been diagnosed, germline and somatic genetic testing is performed to identify targets for therapy. A treatment plan is formulated, and psychosocial assessment and support should be provided.

Generally, ipsilateral recurrences, when operable, are treated with repeat ("salvage") mastectomy. The challenges of performing salvage mastectomy after prior surgery and/or local radiation include compromised blood supply to the skin flap, the loss of typical tissue planes between subcutaneous fat and breast tissue, and the need for negative margins that may necessitate creation of large skin defects that cannot be closed primarily. In these situations, reconstruction may necessitate tissue flaps or a staged closure using an allograft and negative pressure wound therapy, followed by a skin graft. A history of prior radiation increases the risk of skin necrosis and poor wound healing. In the elderly or those with prohibitively high surgical risk, repeat lumpectomy with or without additional radiation therapy can be considered. The majority of ipsilateral recurrences present as "first-failure" events and usually are localized and resectable. They may present on routine surveillance mammogram, MRI, or on physical exam as skin changes, palpable masses, lymphadenopathy, or localized discomfort, usually within 5 cm of the original tumor bed.

The treatment approach of ipsilateral breast cancer recurrences depends on prior treatment history and the location of recurrence. The National Comprehensive Cancer Network (NCCN) classifies ipsilateral recurrences into three categories based on prior therapy: (1) recurrences that occur after (1) BCT, (2) after mastectomy and axillary lymph node dissection (ALND) only, and (3) after mastectomy and ALND and Radiation Therapy (RT). For patients who initially underwent BCT, a total mastectomy is recommended, with ALND if not previously performed at the index cancer operation. Repeat BCT with radiation therapy is not the standard of care. There is some evidence, however, that for recurrences in tumors that were initially treated with lumpectomy without radiation therapy, a completion mastectomy offers no survival benefit over BCT (lumpectomy with radiation therapy). If a mastectomy and ALND were initially performed, resection of the local recurrence and radiation therapy to the chest wall and regional LN basin is recommended. For those who underwent mastectomy, ALND, and prior RT, surgical resection of the recurrence is recommended when technically feasible. The CALOR trial, a prospective randomized study that used adjuvant chemotherapy after surgical excision of recurrent breast cancer, showed survival benefit and reduced risk of second treatment failure for patients with ER– recurrent tumors and no benefit in those with ER+ tumors (who received adjuvant endocrine therapy). When a tumor is diagnosed distant to the initial tumor, or when it presents more than 5 years after the initial tumor was treated, or when it is found to have discordant receptors, a new primary is suspected (rather than a recurrence of the initial tumor). In these cases, a sentinel lymph node biopsy (SLNB) can be attempted if an ALND had not been performed at the initial surgery. Lymphoscintigraphy can be used to aid in operative planning given anatomical changes in lymphatic drainage. If a SLNB cannot be performed, consideration should be given to performing an ALND.

RT is discouraged for those who previously received RT given the cumulative risk of tissue toxicity with repeated course of radiation.

More aggressive recurrences may invade underlying nerve, bone, or muscular structures, which can render them unresectable. Systemic therapy can be used with the goal of converting a nonresectable tumor into a resectable one.

AXILLARY LYMPH NODE DISSECTION IN RECURRENT DISEASE

Axillary lymph node status is one of the most important prognostic factors in breast cancer; traditionally, surgical management of breast cancer involves resection of the primary tumor followed by ALND. Over the years, SLNB has been demonstrated to be sufficient in ruling out axillary lymph node metastases, sparing patients from the morbidity associated with ALND. SLNB has now replaced ALND for the staging of clinically node-negative breast cancer patients, and routine ALND is not performed as the initial staging procedure in clinically node-negative patients. In patients who have positive axillary nodes by biopsy, ALND or SLNB are options depending on the planned surgery and extent of nodal disease. Those with 1 or 2 positive sentinel lymph nodes who are willing to undergo standard whole-breast irradiation and standard adjuvant systemic treatment following BCT may avoid ALND, based on evidence from the Z0011 and IBCSG 23-01 trials demonstrating similar disease-free survival, overall survival, and locoregional recurrence rates between ALND and SLNB-only treatment groups.

Nodal recurrences generally occur in the axillary nodes among patients who underwent a SLN resection; they may also recur in the contralateral axilla or in the interpectoral, internal mammary, and infraclavicular nodal basins due to altered lymphatic drainage following SLNB or axillary dissection. Repeat SLNB in patients with ipsilateral breast tumor recurrence (IBTR) after BCS with SLNB has been shown to be accurate with a false negative rate of less than 10% (Chang, 2020). If a prior ALND was performed at the index surgery, then surgery to resect the recurrent tumor is recommend and no further axillary dissection is warranted. Axillary nodal recurrences and chest wall recurrences are occasionally also amenable to repeat surgical resection. Adjuvant radiation is often utilized, and systemic therapy is employed based on the molecular characteristics of the tumor. Isolated axillary recurrence is rare, occurring in an estimated 1% to 3% of cases within the first 3 or 4 years after treatment (with a median interval of 2.2 years). The 5-year overall survival rate following isolated axillary LN recurrence is about 50%, with a mean survival of approximately 5 years. There are extremely limited data on the optimal management strategy in these patients, and options include completion ALND, isolated axillary lymph node excision, radiation therapy to the regional nodal basin, and systemic therapy. In a Canadian retrospective study examining factors affecting survival after isolated axillary LN recurrence (that is, no other local recurrence, regional recurrence, distant metastasis, or contralateral new breast primary), there was no difference in survival when comparing isolated axillary LN excision versus completion ALND. When comparing surgery alone versus radiation therapy alone versus both surgery and radiation, those treated with both surgery and radiation saw an overall survival benefit. Despite treatment, patients with isolated axillary recurrence had nearly a 50% incidence of distant metastases on subsequent follow-up. Of note, there is no prospective trial to date comparing a completion ALND with a targeted lymphadenectomy. Based on traditional treatment paradigms, the current standard of care is to perform a full ALND. In the setting of modern systemic chemotherapy, however, prospective studies should aim to investigate whether full ALND provides additional survival benefit beyond a targeted lymphadenectomy in the setting of an isolated axillary recurrence.

Current NCCN guidelines recommend surgical resection and RT when feasible. For recurrences in the supraclavicular or internal mammary nodal basins, RT is recommended when possible. When recurrences are not technically amenable to resection or when recurrence presents in the form of stage IV disease, the mainstays of treatment involve endocrine therapy or systemic treatment tailored to hormone and HER2 receptor status.

ROLE OF LOCOREGIONAL THERAPY IN METASTATIC DISEASE

IBTR predicts high likelihood of distant metastatic spread, and therefore systemic therapy remains the mainstay of care. Systemic therapy and palliative care have been the mainstay of therapy for stage IV disease, with locoregional therapy (LRT) generally offered

for palliative intent for symptom control. LRT refers to surgery for the primary tumor, local radiation therapy, or a combination of the two modalities. Hormone receptor–positive tumors also receive endocrine therapy, and HER2+ tumors also receive trastuzumab. The goal of these systemic therapies is to make inoperable tumors operable. A PET CT is obtained to assess for the presence of synchronous metastases, and a repeat scan obtained after a full course of adjuvant systemic therapy can help guide the appropriateness of reoperation. Palliative surgery is an option for those with persistent residual disease to address wound and bleeding complications secondary to locally advanced/destructive tumors.

The traditional belief is that once a cancer metastasizes, there is no therapeutic survival benefit to surgical resection of the primary tumor. However, there is evidence for survival benefit for patients who underwent resection of their primary tumor in stage IV disease. In particular, patients with early metastatic disease limited to bone, *HER*2+ disease, and a positive response to systemic therapy with a resectable primary tumor may benefit from LRT. The proposed mechanisms include (1) reduction of the tumor burden and propagation of clonal heterogeneity (implicated in development of resistance to therapy), (2) disruption of tumor cell movement between the primary tumor and metastatic sites, and (3) elimination of cancer stem cells (CSCs) and their tumor-promoting activities. Although a review of CSCs is beyond the scope of this chapter, CSCs are a subgroup of cells thought to be localized in the primary tumor that differentiate, self-renew, and maintain the tumor microenvironment, thus playing an important role in disease propagation. By depleting the CSC pool, resection of the primary tumor may disrupt the process of metastatic spread and remove a source for possible new metastases.

Animal models have also suggested that removal of the primary tumor reverses the tumor-induced immunosuppression that normally promotes metastatic spread. This effect is seen in early stages of metastatic disease, with little to no positive impact on survival in late stages. That there is a survival benefit for LRT even in metastatic disease suggests that surgical intervention should be considered in early metastatic disease. Khan et al. (2002) reported that most patients had a total mastectomy, but there was no survival benefit compared with patients who underwent partial mastectomy with clear margins achieved. Both partial and total mastectomy had improved survival compared with no surgery, and neither tumor size nor extent of nodal involvement was predictive of survival. Kommalapati et al. (2018) similarly demonstrated no survival difference between breast conserving therapy (partial mastectomy followed by radiation therapy) and total mastectomy in metastatic disease; however, the study also demonstrated worse survival in patients with severe/aggressive disease. Similarly, Wang et al. (2018, 2019) noted worse survival in stage IV patients with liver/lung metastases who underwent surgical resection of the primary tumor.

Several retrospective studies have aimed to identify which patients with metastatic disease benefit from LRT. Arciero et al. (2018) reported that among those who underwent surgical LRT, increased survival was seen in those who had hormone receptor-positive tumors, those who underwent radiation therapy, and those who had clear margins. The greatest increase in survival was seen in those who underwent both surgery and systemic therapy, but survival benefit was seen in those who underwent surgery regardless of systemic therapy. Lane et al. (2017) similarly noted the greatest survival benefit in ER+ patients who underwent surgery after systemic therapy to reduce the burden of disease, and surgery alone compared with systemic therapy alone was associated with improved survival. Importantly, the patients who underwent surgery before systemic therapy had worse survival, despite smaller primary tumor size and lesser degrees of lymph node involvement. Wu et al. (2017) demonstrated that well-differentiated, small tumors with low nodal burden had survival benefit across all breast cancer subtypes (regardless of receptor status). Thomas et al. (2016) found that tumors <2 cm had an additional survival improvement of 11 months after surgical resection of the primary tumor. Tan et al. (2016) found the greatest survival benefit in those who underwent joint primary and metastatic resection; they also noted that in hormone receptor-negative patients, primary and metastatic resection had no additional benefit compared with primary resection alone. Pons-Tostivint et al. (2019) showed that LRT conferred a survival benefit in those who had more than 1 year of controlled disease on their systemic regimens, even when there were more than 2 metastatic sites present. The group found no survival benefit of LRT for TNBC. Co et al. (2019) identified ER+ status as a positive prognostic factor.

Despite numerous studies demonstrating a survival benefit of surgical resection, the evidence is limited by the dearth of high-quality prospective data. In the largest meta-analysis on the topic to date, LRT in stage IV disease was reported to reduce mortality by 31.8%, and surgery specifically was reported to reduce mortality by 36.2%. However, when only the prospective studies were included in the meta-analysis, the reported mortality benefit was only 19.2% in LRT compared with no LRT. Of these, Badwe (2015) demonstrated in a randomized control trial that LRT conferred no survival benefit and increased distant metastases, possibly due to tumor shedding/seeding during surgery. Fitzal (2007) reported significant worse survival following surgery for luminal A subtypes. In contrast, the third study by Soran (2018) reported a significant survival benefit for the LRT arm in patients with HR+, HER2− tumors with solitary bone metastases. Most recently, Khan (2020) demonstrated in a randomized control trial that there was no difference in survival in women with stage IV disease who underwent LRT. It also found no difference in quality-of-life measures in the LRT arm. Importantly, Cady (2008) performed a case-matched analysis of LRT in stage IV breast cancer and reported that case-selection bias accounted for all, if not most, of the apparent survival benefit in patients receiving LRT. Current NCCN guidelines cautiously recommend consideration of locoregional surgery in certain subsets of patients with stage IV breast cancer.

Preliminary results from a handful of more recent prospective studies are promising. Hotton (2021) comparing patients with stage IV breast cancer found that surgery within 12 months of diagnosis was associated with a longer overall survival and progression-free survival. Of note, patients undergoing surgery had fewer distant metastatic sites. Yu (2021) similarly demonstrated longer progression-free survival for those who underwent locoregional surgery, but a survival benefit only in patients whose metastases were limited to bone. Several other prospective trials evaluating the benefit of LRT are actively recruiting, with estimated study completion dates in the next 5 years.

The challenge remains to identify which subset of patients with stage IV disease benefit from LRT. Based on current evidence, LRT appears to provide benefit in those with hormone receptor positivity, younger age, and more indolent disease (as defined by both longer periods of progression-free survival on systemic therapy as well as fewer distant metastatic sites). Other questions include the optimal sequence and timing of LRT, as well as effects of delay of systemic therapy due to complications secondary to LRT. Additional investigation is needed to identify more specific subsets of patients who will likely benefit from LRT based on their clinicopathologic characteristics.

FUTURE QUESTIONS TO ANSWER

Ongoing prospective trials aim to further characterize the role for adjuvant treatments in recurrent and metastatic disease. The ongoing phase III clinical trial (NSABP B51/RTOG 1304) is examining the role of regional nodal radiation therapy after mastectomy for patients who achieve a pathologic complete response to neoadjuvant chemotherapy. The Alliance A001202 trial is a randomized clinical phase III trial comparing ALND to axillary radiation in those who

have positive sentinel lymph nodes after neoadjuvant chemotherapy. Early results from the ongoing OlympiA trial have demonstrated survival benefit of adjuvant treatment with PARP inhibitor olaparib after completion of multimodal therapy with surgery, radiation therapy, and chemotherapy in high-risk, *HER2*–, and *BRCA1/2*-mutated breast cancers.

RECONSTRUCTION IN ADVANCED AND RECURRENT DISEASE

For patients with localized breast cancer, breast reconstruction is a commonly offered and often preferred pathway of care. However, with regard to metastatic breast cancer, breast reconstruction as an option is not always offered to the patient.

The literature in the past has been split regarding reconstruction in the metastatic population. However, more recent literature has suggested increasing rates of reconstruction, from 5.2% in 2004 to 14.3% in 2013. Reconstruction rates were lower in patients with higher tumor (T) and nodal (N) stages, but this may have been due to lower rates of mastectomy among these patients. Some of the well-described barriers to reconstruction include the type of cancer center referred to, insurance coverage, and area of residence. Type and timing of reconstruction can be variable in patients with advanced disease.

The type of mastectomy is also pertinent to breast reconstruction. There has been no clear evidence that nipple-sparing mastectomies (NSM) are associated with a higher risk of locoregional recurrence compared with skin-sparing mastectomy (SSM), even in advanced disease. From a reconstruction standpoint, NSM is associated with significantly better aesthetic outcomes. Thus, in the absence of any clear contraindications, NSM may be considered in suitable patients.

In the case of recurrent breast cancer, the approach to reconstruction varies significantly based on recurrent tumor size and the extent of resection. In the most straightforward case, postlumpectomy recurrence may be treated with mastectomy and reconstruction. If the patient previously underwent radiation therapy, then autologous breast reconstruction is the preferred reconstructive path due to significantly increased risk of capsular contracture with implant-based reconstruction. In advanced cases, a complex staged



FIG. 1 A 58-year-old woman with an ipsilateral breast tumor recurrence of the left breast, 26 months after the primary tumor was treated with breast conserving surgery followed by radiation and adjuvant chemotherapy for 1.5 cm triple negative breast cancer.

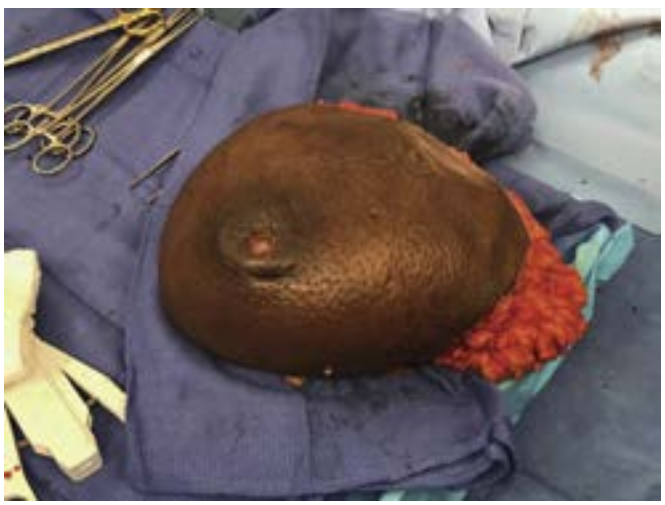


FIG. 3 Mastectomy specimen.



FIG. 2 Salvage mastectomy after lack of response with systemic chemotherapy.

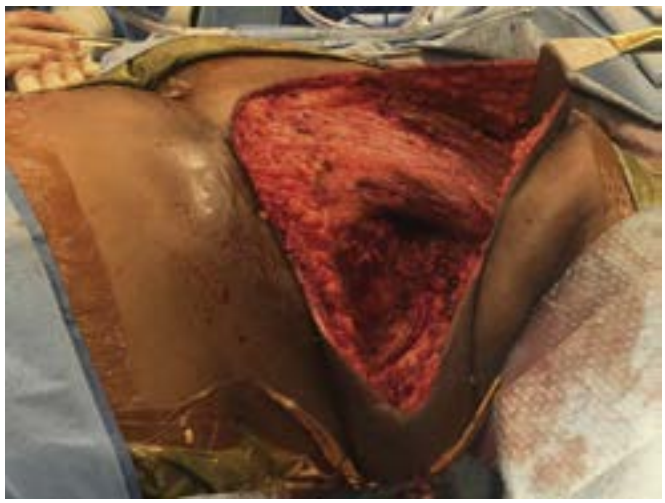


FIG. 4 Resection bed, with all the involved skin resected to achieve negative margins.



FIG. 5 Additional skin resected to achieve negative margins.

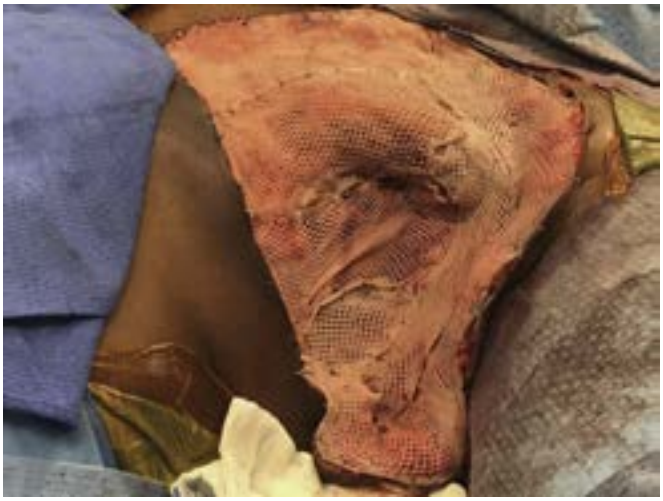


FIG. 6 Application of meshed allograft to assist with promotion of generating granulation tissue and healing for delayed split thickness skin graft.



FIG. 7 Covering the allograft with a layer of meshed nonadhering dressing.



FIG. 8 A negative pressure wound therapy system was applied with biweekly changes with significant decrease in size of open wound in 2 to 3 months period at which time a 7 × 28 cm area of open residual open wound was grafted with split-thickness skin graft.

reconstruction may require initial skin grafting, followed by negative pressure wound therapy before final coverage with skin graft. Figures 1–8 depict a case of advanced recurrence involving skin that required such an approach. Another group of patients who may require salvage mastectomy are patients who report recurrence after breast reconstruction. Last but not least, little is known about breast reconstruction and quality of life, specifically in the population of patients with metastatic or advanced recurrent breast cancer. A greater understanding of quality of life considerations in this patient population can help guide patient-centered reconstructive plans.

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Management of Male Breast Cancer

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INTRODUCTION

Accounting for only about 1% of all breast cancers diagnosed in the United States, male breast cancer (MBC) is a relatively rare disease. Compared with the 1:8 lifetime risk for females, males have an approximately 1:1000 lifetime risk of developing breast cancer, though evidence suggests that, in recent decades, the incidence of MBC may be rising. While the United States documented an estimated 1970 new cases in 2010, there were 2620 new diagnoses in 2020.

Because there are no breast cancer screening algorithms for men, elucidating the risk factors for MBC has been a focus for clinical researchers attempting to identify men at higher risk for developing breast cancer. Advanced age, increased estrogen exposure (e.g., obesity, cirrhosis, Klinefelter syndrome), and history of radiation exposure all increase the risk of breast cancer. Importantly, about one in five men diagnosed with breast cancer has a family history of the disease, and, while most cases may be sporadic, the recent increase in genetic testing has identified several gene mutations linked to increased risk for MBC. An estimated 4% to 40% of MBC are associated with inherited mutations in the *BRCA1* or *BRCA2* genes, which are important in DNA repair and recombination. Specifically, male *BRCA1* carriers have a 1:100 chance of developing breast cancer, while those with *BRCA2* mutations have a 7:100 chance, corresponding to a relative risk of 12 and 42 times that of men with wild type genes, respectively. Mutations in *PALB2*, a gene coding for a chaperone protein in the BRCA protein complex, are encountered in approximately 1% of women with breast cancer but in 16% of men. Mutations in *CHEK2*, which codes for a cell cycle checkpoint peptide, have also recently been linked to an increased risk of MBC, but more work is needed to determine its true clinical implications.

The rarity of MBC has limited the development of comprehensive diagnostic and treatment algorithms specific to men, so clinicians extrapolate from randomized controlled trials performed in women. Several recent reviews of the protocols for breast cancer clinical trials have demonstrated that men have actively been excluded, though there appears to be an increased interest in recruiting men to ascertain the nuances in the clinicopathology and treatment of MBC. There is, however, evidence that MBC may be a distinct entity. Approximately 90% of MBC are estrogen receptor (ER) and progesterone receptor (PR) positive and HER2 negative, compared with approximately 70% of female breast cancers. Given the anatomic differences between the male and female breast, histologically MBC are much more likely to be ductal (~95%) rather than lobular in origin. Broad genomic analyses of MBC have revealed a different distribution of somatic mutations when compared with breast cancers in women, including amplification of the gene *EMSY*, a transcription repressor that interacts with *BRCA2*, which is found in 13% of female breast cancers but 35% of MBC. In contrast, other studies have demonstrated that the distribution of the recurrence score derived from the validated 21-gene expression assay is similar between men and women, bringing the clinical impact of the mutational analyses into question. Additional large cohort studies have demonstrated that, unlike in women, tumor grade is not associated with breast cancer outcomes in men, further strengthening the argument that MBC may have different tumor biology.

Because MBC is typically not screen-detected, men tend to have higher stage cancers at presentation than their female counterparts. In an analysis of the National Cancer Database (NCDB), 18.2% of men had clinical stage III or IV disease at the time of diagnosis compared with 10.2% of women (Table 1). These differences at presentation extend into long-term disparities in which 5-year survival for men was 77.6% and 86.4% for women, which persist even when analyzed stage-for-stage.

DIAGNOSIS

No guidelines for breast cancer screening currently exist, though recent work suggests a potential benefit of the development of a screening protocol for men with high risk. Therefore, the diagnosis of MBC is typically made after the self-palpation of a painless, unilateral, subareolar breast mass. Because 40% of MBCs present stage III or IV, signs of advanced disease, such as invasion into the skin or muscle and axillary adenopathy, may also prompt evaluation (Fig. 1).

The differential diagnosis of a breast mass in a male includes gynecomastia, which typically presents as bilateral breast enlargement with or without a mass. The masses that present in patients with gynecomastia tend to be firm and mobile, are more likely to be tender than those related to a malignancy, and may also be transient in nature. Aside from men who have a clear physiologic or pharmacologic etiology for their gynecomastia, malignancy cannot be ruled out with examination alone.

The workup of a breast mass in a male patient is similar to the workup in women and includes mammogram and ultrasound. If the mass appears benign, biopsy can be deferred, and the patient can be instructed to perform serial self-examinations, as the majority of the masses will resolve over time. Core needle biopsy is indicated if there are any concerning findings on imaging or in situations of high clinical suspicion for malignancy, with a localizing clip placed at the biopsy site. Pathologic analysis of the specimen should be compared with the imaging findings for concordance, and if radiographic-pathologic discordance is present, the patient should undergo excisional biopsy. ER, PR, and human epidermal growth factor 2 (HER2) assays should be performed on all biopsy specimens to aid in directed therapy.

Ultrasound of the axilla is indicated if any lymphadenopathy is present on physical examination, and fine needle or core biopsy should be performed of any abnormal lymph nodes. Institutional protocols vary based on whether a localizing clip should be placed in the biopsied lymph node for future targeted axillary dissection.

Finally, patients who present with locally advanced disease require a metastatic workup with either a CT scan of the chest,

TABLE 1 Clinical and Pathologic Stage of Breast Cancer in Male and Female Patients as Recorded in the National Cancer Database from 2004–2017: ***Data are Presented as [Frequency (%)]***

Clinical Stage			Pathologic Stage		
	Male	Female		Male	Female
0	1850 (11.5)	375,626 (19.6)	0	1941 (12.0)	396,817 (20.7)
1	5438 (33.7)	864,979 (45.0)	1	6444 (40.0)	929,133 (48.4)
2	5902 (36.6)	483,279 (25.2)	2	5778 (35.8)	448,471 (23.4)
3	2254 (14.0)	150,364 (7.8)	3	1246 (7.7)	98,596 (5.1)
4	684 (4.2)	46,165 (2.4)	4	719 (4.5)	47,396 (2.5)



FIG. 1 Inflammatory breast cancer in a male patient.

abdomen, and pelvis plus a bone scan, or with a positron emission tomography (PET/CT) scan.

TREATMENT

Preoperative Considerations

Discussion of MBC patients at a multidisciplinary tumor board and preoperative referral to medical oncology and radiation oncology provide patients the opportunity to review their treatment options and formulate a comprehensive plan. Referral to a plastic and reconstructive surgeon should also be considered to discuss options for simultaneous reconstruction during the index operation.

All MBC patients should be referred for genetic counseling and testing. Although not necessary to be completed preoperatively, a discussion should be held with the patient about whether the results of genetic testing will impact their decision making as related to the operative approach to treating their cancer. For example, in an analysis of the National Surgical Quality Improvement Project, 6.7% of MBC patients opted for contralateral prophylactic mastectomy, and, as in women, these decisions are likely impacted by the presence of a high-risk genetic mutation.

Although surgery is the mainstay of treatment for MBC, neoadjuvant chemotherapy (NAC), anti-HER2 therapy, or antihormonal therapy may be considered in those who present with advanced tumor or nodal stage. As in women, the goal of neoadjuvant therapy is to downstage the primary breast tumor or axilla to offer the patient breast conservation or sentinel lymphadenectomy (SLNB). The ultimate goal of NAC would be a complete pathologic response as these patients have the best oncologic outcome; however, this can only be achieved between 20% and 65% of the time depending on the tumor type and neoadjuvant regimen. There are very few data related to the use of neoadjuvant therapy for MBC in the literature, and guidelines for administration are extrapolated from those in female patients. Fewer male patients may benefit from neoadjuvant therapy given the smaller proportion of patients for whom breast conservation is an option, though recent data from the NCDB do demonstrate lower mastectomy rates for males with locally advanced cancers after NAC. One limitation of neoadjuvant therapy for MBC is that most tumors are hormone receptor positive, which is associated with the lowest pathologic complete response rate (15%–20%) when compared with other subtypes.

Operative Management

Mastectomy

Historically, men with breast cancer have undergone mastectomy more often than breast conserving surgery (BCS); however, breast conservation is increasingly being performed in men, and evolving data indicate safety and feasibility. Decisions about breast conservation versus mastectomy in men should be made according to similar criteria as for women.

The mastectomy is typically performed through a transversely oriented elliptical incision encompassing the nipple and areola. The incision width is dependent on the volume of breast tissue in the individual with a smaller incision used in patients with smaller breast mass. Skin flaps are raised sharply or with electrocautery and are typically thicker in men than women given the general distribution of breast parenchyma. In obese patients, flaps should become progressively thicker laterally to avoid a sharp "drop-off" deformity at the lateral margins. As in females, the breast is dissected off the underlying pectoralis major with removal of the pectoralis fascia. If muscle invasion of the tumor is identified intraoperatively, this adherent portion should be removed from the pectoralis muscle. Resection of the pectoralis major (radical mastectomy) is rarely needed in current treatment paradigms, but postmastectomy radiation therapy is indicated for all patients with muscle invasion. Although uncommonly used, reconstruction options should be made available to men undergoing mastectomy since cosmetic outcomes can be improved with the use of multiple strategies, including fat grafting and implants (Fig. 2).

Breast Conservation

Due to its low incidence, the safety and feasibility of BCS in MBC has been difficult to evaluate in a prospective manner, but reduced morbidity has been documented for men undergoing BCS when compared with mastectomy. As in female breast cancer, BCS should be avoided if the tumor is close to the nipple or encompassing a significant volume of the existing male breast as a cosmetic outcome may not be feasible. In contemporary studies, the rates of BCS are lower in men than women given the more commonly unfavorable tumor-to-breast ratio, but local recurrence and disease-free survival among those undergoing BCS is similar. Despite being an integral part of breast conservation, adjuvant radiation has been historically underused in MBC due to concerns regarding the use of tangential-field radiotherapy to the smaller male breast and the proximity of chest wall, heart, and lung. These concerns are negligible with the contemporary delivery of CT-guided treatment planning; therefore, adjuvant radiation should be offered to men undergoing partial mastectomy according to current breast conservation guidelines.

Axillary Management

Management of the axilla in MBC is comparable to that of female breast cancer. As with women, separate incisions for the breast and axilla often provide improved cosmesis in those undergoing mastectomy.

SLNB is appropriate for all operable invasive MBC with clinically negative axillary nodes (cT1-3N0). Rates of SLNB in men have historically lagged behind those for women, with only 18% of men in one cohort undergoing SLNB between 1990 and 2010, but rates have been increasing. There is controversy over the application of the results of the ACOSOG Z0011 trial to men with clinically



FIG. 2 Postoperative outcomes in men with breast cancer after breast conserving surgery **(A)**, modified radical mastectomy **(B)**, and modified radical mastectomy with reconstruction with fat grafting **(C)**.

node-negative disease. Further investigation is needed to clarify whether men with one or two positive sentinel lymph nodes benefit from completion axillary lymph node dissection (ALND), but patients with three or more positive sentinel nodes should undergo completion ALND.

For patients with clinically node-positive disease, a preoperative biopsy of concerning nodes can be performed, and if any nodes are found to contain metastatic carcinoma, an ALND is recommended. If carcinoma cannot be confirmed, we recommend a SLNB with patient understanding that a completion ALND may be warranted based on final pathology.

For patients who underwent NAC for locally advanced disease, we recommend axillary staging before initiation of chemotherapy with fine-needle or core biopsy rather than SLNB. Up to 40% of patients with positive axillary nodes will have a complete pathologic response in the nodal basin, though this varies by breast cancer subtype. Subsequent SLNB is then performed at the time of definitive surgery with the goal of obtaining three or more lymph nodes for evaluation. Targeted lymphadenectomy is used at some institutions if the positive lymph node was marked before neoadjuvant therapy. Patients with a positive sentinel node or those in whom three sentinel nodes cannot be identified require a completion ALND.

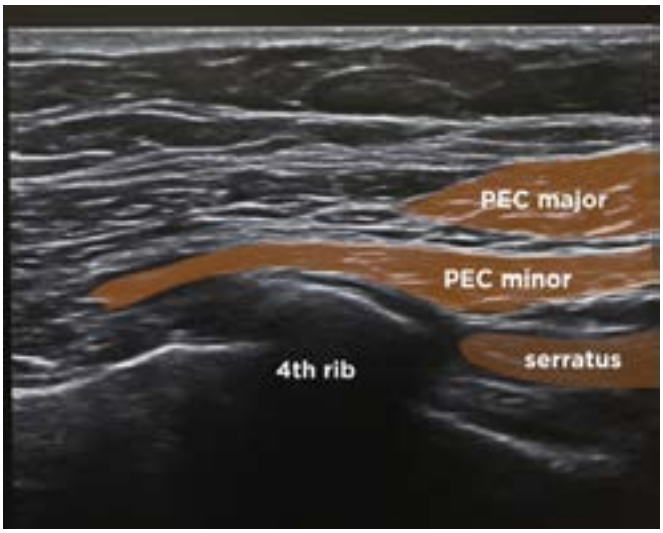


FIG. 3 Sonographic view of the muscle bellies of pectoralis major, pectoralis minor, and serratus anterior used to perform a PECS II block.

Analgesia

Pain control in the perioperative period is essential for patient satisfaction and improved recovery. A perioperative enhanced recovery after surgery protocol is recommended, several protocols for which exist. In most protocols, patients receive preoperative oral analgesics and pain modulators such as acetaminophen, celecoxib, and gabapentin. Before incision, a pectoralis II (PECSII) block can be used

as a regional block to mitigate the need for opioids in both BCS and mastectomy. To perform this block, a total of 20 cc of 0.25% bupivacaine is infiltrated between the muscle bellies of pectoralis major and pectoralis minor and between the pectoralis minor and serratus anterior under ultrasound guidance (Fig. 3).

Postoperative Considerations

Immediate postoperative care includes pain control, management of any drains, and routine wound care. Adjuvant radiation therapy and chemotherapy typically begin several weeks postoperatively for those in whom it is indicated.

The development of a contralateral breast cancer is much rarer among MBC survivors than for females, and there are no data to support the use of postoperative mammographic screening in men. However, MBC survivors should undergo lifelong routine follow-up with history and physical examination aimed at the early detection of local or distant recurrence. Survivorship programs specifically for men are sponsored by several national organizations and should be made available given the excellent prognosis for men who are diagnosed with early-stage disease.

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A Surgeon's Practical Guide to Breast Imaging

Michael D. Grant, MD, and Ronald C. Jones, MD

This chapter serves as a surgeon's guide for the appropriate use of imaging modalities in the evaluation and management of a potential breast disorder. Due to widespread screening, more than half of breast lesions that require assessment are nonpalpable. Therefore, it is important for the clinician to be aware of the available tools to further diagnose and manage specific breast abnormalities. Likewise, the interaction of the surgeon with the radiologist is of paramount importance in optimally managing patients with breast disease. Selecting the appropriate application of these various imaging modalities is beneficial in efficiently and economically obtaining a diagnosis.

For the purposes of this review, mammography refers to either 2D digital or 3D digital breast tomosynthesis (DBT) methods unless otherwise specified. Sonography is performed with specialized high-resolution handheld equipment designed specifically for breast imaging. MRI is accomplished with IV contrast and specialized breast coils.

THE ABNORMAL SCREENING MAMMOGRAM

A screening mammogram may identify an abnormality that requires further diagnostic evaluation. The radiologist will then give a specific recommendation for a diagnostic workup requiring an order from a physician. Breast calcifications are common abnormalities, and although most are benign, they can also be one of the earliest signs of a developing cancer. Magnification views are necessary to further define the characteristics based on size (macro vs. micro), shape (round, punctate, irregular, rod-shaped, pleomorphic), distribution (focal, scattered, clustered, linear, segmental), and behavior (stable, new, developing) and serve as the basis to judge whether a biopsy will be required. Suspicious microcalcifications are consistently irregular, represent a change in comparison to prior studies, and occur in a clustered or ductal distribution. The next step is a percutaneous needle biopsy using a stereotactic-directed, vacuum-assisted device; if the target is not easily identified using this approach, localized excision may be recommended as an alternative procedure.

Screening mammograms may also reveal abnormal densities that are classified as masses, asymmetries, or architectural distortions. A mass is a three-dimensional space-occupying lesion (seen in two views) and categorized as round, oval, or irregular in shape. Further evaluation by sonogram is then used as a diagnostic study to determine if this is solid, cystic, or complex. A mammographic asymmetry is a density that is visualized in one or two views and is usually caused by superimposition of normal breast tissue. This is clarified by special spot compression or rolled views and, if persistent, may lead to a biopsy recommendation. Architectural distortions are caused by tethering or indenting of breast parenchyma. The etiologies can be benign or malignant, but additional evaluation by special mammographic views, tomosynthesis, sonography, or MRI is required for further characterization. For all of the previously discussed abnormalities, BIRADS category of 2 or 3 will need follow-up imaging in 6 to 12 months, whereas BIRADS category 4 or 5 requires a biopsy.

PALPABLE MASS

A palpable mass is a frequent presenting complaint, either self-discovered or found by a clinician during routine examination. In addition to a thorough physical examination, a diagnostic mammogram (age >30) and sonogram should be obtained. Due to limitations with dense breast tissue, a mammogram may not be necessary if the patient is <30 unless there are adverse features on sonography. If the mass is found to be purely cystic and asymptomatic, observation is appropriate and many will resolve spontaneously; if the patient is symptomatic (pain, concern), percutaneous aspiration is recommended. A complex lesion also requires aspiration under sonographic guidance to rule out the possibility of an intracystic mass that, if present, will need to be biopsied. A solid mass necessitates a

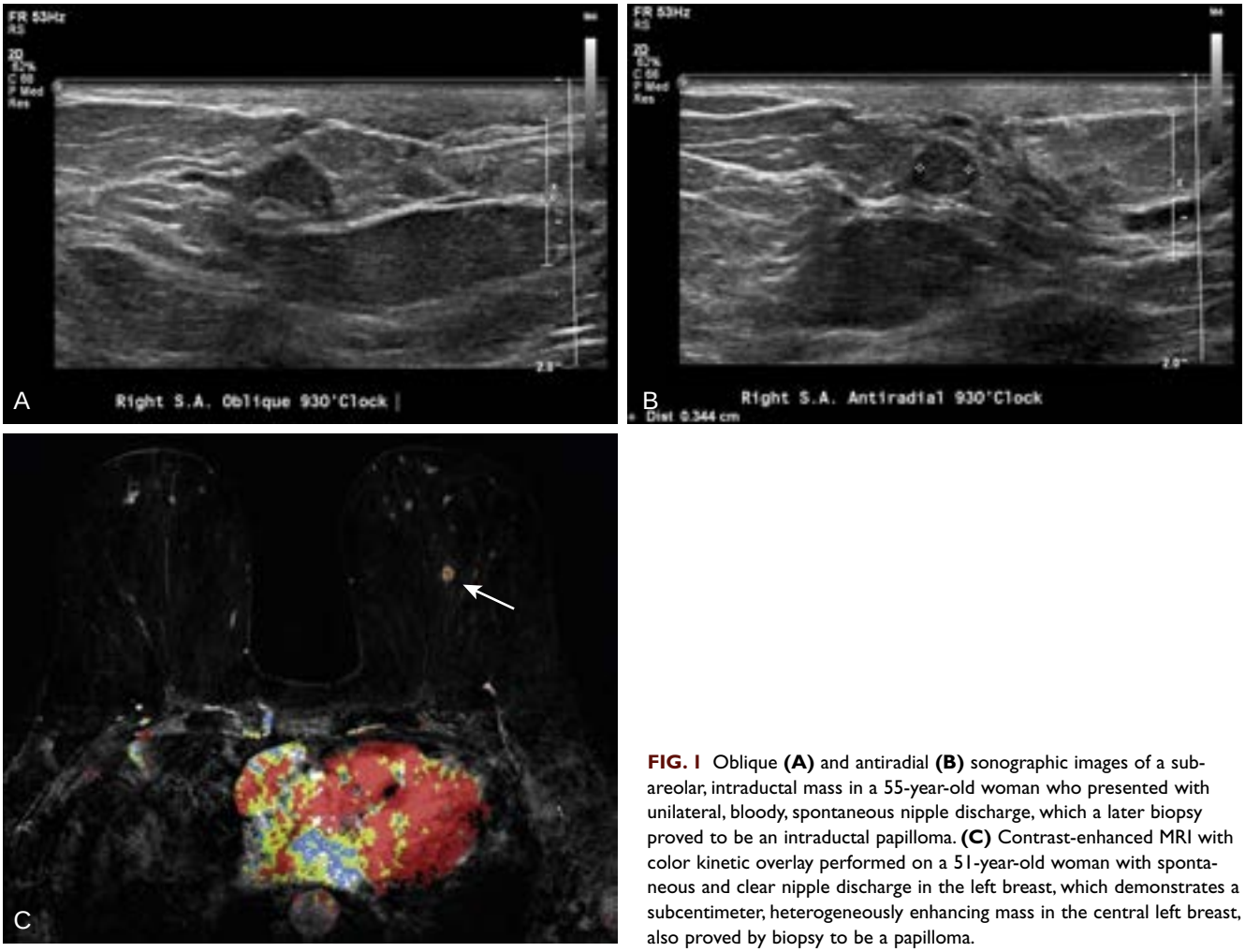


FIG. 1 Oblique **(A)** and antiradial **(B)** sonographic images of a subareolar, intraductal mass in a 55-year-old woman who presented with unilateral, bloody, spontaneous nipple discharge, which a later biopsy proved to be an intraductal papilloma. **(C)** Contrast-enhanced MRI with color kinetic overlay performed on a 51-year-old woman with spontaneous and clear nipple discharge in the left breast, which demonstrates a subcentimeter, heterogeneously enhancing mass in the central left breast, also proved by biopsy to be a papilloma.

tissue diagnosis either by fine-needle aspiration (FNA) or preferably core biopsy. If a biopsy is performed and the lesion is benign, a 6- to 12-month follow-up is recommended. Any lesion showing atypical features is further analyzed by excision. A diagnosis of malignancy calls for further multidisciplinary management. If neither the mammogram or sonogram is diagnostic, an attempt to obtain a tissue diagnosis should be entertained (core biopsy or excision).

NIPPLE DISCHARGE

Nipple discharge is the third most common complaint resulting in surgical and diagnostic radiologic evaluation. Most of the etiologies are benign and can be classified as physiologic or nonphysiologic. Physiologic nipple discharge is typically bilateral, spontaneous (not elicited), emanates from several duct openings, and is white, milky, yellow, or green in color. On the other hand, nonphysiologic discharge arises from a single duct opening and is usually unilateral, serous, or bloody. The radiologic evaluation should start with a diagnostic mammogram (age appropriate) in both circumstances. In the case of physiologic discharge, if the findings are negative, no additional radiology studies are necessary and a search for the underlying etiology should progress medically.

With nonphysiologic discharge, additional evaluation with directed subareolar sonography is also warranted (Fig. 1). If the mammogram and sonogram are negative, further evaluation with ductogram (galactography) or MRI should be considered.

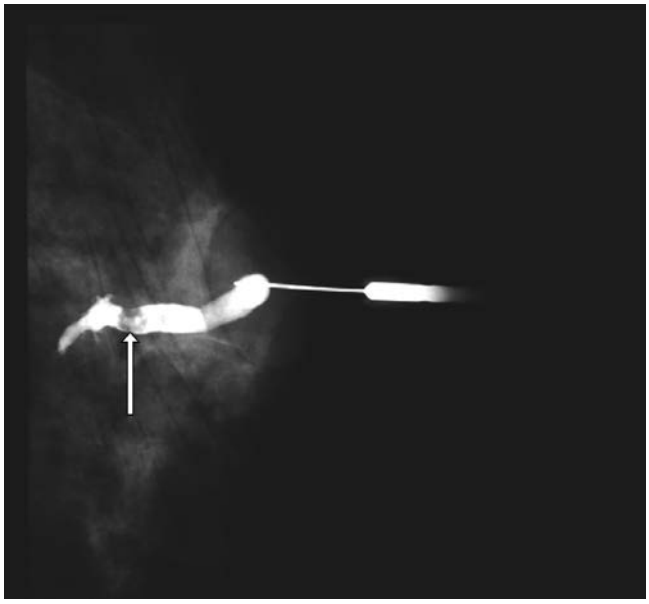


FIG. 2 Ductogram illustrating an intraductal filling defect *(arrow)* that proved to be a papilloma on subareolar resection. *(Courtesy Joe Spigel, MD, and Jean Wang, MD.)*

Ductography utilizes a thin cannula to access the duct in question and instilling a small amount of contrast material that opacifies the duct system for visualization on a mammogram. An abnormal study will identify a filling defect or abrupt truncation of the duct (Fig. 2). MRI can be used as an alternative to ductogram, identifying underlying pathology in 19% to 96% of cases where mammogram and sonogram are negative (see Fig. 1). Focal abnormalities discovered with any of these studies provides a target for obtaining a tissue



FIG. 3 **(A)** Axial MRI of an extracapsular rupture shows extravasated silicone, seen as a bulge in the axillary portion of the implant. The linguine sign is seen within the implant. **(B)** In a different patient, axial three-point Dixon MRI shows bilateral extracapsular rupture with the linguine sign and extravasated silicone in the lateral aspect of the implant *(arrow)*. **(C)** A more inferior slice on the axial three-point Dixon MRI shows the bilateral extracapsular rupture with extravasated silicone in the lateral aspects of the implants *(arrows)*. **(D)** Sagittal three-point Dixon MRI shows intracapsular and extracapsular rupture, with extravasated silicone anterior to the implant *(arrow)*. **(E)** Sagittal three-point Dixon MRI shows extravasated silicone far lateral to the implant within the breast tissue *(arrow)*. *(From Ikeda DM: Breast Imaging:* The Requisites*, 2nd edition. Philadelphia: Elsevier, 2011, Fig. 9.17.)*

diagnosis by image-directed needle biopsy or surgical subareolar excision.

The most common etiology is an intraductal papilloma (35%–48%), followed by duct ectasia (17%–36%), and then rarely malignancy (5%–20%). The risk of malignancy escalates with increasing age as well as the presence of a palpable mass. If all studies are negative and a spontaneous, nonphysiologic discharge is persistent, surgical biopsy by localized duct excision or subareolar resection can be considered.

An isolated nipple discharge in the male breast is very abnormal and requires diligent evaluation to rule out malignancy. Up to 9% of malignancy in males presents as a nipple discharge. Mammographic and sonographic evaluation should be performed followed by subareolar resection if the results are negative.

THE AUGMENTED BREAST

Surgeons are frequently consulted to diagnose breast abnormalities in patients with breast implants. These findings may or may not be related to a problem with the implant material, while the goal may also be to determine the presence or absence of implant rupture. Rupture of a saline implant is frequently diagnosed through physical exam alone since the patient will present with obvious asymmetry that spontaneously occurred. When the clinical exam is equivocal, mammography can be useful since the collapsed implant is easily visualized with routine imaging. In younger patients (<30), sonography is sensitive enough to detect a collapsed implant shell.

Silicone implant rupture may be more challenging to diagnose depending on whether it is intracapsular or extracapsular. If the rupture is intracapsular, it may not present with asymmetry on physical exam or routine mammographic imaging due to the low sensitivity for this entity (11%–69%). Sonography can be more helpful with a sensitivity of up to 75% but is more limited in diagnosing intracapsular ruptures where the accuracy is highly operator-dependent.

Extracapsular ruptures are frequently more easily diagnosed because of the classic "snowstorm" appearance of extracapsular silicone. MRI has the highest sensitivity (80%–90%) and specificity (90%–97%) but is expensive (Fig. 3). Finally, sonography is highly sensitive in determining the presence of periimplant fluid that is the common presentation of breast implant–associated anaplastic large cell lymphoma (BIA-ALCL), a rare T-cell lymphoma recently identified in association with textured implants.

LOCALIZATION

Preoperative localization is an integral component of surgical procedures to remove nonpalpable breast lesions. This is typically performed by a radiologist on the same day of surgery in an imaging center that may or may not be close to the surgical suite. The most common method is the percutaneous placement of one or more thin localization wires through or adjacent to the target area under a local anesthetic using mammographic, sonographic, or MRI guidance. This approach is accurate, effective, and relatively inexpensive assuming the expertise of the radiologist, cooperation of the awake patient, and scheduling logistics are all optimal. Disadvantages include inadvertent wire displacement, suboptimal wire placement, risk of vasovagal reactions of the patient during placement, and timing limitations when scheduling the surgical procedure. Some surgeons choose to perform their own localizations intraoperatively under sonographic guidance after induction of the patient's anesthetic; this is possible only if the target lesion can be adequately visualized sonographically.

As an alternative to wire placement, new technologies enable breast lesion localization before the day of surgery. These include radioactive seed localization, SAVI SCOUT, Magseed, and LOCalizer. Radioactive seed localization utilizes a weakly radioactive (I^{125}) seed that is placed percutaneously at the target area and then located intraoperatively using a handheld gamma probe. Although this localization procedure can be performed several days before surgery, the main disadvantage is difficulty of implementation due to stringent Nuclear Regulatory Council guidelines for handling of radioactive materials. The other devices are nonradioactive and use various technologies to detect percutaneously placed targets. LOCalizer utilizes a radiofrequency identifier tag (RFID) and a handheld detector for pinpointing the objective. Magseed is a tiny surgical steel marker that is placed up to 30 days before the surgical procedure and is located intraoperatively with a probelike sensor. The SAVI SCOUT apparatus is an implantable reflector paired with a radar detector. While these devices allow placement at a time other than the day of surgery, they are also expensive, require specialized equipment, and each have their own limitations. All of these techniques can also be applied to localization of clipped lymph nodes for targeted removal after preoperative chemotherapy treatment.

SUGGESTED READINGS

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Genetic Counseling and Testing

Katherine deAngeli, MD, and Elisa Port, MD

The identification of the *BRCA* genes in the 1990s was a monumental step forward in the care of breast cancer patients. And while *BRCA1/2* are still the most important genes associated with increased risk of hereditary breast cancer, many other genes have been identified in the past 25 years. As more genes have been identified, genetic testing has become more extensive. The field changes quickly enough that many women who originally tested negative before 2014 are being offered repeat testing with contemporary panels.

IMPLICATIONS OF GENETIC TESTING

Genetic counseling must be done in conjunction with testing and includes discussing the implications for the patient and their family. The Genetic Information Nondiscrimination Act (GINA) was passed in 2008 to protect patients from discrimination in health insurance and employment opportunities based on their genetic results. However, it does not cover life insurance, disability insurance, or long-term care insurance.

For patients who wish to proceed with testing, the good news is that it has become much more affordable and accessible in the past several years. There are three possible outcomes of genetic testing: negative, positive pathogenic mutation, and variant of unknown significance (VUS). A VUS is a genetic variant that has been identified but not necessarily associated with a negative clinical result. As the field of genetics expands, many of these VUS results are reclassified. Fortunately, most are downgraded to a negative result. Patients who are found to have a VUS are encouraged to reach out every few years to see if their specific VUS has been reclassified.

Genetic testing also has potential implications for other family members, particularly when testing results reveal a pathogenic mutation. The decision to undergo testing and the disclosure of the positive result can be quite sensitive among family members who are estranged or have made different decisions about when to test or whether to test at all. These issues related to complex family dynamics and the ripple effect on other family members (siblings, parents, offspring, and even those more distant such as cousins) are best handled in the context of genetic counseling.

GENETIC COUNSELING

Counseling is done before and after testing. Pretest counseling involves discussing the implications, getting a detailed medical history, and developing a pedigree with at least three generations. Posttest counseling addresses the significance of the results for the patients and their family members. The lack of availability and accessibility of genetic counseling services has been cited as a barrier to implementing more widespread genetic testing. Some insurance companies even mandate genetic counseling as a prerequisite for determining eligibility for testing based on National Comprehensive Cancer Network (NCCN) criteria and reimbursement. There are some geographical locations in the United States where in-person genetic counseling is of quite limited availability due to lack of genetic counselors. At our institution, we partnered with a company that provides an explanatory video to assist with pretest counseling and then a genetic counselor to perform remote/telephone posttest counseling once the test results are available. This helps offload the volume of patients with negative results so our in-house genetic counselors can spend their time on complex families and positive results.

WHO SHOULD GET TESTED?

According to NCCN guidelines, patients with a new diagnosis of in situ or invasive breast cancer qualify for genetic testing if they are male, of Ashkenazi Jewish ancestry, diagnosed with triple negative breast cancer, diagnosed young (≤45), or diagnosed at any age with a first-degree relative with young or male breast, ovarian, pancreatic, or metastatic prostate cancer. Patients can also be tested without a diagnosis of breast cancer if they have a known mutation in their family or a first or second degree relative who qualifies for testing. The American Society of Breast Surgeons released a consensus statement in 2019 that recommended testing everyone with a diagnosis of breast cancer to increase the identification of patients with a clinically meaningful mutation who do not fall into strict NCCN guidelines.

WHO ARE WE MISSING?

Despite these guidelines, genetic testing is underutilized. At our own institution with resources for testing and several genetic counselors, we found that age over 45 and having no identifiable Ashkenazi Jewish heritage were both associated with a missed referral.

WHICH GENES ARE TESTED FOR?

Genetic testing can range from testing only for *BRCA1/2* to a panel of more than 77 different genes. Genetic counselors typically discuss how extensive of a panel to send during pretest counseling. A smaller panel can answer the immediate question of hereditary breast cancer risk. A larger panel can inform a patient's risk and screening recommendations for several other hereditary cancers. Some patients prefer to keep a narrow focus when undergoing genetic testing while others prefer to know as much information as possible.

To assess breast cancer risk, a commonly run panel is Ambry's *BRCA+*, which includes eight genes for breast cancer: *BRCA1, BRCA2, CHEK2, PALB2, ATM, CDH1, PTEN,* and *TP53*. All are tumor suppressor genes. *BRCA1/2, PALB2*, and *ATM* are involved in repair of double-stranded DNA breaks. A mutation in *CDH1* causes a loss in E-cadherin, a protein that allows cell adhesion and is associated with hereditary diffuse gastric cancer and lobular breast cancer specifically. Staining for E-cadherin is one of the ways pathologists differentiate lobular breast cancers, which stain negative, from ductal breast cancers, which stain positive. *CHEK2, PTEN,* and *TP53* are involved in regulation of cell division. There are several known mutations in *CHEK2*, but the most studied mutation increases breast cancer risk as the number of affected family members increases. *PTEN* is associated with Cowden's syndrome, and *TP53* is associated with Li Fraumeni syndrome.

In our practice, the smaller, eight-gene panel is run in the peridiagnostic period of a newly diagnosed breast cancer when the results of testing could affect plans for surgical management. Results typically take 10 to 12 days, which allows patients to proceed to surgery in a timely fashion without significant delay. However, the selection of a surgery date should allow enough time for discussion for those with a high likelihood of testing positive and for whom results would affect recommendations for management by the physician or desire for different operative management by the patient.

WHAT TO DO WITH A POSITIVE RESULT

Although most breast cancers are not associated with an identifiable gene, as discussed earlier, positive genetic results can drastically influence surgical management. For example, a patient with a small breast

cancer who originally planned on having a lumpectomy may choose a bilateral mastectomy instead if she learns she carries a *BRCA* mutation. A positive genetic result is also informative for any children the patient may have. We generally recommend that the children of someone with a mutation wait until they are 25 before getting tested because this is the age at which screening would likely begin.

For an asymptomatic patient who tests positive for a pathogenic mutation, we offer high-risk screening. This involves a yearly mammogram alternating with a yearly MRI so they are getting imaging every 6 months. In addition to imaging, they come for a yearly breast examination. It is important to explain that high-risk screening does not change a person's risk of getting breast cancer. We counsel our patients that the goal of high-risk screening is to identify breast cancer early when it is very treatable but is not in any way preventive of breast cancer development. In addition, identifying early breast cancer is a goal but not a guarantee. Interval cancers that are identified by physical examination between "normal" screening tests are notorious among the *BRCA*-positive population. In particular, estrogen receptor/progesterone receptor/Her2-neu negative cancers (also known as triple negative breast cancers) that make up approximately 75% of cancers developed by *BRCA1* carriers can be particularly aggressive and defy screening and even rigorous early detection regimens. The only way to substantially reduce risk is with surgery, specifically by removing the vast majority of the tissue at risk for developing the disease. Although bilateral mastectomy cannot completely prevent breast cancer, it can reduce a patient's risk of breast cancer to approximately 1%. Historical series of subcutaneous mastectomy have shown risk reduction of approximately 90%. However, more recent series show a risk reduction closer to 99%, most likely based on current techniques and commitment to removing all breast tissue.

For a patient who learns she has a pathogenic mutation peridiagnostically, the pathway involves treating the current breast cancer followed by high-risk screening postoperatively if she decides to have a lumpectomy or yearly physical examination if she decides to have a bilateral mastectomy.

WHO IS OFFERED RISK-REDUCING MASTECTOMY?

Current NCCN guidelines recommend offering risk-reducing mastectomy for asymptomatic patients with *BRCA1/2, PTEN*, and *TP53* mutations. For *BRCA* patients, it is important to refer them to gynecology to discuss bilateral salpingo-oophorectomy as well. Although there is excellent screening for breast cancer, there is not for ovarian cancer. Therefore, women with *BRCA* mutations are generally recommended to have their ovaries removed after they have completed childbearing and before age 40 to 45. When they are ready for their mastectomies, we make sure to have updated imaging, which is usually a bilateral mammogram and ultrasound or bilateral mammogram and MRI within the last 6 months.

WHAT ARE THE SURGICAL OPTIONS?

For patients who are undergoing risk-reducing mastectomy, nipple-sparing mastectomy with reconstruction is a safe option. The two incisions we most commonly use are an inframammary fold incision or a radial incision on the lateral breast. The best candidate for nipple-sparing mastectomy is someone with a smaller, nonpendulous breast where the nipple-areolar complex (NAC) is in anatomic position. This type of NAC has the most robust blood supply and thus the best chance of surviving. If a woman is not a nipple-sparing mastectomy candidate because her breasts are too large and pendulous, she may choose to have a breast reduction and lift in preparation for nipple-sparing mastectomy several months later. The delay of a two-stage mastectomy is acceptable in a prophylactic setting, whereas it would be inappropriate for a patient with breast cancer.

Suggested Readings

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Contralateral Prophylactic Mastectomy

Thomas W. Smith Jr., MD, MS, and Swati A. Kulkarni, MD

Contralateral prophylactic mastectomy (CPM) is a surgical procedure that is most often performed when the unaffected breast is removed at the time of a therapeutic mastectomy for a unilateral cancer. The rates of CPM have continued to rise in recent years, largely driven by younger, average-risk women. Misconceptions about cancer risk, peace of mind, and interest in symmetry are among the primary reasons women opt for CPM. Importantly, the number of women who develop contralateral breast cancer has been decreasing in recent years, and there is little evidence that CPM improves survival. CPM should be discussed with women who have a high risk of contralateral breast cancer but should be discouraged in average-risk women (Fig. 1).

INDICATIONS FOR CONTRALATERAL PROPHYLACTIC MASTECTOMY

Pathogenic Variants in Breast Cancer Susceptibility Genes

Some genetic counselors and surgeons recommend a more tailored approach to genetic testing for breast cancer susceptibility genes based on age of diagnosis, family history of cancer, Ashkenazi Jewish decent, histology, and tumor biology. Others test all women with a newly diagnosed breast cancer. As a result, multigene panel testing is currently performed before surgical planning for a significant proportion of women with a newly diagnosed unilateral breast cancer.

Pathogenic variants in *BRCA1* and *BRCA2* carry increased risk of contralateral breast cancer after breast cancer diagnosis. *BRCA1* mutation carriers have a higher risk of contralateral breast cancer compared with *BRCA2* mutation carriers. The cumulative 10-year risk is 20% for *BRCA1* and 10% for *BRCA2*. Moreover, this cumulative risk increases with early age of primary cancer diagnosis. Women carrying a pathogenic variant of *BRCA1* or *BRCA2* under

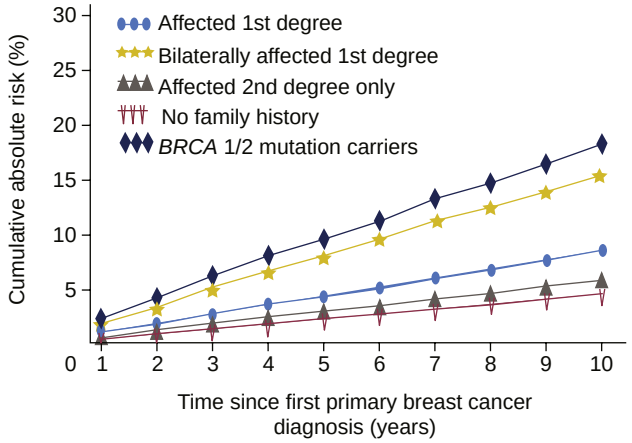


FIG. 1 Risk of contralateral breast cancer. *(Data from Reiner AS, John EM, Brooks JD, et al. Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: a report from the Women's Environmental Cancer and Radiation Epidemiology Study. J Clin Oncol. 2013;31:433–443.)*

40 years of age have a 10-year cumulative risk of contralateral breast cancer of 25% compared with approximately 6% in noncarrier women of the same age demographic. Additional highly penetrant mutations associated with contralateral breast cancer, identified in multigene panel testing, include pathogenic variants in *TP53* (Li Fraumeni syndrome), *PTEN* (Cowden's syndrome), *CDH1* (associated with hereditary diffuse gastric cancer), and *PALB2*. The option of CPM should be discussed with these women to reduce their risk of developing contralateral breast cancer. There is insufficient data to recommend CPM to women with mutations of moderate penetrance genes such as *CHEK2*, *ATM*, *BARD1*, *STK11*, and *NF1*. These women can be managed with clinical breast exam, yearly screening mammography, and MRI.

Variant of Unknown Significance

A variant of unknown significance (VUS) is a mutation in a gene that has not yet been classified as pathogenic or benign because there is insufficient data on the cancer risk associated with the mutation. It is important to counsel patients on the significance of a VUS identified on panel testing. The vast majority of VUS that are identified are ultimately reclassified as benign; therefore, the presence of a VUS is not an indication for a CPM.

History of Chest Wall Radiation

Women diagnosed with Hodgkin's lymphoma as adolescents and young women treated with mantle field radiation have a 25% to 30% risk of developing breast cancer before the age of 50. Bilateral breast cancer is common in these women, with half of women presenting with synchronous breast cancer and about 20% of women presenting with metachronous breast cancer at 5 years. Because of the excess risk of contralateral breast cancer in Hodgkin's lymphoma survivors treated with mantle radiation, CPM should be discussed with those women who present with a unilateral breast cancer.

Family History

The Women's Environmental Cancer and Radiation Epidemiology (WECARE) study found a strong relationship between family history of breast cancer and risk of contralateral breast cancer. Women without a pathogenic variant (specifically in *BRCA1* and *BRCA2*) and a first-degree relative with breast cancer had a two times greater risk of contralateral breast cancer compared with women without family history of breast cancer. The risk of contralateral breast cancer varied depending on the degree of relationship to the women, with first-degree relatives imparting the highest risk of contralateral breast cancer (see Fig. 1). Polygenic Risk Scores are emerging as a clinical tool to further stratify risk in women with a strong family history without an identified pathogenic variant in breast cancer susceptibility genes. At present, there is no evidence to support the use of polygenic risk to recommend CPM.

Age

The WECARE study also demonstrated an increased risk of contralateral breast cancer with earlier age of diagnosis. In women less than 45 years old at time of initial breast cancer diagnosis, the risk of developing contralateral breast cancer is higher than women greater than 45 years of age. This elevated risk is likely due to the increased life span of the woman, presence of a known genetic predisposition, and a family history of breast cancer.

Average Risk Women with Sporadic Breast Cancer

For the average-risk woman with a newly diagnosed breast cancer, the risk of contralateral breast cancer is low, and it has been declining steadily since 1985. Overall, women diagnosed with unilateral stage I–III breast cancer from 1990 to 2015 in the Surveillance, Epidemiology, and End Results (SEER) database were found to have a 0.37% annual risk of contralateral breast cancer, with a 25-year risk estimated to be below 10%. This decline is due in large part to advances in adjuvant endocrine therapy for estrogen receptor (ER)+ women. Even in ER– patients, cytotoxic chemotherapy and targeted therapies such as trastuzumab have been shown to reduce contralateral breast cancer risk by 30% to 40%.

Male Breast Cancer

Overall, male breast cancer is exceedingly rare in the general population, occurring in approximately 1:1000 males. Even in men with a pathogenic variant in *BRCA2* or *BRCA1,* the cumulative lifetime risk of developing a primary breast cancer is only 5% to 10% and 1% to 5%, respectively. Of those men diagnosed with unilateral breast cancer, only 2% to 4% develop contralateral breast cancer, and even though the numbers are small, it appears to be independent of the presence of a pathogenic variant or family history. Therefore, CPM is not recommended in men diagnosed with unilateral breast cancer.

OUTCOMES OF CONTRALATERAL PROPHYLACTIC MASTECTOMY

Risk Reduction for Contralateral Cancer

CPM confers a 95% relative risk reduction for developing a new breast cancer for all women. This can be impactful for women who have a pathogenic variant such as *BRCA1* or *BRCA2* because they have a high risk of developing a contralateral breast cancer. However, for women with average risk, who may have a 3% to 4% risk of developing a contralateral breast cancer over 10 years, the absolute of CPM benefit is very low.

Survival

There is little evidence that CPM improves breast cancer specific survival. Retrospective studies demonstrating improved survival should be viewed cautiously as there is likely significant selection bias towards healthy patients. Survival is largely driven by the index cancer because most subsequent cancers are early-stage invasive cancers or ductal carcinoma in situ (DCIS) detected by increased

surveillance after breast cancer diagnosis. A Markov model was developed by Portschy et al. to reduce the effect of selection bias seen in retrospective studies. The model estimated that the benefit of CPM in women with early-stage breast cancer was less than 1% regardless of age, stage, or biomarker status.

Local and Distant Recurrence of the Index Cancer

Patients often cite the desire to reduce the risk of local recurrence and distant recurrence after breast cancer diagnosis as a reason to perform CPM. CPM does not prevent local recurrence or distant recurrence from the primary tumor. It is important to counsel patients that CPM only prevents the development of a new breast cancer in the contralateral breast.

SURGICAL RISKS ASSOCIATED WITH CONTRALATERAL PROPHYLACTIC MASTECTOMY

A number of single-institution, retrospective studies have reported an increased risk of complications and higher rates of planned and unanticipated reoperations in women undergoing CPM compared with women who undergo unilateral mastectomy. Because women undergoing CPM are more likely to have breast reconstruction, and reconstruction is associated with more postoperative complications, the question of whether the increased risk is due to the increased risk of having a CPM alone or the addition of breast reconstruction was addressed in two American College of Surgeons National Surgery Quality Improvement Program (NSQIP) database reviews. Osman et al. identified 4291 patients who had either a unilateral mastectomy or CPM without reconstruction from 2007 to 2010. The 30-day complication rate was 4.2% versus 7.6%. A second study by Silva et al. analyzed 20,501 patients undergoing unilateral and bilateral mastectomy with immediate reconstruction and found a statistically significant increase in return to operating room, overall rate of complications, hospital stays, and transfusion rates for bilateral mastectomy patients compared with patients undergoing a unilateral mastectomy with immediate reconstruction. Overall, CPM confers a 2-fold risk of complications compared with unilateral mastectomy. Significant complications could negatively affect the start of therapy for individual women with high-risk breast cancer. However, overall, CPM does not appear to significantly delay the onset of adjuvant therapy.

IMPACT ON QUALITY OF LIFE AND PATIENT SATISFACTION

Eighty to ninety percent of women were satisfied with their decision to undergo CPM at 10 to 20 years after procedure, and more than 90% would choose CPM again. Women who have undergone CPM are generally satisfied with the appearance of their breasts and they have reduced cancer worry. However, women do not appear to have an improvement in overall quality of life, and about 20% to 30% of women cited decreased satisfaction with body appearance and femininity. Moreover, CPM appears to impact the sexuality of younger women. This could be a result of the loss of sensation in the breast skin that occurs with mastectomy.

ALTERNATIVES TO CPM

Patients cite fear of contralateral breast cancer as an indication for CPM; however, there are alternative approaches to reducing risk. Improved radiographic screening has increased breast cancer detection rates with the onset of 3D digital breast tomosynthesis and contrast-enhanced breast MRI. Beyond improved screening, alternatives to surgical risk reduction for contralateral breast cancer include improvements in systemic therapies. Women with hormone receptor-positive breast cancers have increased options for preventative techniques with endocrine therapy. Multiple randomized controlled trials have shown that women with ER+ breast cancers can halve their risk of contralateral breast cancer by taking tamoxifen, a selective estrogen receptor modulator (SERM) or aromatase inhibitors for 5 years. More recently, for women concerned about the risk of side effects of tamoxifen, a recent study found that 5 mg PO daily was as effective at reducing risk of breast cancer as the standard dose (20 mg PO daily) but was associated with fewer side effects. There are also surgical alternatives to CPM. Many women believe the only way to achieve symmetry is through CPM. Those women may be eligible for symmetrizing surgery such as mastopexy, augmentation, or reduction mammoplasty. Alternative surgical approaches to achieving symmetry should be included in the discussion with women who request CPM for symmetry.

COST-EFFECTIVENESS OF CONTRALATERAL MASTECTOMY

Beyond the effects on the individual patient, what is the cost of performing CPM compared with continued surveillance of the contralateral breast? Patients treated with unilateral mastectomy have continued costs after surgical intervention, including regular physician visits, screening breast imaging (mammogram, ultrasound, and MRI), and potential diagnostic biopsies for imaging detected or palpated abnormalities. Model-based studies have been used to compare cost of CPM with surveillance of the contralateral breast. For average risk women with early-stage, node-negative breast cancer, the cost-effectiveness over a patient's lifetime is controversial within the literature; however, it has been shown to decrease with age. For women aged 45 years old and younger, the cost of surveillance over a lifetime was equal to the breast cancer-related treatment costs with CPM. However, it was shown that CPM offers increased quality adjusted life years (QALYS) compared with surveillance (one QALY equals 1 year spent in perfect health, other health states equal a fraction of a QALY). It was estimated that women aged 70 years and older have no cost benefit, financial or QALY, with CPM compared with surveillance. Although the exact difference of cost-effectiveness of CPM and surveillance is unknown for average risk women, for high-risk women (including *BRCA1* and *BRCA2* genetic mutations) CPM has been shown to offer significant cost-effectiveness with increased QALYS for women of all ages.

SURGICAL OPTIONS FOR CONTRALATERAL PROPHYLACTIC MASTECTOMY

Types of Mastectomies

Simple mastectomy is performed for those women who do not want to have reconstruction. It involves removing the nipple-areolar complex, excess skin, and underlying breast tissue with an elliptical skin incision. Care should be taken to align the linear scars from both breasts and to avoid dog ears on the lateral and medial aspects of the incision. Skin-sparing mastectomy involves resection of breast tissue and the nipple-areolar complex while preserving the majority of the overlying skin to create a skin envelope for immediate breast reconstruction. For those women who are eligible based on bra size and amount of ptosis, nipple-sparing mastectomy can be performed through an inframammary incision. Care must be taken to remove all breast tissue, especially in the axillary tail. Mastectomy can be carried out with electrocautery or with tumescence depending on surgeon preference. At this time, there is insufficient evidence that robotic mastectomy improved outcomes of mastectomy and these should only be performed as part of a clinical trial.

Axilla

A meta-analysis by Nagaraja et al. found that occult invasive disease in the contralateral breast was identified in 1.8% of cases, and the rate of sentinel node positivity was 1.2%. Therefore, staging of the

axilla with sentinel lymph node biopsy (SLNB) is not recommended with CPM when preoperative imaging does not identify any suspicious or indeterminant lesions due to the low occult malignancy rate and the potential for short- and long-term surgical complications such as seroma, hematoma, sensory changes in the skin, and lymphedema.

Breast Reconstruction

Patients interested in reconstruction after mastectomy can undergo implant-based reconstruction or autologous reconstruction. Implant-based reconstruction generally involves a shorter operative time and shorter hospital stay. Tissue expanders are often placed at the time of mastectomy followed by permanent implants after adequate expansion. Occasionally, direct to implant reconstruction can be performed. Autologous reconstruction can be performed in women with adequate abdominal fat for reconstruction using free flaps such as deep inferior epigastric perforator (DIEP) flap or rotational flaps such as transverse rectus abdominis muscle (TRAM). Operative time and hospital stay tend to be longer, and the patient will have an additional surgical incision in the abdomen, but autologous reconstruction generally results in more natural appearing and feeling breasts. More recently, nerve preservation and grafting has been incorporated to preserve sensation after mastectomy. Consultation with a reconstructive surgeon should be part of the decision process for CPM as the recommendation for autologous versus implant-based reconstruction can differ depending on whether the patient chooses a unilateral mastectomy or bilateral mastectomy.

SHARED DECISION MAKING AND PATIENT EDUCATION

The goal of surgical planning is to come to a shared decision from medical understanding leading to the best oncologic outcome. Patients view surgeons among the most important source of information about their care. Surgeons should take the opportunity to include a discussion of CPM as part of their consultation. It is important to understand why a patient is requesting a CPM. The most common reasons women choose CPM are cancer worry, wanting peace of mind, and cosmetic outcome. Many patients overestimate risk of contralateral breast cancer and the benefits of CPM. If there are misconceptions about their risk of contralateral breast cancer, survival advantage, and/or reduction in local and distant recurrence, the surgeon should address them with the patient and provide them with their absolute risk of breast cancer when possible. For patients with more advanced disease who are requesting CPM, it can be helpful to inform patients that their risk of recurrence from their known index cancer is higher than their risk of contralateral breast cancer. It is also important to remind patients that the systemic treatment they will take to treat their index cancer will also reduce the risk of contralateral breast cancer. The surgeon should then discuss the risks and benefits, including the risk of additional surgical complications and lengthy recovery compared with breast conservation versus the benefits the patient will receive from CPM. The use of decision aides for CPM may also be helpful for the patient to focus on why they are choosing CPM. Overall, it is important for the surgeon to provide the patients with adequate information and support, so that the patient can make an informed decision about CPM (Fig. 2; Table 1).

CONTRAINDICATIONS TO CONTRALATERAL PROPHYLACTIC MASTECTOMY

CPM is contraindicated in patients with advanced stage disease, including stage IIIB (T4 disease, inflammatory breast cancer), stage IIIC (N3 disease), and stage IV (metastatic disease) breast cancers because initiation of oncologic medical therapy is crucial in overall survival. No potential risk of contralateral breast cancer outweighs risk of advanced primary disease and risk of distance recurrence and death (see Fig. 1; Table 1). Furthermore, CPM is relatively contraindicated in patients with severe medical comorbidities increasing the morbidity and mortality of surgery, including cardiac, pulmonary, hepatic, and renal dysfunction. A multidisciplinary team discussion is paramount in balancing desire for CPM versus risk of a poor outcome for the patient.

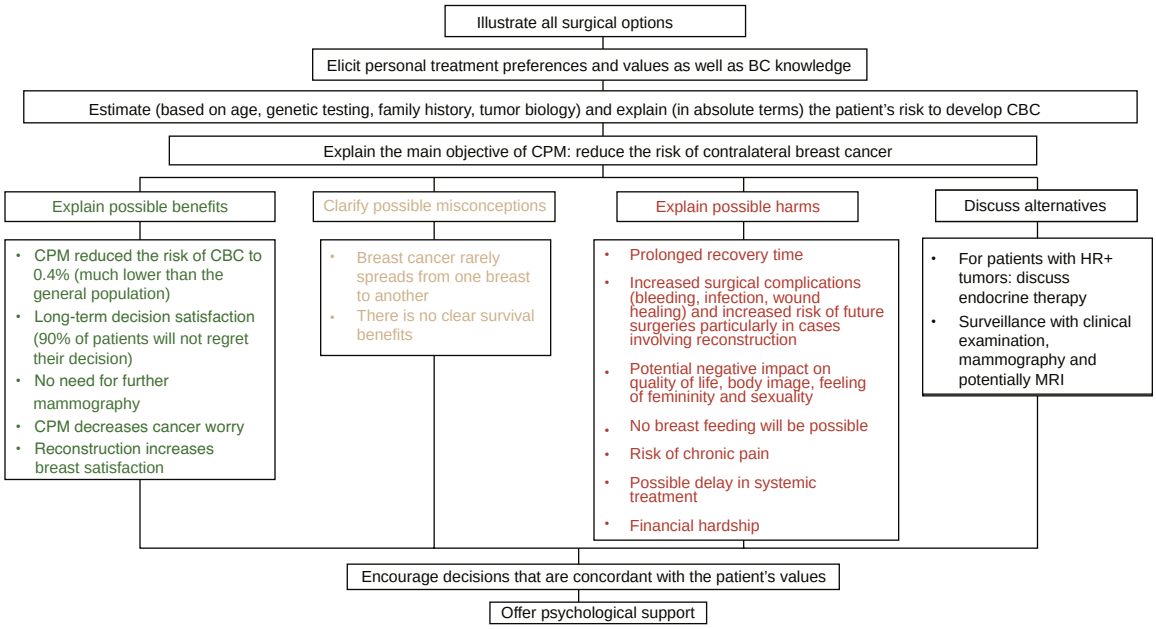


FIG. 2 Framework for a stepwise informed discussion with patients with sporadic unilateral breast cancer who are considering CPM. *BC*, Breast cancer; *CBC*, contralateral breast cancer; *CPM*, contralateral prophylactic mastectomy. *(From* Expert Rev Anticancer Ther. 2020;20:159–166.)

TABLE 1 Consensus Guidelines

	ASBrS	NCCN
CPM Discouraged	1. Average-risk women with unilateral breast cancer 2. Women with advanced index cancer (e.g., inflammatory breast cancer, T4 or N3 disease, stage IV disease) 3. Women at high risk for surgical complications (e.g., patients with comorbidities: obesity, smoker, diabetes) 4. Woman tested *BRCA* negative with a family of *BRCA*+ carriers 5. Male breast cancer, including *BRCA* carriers	
CPM Considered	1. Deleterious mutations of *BRCA1/2* 2. Greater than 25 % lifetime risk (Gail Model) of breast cancer primarily due to family history in the absence of deleterious mutations 3. History of mantle radiation (typically for Hodgkin lymphoma) before age 30 4. Gene carrier of non-*BRCA* gene (e.g., *CHEK-2, PALB2, p53, CDH1*).	Women with a known *BRCA1/2* pathogenic or likely pathogenic variant, typically between 35 and 40 years of age

ASBrS, American Society of Breast Surgeons; *NCCN*, National Comprehensive Cancer Network.

CONCLUSION

There are no absolute indications for CPM. It is an elective procedure that should only be discussed in a limited subgroup of women who have significant risk of developing contralateral breast cancer. For these women, the stage of the index cancer, patient age, medical comorbidities, and reconstructive options should be incorporated into the decision to undergo CPM. For the average-risk woman who requests a CPM, it is incumbent on the surgeon to understand the patient's motivations for CPM, educate the patient on the perceived versus actual risks and benefits of CPM, discuss alternative treatments, and discuss potential outcomes so the patient can make an informed decision about proceeding with CPM.

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Margins: How to and How Big?

Patricia A. Cronin, MD, and Richard J. Gray, MD

Complete cancer resection with negative margins is the goal of any surgical oncologist. It is an important component of breast cancer surgery, with local recurrence rates significantly higher in patients with positive margins. One of the more difficult conversations to have with a patient postoperatively is informing her of the presence of a positive margin and advising that further surgery is required. However, in breast conserving surgery (BCS), taking margins that are wider than necessary does not improve local control and may significantly worsen cosmesis. The volume of resection is the biggest driver of poor cosmetic outcome. Therefore, the balance in BCS is achieving optimal margins to maximize local control while maintaining the best possible cosmetic outcome.

Achieving negative margins and an acceptable aesthetic outcome requires careful interpretation of imaging, wise patient selection, regimented operative technique, coordinated specimen handling and communication with pathologists, and multidisciplinary interpretation of the pathologic findings that incorporates the best evidence in the context of the individual patient.

PREOPERATIVE PLANNING

Imaging

Evaluation of the available breast imaging is invariably the first step in assessing a new diagnosis of breast cancer. A complete and adequate set of mammographic views of both breasts should be obtained. The surgeon should review the imaging personally, but we encourage review with the breast radiology team. This can be done directly or at a multidisciplinary conference where new cases are discussed. This multidisciplinary assessment ensures adequacy of the imaging to determine whether further views are required. Multidisciplinary review helps optimize any further evaluation such as biopsies to confirm extent of disease or evaluate additional ipsilateral or contralateral lesions. Review in conjunction with breast imaging colleagues helps all parties to better appreciate the location and extent of disease within the breast. One must confirm pathologic concordance of the biopsy or biopsies, whether the clip placement was accurate, and the sites and types of clips if multiple clips were placed for multiple biopsies. In planning for preoperative radiologic localization, direct discussion with the breast imager performing the localization is invaluable, especially with multiple lesions or lesions in need of bracketing techniques.

For patients with ductal carcinoma in situ (DCIS), mammographic imaging alone is typically sufficient to establish the extent of disease based on microcalcifications. For those with invasive disease, mammography with ultrasound is the standard assessment. The use of adjunct imaging such as MRI should not be routinely performed. MRI does not improve margin reexcision or local recurrence rates. It is associated with false positives, second look ultrasounds, additional biopsies, and recommendations for short interval imaging. It may overestimate the extent of disease, especially with postbiopsy change having the potential to confound the reviewer. Clarification and investigation of MRI findings may delay surgery and can increase patient anxiety. The use of preoperative MRI has been associated with increased mastectomy rates.

MRI use should be limited to cases with complex radiologic findings on mammography and ultrasound for which MRI can help clarify and troubleshoot. The most common situations in which we would request additional imaging include mismatch between the clinical and the radiology findings, mammographically dense breasts that make the extent of disease difficult to assess, and in many cases of invasive lobular carcinoma where extent of disease may be underappreciated by conventional imaging. In our practice, we commonly utilize contrast-enhanced digital mammography (CEDM) in these cases as an alternative to MRI. MRI is clearly indicated for mammographically occult primary tumors in patients presenting with metastatic axillary disease.

Patient Selection

Patient selection for BCS is an important part of margin management. Essentially this comes down to a decision that the patient desires BCS and the surgeon can achieve negative margins with a reasonable cosmetic result. There is no defined tumor size for which BCS should not be considered, rather the ratio between the expected volume of resection to the size of the breast must be considered. A larger breast may accommodate a large resection that would be unacceptable in a smaller breast. Resection of volumes over an estimated 20% of breast volume is likely to result in asymmetry. For patients who will benefit from systemic therapy, this should be considered in the preoperative setting if the tumor size is too large or borderline for BCS and the patient would like to achieve breast conservation. Oncoplastic techniques, such as a combined reduction mammoplasty with BCS, can also help facilitate resection of tumors that are large in relation to the total breast volume. The tumor bed of any resection done with oncoplastic reconstruction should be carefully marked with clips to facilitate reexcision should a positive margin be found on final pathology. BCS may be attempted for multifocal and/or extensive disease but these circumstances are associated with an increased risk of positive margins and BCS should be reserved for well-informed, motivated patients.

Preoperative Localization

Lesions that are clearly palpable do not require additional localization. One must be mindful of clinical assessment after core biopsy when postbiopsy inflammation or hematoma may give the impression of a palpable lesion that will not be evident later. When in doubt, perform preoperative localization. For impalpable lesions, we use radioactive seed localization with iodine-125 radioactive seeds (Fig. 1). Single seeds can be used in most straightforward cases. In cases of multifocal or extensive disease or a linear distribution of microcalcifications, one should not hesitate to localize with multiple seeds or bracketing seeds around the lesion(s). Other localization devices are now available that do not use radiation, such as magnetic seeds. Wire localization is still an excellent option, but it must be placed on the morning of surgery, which affects timing and perioperative logistics, and it can be potentially dislodged inadvertently.

OPERATIVE TECHNIQUE

On the day of surgery, the surgeon should review the preoperative imaging, biopsy results, and clinical findings. The surgeon should have a clear understanding of the biology of the target lesion, its estimated size, the position of the lesion, the location and appearance of all clips, and the method of localization. Preoperative imaging including the craniocaudal (CC) and mediolateral oblique (MLO) views should be displayed in the operating room for review throughout the case. Displaying and reviewing CEDM and/or MRI imaging, if obtained, can be also useful.

Breast Conserving Surgery

There are many approaches to incision placement in BCS. It comes down to a balance between allowing sufficient access for adequate tumor resection with negative margins and a good cosmetic result. One should keep in mind the possibility of having to return to the OR to reexcise margins and thus how your approach now may help or hinder you in the future. Incision placement away from the tumor means tunneling; it may give a more hidden scar but may limit your ability provide adequate resection at the first procedure and hinder access at any needed subsequent operation. We typically utilize periareolar incisions for central tumors. In the upper pole of the breast, a transverse or curvilinear incision over or just inferior to the targeted lesion works well. In the upper outer quadrant with large tumors, a radial incision can give an excellent cosmetic result and may also allow for access to the axilla for sentinel node biopsy. For upper inner quadrant lesions, one should try to avoid incisions in the decolletage that may be visible later and a periareolar incision, or a crescent or batwing mastopexy approach, can be employed. For tumors in the lower pole of the breast, radial incisions give good access, facilitate cavity closure, and heal well.

BCS is typically performed either with a single specimen maintaining circumferential margins of 5 to 10 mm or a close excision of the targeted lesion followed by separate shaves of the cavity margins. The latter technique is the approach we will describe here. Following incision, dissect down to a level just anterior to the tumor. From preoperative imaging, one should already understand if the

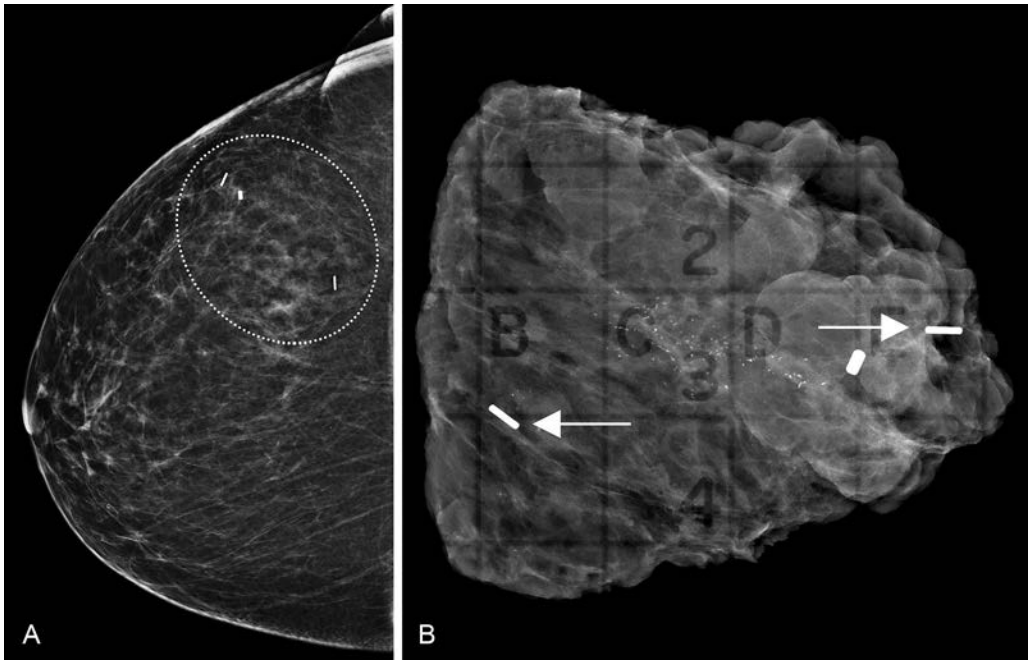


FIG.1 **A,** Localization mammogram demonstrating bracketing radioactive seeds demarcating an area of extensive ductal carcinoma in situ with the microcalcifications being targeted for resection. **B,** Specimen radiograph after resection demonstrating the bracketing radioactive seeds *(arrows),* microcalcifications and biopsy clip.

lesion is in the anterior, middle, or posterior depth. The localization technique then provides more precision during dissection through palpation, ultrasound, or position of the radiologic localization device. We utilize a measure of the gamma signal from the radioactive seed to determine distance from the seed and therefore the lesion. One must assure the gamma probe is directly aimed at the seed, not oblique to it, for accurate margin distance determination. One can then perform circumferential flaps at that depth anterior to the tumor. Aim to leave sufficient anterior margin on the main resection specimen while maintaining anterior tissue on the skin flaps to improve cosmesis. One need not routinely resect from the skin to the chest wall.

For palpable tumors, "hug" the tumor during the initial excision, using the nondominant index finger to feel as you go with frequent repositioning. Visual clues can also be evident with cicatrization of the tissues closer to the tumor. Many clinically impalpable lesions may be palpable intraoperatively when closer to them during dissection. For nonpalpable tumors with radioactive seed localization, continued measurements of gamma signal during dissection can maintain appropriate distance from the lesion. One should also use the preoperative imaging and the estimated size of the lesion to help guide the extent of resection.

The cavity is reviewed following resection of the main specimen. Five separate, uniformly 5- to 7-mm thick specimens are taken around the four radial margins and posteriorly. One should avoid creating any crevices on the true margin side that ink may penetrate and thus interfere with interpretation of the margin. A separate anterior margin can be taken if one is concerned about that margin on the main specimen or if the intraoperative pathologic assessment is that this margin is close or positive. If the main tumor is very close to or involves skin, then skin excision may be required. Incision placement should be planned preoperatively in the situation of superficial carcinomas to allow for this possibility and still minimize the effect on cosmesis. For invasive tumors found to be abutting or invading the underlying muscle, a portion of pectoralis or serratus may need to be taken to achieve negative margins.

Mastectomy

Even when performing a mastectomy, the surgeon should be mindful of the tumor location within the breast. If a skin paddle is excised, it may need to be adjusted to maximize the anterior margin. Areas of concern during dissection of the mastectomy flaps or posterior margin should be marked with ink and/or clips to make subsequent interoperative or reoperative reexcision more accurate should pathologic interrogation of the specimen reveal a close or positive margin. Such areas of concern should also be documented in the operative note with measurements from the nipple or other landmarks for future reference.

The anterior resection margin for nipple-sparing mastectomy (NSM) at the nipple is at the base of the nipple. It is not necessary to routinely core out the nipple as minimal duct tissue, if any, is present depending on the size of the nipple. The nipple margin is subjected to intraoperative frozen section. A positive margin may be improvable in patients with a substantial nipple by coring it out with an 11-blade scalpel. For most patients, a positive nipple margin will result in excision of the nipple, but the areola can be spared. In NSM cases with a lesion in proximity to the nipple on preoperative imaging, we recommend considering a lateral transverse incision to better accommodate possible nipple or nipple-areolar excision. An inframammary incision is an excellent approach for most patients to achieve the best cosmesis, but excising the nipple-areolar complex in these cases will result in two scars that may compromise the perfusion of the inferior mastectomy flap.

Borderline Lesions

Atypical ductal hyperplasia and classic lobular carcinoma in situ (LCIS) are lesions that are often excised for evaluation of the whole lesion due to the risk of upstaging to DCIS or invasive cancer. These lesions should be excised with narrow margins since they do not require a negative margin. Nonetheless, one should be mindful that if the lesion is upstaged the excision margins will become essential.

Thus, the specimen must still be carefully and accurately orientated for margin assessment. Cavity shaves need not be performed for these lesions unless for a specific intraoperative finding. Pleomorphic LCIS differs from the classic type and likely behaves more similarly to DCIS. Therefore, therapeutic excision with negative margins should be the goal of surgery for the vast majority of these patients.

SPECIMEN HANDLING AND PROCESSING

All specimens must be clearly oriented by the operating surgeon. Most use suture markings, clips, inks, or a combination of these. We place a long stitch in the center of the lateral margin, a short stitch on the superior margin, and a double stitch on the anterior margin of the main specimen. For cavity shave specimens, the new, true resection margin is marked with a medium clip for efficiency and further oriented on a piece of paper with written labels. More important than the method used is that orientation is done in a standardized fashion in one's practice and preferably at one's institution. This will minimize errors in labeling or interpretation by the pathology team.

Impalpable, localized lesions undergo specimen radiography. The specimen radiograph confirms retrieval of the seed(s) and the clip(s). It can also be useful to further assess the adequacy of margins, particularly for specimens containing microcalcifications. To better facilitate this assessment, the orientation of the specimen for the specimen radiograph should also be standardized. We place the specimen on the x-ray board with superior at 12 o'clock and lateral at 3 o'clock (for left-sided lesions) or 9 o'clock (for right-sided lesions). If the mass, calcifications, or the clip/seed are close to the edge of the specimen, this guides us in closer pathologic examination of that margin, a wider cavity shave margin at that site, or even a reexcision based on the imaging findings.

The main specimen and the five additional shave margins are brought to surgical pathology for processing and are assessed intraoperatively. As with orientation by surgeons, pathologists should have a standardized procedure for inking and processing specimens. In our practice, main specimens are inked with six colors, each standardized in designation of one of the six margins to be assessed. All specimens undergo gross pathologic examination and, depending on gross findings, tumor biology, and consultation with the surgeon, are subjected to targeted frozen section analysis. Although labor intensive and time consuming, targeted intraoperative frozen section further reduces the risk of reoperation for positive margins.

REEXCISION OF MARGINS BASED ON FINAL PATHOLOGY

When reoperation for margin reexcision is planned, it should be performed reasonably soon after the initial operation, especially when the cavity has been closed. The underlying mastopexy can then be taken down and the tumor bed reidentified. Then the face of the involved margin can be taken as a cavity shave and the new margin oriented. This should be performed similarly to what is described earlier for resecting cavity shave margins with intraoperative pathologic consultation.

For patients undergoing reexcision who had extensive microcalcifications, a postoperative mammogram should be performed to identify any residual calcifications that can be localized for the second operation to assure adequate resection of all disease. If a patient underwent an oncoplastic procedure, such as a reduction mammoplasty, reidentification of the tumor bed will rely on clips placed at the time of tumor resection. If identification of the site of needed reexcision cannot be done in a reliable fashion, mastectomy may be required to ensure the resection of all disease.

Breast Conserving Surgery for Invasive Cancer

We routinely follow the guidelines published in 2014 by the Society of Surgical Oncology (SSO) and the American Society of Radiation Oncology (ASTRO), which were subsequently endorsed by American Society of Clinical Oncology (ASCO) and the American Society of Breast Surgeons (ASBrS) and incorporated into the National Comprehensive Cancer Network clinical practice guidelines. For early-stage invasive breast cancer, no ink on tumor is a sufficient margin for women undergoing BCS with whole breast radiation. Achieving wider margins than no tumor on ink does not appear to reduce local recurrence rates. Of note, these guidelines do not apply to patients who plan to undergo no radiation or partial breast irradiation or patients who underwent neoadjuvant chemotherapy. The best practice for patients in these circumstances, as well as for all patients with close (<2 mm) final margins, is to undergo multidisciplinary review to impartially consider patient and tumor factors to finalize the decision on reexcision of margins. For some patients, a deviation from these general guidelines will be in their best interest, but a multidisciplinary review helps assure the best judgment for these exceptions. The decision to return to the operating room for margin reexcision should balance the risk of residual disease and local recurrence with the morbidity, cosmetic effect, and cost of reexcision.

Breast Conserving Surgery for Ductal Carcinoma In Situ

Likewise, we routinely follow the guidelines published in 2016 by SSO-ASTRO-ASCO regarding the optimal margins for pure DCIS lesions. DCIS has an excellent prognosis, but local recurrence rates are higher following BCS for DCIS lesions compared with invasive cancers, and half of all local recurrence events are invasive. The growth pattern of DCIS may be different, and the receipt of adjuvant therapies is less than that for invasive cancer. Thus, margins of at least 2 mm are associated with a reduced risk of local recurrence compared with narrower margins, and we routinely reexcise for margins less than this width. Margins greater than 2 mm do not significantly improve local control. This guideline does not apply to women who plan for to forego radiation. There are mixed data as to whether margins wider than 2 mm in that population would improve local control rates. Again, the best practice for patients with DCIS who plan to forego radiation, as well as for all DCIS patients with close (<3 mm) final margins, is to undergo multidisciplinary review to be sure to consider all patient and tumor factors. A 2-mm margin for DCIS is ideal, but the value of reexcision of a single focus of microscopic DCIS 1 mm from the margin in an octogenarian, for example, should be questioned.

Breast Conserving Surgery After Neoadjuvant Chemotherapy

The appropriate margin width for BCS after neoadjuvant chemotherapy is not known. Preoperative imaging is important to assess the pattern of tumor response. The effect of chemotherapy on primary tumors can differ with some tumors downsizing in a concentric fashion and others in a more "swiss cheese" pattern. This should be factored into assessment of appropriateness for BCS and preoperative planning. We routinely use a "no ink on tumor" criterion for the adequacy of margins in these circumstances since the National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and B27 trials used no ink on tumor as their margin definition with high local control rates and other published institutional data further support this criterion. But patients with close (<2 mm) margins should again undergo multidisciplinary review.

Mastectomy

Positive margins after mastectomy should be infrequent but can be challenging. There are no guidelines for what constitutes an adequate margin of excision for patients undergoing mastectomy, but positive margins are associated with increased recurrence risk, and many patients do not meet criteria for postmastectomy radiation. We

therefore ensure negative margins (no ink on tumor) for mastectomy patients and routinely perform reexcision for positive margins after multidisciplinary review. Reexcision is preferable to adjuvant radiation, which should be reserved for cases where the site of positive margin cannot be identified and improved.

Reoperation should be done early in the postoperative phase when the mastectomy cavity is more readily accessible with minimal dissection. Reoperation for positive mastectomy margins requires careful rereview of the original imaging; measurements from landmarks like the nipple in preoperative imaging, the operative report, and the pathology report; and the surgeon's recollection, and hopefully marking with clips, of the intraoperative findings. The surgeon should significantly overlap the targeted area of reexcision to allow for postoperative changes in orientation and the imprecision of such targeting. If a positive nipple margin is detected following NSM, then the nipple should be excised. The areola can be spared if desired. This should be planned in conjunction with the patient's reconstructive surgeon.

CONCLUSION

With modern management of breast cancer, local control rates are excellent. A better understanding of biology and use of systemic therapy have certainly played a role, but a robust, multidisciplinary approach to the primary tumor has been essential in these improvements. Surgeons should routinely reexcise for positive margins or for margins <2 mm when performing BCT for DCIS. But decisions to reoperate are best made with multidisciplinary review to dispassionately account for patient, tumor, and treatment characteristics, rather than margin width in isolation.

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Breast Reconstruction Following Mastectomy: Considerations, Techniques, and Outcomes, Part 1

Salih Colakoglu, MD, and Gedge Rosson, MD

Breast cancer remains the most common cancer and the second most common cause of cancer death in women. In recent years, breast cancer incidence rates have increased by 0.5% per year, however; the death rate decreased by 1% per year. The Agency for Healthcare Research and Quality reported a significant increase in overall mastectomy rates and, in particular, bilateral mastectomies more than tripled in less than a decade. This can potentially be attributed to an increase in genetic screening and improved patient awareness of breast reconstruction options after mastectomy.

Although the demand for breast reconstruction continues to increase, and the beneficial effects of reconstruction on quality-of-life and self-esteem are now well established, as of 2017 fewer than half of all women who required a mastectomy were offered breast reconstruction surgery in the United States. Studies revealed that a breast surgeon's decision to refer a patient for reconstruction significantly affects whether the patient will receive breast reconstruction. Because many women are unaware of insurance coverage for breast reconstruction provided by federal law (The Women's Health and Cancer Rights Act) and do not know how to access to such procedures, breast surgeons assume a crucial role by providing patients with appropriate referrals.

PREOPERATIVE CONSIDERATIONS

Mitigating Preoperative Risks

Although reconstruction of a new breast is a powerful adjunct of breast cancer treatment, it is still an elective procedure. Therefore, an operative risk assessment should be made accordingly. Elevating large skin flaps, performing large incisions, and placing foreign bodies such as implants and acellular dermal matrices (ADMs) require an optimized healing environment for satisfactory results. Although radiation and chemotherapy treatments cannot always be avoided, surgeons should identify and optimize the modifiable risk factors to minimize the risk of complications.

Because there is no distinct anatomic plane between the breast tissue and the subcutaneous fat, a breast surgeon's desire to remove the entire breast tissue to minimize the risk of local recurrence frequently results in thin mastectomy skin flaps. Because the mastectomy skin flap relies on the subdermal plexus for the blood supply, a thin and large flap becomes vulnerable to ischemia. Additionally, surgical retraction– and reconstruction-related mechanical stresses can further diminish tissue perfusion.

Patients with microvascular disease have a very high risk for partial or total mastectomy skin necrosis. Active smoking status has a strong association with infection, delayed wound healing, and skin necrosis complications. An infected breast implant, partial or total loss of mastectomy skin flaps, or partial or total loss of donor site skin flaps after autologous breast reconstruction can result in poor cosmetic outcomes and months of delay in postmastectomy breast cancer treatment. Although there is no high-level evidence behind different smoking cessation protocols, many surgeons require their patients to stop smoking 6 to 12 weeks before and after surgery. If a patient fails urine nicotine test before surgery, a delayed breast reconstruction can always be offered in the future.

Poorly controlled diabetes, high BMI (especially over 35), and poor nutritional status can all cause delayed wound healing and skin

necrosis, which ultimately results in loss of breast reconstruction, whether it is implant or autologous based. The impact of such major complications on a cancer patient's emotional status and overall outcomes can be destructive; therefore, patient optimization should be a crucial part of the surgical decision-making process.

AESTHETIC CONSIDERATIONS

Unilateral versus Bilateral Reconstruction

Whether it is an autologous- or implant-based reconstruction, achieving symmetry with a natural breast on the contralateral side creates a challenge for the reconstructive surgeon. This usually requires some revision surgeries including both the reconstructed and the contralateral breast. Although both reconstruction types can give satisfactory results, when aging-related changes are considered, it is not surprising that studies show higher general and aesthetic satisfaction rates with autologous flaps for unilateral reconstruction. Nevertheless, studies show that long-term quality-of-life scores are the same for both unilateral and bilateral reconstruction.

Nipple-Sparing versus Simple Mastectomy

Studies have shown that when certain tumor characteristics criteria are met, nipple-sparing mastectomy can be a safe option with similar recurrence and survival outcomes compared with traditional mastectomy techniques. Although this encourages patients to preserve their nipples to improve cosmetic outcomes, this can only be a feasible option for patients with small to moderate breast tissue volume and with low-grade breast ptosis. When patients have high-grade ptosis, nipple-sparing procedures may not be possible. Patients should be informed about several types of nipple reconstruction techniques and/or three-dimensional nipple tattoos that can be performed as a last stage of reconstruction in the future.

Patients who undergo bilateral prophylactic mastectomy because of genetic predisposition can be offered a breast reduction or breast lift procedure to improve the nipple position on the chest wall 3 to 6 months before the mastectomy. In this fashion, a nipple-sparing mastectomy can then be utilized for satisfactory cosmetic outcomes for patients with high-grade breast ptosis and/or macromastia. Because these procedures can delay the mastectomy 3 to 6 months, they usually cannot be offered to patients with active cancer.

RADIATION THERAPY

Radiation therapy creates a significant challenge to breast reconstruction by increasing almost any surgical complication rate and adversely affecting cosmetic outcomes. Although radiation therapy requires an entire chapter to discuss, two main points should be highlighted for the purposes of this textbook. First, when there is planned radiation therapy after mastectomy or just a possibility of radiation therapy based on the final pathology results, an autologous flap-based reconstruction typically should be delayed. The well-vascularized abdominal skin and soft tissue should be preserved to replace the radiated, unhealthy tissue after the radiation therapy is completed. Studies show that the long-term results of autologous reconstruction are more favorable than implant-based reconstruction for the radiated breast.

TIMING OF RECONSTRUCTION

Immediate Reconstruction

In an appropriate setting, any type of breast reconstruction technique can be utilized at the same time as the mastectomy surgery. Because the breast pocket is preserved, the reconstructive surgeon can have better control while shaping the new breast, thus providing a more natural aesthetic outcome. Overall, patients require fewer surgical procedures and a shorter, cumulative hospital stay. Also, women who opt to undergo immediate reconstruction avoid the experience of a flat chest altogether. The viability of mastectomy skin flaps is a greater consideration in the immediate setting because of the risk of infection and skin necrosis, as mentioned previously.

Delayed Reconstruction

Delayed breast reconstruction offers the ability to deliver adjuvant therapies without compromising the reconstructed breast. Especially with autologous breast reconstruction, radiated breast skin and soft tissue can be exchanged with healthy tissue when the patient recovers from adverse effects of adjuvant therapy. Also, it was seen to be a reasonable option when patients were unsure about their wishes or when they were overwhelmed with the ongoing breast cancer treatment. Loss of the breast envelope and need of a larger skin paddle with autologous flap reconstruction are two main disadvantages of delayed reconstruction. Today, truly delayed reconstruction is usually performed when there is no plastic surgeon readily available at the time of mastectomy. In high-volume centers, delayed-immediate reconstruction is a variant that is becoming the standard of care because it has several emotional and cosmetic outcome advantages over truly delayed reconstruction.

Delayed-Immediate Reconstruction

The delayed-immediate paradigm aims to circumvent the problems associated with loss of the breast envelope encountered with immediate reconstruction and the risk of radiating a newly reconstructed breast with healthy autologous tissue. A temporizing tissue expander is placed at the time of mastectomy to maintain the skin envelope in case the patient needs adjuvant radiation therapy. If final pathology results mandate radiation therapy, the expander can be deflated to facilitate the treatment. Once radiation therapy is completed, if the envelope has contracted it can be reexpanded gently to accommodate an implant, or the expander can be removed and replaced with autologous tissue. The latter route is perhaps preferable because of the significant risks of both short- and long-term reconstructive failure with implant-based reconstructions in the irradiated breast.

RECONSTRUCTIVE TECHNIQUES (FIG. 1)

Oncologic Reconstruction

This method refers to performing a lumpectomy surgery by utilizing breast reduction techniques. A plastic surgeon helps the surgical oncologist design a resection pattern that will remove the breast pathology with necessary margins while leaving enough and appropriately distributed breast tissue behind for a cosmetically acceptable breast shape and volume. Because the majority of these patients will require adjuvant radiation therapy, patients should be informed adequately regarding complications related to delayed wound healing.

Implant Based Reconstruction

Two-Stage Reconstruction

This more traditional implant-based breast reconstruction technique involves placing an expander into a subpectoral or prepectoral pocket as the first stage. Around 3 weeks after surgery, the patient returns to the clinic, and the expansion process starts by injecting saline (usually 50–150 mL per visit) into the expander port. Once the desired volume is achieved, the patient is scheduled for the second stage, which involves exchange of the expander with an implant. Although this might be a time-consuming process with several office visits, it offers better control over breast position, size, and shape. Also, arguably a tissue expander puts less stretch on fresh mastectomy flaps during the first-stage surgery.

Whether to choose a subpectoral versus prepectoral plane is an ongoing debate in the field and requires shared decision making

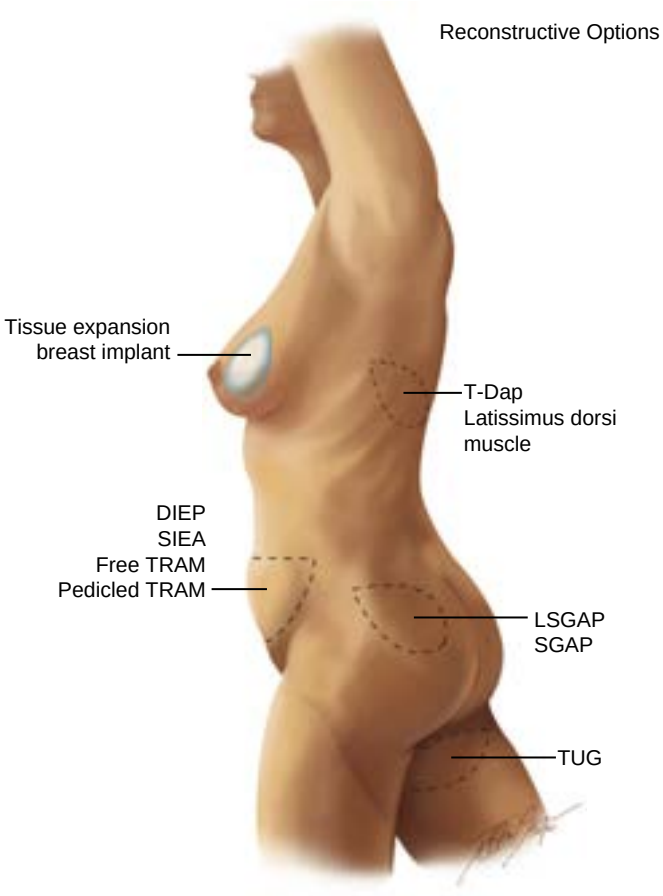


FIG. 1 Reconstructive options.

between the surgeon and patient with meticulous examination of the patient's skin and body habitus. For patients with thin mastectomy skin flaps, especially when there is concern for tissue viability, an additional muscle layer covering the expander can avoid exposure and potentially salvage the expander in case of tissue necrosis. Also, muscle coverage usually gives a smoother and more natural transition to implant on the superior pole. On the other hand, implants placed in the subpectoral plane usually create more discomfort during the expansion period given the increased muscle tension. Also, physically active women often complain about the animation deformity and displacement of implants superiorly with pectoralis muscle contraction. Because the subpectoral technique requires use of only a small piece of ADM (usually 8 × 16 cm) as a sling to cover the lower outer portion of the implant, it usually carries less seroma risk, with decreased cost compared with the prepectoral technique in which the entire anterior surface of the implant is covered with ADM. The prepectoral plane offers less discomfort during the expansion period but carries its own disadvantages. With mastectomy skin flap loss, expander salvage would be less likely, seroma formation can be problematic with extended drain stay, and a rippling deformity on the skin can result from inadequate soft tissue coverage over the implant. Revision surgeries with fat grafting can greatly mitigate these issues.

Single-Stage Reconstruction

Because the prepectoral plane precludes a tight inadequate submuscular space, a single-stage direct implant placement can be possible with this technique. Once again, because of mastectomy flap–related concerns, this is a less preferred technique, particularly for surgeons in a breast center where the oncologic surgeon creates these skin flaps. A small- to medium-size implant can be placed under thick and well-perfused mastectomy skin flaps after wrapping circumferentially with ADM. An indocyanine green angiogram can be utilized to assess viability of skin flaps before proceeding with implant placement.

Acellular Dermal Matrices

ADMs are cadaver-derived biologic sheets of dermis that support revascularization by ingrowth of blood vessels from adjacent tissues and, ultimately, integrate into the skin. Although there is controversy in the literature regarding their impact on increased infection and seroma formation rates, they are usually an essential part of implant-based breast reconstruction with acceptable risks.

COMPLICATIONS

Capsular Contracture

Capsules forming around the implants are normal physiologic responses to the insertion of foreign material in the body. Hematoma formation, radiation therapy, infection, subclinical bacterial contamination of the implant, implant rupture, and patient-related factors can all trigger an exaggerated physiologic response resulting in a firm, tight, and displaced breast pocket. This can create a wide spectrum of symptoms from mild firmness with palpation to chronic pain based on the severity of capsular contracture. A plastic surgeon may need to remove the entire capsule (capsulectomy) or revise it (capsulotomy). Sometimes a change in the tissue plane can create the most predictable and satisfying outcomes with complete resolution of the symptoms.

Infection

Implant infections usually arise in the subacute postoperative period (20–30 days), and patients commonly present with a red breast and a history of pyrexia or feeling generally unwell. Implant infections without systemic manifestation should be managed by oral antibiotics first, most commonly linezolid and high-dose ciprofloxacin. Signs of sepsis, recurrence of symptoms after completion of antibiotic course, or no improvement with initial antibiotics all warrant explantation of the implant. In exceptional circumstances, it might be possible to irrigate the breast pocket and place a new implant in the immediate setting, but reinfection rates are generally high, and patients must be counseled accordingly.

Implant Rupture

Implant rupture rates have been reported to be to be as high as 10% to 20% at 10 years after breast reconstruction. The US Food and Drug Administration (FDA) recommends performing the first ultrasound or magnetic resonance imaging (MRI) examination at 5 to 6 years postoperatively, and then every 2 to 3 years thereafter for asymptomatic patients. For symptomatic patients, an MRI is recommended at any time postoperatively.

Clinical signs of a ruptured saline implant are usually very clear, with significantly decreased breast volume and distortion in the breast shape on the affected side. However, a silicone implant rupture can be clinically asymptomatic, with minimal symmetry issues or physical examination findings.

Breast Implant-Associated Anaplastic Large Cell Lymphoma

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a new form of T-cell, non-Hodgkin lymphoma arising within the capsule of breast implants and is currently thought to arise in relation to primarily textured implants. The true incidence is unknown, but current estimates range between 1 in 3187 to 30,000 women with textured implants. The etiology of BIA-ALCL remains elusive, but tonic activation of the immune system in relation to either subclinical infection or inflammation is considered as the

underlying drive for lymphomagenesis. Patients commonly present with late-onset seroma formation on the effected breast (on average 7 years after insertion). Needle-guided aspiration with cytologic evaluation for CD30-positive cells confirms the diagnosis. Capsulectomy alone is curative for disease confined to the capsule, but adjuvant therapies such as chemotherapy or monoclonal antibodies may be required for extracapsular spread.

AUTOLOGOUS RECONSTRUCTION

Although over 70% of breast reconstructions performed in the United States are implant based, free flap reconstruction has advanced significantly in the past two decades, and abdominal-based perforator flaps have become increasingly common in autologous breast reconstruction. Autologous reconstruction is commonly accepted as a preferred technique after radiation therapy because it exchanges the thin, discolored, and contracted skin and soft tissue with healthy tissue. The primary advantage of autologous reconstruction is absence of prosthetic device–related complications with more natural feel as they are made of vascularized tissue. Long recovery time, emotional and physical distress in case of flap loss, donor site morbidities, and wound healing–related problems are main disadvantages of autologous breast reconstruction. Although autologous reconstructions require a greater investment of time at the time of reconstruction, over a lifetime they can offer more favorable outcomes and incur less of a healthcare and economic burden than implant-based reconstructions, particularly in patients who underwent radiation therapy.

Abdominal Free Flaps

Replacing tissue loses is essential to achieve functionally and aesthetically pleasing outcomes; therefore, the ideal tissue for breast reconstruction is fat with or without skin (Fig. 2). Because of the availability and quality of the soft tissue with an acceptable postsurgical scar pattern, abdominal-based flaps are the most commonly used autologous tissues for breast reconstruction. In the past two decades, advancements in microsurgical skills have allowed reconstructive surgeons to raise the abdominal skin and the underlying fat tissue without damaging the rectus muscle as much as in previous techniques. Several studies reported superior donor site outcomes (less ventral hernia, abdominal bulging, and pain) and patient satisfaction rates with deep inferior epigastric artery perforator flaps (DIEPs) compared with the more conventional pedicled transverse rectus abdominis muscle (TRAM) flaps.

The skin of the abdomen is supplied by blood vessels that are originating from the deep epigastric artery and perforating through the rectus abdominis muscle and its fascia in a predictable manner. The skin and fat of the abdomen can be raised by dissecting these perforators with a varying degree of accompanying muscle and following the deep inferior epigastric artery to its origin at the external iliac artery. In the majority of patients, it is possible to raise this flap without sacrificing muscle because of the suitable trajectory and caliber of the perforators. Therefore, the donor site morbidity is minimized by preserving the musculature and its innervation. However, in some instances, the caliber of perforators is too small; therefore, some or all of the rectus muscle must be included to ensure adequate blood supply to the flap. Both sides of the abdomen can be harvested to reconstruct both breasts at the same time, or both sides can be used to reconstruct one breast where greater volume is required. Abdominal flaps can also be raised with cutaneous nerves that pierce the anterior rectus fascia to supply the overlying skin. These can be coapted to nerves at the recipient site with a view to restoring protective and proprioceptive sensation to the breast.

The incidence of abdominal bulge/hernia is reported to range from 1% to 3% for DIEP flaps to up to 20% with TRAM flaps. It is therefore recommended that where muscle is taken, a formal

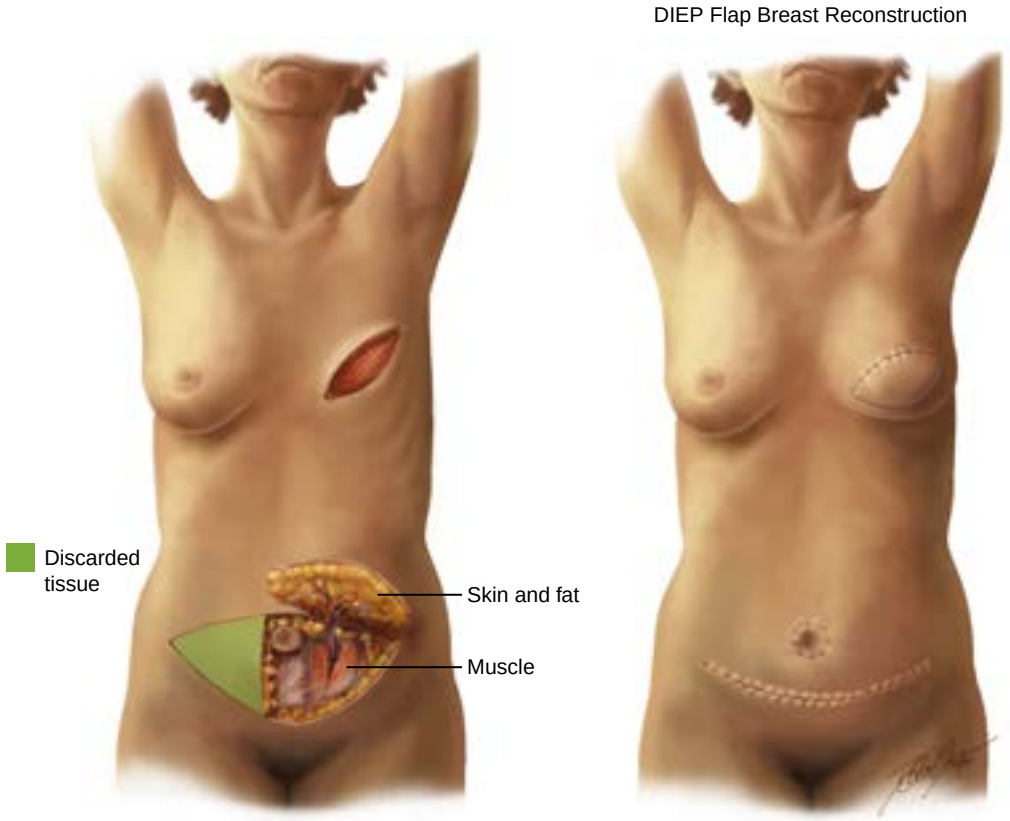


FIG. 2 Deep inferior epigastric artery perforator (DIEP) flap.

permanent mesh repair is performed to reduce this risk. The resultant donor site scar from an abdominal flap harvest is designed to stay as low as possible based on the perforator location seen on three-dimensional computed tomography angiogram or MRI angiogram and extends from hip to hip.

Before starting the ischemia time by clipping the vascular pedicle at the abdomen, the breast pocket should be prepared for flap inset, and the recipient vessels should be exposed and prepared for microsurgical anastomosis. The internal mammary artery and vein are the most common recipient vessels, and the preferred location for exposure is the second or third intercostal space (Fig. 3). Thoracodorsal vessels are the second most commonly used vessels in the axilla. Once the recipient vessels are ready for anastomosis, the ischemia time is started by clipping the deep inferior epigastric vessels as proximal as possible to obtain an adequate pedicle length. Venous anastomosis is usually performed first to avoid perfusing the flap without outflow, which might result in early congestion. For arterial anastomosis, 8-0 or 9-0 nylon sutures are usually placed in interrupted fashion. The flap is then inset loosely and carefully inside the breast pocket to avoid vessel kinking and congestion. The patient usually is transferred to a floor where hourly flap monitoring is available. Patients are usually discharged to home in 3 to 5 days.

Other Perforator Flaps

Gluteal soft tissue has been considered as a viable option when the abdominal donor site is not available because of inadequate tissue volume or damaged perforators caused by prior surgical procedures. Gluteal flaps like the superior gluteal artery perforator (SGAP) and the inferior gluteal artery perforator (IGAP) can sustain soft tissue with consistent vascular anatomy, good skin color match, and excellent thickness and texture of subcutaneous fat. However, difficult dissection of perforators, short pedicle length, and patient positioning–related problems make them less favorable choices compared with the new-generation perforator flaps such as the transverse upper gracilis (TUG) and profunda artery perforator (PAP) flaps in our practice.

The medial thigh is currently regarded as the second-line choice for autologous tissue. Thigh-based perforator flaps offer a discrete donor site scar in the groin crease. The TUG myocutaneous flap is based on perforating blood vessels traversing the gracilis muscle to supply the overlying skin. The profunda artery perforator flap is also raised from the medial thigh but sits posteriorly to the TUG flap. It is supplied by the perforating branches (second or third) of the profunda artery that pierce the adductor magnus posterior to the gracilis. The advantage of this over the TUG flap is that it usually offers a longer pedicle; however, both medial thigh flaps usually offer only a small amount of volume for transfer.

Pedicled Latissimus Dorsi Flap

The latissimus dorsi flap was more commonly used in the late 80s and 90s. It is raised based on the thoracodorsal vessels. A skin paddle can be designed transversely below the tip of the scapula so the scar can be hidden in the bra line when closed. This robust flap can be harvested in a short period because of its reliable anatomic landmarks. Although the latissimus flap rarely provides sufficient volume to reconstruct a breast, it becomes a viable option after failed microsurgical flaps. An implant can also be placed to increase the breast volume under the latissimus muscle at the anterior chest wall. The donor site can sometimes be problematic with prolonged seroma drainage. Also, studies suggest that there may be some degree of upper-limb/shoulder weakness, and up to 30% has been reported.

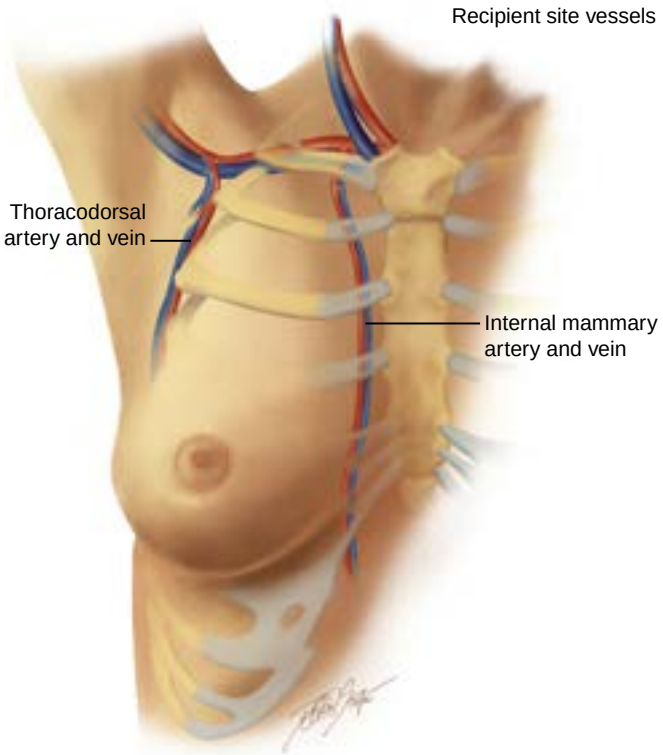


FIG. 3 Recipient vessel options.

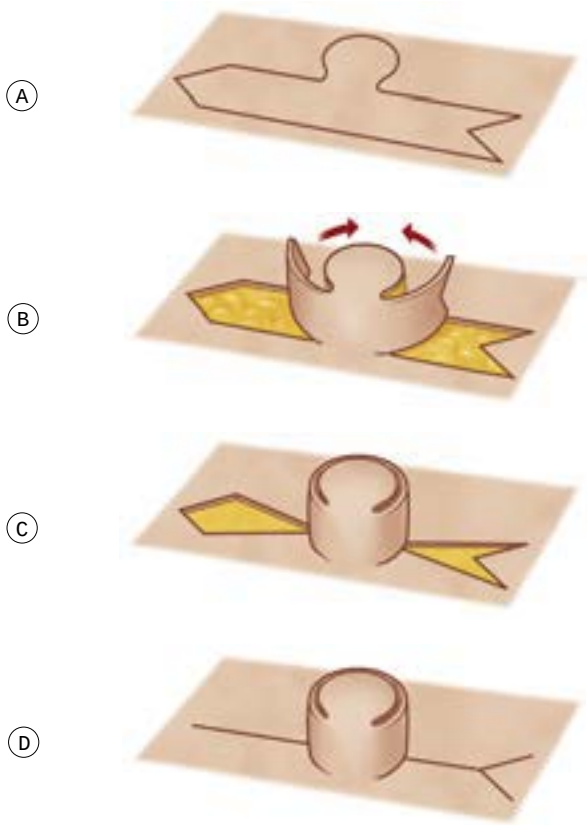


FIG. 4 Nipple reconstruction. *(From Neligan P. Plastic Surgery, 4th ed. Volume 5. Philadelphia: Elsevier; 2018.)*

REVISION SURGERIES

Fat Grafting/Lipofilling

A thin mastectomy skin flap that is inadequate to cover the underlying implant can give an unnatural appearance to the breast reconstruction with prominent implant borders, especially in the upper and medial poles. Also, patients with upper-pole deflation can require additional tissue to improve cosmesis. Liposuction of excessive fat from the abdomen, flank, and/or inner thighs can usually provide high-quality fat to improve these contour deformities. In a single stage, 100 to 150 cc of fat can be injected safely. Patients should be counseled that up to 30% to 40% of injected fat might disappear in time as a result of inadequate perfusion. Therefore, surgeons should consider multiple sessions to correct the deformities.

Nipple Reconstruction

Sparing the nipple during mastectomy may not be feasible, either because of tumor-related factors or advanced-grade breast ptosis. Patients should be counseled that there are variety of techniques available to create a new nipple as a final stage of breast reconstruction including local skin flaps, ADM-based reconstruction, or tattooing (Fig. 4).

BREAST CANCER SURVEILLANCE AFTER BREAST RECONSTRUCTION

Reconstruction with a variety of methods were found to be safe without any adverse effects on the incidence or time to detection of recurrent breast cancer. Mammogram and other imaging studies are usually not recommended to evaluate the reconstructed breast. However, patients and clinicians should continue routine examinations to detect locoregional metastasis on the chest wall, native breast skin, and regional lymph nodes.

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Breast Reconstruction Following Mastectomy: Considerations, Techniques, and Outcomes, Part 2

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INTRODUCTION

Breast reconstruction decreases psychological stress following extirpation of breast cancer and has been shown to not have a negative impact on cancer recurrence or survival. As a patient navigates the reconstructive process, there are many decisions to be made including the method and timing of breast reconstruction desired, which some patients find a source of additional stress on top of the cancer itself. The breast surgeon or general surgeon is often the patient's initial point of contact regarding reconstructive options, and it has been demonstrated that collaborative decision making, with medical professionals providing information regarding advantages and disadvantages of reconstructive options and patients expressing their desires for reconstruction and risk, helps patients move more smoothly through the reconstructive process. As such, it is imperative that the ablative surgeon have a sound grasp on potential reconstructive options and outcomes.

RECONSTRUCTIVE METHODS

Many different options for replenishment of lost breast volume due to mastectomy exist. Each has different advantages and disadvantages as well as ability to provide a satisfactory result both emotionally and physically for an individual patient (Table 1). Patients may have different goals for reconstruction including, but not limited to, complexity and length of the reconstructive process, tolerance to risk and potential complications, additional operative sites and scars, time in the hospital or off of work, and expectations for the final result. Additionally, patients have different comorbidities, body habitus, and potential need for breast radiation. It is important to understand all of the reconstructive options so the chosen reconstruction can be the one best suited to the patient's factors. While it is not unusual for a patient to tell their surgeon, "I just want whatever reconstruction is best!", one must understand that although there is not a *"best reconstruction,"* there may be a *"best reconstruction for this patient."*

Alloplastic Reconstruction

Alloplastic, or implant-based, reconstruction is the most common modality for breast reconstruction in the United States and is traditionally a two-stage reconstruction process. The first reconstructive procedure following mastectomy entails a tissue expander being placed in the breast pocket, either above or below the pectoralis major muscle, with or without the support of a scaffolding such as human acellular dermal matrix (ADM). The tissue expander is slowly filled with saline during serial outpatient office visits over several months to expand the remaining breast skin, which gives the patient the advantage of having some control over size and symmetry but results in an elongated timeline from start to finish. Following this, the tissue expander is removed, and a permanent implant is placed in the pocket created by the inflation of the tissue expander.

With the goal of circumventing the additional time and office visits required for traditional two-stage alloplastic reconstruction, single-stage implant-based reconstruction in which the patient goes "direct to implant" following mastectomy is becoming increasingly popular. With this technique, immediately following mastectomy, the reconstructive surgeon creates a pocket or "sling," typically with ADM, in which the permanent implant is secured to the pectoralis major muscle in the desired footprint of the breast. The native breast skin is then loosely draped over the implant, providing soft tissue coverage while the ADM scaffold supports the implant and prevents

TABLE 1 Comparison of Reconstructive Methods

	Reconstructive Method	Advantages	Disadvantages
Technique	**Expander-implant**	Smaller, low-risker operations/minimal down time; no donor site; more control of breast size	Requires foreign body; will need additional surgeries over time; poor radiation tolerance; longer time to completion; less patient satisfaction in obese
	Straight to implant	One stage to completion/minimal down time; lower-risk; no donor site	Requires foreign body; will need additional surgeries over time; poor radiation tolerance; requires careful patient selection
	Autologous	No foreign body; tolerates radiation well; behaves more like natural breast; higher patient satisfaction rates in obese	Donor site; longer, more complicated operations; more down time
	Hybrid	Very reliable (LMF); excellent implant protection/radiation tolerance; additional control of size/symmetry	Requires foreign body; donor site; more down time vs. IBR
Timing	**Immediate**	Improved psychosocial immediately after mastectomy; reduces overall number of surgeries/time to completion	Less time for patient decision-making; less time for patient optimization, surgeon coordination, increased postoperative complications compared with mastectomy alone
	Delayed	No delays to cancer extirpation; no additional complications to mastectomy	Worsened psychosocial immediately following mastectomy; issues with breast prosthesis
	Delayed-Immediate	Patient has breast(s) following immediately after mastectomy; simplifies initial reconstructive decision-making/scheduling	May cause unnecessary steps/delay to completion of reconstruction in some patients

IBR, Implant based reconstruction; *LMF*, latissimus myocutaneous flap.

excessive tension on the fresh mastectomy skin flaps. This method of reconstruction provides an immediate, one-stage reconstruction while avoiding the prolonged tissue-expansion process of the traditional two-stage technique.

Advantages to alloplastic reconstruction include the lack of a donor site from harvesting tissue as with autologous flaps and therefore a lack of pain, scars, or risk of complications anywhere except the breast(s) being reconstructed. The operation tends to be shorter and of lower risk with minimal to no time in the hospital and potentially less time off of work.

One of the biggest concerns with implant-based reconstruction is the prevention of infection. Maintaining sterility of the implants with sound surgical technique at the time of placement, healthy skin/soft tissue coverage with well-vascularized mastectomy flaps, and facilitation of good wound healing are vital to success when using a prosthetic device. Additionally, utilizing an implant-based reconstruction in a radiated breast field must be carefully considered, as alloplastic reconstructions that are radiated have a more than 4-fold risk of complications including infection, mastectomy skin flap necrosis, and capsular contracture compared with irradiated alloplastic reconstructions.

Breast Implant-Associated Anaplastic Large Cell Lymphoma

Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is a non-Hodgkin T-cell lymphoma first described in 1997 and was recognized as a distinct disease associated with breast implants by the World Health Organization in 2016. As of the current literature, there have been 573 reported cases, all of which were associated with textured implants, regardless of whether they were saline- or silicone-filled. No cases have been reported in smooth implants. The risk for patients with exposure to textured breast implants is estimated at 33 per 1,000,000 in the United States. Theories of etiology include chronic inflammation and preexisting lymphoproliferative disorders. Patients may present 7 to 10 years after texture implant exposure with breast seroma, swelling, or pain around the implant, and one-third of patients have a palpable mass of the implant capsule. In rare cases, regional lymph node involvement has been reported. Diagnosis is usually derived via cytology from aspirating the periprosthetic seroma or from histologic examination of the capsule. Treatment in most cases is accomplished with implant removal and complete capsulectomy. In cases where there is significant capsule infiltration or residual disease left in the patient, adjuvant radiation should be considered. Chemotherapy is typically reserved for those cases with lymph node involvement (CHOP). This disease is rare, and typically patients tend to do very well with survival rates of 93% at 3 years and 89% at 5 years. For asymptomatic patients, even those with implants that are currently under worldwide recall, serial follow-up with history and physical is recommended rather than prophylactic removal of the implants.

Autologous

Purely autologous reconstruction utilizes the patient's own tissue to replace the breast volume lost to mastectomy without use of an implant. Autologous reconstruction provides a single-stage breast reconstruction in which the reconstructed breast is the patient's own *living* tissue. As opposed to implants, autologous tissue tends to feel more like breast tissue, will gain weight and lose weight with the patient, and be less likely to need additional revisions years after the reconstruction. Women undergoing autologous breast reconstruction have higher satisfaction with their reconstructed breast, as well

as increased psychosocial and sexual well-being years later when compared with alloplastic reconstruction.

Abdomen

The most common donor site for autologous breast reconstruction is the abdomen, where the epigastric arterial system supplies the flaps. This system consists of the superior and inferior epigastric vessels that run on the deep surface of the rectus abdominis muscles. The superior and inferior epigastric vessels are in continuity with each other via smaller "choke" vessels. The epigastric system also sends perforating vessels through the rectus abdominis muscle that helps supply the skin of the fat and abdomen. All abdominal-based breast reconstructions take advantage of this epigastric system.

The most traditional option in abdomen-based reconstruction is the *Transverse Rectus Abdominus Myocutaneous (TRAM)* flap that can be transferred either pedicled or via free tissue transfer. Both methods entail a flap design where a transverse ellipse is marked out on the lower abdominal skin with a height extending from just superior to the umbilicus to the lower abdomen several centimeters above the mons and spanning laterally from hip to hip, utilizing tissue similar to what would be removed in a cosmetic "tummy tuck" operation. The skin, fat, and entire rectus abdominis muscle is included with the TRAM flap and can be transferred in one of two manners. The simplest method of transfer is a *pedicled TRAM*, in which the inferior epigastric vessels are divided and a subcutaneous tunnel from the abdominal donor site up to the breast pocket is created through which the flap is transferred and supplied by the superior epigastric vessels. The second potential mode of transfer is to divide both the superior and inferior epigastric vessels and separate the flap completely, moving the tissue up to the breast pocket and reconnecting the flap's inferior epigastric vessels to recipient vessels near the breast (typically the internal mammary or thoracodorsal vessels) under microscopic magnification, known as a *free TRAM*. The advantage of TRAM flaps in general over other autologous options is their ease of harvest and reliability. Pedicled TRAMs do not require specialized equipment or microvascular surgical skills, while free TRAMs do. Free TRAMs, however, have a better blood supply because the inferior epigastric vessels supply the lower abdominal soft tissue directly, as opposed to depending on the superior epigastric that must travel through choke vessels. The problem with TRAM flaps compared with other autologous options from the abdomen are postoperative abdominal wall weakness, abdominal bulging, and potential need for permanent mesh for closure of the anterior rectus sheath.

The donor site problems with TRAM flaps described earlier, as well as the advancement of perforator flap dissection techniques, led abdominal-based breast reconstruction to evolve from the traditional TRAM flap to the *Deep Inferior Epigastric Artery Perforator (DIEP)* flap. This technique employs the same flap design as the TRAM flap described before, but rather than harvesting the entire rectus muscle to include *all* of the blood vessels perforating the rectus muscle from the epigastric vessels as with the TRAM, only the main one to three perforating vessels are identified during the dissection and preserved with the flap. The fascia of the anterior rectus sheath is opened vertically around the perforating vessels, exposing the rectus abdominis muscle and removing essentially no fascia. The rectus abdominis muscle is split along its fibers (with minimal division of muscle fibers) around the preserved perforating vessels to allow these perforators to be dissected down to the underlying inferior epigastric vessels. Through the split rectus abdominis muscle, the full length of the inferior epigastric vessels are dissected and included with the flap. The DIEP flap consists only of skin and fat without harvesting any of the rectus abdominis muscle or overlying fascia. It is then transferred to the breast where microvascular anastomoses and inset are carried out, similar to that described for a free TRAM flap earlier. At the abdominal donor site, the anterior rectus sheath is closed primarily with no need for synthetic mesh, even in cases of bilateral DIEP flap harvest. Because no muscle is harvested, the abdominal weakness and bulging following a TRAM is typically significantly reduced or avoided. The use of abdominal tissue in breast reconstruction leaves an acceptable scar on the lower abdomen, as well as excellent abdominal soft tissue contour that is actually sought after by some patients for cosmetic purposes. DIEP flaps have become the gold standard for autologous breast reconstruction.

Lower Extremity

In cases where an abdominal donor site is not possible (previous abdominoplasty, previous free flap from the abdomen, or a patient too thin to harvest adequate abdominal tissue for breast reconstruction), the use of the thigh is a second donor site option for autologous breast reconstruction. Options such as the *Transverse Upper Gracilis (TUG)* flap and the *Profunda Artery Perforator (PAP)* flap utilize the medial and posterior-medial skin and soft tissue of the upper thigh, respectively. Other lower extremity donor site options are *Superior Gluteal Artery Perforator (SGAP) and Inferior Gluteal Artery Perforator (IGAP)* flaps, which are harvested from the buttock.

Advantages to autologous reconstruction are that it provides a single-stage reconstruction with higher overall satisfaction rates than alloplastic techniques. The lack of a prosthetic implant significantly reduces the consequences of infection. Disadvantages are the requirement of a flap donor site with associated scarring, pain, and potential complications remote from the reconstructed breast. Additionally, autologous reconstruction requires longer, more complicated operations, in some cases requiring specialized microvascular skills as well as longer operative times, hospital stay, and time off of work.

Hybrid

Hybrid breast reconstruction refers to the use of both autologous tissue as well as some form of breast implant. The most common example of hybrid breast reconstruction is the use of a *latissimus dorsi myocutaneous* flap (LMF). In this technique, an elliptical skin paddle is designed over the latissimus muscle on the side of the breast to be reconstructed. The skin paddle is cut away from the surrounding skin but left in continuity with the underlying latissimus muscle. The surrounding skin is elevated off of the superficial surface of the latissimus muscle, and the entire muscle along with the attached skin paddle is mobilized all the way up to the humoral attachments of the muscle. Care is taken not to disrupt the thoracodorsal blood supply to the flap. A subcutaneous tunnel is then created along the axilla from the flap donor site in the back to the breast pocket, and the muscle and skin are simply passed through this tunnel to the breast. The donor site is closed primarily, and the flap is inset at the breast. As opposed to abdominal and thigh donor sites, there is typically a paucity of soft tissue associated with this flap that does not usually allow enough volume to reconstruct a breast, and as such an implant is typically used in addition to a latissimus flap breast reconstruction. A tissue expander may be positioned deep to the flap at the time of transfer, or a permanent implant may be placed immediately if there is enough tissue laxity. The latissimus flap is highly reliable with acceptable donor site morbidity. This is a reasonable first-line option for breast reconstruction, although it is becoming less popular in this regard, losing ground to pure implant-based and DIEP flap options. It is an outstanding choice to cover an implant and significantly reduce complications in a radiated breast for a patient who prefers an implant-based reconstruction or for salvage of a previously failed breast reconstruction. The only absolute contraindications for the use of this flap are previous harvest, the thoracodorsal vessels having been sacrificed from previous axillary dissection, or attempt at free tissue transfer where these vessels were used as recipients.

TIMING OF RECONSTRUCTION

Immediate

Immediate breast reconstruction typically requires coordination between the ablative surgeon and the reconstructive surgeon, with the breast surgery team performing the extirpative operation and the

reconstructive team following immediately in the same operative setting. This method allows the patient to wake up from cancer surgery with a completed, or at least in-process, reconstruction, and may help to alleviate some of the stress many patients have at the thought of waking up with no breast(s). Immediate reconstruction also reduces the total number of surgeries required and provides a faster time to completion of the reconstruction process.

There are some challenges to immediate reconstruction, however. First and foremost, the requirement of schedule coordination between the cancer surgeon and reconstructive surgeon can be an obstacle that leads to delays in a patient's cancer resection. For implant-based reconstruction, with its relatively short operative time and much lower rate or intraoperative problems and complications, this delay is typically minimal. For autologous reconstruction, especially in the setting of free tissue transfer, the need for large amounts of scheduled time on both the part of the reconstructive surgeon as well as the operating room team can cause further delays. Although these delays are typically minimized between experienced practices, they are a consideration. Additionally, reconstructive surgeons managing patients who are active smokers, or have medical issues that could otherwise be optimized such as poorly controlled diabetes or obesity, may feel more comfortable delaying a patient's reconstruction to give them the best chance for a successful result. Care must be taken not to compromise a patient's cancer care for the sake of the reconstruction. Additional considerations to immediate reconstruction are a longer operative time for the patient at the time of mastectomy, potentially a longer hospital stay, and increased risk for postoperative complications vs. mastectomy without immediate reconstruction. In some instances, a patient may have difficulty deciding what type of reconstruction they wish to undergo or feel confusion or pressure from family, friends, a spouse, other doctors, or society in general that they *must* have their breasts reconstructed. If patients are sure they wish to undergo reconstruction but are not certain which route they would like to pursue, the most reasonable option may be delayed or delayed-immediate reconstruction.

Delayed

Delaying the start of the reconstruction of the breast is an option for patients that conveys advantages and disadvantages, which are the inverse of immediate reconstruction. From the surgeon standpoint (both the ablative as well as the reconstructive), scheduling becomes less of a challenge, especially for longer autologous reconstructive plans. The breast surgeon is free to perform the cancer operation as soon as appropriate without the added concern of coordinating with the reconstructive surgeon. In turn, the reconstructive surgeon can do the same at a future date without delaying or impacting the patient's care. Additional benefits to delaying reconstruction include the opportunity for improvement of patient-related factors such as smoking cessation, weight loss, or improved control of medical issues such as diabetes before reconstruction, where these problems can have a detrimental effect on outcome. Delaying the reconstruction may also be an advantage for those patients who feel overwhelmed by all of the decisions required in planning their reconstruction and do not want to be burdened with these decisions while they are undergoing cancer treatment. Others do not feel overwhelmed but simply do not want the added surgery, visits to the reconstructive surgeon's office, or potential complications of reconstruction until their cancer treatment is further along or even complete. Reconstructive delay is also an advantage in many cases when a patient is likely to need adjuvant radiation treatment. Radiation in the setting of a purely implant-based reconstruction is a significant source of complications and reconstructive failure (see later). Even in the setting of a purely autologous reconstruction, radiating the flap can lead to changes to size, position, and feel of the reconstructed breast, which may have been improved or avoided if the reconstruction was performed after radiation.

Disadvantages to waiting for reconstruction are several as well. Many patients find the thought of waking up from mastectomy without any form of reconstruction disheartening or even completely unacceptable and may be better served with some form of immediate reconstruction. Additional skin and breast pocket space that may be available immediately at the time of mastectomy may have been resected by the breast surgeon to facilitate closure or lost to wound healing, making delayed reconstruction of the breast more difficult due to less space for the reconstructive volume and loss of tissue pliability. The number of overall planned surgeries the patient will require is also increased because the patient's initial surgery was not used as part of the reconstruction.

Delayed-Immediate

Delayed-immediate reconstruction is a method of reconstruction that attempts to take advantage of the advantages of both of the traditional *immediate* and *delayed* timing options. In this method, most reconstructive candidates have a tissue expander placed immediately at the time of mastectomy. This allows all patients to wake up from mastectomy with a reconstruction started, and because of the speed and simplicity of the reconstructive part of the process, there initially are few decisions to be made on the part of the patient. Also, coordination of the schedules between the breast surgeon and reconstructive surgeon becomes much less of an obstacle. After this, all reconstruction options are open to the patient: if they wish to continue with expander-implant reconstruction, expansion proceeds as normal, and the reconstructive process continues uninterrupted. If patients decide to have autologous reconstruction, the tissue expander preserves the breast pocket, and the reconstructive procedure can be scheduled electively without the concern of delaying the patient's cancer operation. If the patient turns out to require adjuvant radiation therapy, the tissue expander can be left in place and postradiation reconstructive plans can be made.

RISK MANAGEMENT CONSIDERATIONS

Smoking

Cigarette smoking increases the risk of postoperative complications in both alloplastic and autologous breast reconstruction. In implant-based reconstructions, smoking increases the risk of postoperative wound healing delay, mastectomy skin flap necrosis, and implant infection by 8-fold, and the risk of these complications increases exponentially when smoking is combined with obesity or breast radiation. For autologous reconstructions, smoking-related complications include both mastectomy and abdominal skin flap necrosis and hernias. The risk of smoking-related postoperative complications improves with each week of smoking cessation up to 6 weeks, and patients who quit smoking at least 4 weeks before surgery have similar complication rates to nonsmokers. Smoking cessation should be encouraged before attempt at breast reconstruction, and many surgeons refuse to perform breast reconstruction in active smokers.

Obesity

Obesity (defined as a BMI >30 kg/m^2) is a major risk factor for postoperative breast reconstruction complications such as wound healing issues, infection, seroma, and reconstructive failure. Implant complications increase with increasing BMI and jumps significantly with BMI over 35 kg/m^2. These complications are increased regardless of the reconstructive technique or timing. Additionally, obese women have greater operative time, anesthesia risk, length of hospital stay, and perioperative morbidity, with obese women being nearly twice as likely to require reoperation than nonobese. Although failure rates are elevated with both implant-based and autologous reconstruction in obese women, they are less elevated with autologous reconstruction. In addition to the higher complication rates, patient satisfaction

with their postoperative breasts is lower for obese women as well, especially with implant-based reconstruction. Immediate microsurgical autologous breast reconstruction has been shown to yield higher satisfaction rates.

Patient Age

With approximately 75% of breast cancer diagnoses made in patients older than 65 years old, use of age alone as exclusion criteria for reconstruction results in a substantial portion of mastectomy patients without the option of reconstruction. While some studies have revealed complications rates similar between young and elderly groups when comorbidities are controlled for, other research has suggested patients older than 65 years of age may be a risk factor for perioperative complications following expander/implant reconstruction but not for autologous breast reconstruction where no difference in complications rates were found between those over or under 65 years of age. While there is some conflicting data, the use of the 5-factor modified frailty index (mFI-5),which looks at functional status, diabetes, chronic obstructive pulmonary disease, congestive heart failure, and hypertension requiring medication, appears to have a stronger predictive ability for complications than age alone.

Radiation

Patients who have breast reconstructions complicated by breast radiation therapy have typically either failed breast conservation efforts and required subsequent mastectomy or required postmastectomy radiation therapy (PMRT), which may be performed either before or after the patient's reconstruction. The use of radiation increases complications for all forms of breast reconstruction, regardless of timing, but can be especially problematic with implant-based reconstructions where they elevate the risk of mastectomy skin necrosis, infection, seroma, and capsular contracture. When radiation is performed before implant-based reconstruction, reconstructive failure in this setting is reported at 14%, and complications overall at 36%. In cases where PMRT was delivered after implant reconstruction, reconstructive failure was 19% versus 3% for nonradiated patients. Risk of reconstructive loss was higher when a tissue expander was radiated vs. the permanent implant, but cosmesis was worse when radiation was delivered to the permanent implant. For patients who wish to have an implant-based reconstruction in the setting of radiation, hybrid options such as utilizing a latissimus dorsi myocutaneous flap to cover implant-based reconstructions should be considered. This option reduces implant infection and reconstructive failure by over 70%.

Autologous reconstructions fare much better in radiated fields than do implant-based reconstructions. Microvascular free flaps placed in a radiated field have been shown to have minor postoperative complications such as mastectomy skin loss or infections. They may also have higher intraoperative arterial complications requiring further arterial dissection and anastomotic revision but no increase in flap loss or fat necrosis. Additionally, these patients will not have radiation changes to the breast flap such as pigment changes or fibrosis of the skin and subcutaneous tissue. Autologous flaps placed before PMRT tolerate radiation very well and may have some increased fat necrosis but otherwise minimal increase in problems. Autologous breast reconstruction is considered by many to be the gold standard for reconstruction in a radiated field.

SUMMARY

Although more than 60% of patients choose to undergo some form of reconstruction following mastectomy, others do not feel the need to undergo reconstruction at all and others simply want to focus on dealing with their cancer treatment and not be distracted with the decisions, additional doctors, and potential complications that accompany breast reconstruction. Although all patients should be given the opportunity to understand their breast reconstruction options, a decision to forgo or delay the reconstructive part of the process should be supported.

All of our patient's concerns are valid and it is the job of the reconstructive surgeon to use the tools and techniques available to us to help fill our patients desires for breast reconstruction as best as possible, while being observant of their emotional needs as they go through this process.

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Breast Implant-Associated Anaplastic Large Cell Lymphoma

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INTRODUCTION

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) was first reported in 1997, and it has emerged as a distinct type of T-cell lymphoma that develops in association with breast implants. The World Health Organization (WHO) initially categorized BIA-ALCL as a new class of lymphoma in 2016, and the National Comprehensive Cancer Network (NCCN) established the first set of evidence-based guidelines for the evaluation and management of BIA-ALCL the same year. Awareness of BIA-ALCL has gained traction over the last several years, resulting in an increased recognition and reporting of cases. This chapter will summarize the present knowledge regarding BIA-ALCL, review the current algorithm for diagnosis and treatment as published in the NCCN Guidelines version 1.2021 (last updated October 5, 2020), and address decision making regarding prophylactic management of patients who currently have breast implants.

SCOPE

BIA-ALCL is a rare peripheral T-cell lymphoma that most commonly arises in association with a current or prior textured breast implant. As of January 2020, the US Food and Drug Administration (FDA) has reported a total of 733 cases and 36 deaths from BIA-ALCL. BIA-ALCL can develop in association with breast implants that are placed for either aesthetic augmentation or reconstructive purposes and can occur with both saline and silicone implants. Implant manufacturer and shell type numbers associated with cases of BIA-ALCL are not currently evenly distributed.

EPIDEMIOLOGY

The actual incidence and prevalence of BIA-ALCL are challenging to ascertain due to multiple factors. Concerns exist regarding the accurate reporting of the overall prevalence of patients with implants, the level of detail recorded specifying the type of implant, the lack of robust implant and BIA-ALCL registries secondary to the voluntary nature of reporting, and the potential for underreporting due to lack of awareness of BIA-ALCL by providers and patients. Data collected over the years has estimated the risk of BIA-ALCL from 1 in 1 million (for all types of implants) to more recently as ranging from 1 in 3000 (for patients in Australia and New Zealand with textured implants) to 1 in 30,000 (for patients in the United States with textured implants).

Textured implants were initially developed with the premise that normal tissue growing into the textured surface would decrease capsular contracture, but it remains controversial as to whether the rate of capsular contracture is notably different for smooth versus textured implants. The classification system for implant surfaces ranges from grade 1 to grade 4 and is based on the surface area as well as the roughness of the surface, with 1 representing smooth implants and 4 representing the most textured surface. BIA-ALCL appears to be most associated with implants of grade 3 and 4 surfaces. It is postulated that the more highly textured surfaces allow for attachment of bacteria and development of a biofilm, stimulating a chronic inflammatory response and eventually leading to T-cell transformation and development of BIA-ALCL. Studies have examined the bacterial biofilms of breast implant capsules in patien' with BIA-ALCL as well as in patients with capsular contracture and have noted that gram-negative rods of the *Ralstonia* species are far more common in BIA-ALCL compared with *Staphylococcus* species in capsular contracture.

Given the rare nature of BIA-ALCL, the FDA recommends reporting of confirmed cases to the American Society of Plastic Surgeons BIA-ALCL Patient Registry and Outcomes for breast Implants and anaplastic large cell Lymphoma etiology and Epidemiology (PROFILE) registry, available at www.thepsf.org/PROFILE. Tracking of cases over time will hopefully allow for a more accurate assessment of the incidence and prevalence of BIA-ALCL.

PRESENTATION

The most typical clinical presentation of BIA-ALCL is a patient with a breast implant who develops a new fluid collection surrounding the breast implant or asymmetric breast swelling, occurring at least 1 year after the implant was placed and unexplained by other etiologies such as infection or recent trauma to the chest. The average length of time from implant placement to development of BIA-ALCL is 7 to 9 years. Far less commonly, BIA-ALCL can present as a palpable mass, lymphadenopathy in the regional lymph node basins (axillary, supraclavicular, or internal mammary), overlying skin changes such as a rash, or capsular contracture.

DIAGNOSIS AND WORKUP

For patients with breast implants presenting with a delayed fluid collection, asymmetric breast swelling, or less commonly a palpable mass, the initial step in diagnostic evaluation should be an ultrasound of the breast and ipsilateral axilla. Ultrasound can detect a fluid collection surrounding the implant, characterize a palpable mass (if present), and identify any lymphadenopathy. If ultrasound is inconclusive or indeterminant, then an MRI of the breast can be considered.

If a fluid collection is detected on ultrasound, aspiration of the fluid should be performed and the fluid sent for histopathologic evaluation. If there is any suspicion for potential infectious etiologies, a sample of fluid can also be sent for gram stain and culture. For the most accurate diagnosis of BIA-ALCL, at least 50 cc of fluid should be aspirated and sent for evaluation by cytology, immunohistochemistry, and flow cytometry. The specific tests to request include ALK (anaplastic lymphoma kinase), CD2, CD3, CD4, CD5, CD7, CD8, CD30, and CD45. BIA-ALCL is always ALK-negative and CD30-positive, and cytologic evaluation will demonstrate large anaplastic cells that express CD30. CD30 expression is nonspecific, however, and can be associated with other types of lymphoma as well as with benign inflammatory cells. BIA-ALCL will have a single clone of T cells present on flow cytometry. Correlation of the appropriate clinical context in conjunction with the cytology findings of large anaplastic cells that are ALK-negative and CD30-positive is necessary for the diagnosis of BIA-ALCL.

Patients with breast implants presenting with a breast mass on clinical examination or detected on imaging should undergo further evaluation with core needle biopsy of the mass. Pathologic evaluation should be performed using the biomarkers previously listed if there is clinical concern for BIA-ALCL, and other etiologies such as breast cancer should also be ruled out.

TREATMENT

Following histopathologic confirmation of a diagnosis of BIA-ALCL, a multidisciplinary treatment approach involving plastic surgery, surgical oncology, and medical oncology is recommended. Further imaging evaluation with a PET CT is indicated to evaluate for the

presence of any associated masses in the breast implant capsule, involvement of the chest wall, regional lymphadenopathy, and distant metastatic disease. For disease that is localized to the breast implant capsule and/or breast, the mainstay of treatment is complete surgical resection including the breast implant, total capsulectomy of the implant capsule, and resection of any masses associated with the breast implant capsule. Any suspicious regional lymph nodes should also be excised. The implant capsule, any fluid surrounding the implant, and any lymph nodes that are excised should be evaluated pathologically for complete staging of BIA-ALCL. For patients who have undergone complete surgical resection with no concern for residual disease, adjuvant therapies are not indicated. Close follow-up with clinical evaluation and examination every 3 to 6 months for 2 years, as well as consideration of annual systemic imaging with a CT scan of the chest/abdomen/pelvis or PET CT, is recommended.

If BIA-ALCL involves regional lymph nodes, or if complete surgical resection is not feasible and a portion of the capsule or residual disease remains, then adjuvant therapy is indicated. Radiation therapy can be utilized to treat local residual disease that is not amenable to surgical resection. Adjuvant systemic therapy is recommended for patients with node positive disease or in cases where radiation may not be possible to treat local residual disease. Systemic therapy is also indicated as first line treatment for patients with more advanced disease for whom surgical resection is not an option. Systemic therapy regimens that are utilized to treat BIA-ALCL include anthracycline-based regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or brentuximab vedotin (a CD30-targeted therapy) in combination with CHP (cyclophosphamide, doxorubicin, and prednisone).

Although the vast majority of cases of BIA-ALCL present with early-stage disease confined to a fluid collection surrounding the implant and/or involving the implant capsule, up to about 18% of cases can present with more advanced disease such as regional lymph node involvement or distant metastatic disease. As demonstrated by one study, patients with advanced BIA-ALCL were more likely to have a longer length of time from diagnosis to surgery and were less likely to have complete surgical resection compared with patients with early-stage disease.

With respect to prognosis, there are limited data regarding the overall survival for BIA-ALCL due to the rarity of the disease and the paucity of long-term follow-up. In one study of 87 patients with BIA-ALCL, the overall survival was reported as 94% at 3 years and 91% at 5 years. The ability to achieve complete surgical resection has been associated with improved overall survival and disease-free survival, as compared with incomplete surgical resection with or without adjuvant therapies. Locally recurrent BIA-ALCL is most commonly seen in patients who undergo incomplete surgical resection or partial capsulectomy.

For patients with bilateral breast implants, removal of the contralateral implant and capsule may be considered, as BIA-ALCL has been identified in the contralateral breast implant in approximately 4.6% of cases

STAGING

BIA-ALCL was initially staged according to the Ann Arbor Staging System for hematologic malignancies. Due to the behavior of BIA-ALCL being more in line with that of a solid tumor, the proposed staging system developed by Clemens et al. and included in the NCCN guidelines is based on American Joint Committee on Cancer TNM staging system. Tables 1 and 2 depict the TNM category descriptions and associated staging.

TABLE 1 Proposed TNM Category Descriptions for BIA-ALCL

TNM	Description	
T: Tumor extent	T1	Confined to effusion or a layer on luminal side of capsule
	T2	Early capsule infiltration
	T3	Cell aggregates or sheets infiltrating the capsule
	T4	Lymphoma infiltrates beyond the capsule
N: Lymph node	N0	No lymph node involvement
	N1	One regional lymph node involved
	N2	Multiple regional lymph nodes involved
M: Metastasis	M0	No distant spread
	M1	Spread to other organs or distant sites

TABLE 2 Proposed TNM Staging for BIA-ALCL

Stage Designation	Description
IA	T1 N0 M0
IB	T2 N0 M0
IC	T3 N0 M0
IIA	T4 N0 M0
IIB	T1-3 N1 M0
III	T4 N1-2 M0
IV	T any N any M1

FDA WARNINGS ON IMPLANTS

In response to concerns regarding the association between textured implants and BIA-ALCL, the FDA requested that Allergan recall Natrelle BIOCELL textured breast implants and tissue expanders in July 2019. The FDA's recommendation was based on the report of 481 out of 573 cases of BIA-ALCL worldwide being attributed to Allergan breast implants, resulting in a 6-fold higher risk of BIA-ALCL with Allergan textured implants compared with textured implants produced by other manufacturers. In addition, 12 of 13 deaths in patients with BIA-ALCL where the manufacturer of the implant was known had Allergan implants. The manufacturer was unknown for 20 additional deaths. Allergan complied with the FDA's request, and removed the specified Natrelle BIOCELL textured breast implants and tissue expanders from the worldwide market. BIOCELL is a unique textured surface that is found only in Allergan textured implants.

In the United States, textured implants represent approximately 10% of all breast implants. The FDA released labeling guidance for all breast implants (textured and smooth) in September 2020, with recommendations for a boxed warning stating that breast implants have been associated with BIA-ALCL, that BIA-ALCL occurs more commonly in patients with textured as opposed to smooth implants, and that deaths have occurred from BIA-ALCL. Moreover, the FDA recommends that breast implant information brochures provided to patients contain a decision checklist that indicates the risk of BIA-ALCL.

DECISION MAKING REGARDING PROPHYLACTIC MANAGEMENT

For patients who currently have breast implants (textured or smooth) and are asymptomatic, removal of implants as a precautionary measure is not recommended. Rising public awareness, discussion amongst medical professionals, and media coverage of BIA-ALCL have led to increasing inquiries regarding prevention of BIA-ALCL among patients, in educational forums, and during patient-physician encounters. Methods to potentially mitigate risk are frequently queried in the absence of any worrisome clinical symptoms and signs. Management of these concerns encompasses addressing patients' fears regarding potential development of BIA-ALCL in the future, rather than simply appropriately diagnosing and treating the disease if it occurs. Moreover, patient concerns related to BIA-ALCL are often intertwined with concerns regarding a constellation of symptoms commonly referred to as "breast implant illness." Literature in these areas is increasing, but consensus is not easily defined and controversy still exists.

Patients may request explantation, without replacement, of their breast implants. Recently, the number of implant explantation surgeries has been increasing (33% increase from 2018 to 2019, with more than 33,000 explantations performed in 2019). These surgeries can be associated with significant negative implications regarding chest aesthetics, and the true effect on risk mitigation is difficult to quantify. As a result, careful consideration of all options and thorough discussion with patients remains critical.

Patient-reported outcomes are integral to the justification of surgical decision making when considering explantation of implants for prophylactic reasons. Existing literature has demonstrated increased patient satisfaction and well-being following breast implant explantation in both symptomatic and worried patients. Studies have shown statistically significant subjective health improvement (in the realms of vitality, mental health, and body area satisfaction) and breast implant illness symptom resolution after explantation in patients experiencing preoperative concerns; with increased postoperative improvement associated with a greater magnitude of preoperative concern. Additionally, explantation regret has been minimal in several studies. The quality of the literature, however, is plagued by small sample sizes, complex and nebulous clinical scenarios, and questionable broad applicability of findings. Documented opportunities for psychological and physical improvement, or simply respect for patients' wishes, can justify explantation as a viable treatment option when considering the entire patient, rather than just the breast. Previously, Slavin and Goldwyn wrote, "Satisfying the needs in these patients emphasizes the importance and necessity of the surgeon taking the time to understand what the patient wants." Patient desire for removal of their implants may be an adequate sole justification for explantation.

SOFT TISSUE MANAGEMENT FOR PROPHYLAXIS

While en bloc capsulectomy is recommended for suspected or proven cases of BIA-ALCL, the appropriate management of the implant capsule in prophylactic explantation cases is less clear. Literature is lacking with respect to demonstrating clear benefits of prophylactic en bloc capsulectomy. Standard capsule management for implant revisions and removals includes capsulotomy as well as capsulectomy (partial, complete, or en bloc). Capsulectomy may decrease future risks related to any influence of proinflammatory substances, microbiomes, and genetics of capsules and periimplant tissues. Further confusion arises due to the fact that within the existing literature, "capsulectomy" may actually refer to "partial" capsulectomy, or total capsulectomy performed only in certain circumstances, with many authors accepting remnants of thin capsular tissue in surgical beds of asymptomatic patients.

Focusing solely on the physical results of surgery rather than on reduction of risk for future development of BIA-ALCL, capsulectomy may decrease risk for seromas, palpable or radiographic masses, and silicone retention; but it carries potential additional risks like increased operative time and expense, larger incisions, increased morbidity, pain, increased recovery time, risk of pneumothorax, and thinning of the soft tissue envelope. Potential contraindications to capsulectomy include thin capsules, thin overlying soft tissue of the breast/chest, a capsule that is densely adherent to chest wall structures, and use of the capsule for pocket management (such as lateral plication, inframammary fold revision, or symmastia correction). In reality, factors including characteristics of the implant (such as the composition of the implant contents and outer shell), size and shape of the implant pocket, thickness of the implant capsule, capsular contracture, silicone granulomas, calcification, implant rupture, infection, and carcinoma may affect decision making for any individual patient.

SUBSEQUENT RECONSTRUCTION

Reconstruction after BIA-ALCL is a realistic consideration if complete surgical ablation of the disease is achieved. While some authors have placed smooth implants following a diagnosis of BIA-ALCL, many patients and other authors would advocate for autologous tissue techniques such as mastopexy, fat grafting, and flaps. Patients who elect to undergo explantation of their implants for prophylactic reasons are also likely to look more favorably upon autologous methods of reconstruction.

Explicit patient counseling is recommended regarding the potential for undesirable postexplantation aesthetic results such as ptosis, nipple retraction, skin laxity, and hollow upper poles, as well as wide, deflated, "aged," and laterally displaced breasts. Studies have documented a wide spectrum of patient reactions to explantation, ranging from improvement to satisfaction to dissatisfaction and even feelings of mutilation. Various reconstruction techniques have not been reliably linked to any of these patient reported outcomes. There are many reported reconstruction methods with varied incisions, pedicles, flaps, and management of the implant pocket. The potential options for reconstruction will differ in patients who had implants placed for aesthetic augmentation versus patients who had implants placed for reconstruction following mastectomy. The quality and volume of the remaining soft tissue envelope, nipple and areola ptosis and size, implant size and position, and skin elasticity will all affect aesthetics of the postexplantation results and the available reconstruction options.

Insufficient breast tissue, poor quality skin, and history of radiation therapy are all factors that can make patients less ideal candidates for soft tissue redistribution techniques. Many patients with a history of implants will have the poorest quality tissue in the inferior pole, as a result of mechanical pressure and aging, particularly if the implants have been present for many years. This may make them poor candidates for many described autoaugmentation techniques. Volume can be reintroduced with autologous tissue transfer using distant flaps from donor sites such as the abdomen, but these procedures carry additional scar burdens. Literature has reported techniques for reintroduction of volume using other materials, such as acellular dermal matrix and fat grafting.

Regardless of the planned reconstruction method, timing of these techniques can be debatable. Immediate reconstruction when BIA-ALCL is suspected or proven has been performed, but should be considered only when preoperative workup and imaging demonstrate disease confined to the implant capsule. Otherwise, staging reconstruction 6 to 12 months later is likely prudent. In the setting of implant explantation solely for prophylactic purposes, reconstruction may be pursued in an immediate or delayed fashion based on anatomic considerations. In these situations, it is important to recognize that the scarring and uncontrolled contracture that can occur

in the absence of immediate reconstruction may be challenging to correct at the time of delayed reconstruction.

CONCLUSION

BIA-ALCL is a rare type of lymphoma most commonly associated with textured breast implants. The precise underlying etiology of BIA-ALCL is currently unknown, but it is hypothesized that the interaction between a bacterial biofilm and the textured implant surface may stimulate a chronic inflammatory response leading to transformation of T cells. Although the risk of developing BIA-ALCL is difficult to quantify, it is estimated to be 1 in 3000 to 1 in 30,000. Awareness on the part of patients and providers of the existence of BIA-ALCL and its presenting symptoms are key to early diagnosis and appropriate treatment.

In patients who present with a delayed fluid collection surrounding a breast implant, inclusion of BIA-ALCL in the differential diagnosis as well as appropriate histopathologic evaluation to confirm the diagnosis are essential. The vast majority of cases of BIA-ALCL are diagnosed at an early stage, and achieving complete surgical resection (removal of the implant, total capsulectomy of the breast implant capsule, and any masses associated with the implant capsule) portends an overall good prognosis. For patients who present with more advanced BIA-ALCL, systemic therapy is recommended, and radiation therapy may also be indicated. For patients who desire prophylactic explantation of their implants, a thorough discussion of the risks, benefits, spectrum of potential outcomes, and subsequent reconstruction options is essential.

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Adrenal Incidentaloma

Whitney Sutton, MD, MHS, Shkala Karzai, MD, and Aarti Mathur, MD, PhD

An adrenal incidentaloma is defined as an adrenal mass identified on imaging performed for an indication other than suspected adrenal disease. With increasing utilization of cross-sectional imaging over the past several decades, 40% of adrenal masses are now discovered incidentally. It is estimated that 1% to 8% of adults have an adrenal incidentaloma, and the incidence increases with age.

The initial diagnostic evaluation of an adrenal incidentaloma must (1) assess the risk of malignancy and (2) determine whether it is hormonally active. Of the functional lesions, the most common is Cushing's syndrome followed by pheochromocytoma and aldosteronoma. Once the diagnosis is achieved, if surgery is indicated, the benefits and risks of surgery should be considered and the operative approach determined. Finally, postoperative or nonoperative surveillance must be established.

INITIAL EVALUATION

The initial evaluation of an adrenal incidentaloma consists of: (1) A comprehensive history and physical examination to elicit signs and symptoms of adrenal hormone excess and cancer history, (2) radiologic evaluation, and (3) biochemical evaluation to determine risk of malignancy and functionality (Fig. 1).

The most common signs and symptoms in patients with hypercortisolism include hypertension, obesity, and hyperglycemia/diabetes (Table 1). They can also present with osteoporosis, facial plethora, proximal muscle weakness, easy bruising, weight gain, cutaneous abdominal striae, buffalo hump, and moon facies. Signs and symptoms of catecholamine excess are present in over 60% of patients with a pheochromocytoma and include hypertension, episodes of severe headaches, palpitations, perspiration, anxiety, abdominal pain, and nausea or vomiting. Patients with hyperaldosteronism may present with a history of asymptomatic or symptomatic hypokalemia, refractory hypertension, or fluid retention. In assessing for primary malignancy or metastasis, a personal history of cancer, smoking history, or recent weight loss should be elucidated. Hirsutism or feminization may represent physical signs of sex hormone excess, which can accompany adrenocortical carcinoma. In addition to the aforementioned signs and symptoms, particular attention should paid to the patient's vitals signs as an elevated systolic and diastolic blood pressure and/or heart rate are consistent with hypercortisolism, hyperaldosteronism, and pheochromocytoma.

Radiographic Assessment

The primary goal of imaging studies is to evaluate for radiographic features that portend a higher risk of malignancy. Although CT is the most commonly used imaging modality, MRI is preferred in children, adolescents, and pregnant women (Figs. 2 and 3). A triple-phase CT scan with and without intravenous contrast including arterial-enhanced, venous-enhanced, and delayed images of the adrenal glands is ideal for initial radiographic assessment as this imaging modality is readily available and provides excellent anatomic guidance should patients require surgery. Several specific radiographic features on CT should be considered to assess for malignancy or need for surgical resection. These are discussed in the following sections.

Size

Adrenal mass size >4 cm has been associated with an increased risk for cancer across several studies. Prior studies have approximated a 2% risk of adrenocortical carcinoma in masses <4 cm, a 6% risk in masses measuring 4 to 6 cm, and a 25% risk in masses >6 cm. However, size must be considered along with additional radiographic features in determining the threshold for surgery. The majority of incidentalomas >6 cm should undergo adrenalectomy. Management of benign-appearing, nonfunctional incidentalomas 4 to 6 cm in size is controversial, and either adrenalectomy or active surveillance can be offered for the appropriately selected patient. Myelolipomas, for example, can present as large adrenal lesions, but they have distinct radiographic features and do not necessitate surgery at >6 cm unless the patient is symptomatic.

Computed Tomography Features

CT characteristics that differentiate lesions from one another include margins, shape, heterogeneity, attenuation, and washout. Typical benign features include distinct and smooth margins, round shape, and homogenous composition. Attenuation of <10 Hounsfield units (HU) without contrast and rapid (>60%) absolute washout on 15-minute delayed-phase images is characteristic of lipid-rich benign adenomas. In contrast, lipid-poor lesions, such as malignant tumors, have a density >10 HU without contrast. However, 20% to 30% of benign adenomas can be lipid poor. Contrast enhancement and percentage of contrast washout convey information related to the vascularity of lesions. Lesions with increased vascularity, such as malignant tumors, demonstrate strong arterial enhancement and absolute washout <60% on delayed-phase imaging. Further features suggestive of malignancy include large size, irregular borders, heterogenous composition, central necrosis, and local invasion into surrounding structures. Pheochromocytomas may be difficult to distinguish from malignant lesions on CT as both have a high density, enhance, and have <60% washout. Additionally, central necrosis and calcifications may be present in pheochromocytomas. Pheochromocytomas, however, do not have the same predilection for local invasion as adrenocortical carcinomas and are distinguished by biochemical testing. Myelolipomas are composed of mature adipose tissue and interspersed areas of myeloid tissue. These features provide a characteristic appearance on CT of a well-circumscribed mass with areas of higher attenuation intermixed with areas of predominantly

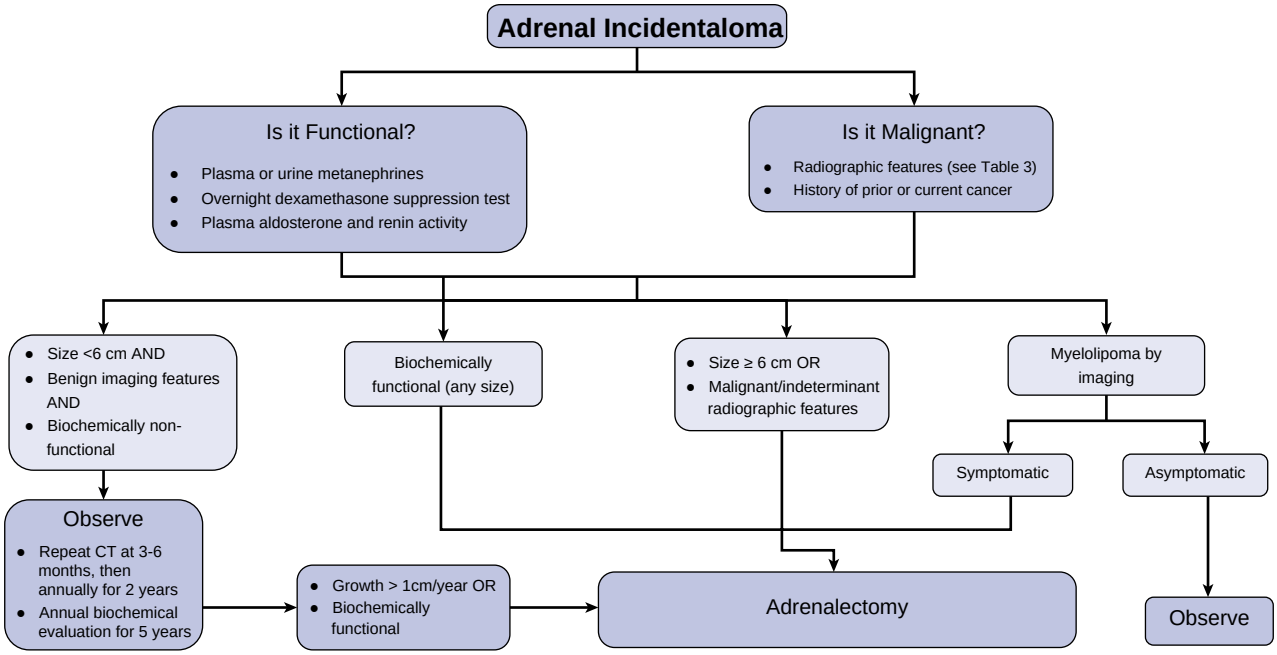


FIG. 1 Initial evaluation for a patient with an adrenal incidentaloma.

TABLE 1 Differential Diagnosis for an Adrenal Incidentaloma

	Nonfunctional	Functional
Benign	• Adenoma • Cyst • Ganglioneuroma • Hemangioma • Hemorrhage • Infection (tuberculosis, fungi) • Granulomatous disease (sarcoidosis) • Lymphangioma • Myelolipoma • Pheochromocytoma • Schwannoma	• Adenoma • Cushing's syndrome • Pheochromocytoma • Aldosteronoma • Micronodular or macronodular hyperplasia
Malignant	• Adrenocortical carcinoma • Metastatic cancer from a non-adrenal primary tumor (lung, renal cell, melanoma)	• Adrenocortical carcinoma • Pheochromocytoma

low attenuation, measuring −130 to −23 HU without contrast. Myelolipomas can be diagnosed on the basis of imaging alone.

Magnetic Resonance Imaging Features

MRI for evaluation of the adrenal glands includes contrast-enhanced and T1- and T2-weighted images of the entire abdomen. In-phase and out-of-phase images of the adrenal glands are also performed to evaluate the fat content of lesions. A loss of signal intensity on out-of-phase images indicates fatty composition, which is compatible with lipid-rich lesions such as adenoma or myelolipoma. A lack of signal drop in out-of-phase images is more suggestive of malignancy or pheochromocytoma. These dense lesions show high signal intensity in T2-weighted images on MRI. Large pheochromocytomas and cancers can demonstrate heterogenous signal intensity that is related to the cystic and necrotic degeneration that may accompany large lesions. A classic "light bulb" T2 signal can be found in 11% of pheochromocytomas. Similar to their appearance on CT, pheochromocytomas and malignant lesions will demonstrate strong contrast enhancement following injection of gadolinium. Myelolipomas appear hyperintense on T1-weighted images (macroscopic fat) with regions of hypointensity caused by the presence of interspersed marrow elements.

Molecular Imaging

[$^{123/131}$I] Metaiodobenzylguanidine (MIBG) scintigraphy, FDG-PET/CT, and DOTA-PET/CT are molecular imaging tests available for the evaluation of adrenal malignancies and neuroendocrine tumors. The clinical utility of molecular imaging includes staging of malignancies (PET/CT) and localization of pheochromocytomas (MIBG). FDG-PET/CT carries a sensitivity and specificity of 100% and 98%, respectively, in differentiation of malignant and benign lesions. FDG-PET/CT should be used in patients in whom a high clinical

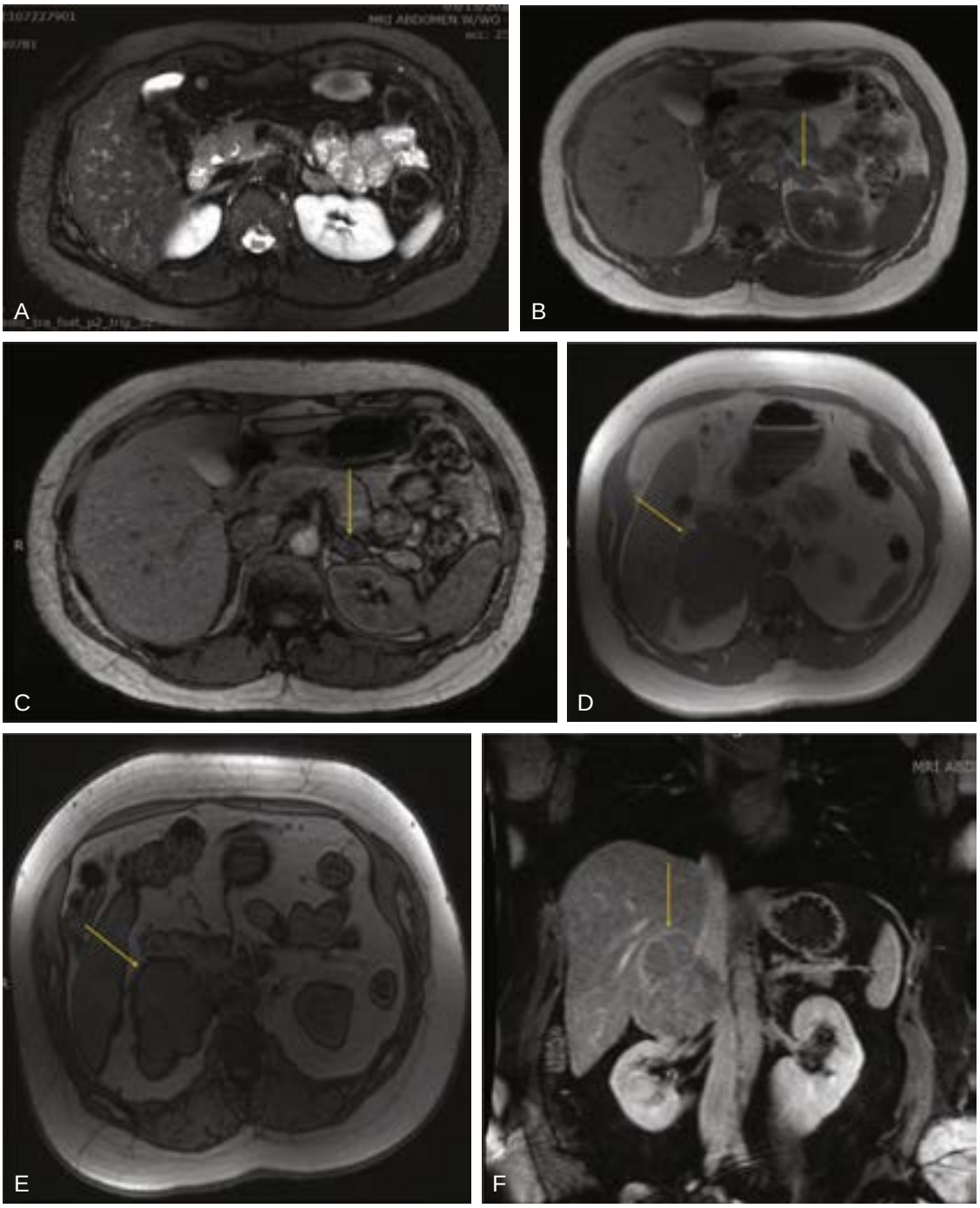


FIG. 2 In a patient with Cushing's syndrome secondary to a benign cortisol-producing adenoma, T2-weighted image **(A)** demonstrates an isointense appearance of the nodule. T1-weighted images demonstrate loss of signal intensity shifting from in-phase **(B)** to out-of-phase **(C). (D-F)** MR images in a patient with right adrenocortical carcinoma. Compared with in-phase imaging **(D)**, out-of-phase imaging **(E)** demonstrates no evidence of signal dropout to suggest that this lesion contains fat. Postcontrast MRI imaging **(F)** demonstrates heterogeneous enhancement. There is mass effect on the adjacent inferior vena cava without discrete infiltration of the inferior vena cava.

suspicion of metastatic adrenal cortical carcinoma or another primary cancer with suspected metastasis to the adrenal gland exists. In the setting of an adrenal incidentaloma, this includes patients with a synchronous malignancy, history of previous cancer, and patients with incidentaloma characteristics highly suggestive of adrenal cortical cancer. MIBG scintigraphy carries a sensitivity of 83% to 100% and a specificity of 95% to 100% for pheochromocytomas. MIBG is useful in the localization of paragangliomas, metastatic pheochromocytomas, and in clinical scenarios in which the diagnosis between a nonfunctional pheochromocytoma and malignancy remains uncertain. MIBG is particularly useful in patients with biochemical findings consistent with pheochromocytoma but without evidence of an adrenal lesion on CT. DOTA-PET, which uses a somatostatin receptor imaging agent, carries a sensitivity of 88% for pheochromocytoma, and it can be used in a similar context as MIBG scintigraphy.

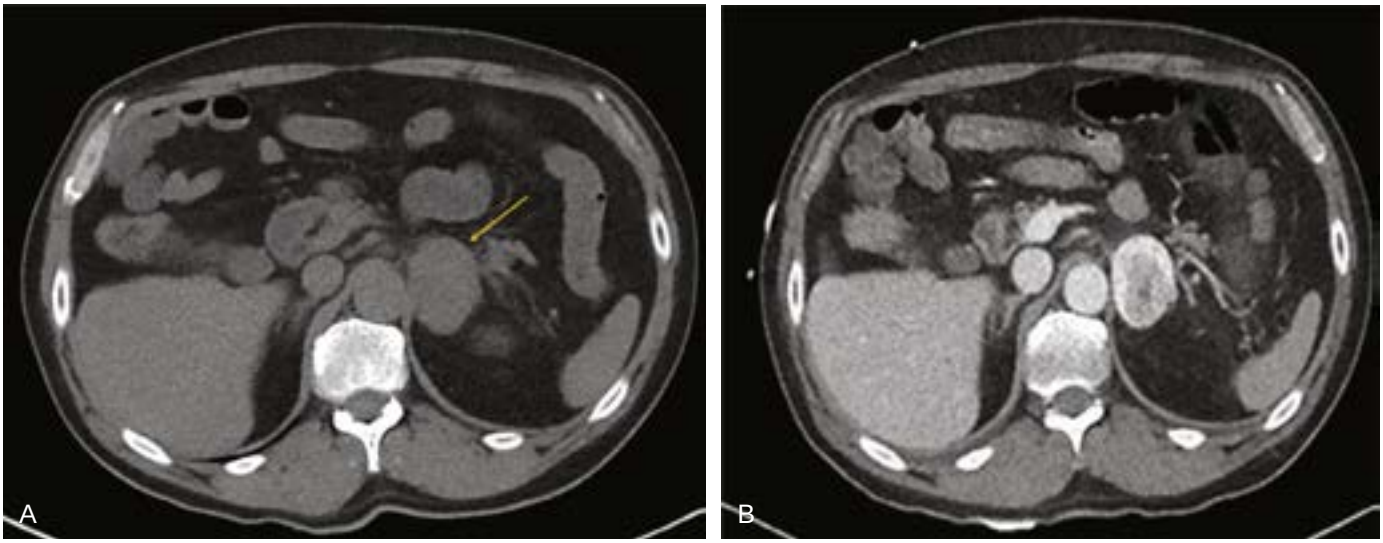


FIG. 3 Classic CT scan findings in a patient with a left pheochromocytoma. The left adrenal mass is well circumscribed; compared with the noncontrast image **(A),** it is heterogeneous and strongly enhances on arterial phase **(B)** with increased attenuation at the periphery, suggestive of a pheochromocytoma.

Fine-Needle Aspiration

There is limited utility in the use of fine-needle aspiration (FNA) biopsy of adrenal lesions, most importantly because it cannot differentiate between benign and malignant disease. If adrenocortical carcinoma is present, a biopsy can cause peritoneal seeding of tumor along the tumor tract. Finally, in the case of pheochromocytoma, adrenal biopsy can cause a physiologically catastrophic release of catecholamines. Unless there is a clinical concern for metastasis in which pathologic confirmation could affect therapy, biopsy should not be performed.

Assessment of Biochemical Functionality

The biochemical workup of adrenal incidentalomas is critical to assess for functionality, and ultimately for surgical decision making (Table 2). It is imperative to identify or rule out pheochromocytoma, cortisol hypersecretion, or primary hyperaldosteronism before an attempted resection of any adrenal mass as it affects perioperative management, guides subsequent medical therapies, and informs surveillance. Positive screening tests should be followed by confirmatory testing.

Screening for Hypercortisolism

All patients with an adrenal incidentaloma should be screened for autonomous cortisol secretion. Screening tests include a low-dose dexamethasone suppression test, midnight salivary cortisol × 2, or urine free cortisol × 2. A 1-mg dexamethasone suppression test involves administering 1 mg dexamethasone at 11:00 PM the night before and drawing blood between 8:00 AM and 9:00 AM the following morning for cortisol and dexamethasone levels. A cortisol level of >1.8 μg/dL is 90.4% to 100% sensitive and 51.8% to 100% specific for autonomous cortisol secretion. Dexamethasone levels are included to confirm proper administration. If results of the dexamethasone suppression test, 24-hour urine cortisol, or midnight salivary cortisol are abnormal, the patient can undergo further confirmatory testing with an adrenocorticotropic hormone (ACTH) level to differentiate ACTH-dependent versus ACTH-independent hypercortisolism. A suppressed ACTH level confirms the diagnosis of autonomous cortisol secretion from the adrenal gland. Although not a routine step in the diagnostic algorithm, low dehydroepiandrosterone sulfate (DHEA-S) concentrations caused by sustained negative feedback on the hypothalamus and pituitary gland can provide further support for the diagnosis.

Screening for Pheochromocytoma

Measurement of plasma free metanephrines (normetanephrines and metanephrines) is the most sensitive test tool to rule out pheochromocytoma. Several physiologic states and medications, such as hypertension, exercise, trauma, amphetamines, antidepressants, and β-blockers can elevate metanephrine levels, leading to false positives. However, they do not typically cause levels as high as two times to four times the laboratory upper normal limit, which are considered diagnostic. If plasma metanephrines are equivocal or mildly elevated, a diagnosis can be confirmed by 24-hour collection of fractionated metanephrines, which carry a higher specificity.

Screening for Hyperaldosteronism

Hyperaldosteronism is less commonly diagnosed from an adrenal incidentaloma, as aldosterone-secreting adenomas tend to be smaller. Concurrent diagnosis of hypertension must be present in patients with an adrenal incidentaloma. Only 9% to 37% of patients present with hypokalemia. Screening involves measurement of aldosterone and renin levels, and computation of the aldosterone-to-renin ratio (ARR). An ARR >20 in the absence of mineralocorticoid antagonists such as spironolactone encourages further investigation. The diagnosis of hyperaldosteronism can be confirmed with aldosterone suppression testing including a saline infusion test or a 24-hour urinary aldosterone test while the patient maintains a high-sodium diet. All mineralocorticoid antagonists should be stopped for at least 6 weeks before confirmatory testing. Once confirmed, surgical candidates older than 35 years of age who wish to pursue surgery must undergo adrenal venous sampling (AVS) to localize the hypersecreting gland. AVS can also be obtained routinely in all patients with hyperaldosteronism in the setting of an adrenal nodule.

Screening for Secretion of Sex Hormones

Screening for sex hormones should only be performed for patients with clinical signs or symptoms of virilization or feminization, or those with masses suspicious for adrenocortical carcinoma. Screening is performed by measuring plasma DHEA-S levels. For men exhibiting features of feminization, estradiol-17 can be measured.

TABLE 2 Biochemical Evaluation for Adrenal Incidentaloma*

	Screening Test	Confirmatory Test
Cushing's syndrome	1. Overnight 1-mg dexamethasone suppression test (AM cortisol ≥ 1.8 μg/dL) 2. 24-hour urine free cortisol (elevated) 3. Midnight salivary cortisol (elevated)	Random ACTH level (low/suppressed)
Pheochromocytoma	Plasma free metanephrines and normetanephrines (≥2–4 × upper limit of normal)	24-hour urine fractionated metanephrines and normetanephrines (≥2–4 × upper limit of normal)
Primary hyperaldosteronism	Serum aldosterone (PA) >15 and serum aldosterone-to-renin ratio (ARR) ≥ 20	Saline suppression test (PA ≥ 10 ng/dL) Salt load test (elevated aldosterone) **Adrenal vein sampling

*Levels in parentheses indicate a positive result indicative of a functional tumor.
**Adrenal vein sampling is used to lateralize an aldosteronoma.
ACTH, Adrenocorticotropic hormone.

Management

Treatment should be individualized according to the patient's comorbidities, preferences, and the clinical expertise available. Surgery is indicated for functional adrenal tumors and adrenocortical carcinoma in the absence of distant metastatic disease. Surgery may be indicated for indeterminate nodules and large, benign, or symptomatic tumors as well (Table 3).

Surgery

Adrenalectomy can be performed with an open or minimally invasive technique (laparoscopic versus robotic) and with either a transabdominal or retroperitoneal approach. Open surgery should be performed in cases of suspected adrenocortical carcinoma or large tumor size. An open approach for suspected adrenocortical carcinoma allows for optimal exposure of surrounding structures should the need arise for more extensive dissection or vascular reconstruction. For presumed benign lesions, minimally invasive techniques, such as laparoscopic or robotic, can be used and choice of technique is a matter of surgeon preference, as there is no additional benefit to robotic-assisted adrenalectomy. The adrenal glands can be approached transabdominally in the lateral decubitus position and retroperitoneoscopically in a modified prone position. A retroperitoneal approach can be particularly useful in patients with a history of multiple abdominal surgeries to avoid the risks of extensive adhesiolysis and in those who need a bilateral adrenalectomy.

Perioperative Management

All adrenalectomy patients should receive chemical deep venous thrombosis prophylaxis. Additionally, each type of functional tumor requires specific considerations in the perioperative period.

Patients with Cushing's syndrome must undergo optimization of blood pressure and glucose control. They may require stress doses of glucocorticoids well into the postoperative period resulting from adrenal insufficiency of the remaining contralateral gland. Preoperative antihypertensives and diabetic medications can slowly and judiciously be adjusted as the patient's blood pressure and glucose trend demand. Patients eventually may not require some or even all of their previous medications.

Patients with pheochromocytomas carry an elevated risk of catastrophic perioperative hemodynamic lability. These patients require preoperative nonselective alpha blockade with agents such as doxazosin or phenoxybenzamine to reduce the risk of a hypertensive crisis for approximately 2 weeks. After alpha blockade is established, beta blockade may be added for patients with tachycardia. Anesthesia plays a critical role in the care of patients intraoperatively; therefore excellent communication with the anesthesia team regarding vascular access, hemodynamic monitoring, and critical steps during surgery is key for optimal patient outcomes. All patients with a pheochromocytoma should be offered genetic testing to include *NF1, VHL, RET, SDHB,* and *SDHD* mutations. Genetic mutations have been reported in 19% of patients with apparently sporadic pheochromocytomas and a negative family history, and the prevalence is much higher in families with known syndromes. Postoperative hypotension may occur; it is transient and more often seen in those treated with phenoxybenzamine preoperatively because of its residual longer-acting alpha-blocking effects in the setting of sudden excess catecholamine withdrawal. Hypotension can be managed with

TABLE 3 Radiographic Characteristics Suggestive of Benign vs. Malignant Adrenal Masses

Characteristics	Likely Benign	Likely Malignant
Size	<4 cm	≥4 cm
Margins	Smooth	Irregular
Heterogeneity	Absent	Present
Rate of growth	<1 cm/year	≥1 cm/year
CT Density (HU)		
Unenhanced density	<10 HU	≥10 HU
Contrast-enhanced density	Low	High
Washout	>60%	<60%
Features on MRI		
T2-weighted intensity	Isointense/ hypointense	Hyperintense
Out-of-phase imaging	Loss of signal intensity	No change
FDG avidity on PET	No	Yes

CT, Computed tomography; *FDG,* fluorodeoxyglucose; *HU,* Hounsfield unit; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.

fluid boluses and vasopressors should it persist despite adequate fluid resuscitation. Rebound hypoglycemia is rare but can occur immediately postoperatively due to preoperative suppression of alpha and beta pancreatic cell function from high catecholamine levels that are no longer present after adrenalectomy.

Patients with aldosteronomas should discontinue any potassium supplements and potassium-sparing diuretics, such as spironolactone, immediately postoperatively. Rebound hyperkalemia is a risk in the postoperative period. Potassium-containing crystalloid solutions and potassium repletion should be avoided. Similar to patients with hypercortisolism, preoperative antihypertensives can be resumed cautiously.

Special Cases

Patients with bilateral pheochromocytomas require bilateral adrenalectomy. The bilateral adrenal glands can be resected during the same anesthetic event. Because pheochromocytomas arise from the adrenal medulla, bilateral cortical-sparing adrenalectomy can be performed to minimize life-long adrenal insufficiency. Ideally, a remnant of adrenal cortical tissue around the adrenal vein should be spared. The management of patients with hypercortisolism is more controversial. Options include: bilateral adrenalectomy, AVS to identify and then excise the more biochemically active gland, or removal of the larger gland. The latter two options require close postoperative surveillance as hypercortisolism can recur requiring contralateral adrenalectomy. Patients with hyperaldosteronism caused by bilateral adrenal hyperplasia are not surgical candidates and should be managed medically.

Follow-up

Both nonoperative and postoperative patients require long-term surveillance, and management varies according to the type of adrenal lesion.

Postoperative Surveillance

After adrenalectomy for pheochromocytoma, patients require life-long follow-up as pheochromocytomas can recur. Surveillance entails annual history and physical examination with particular attention paid to blood pressure, heart rate, and resurgence of symptoms of catecholamine excess. Plasma metanephrines can be assessed periodically, and a rising trend should be evaluated further with cross-sectional imaging.

Patients undergoing adrenalectomy for Cushing's syndrome require short-term glucocorticoid supplementation until normal function of the hypothalamic-pituitary-adrenal (HPA) axis is restored. In the first year after surgery, they should be followed closely by an endocrinologist as they may require frequent medication adjustments because of weight loss, lower blood pressure, and lower glucose levels. Cushing's syndrome may recur, especially in patients status post–unilateral adrenalectomy in the setting of bilateral nodules, and these patients should continue to have routine long-term follow-up with particular attention paid to resurgence of hyperglycemia, worsening hypertension, and weight gain. Patients undergoing bilateral adrenalectomy will require life-long physiologic glucocorticoid supplementation as well as education regarding stress doses during illness, injury, and so on.

After adrenalectomy for hyperaldosteronism, it may take several weeks or months before patients can be weaned off some or all of their antihypertensive agents. In some cases, especially if hyperaldosteronism went unrecognized for a prolonged period causing permanent renal changes, patients will remain hypertensive and continue to require all preoperative antihypertensives. Patients should continue to be seen and evaluated by a clinician to address these potential changes.

Standardized guidelines for surveillance after resection of adrenocortical carcinoma do not exist; however, patients require close life-long follow up to monitor for local and metastatic recurrences. Physical examinations, hormonal studies, and CT of the chest and abdomen should be performed every 3 months, which can be increased to every 6 months after a few years. Surveillance can be extended to every 1 to 2 years after a 5-year disease-free interval.

Nonoperative Management

Observation with repeat imaging and biochemical testing is an acceptable alternative for patients with indeterminate, nonfunctional nodules with low suspicion of adrenocortical carcinoma. Repeat imaging should be performed at 3 months, 6 months, and then annually for 1 to 2 years. Biochemical testing should be repeated annually for up to 5 years. Should the tumor grow more than 1 cm or become hormonally active, adrenalectomy is indicated.

Suggested Readings

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Management of Adrenal Cortical Tumors

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INTRODUCTION

The adrenal cortex is the main source of corticosteroid hormone synthesis, producing both mineralocorticoids and glucocorticoids. These hormones help regulate inflammation, stress response, metabolism, catabolism, as well as electrolyte and water balance, depending on the anatomic adrenal layer from which the hormone is produced. Tumors arising from the zona glomerulosa, zona fasciculata, or zona reticularis can produce increased levels of hormones from the involved layer (functional), or they may be hormonally inactive (nonfunctional). Although they are important in the discussion of surgical management of adrenal tumors, tumors arising from the adrenal medulla (pheochromocytoma and neuroblastoma) are discussed elsewhere.

The prevalence of adrenal cortical tumors has been reported at about 2% (ranging 1% to 9%) in autopsy studies, with higher prevalence noted in the older population. Because of the increased use of diagnostic imaging over the past 3 decades in conjunction with advances in each imaging modality, the prevalence of adrenal tumors on computed tomography (CT) imaging has been reported at 4% to 10%. The majority of these tumors are found incidentally.

Less than 2% of adrenal tumors are found to be adrenocortical carcinomas (ACCs); however, despite the rarity of this malignancy (annual incidence of 1 to 2 per 1 million), the diagnosis of ACC carries a 5-year disease-specific survival (DSS) of approximately 50%. Therefore prompt identification and treatment are critical in these patients.

PREOPERATIVE EVALUATION FOR THE SURGEON

The initial workup of a patient with an adrenal tumor includes a detailed personal history (including a history of malignancy to evaluate for recurrent primary or metastatic disease to the adrenal glands) and a physical examination. A careful family history is important to identify potential underlying genetic syndromes that would require further investigation (multiple endocrine neoplasia, familial paraganglioma syndrome, von Hippel-Lindau disease, neurofibromatosis type 1, Carney complex, Li Fraumeni syndrome). The history should focus on the signs and symptoms that may also help identify the specific adrenal hormone(s) being overproduced. A complete biochemical assessment should be performed to evaluate for elevated adrenal hormone levels (Table 1). For adrenal cortical tumors, it is helpful to always send for serum aldosterone, renin, ACTH, and dehydroepiandrosterone sulfate (DHEAS) as well as perform an overnight low-dose dexamethasone suppression test.

Approximately 10% to 15% of adrenal cortical tumors secrete excess hormone and are considered functional adrenal cortical tumors. These are typically referred for adrenalectomy and can be

TABLE 1 Biochemical Workup of Adrenal Cortical Tumors

Biochemical Abnormality	Layer	Syndrome	Symptoms	Screening Test	Indications For Further Evaluation
Hyperaldosteronism	Zona glomerulosa	Conn's syndrome	Hypertension, weight gain, edema, muscle cramping, weakness, temporary paralysis, headaches, polyuria, polydipsia	**Plasma aldosterone, plasma renin activity**	Plasma aldosterone to renin activity ratio > 20
Hypercortisolism	Zona fasciculata	Cushing's syndrome	Hypertension, weight redistribution (central obesity, "buffalo hump," "moon face"), diabetes, bruising, fatigue, abdominal striae, proximal muscle weakness, hirsutism, amenorrhea, impotence, depression	**ACTH, overnight low-dose (1-mg) dexamethasone suppression test**	Serum cortisol > 1.8 mcg/dL with suppressed ACTH
Increased sex hormones	Zona reticularis	Virilization/feminization	Hirsutism, menstrual irregularities, precocious puberty, postmenopausal bleeding, feminization (gynecomastia, testicular atrophy)	**DHEA-S,** +/–androstenedione, 17-hydroxyprogesterone, testosterone (total and free) for women, estradiol for men and postmenopausal women	Abnormally elevated levels with associated clinical symptoms

ACTH, Adrenocorticotropic hormone; *DHEA-S*, dehydroepiandrosterone-sulfate.
Bolded studies indicate recommended minimum during biochemical workup.

identified via the clinical symptoms and screening tests listed in Table 1. Nonfunctional tumors with indeterminate initial imaging should have additional adrenal-specific imaging including adrenal protocol computed tomography (CT) with timed contrast and multiphase scanning, magnetic resonance imaging (MRI), and/or fluorodeoxyglucose positron emission tomography (FDG-PET). These imaging modalities can help differentiate between benign adrenal tumors that can be observed and suspicious or malignant tumors that should be resected. (Table 2)

Percutaneous fine-needle aspiration (FNA) is not routinely recommended in the preoperative workup of adrenal tumors. Biochemical and imaging findings, in addition to personal/family history and physical examination, are sufficient to make a diagnosis in most cases. Additionally, FNA cytology cannot reliably differentiate a benign adrenal adenoma from adrenal cortical carcinoma (ACC). Finally, adrenal biopsy is associated with multiple risks including malignant seeding of the FNA tract, adrenal hemorrhage that may complicate subsequent adrenalectomy, damage to surrounding organs and vessels, and hypertensive crisis in patients with undiagnosed pheochromocytoma.

There are rare instances in which FNA can be useful, such as for patients in whom surgery is not recommended but a tissue diagnosis will help guide appropriate treatment. For example, tissue diagnosis by FNA may be helpful in the workup of metastatic disease from a non-adrenal primary tumor, an unresectable adrenocortical carcinoma, or for patients who are poor surgical candidates because of multiple medical comorbidities.

In patients with a history of nonadrenal malignancy and a new adrenal lesion, FNA may be useful in determining cell type of origin.

TABLE 2 Differences in Imaging Characteristics of Adrenal Cortical Tumors

Characteristic	Benign	Indeterminant
Size	< 4 cm	> 4–6 cm
Growth	< 3 mm/year	> 5 mm/year
Noncontrast CT (Hounsfield units)	< 10	> 10
Percentage washout on CT (if homogeneous)	> 50%–60%	< 50%–60%
MRI chemical shift	> 50%	< 50%
Internal attenuation	Homogeneous	Heterogeneous
Calcification	Absent	Present
Necrosis	Absent	Present
Borders	Regular	Irregular
Invasion of adjacent structures	Absent	Present
Intravascular tumor thrombus	Absent	Present
Lymphadenopathy	Absent	Present
FDG PET CT: Tumor SUV	< 3.4	> 3.4
FDG PET CT: Tumor/liver SUV ratio	< 1.45	> 1.45

CT, Computed tomography; *MRI*, magnetic resonance imaging; *FDG PET*, fluorodeoxyglucose positron emission tomography; *SUV*, standardized uptake value.

However, if the adrenal lesion is the only evident site of metastasis and clinical suspicion is high, adrenalectomy may be performed without adding the risks associated with FNA. Despite the adrenal glands being the fourth most common location for metastatic disease, a series of studies showed that, on average, greater than 50% (range 9%–76%) of adrenal masses found in these patients are benign adrenal adenomas.

INDICATIONS FOR SURGICAL INTERVENTION

Adrenalectomy is recommended if biochemical evaluation and imaging characteristics are consistent with a hormonally active and/or potentially malignant adrenal lesion, and the patient is a reasonable candidate for surgery (Fig. 1). Patients with functional or suspicious-appearing lesions who are not operative candidates may be managed with observation or medical management.

Although tumor size (>4 or 6 cm) has in the past determined the threshold for adrenal surgery in nonfunctional adrenal lesions, imaging characteristics are also necessary to consider in a complete evaluation. Washout of contrast of >50% to 60% on CT or a loss of signal on out-of-phase images on MRI can reliably identify benign adrenal adenomas. The rate of growth in solid adrenal lesions is another important determinant used to help identify benign and malignant tumors; a growth rate of less than 3 mm/year is consistent with an adenoma, compared with malignant tumors that characteristically grow more than 5 mm/year (see Table 2). Previous size criteria that guided surgical resection for adrenal tumors 6 cm and greater were determined given the greater risk of a malignancy with larger tumors: > 6 cm carries a 22% risk of malignancy, 4.1 to 6 cm carries a 6% risk of malignancy, and ≤ 4 cm has approximately 2% or less risk of malignancy. On the other hand, benign adrenal masses like myelolipomas and simple adrenal cysts have characteristic imaging features, can grow to large sizes, remain asymptomatic, and do not need to be resected. Benign-appearing tumors can be observed with repeat scans in 3 to 6 months and then annually. Biochemical testing should be repeated annually for 5 years to monitor for any changes in hormonal activity.

Functional Cortical Tumors

Functional adrenal tumors, especially in patients with worsening symptoms, should undergo adrenalectomy to remove the source of excess hormone production. The rate of malignant transformation of functional tumors is unknown, with only a few case reports identifying this rare situation.

Nonfunctional Cortical Adenomas

Nonfunctional, stable, benign-appearing adenomas do not need surgical resection. Nonfunctional adenomas that are continually growing or with indeterminant radiographic features should be reevaluated for resection with the surveillance schedule mentioned previously. (Fig. 2A; see Table 2). It is important to note that adenomas are not thought to be premalignant lesions and do not seem to have the potential for malignant transformation.

Adrenocortical Carcinoma

Complete surgical resection is the only potential curative treatment for ACC. It is typically recommended to be done via an open approach, regardless of size and functional status. As further explained later in this chapter, this is done via en-bloc open resection for a decreased rate of recurrence compared with the laparoscopic approach (see Fig. 2B).

Isolated Adrenal Metastases

Lung cancer, breast cancer, melanoma, gastrointestinal malignancies, and renal cell carcinoma are the most common primary malignancies

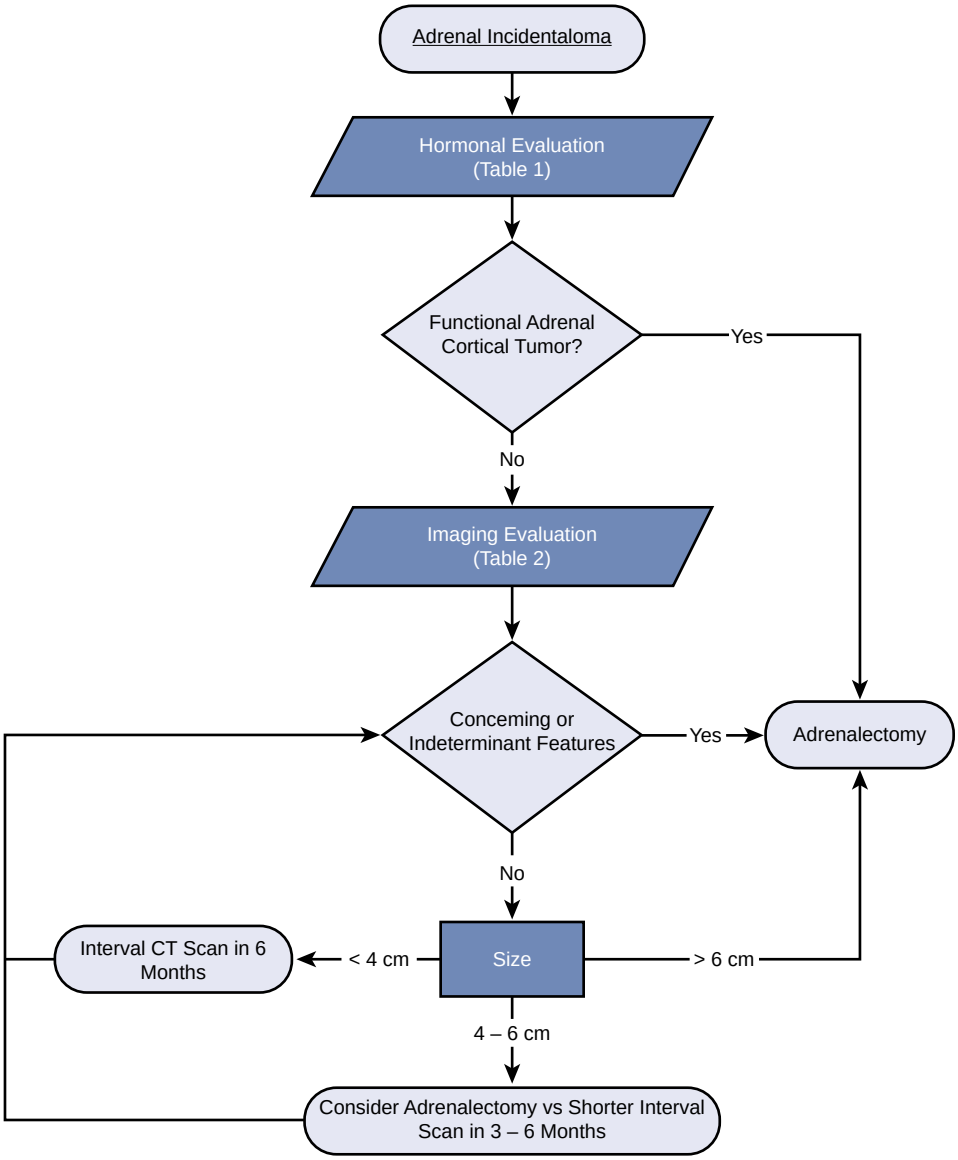


FIG. 1 Adrenal incidentaloma workup and general management algorithm.

that metastasize to the adrenal glands. Approximately 50% of these tumors metastasize to bilateral adrenal glands. Isolated adrenal metastases should be surgically resected in appropriate patients if feasible and can be done so safely via a laparoscopic approach unless characteristics of more aggressive disease are present (e.g., lymphadenopathy, invasion into surrounding organs or vessels), at which time open adrenalectomy is recommended.

IMMEDIATE PERIOPERATIVE MANAGEMENT AND CONSIDERATIONS

There have been very few studies looking at neoadjuvant systemic therapy for ACC, and although they have suggested a potential benefit in patients with borderline resectable ACC, the studies were not randomized controlled trials, and they lacked power; therefore there is no clear consensus on neoadjuvant therapy from the various society guidelines.

It is critical to avoid capsular rupture when handling an ACC as they have a high propensity to seed the entire field, increasing local recurrence rates. For large or invasive ACCs that involve the inferior vena cava (IVC), liver, diaphragm, spleen, or kidneys, a multidisciplinary team approach at a regional center where there is adequate expertise should be considered, and resection should be planned in conjunction with hepatic, vascular, and/or cardiothoracic surgeons as needed. For tumors with extensive IVC involvement, vascular bypass, IVC resection and repair or replacement may be necessary.

SURGICAL APPROACH

Choosing Minimally Invasive versus Open Adrenalectomy

Determining the optimal surgical approach for adrenalectomy should be done on a case-by-case basis, and certain factors may lead to choosing one approach over the other (Table 3). In general, although minimally invasive laparoscopic and retroperitoneoscopic approaches have replaced traditional open adrenalectomy for most presumed benign adrenal tumors, the debate over open versus minimally invasive surgery for ACC continues to evolve. The American



FIG. 2 Adrenal cortical lesions on CT imaging can appear **(A)** benign, hypodense compared with normal adrenal tissue, and generally contained to the adrenal gland, or **(B)** malignant, with areas of hyperintensity and invasion into surrounding structures (such as the liver and retrohepatic inferior vena cava in this example). *(**A** from Mazzaglia PJ. Radiographic evaluation of nonfunctioning adrenal neoplasms. Surg Clin North Am. 2014;94:625–642; **B** from Chagpar R, Siperstein AE, Berber E. Adrenocortical cancer update. Surg Clin North Am. 2014;94:669–687.)*

Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons currently recommend open adrenalectomy for ACC, regardless of size, per their most recent guidelines (published in 2009). The National Comprehensive Cancer Network (NCCN) agrees with these recommendations in their guidelines (Version 1.2021 for Neuroendocrine and Adrenal Tumors), yet also acknowledges that depending on individual surgeon expertise and tumor characteristics, a minimally invasive approach may be used for small tumors, with a plan for converting to an open procedure if local invasion is noted. This indicates that despite their recommendation for open resection of ACC, there is still debate within the guidelines. In contrast, the European Society of Endocrine Surgeons recommends that laparoscopic adrenalectomy may be attempted for stage I or II ACCs < 10 cm.

Benign adrenal masses, both functional and nonfunctional, can be safely approached using a minimally invasive approach, barring any intraoperative concern for malignancy, at which point the procedure should be converted to open. Benign tumors 10 cm or greater can pose technical challenges to minimally invasive resection; however, tumor size alone is not an absolute contraindication to a minimally invasive approach.

Open Right Adrenalectomy

The patient is placed in the supine position with a wedge or bump to elevate and separate the pelvis from the costal margin on the right side. The initial steps involve making a long right subcostal or bilateral subcostal incision and then examining the peritoneal cavity to assess for distant metastases, lymph node involvement, and fixation of the mass to the surrounding tissues. The liver is mobilized by dividing the falciform and right lateral triangular ligaments, allowing for retraction of the liver upward. The hepatic flexure of the colon is mobilized by dividing the lateral gastrocolic ligament and exposing the IVC via the Kocher maneuver. Upon entering the Gerota fascia along the IVC, the adrenal gland can now be examined (Fig. 3). If the adrenal mass does not involve the upper pole of the kidney, the Gerota fascia is opened, and all perinephric fat below the adrenal gland is mobilized upward with the adrenal gland en-bloc to ensure an adequate margin. If invasion into the kidney or renal vessels is found, continuation of the mobilization with en-bloc partial or total resection of the right kidney as needed to ensure capsule integrity and minimize the chance of tumor spillage. If there is IVC invasion, the IVC must be secured superiorly under the diaphragm at the crus as well as distally to the right renal vein inferiorly. If there is invasion into the liver, a limited right hepatectomy may be performed, typically using a multidisciplinary approach. The superior dissection can extend up to the diaphragm, and the inferior dissection should include all perinephric fat over the superior pole of the kidney to ensure an adequate margin. The medial dissection is done very delicately as it is just anterior to the vena cava, and the right adrenal vein is very fragile. The medial attachments are then mobilized and ligated with the right adrenal vein being last, including all fatty tissue medial to the gland and lateral to the IVC. If bleeding does occur after ligation of the right adrenal vein, the surgeon can obtain proximal and distal control of the vena cava and repair the stump primarily via suture ligation.

Open Left Adrenalectomy

The patient is positioned in the same way as described earlier for the open right adrenalectomy resection, with a bump/wedge placed under the left side. A left-sided or bilateral subcostal incision is

TABLE 3 Advantages of Operative Approaches for Adrenal Cortical Tumors

Adrenalectomy	Open	Laparoscopic	Retroperitoneoscopic	Robotic	Single-Port
Advantages	Tactile feedback	Familiar anatomic orientation to open approach	Avoids peritoneal cavity	Increased dexterity	Excellent cosmesis
	Better exposure	Decreased postoperative pain	Shorter distance of dissection	Three-dimensional depth perception	Similar results to laparoscopic
	Decreased local recurrence of ACC with en bloc resection	Decreased hospital stay	Can do bilateral without patient repositioning	Good for obese patients	
	Appropriate for any tumor size	Better cosmesis	Prior abdominal surgery does not hinder this approach	Appropriate for larger tumors (even in RP given dexterity)	
	Can utilize a single midline incision for bilateral adrenalectomy	Shorter operative time compared with robotic/single-port			
	Quicker management if catastrophic injury occurs	Appropriate for larger tumors			
	No CO_2 insufflation for preload-dependent patients	Good for obese patients			
	Good for obese patients				
Disadvantages	Larger incision	Risk of iatrogenic injury to intraabdominal organs	Requires increased insufflation pressure to maintain exposure	Increased cost	Learning curve
	Increased postoperative pain	Increased manipulation of additional organs	Restricted exposure to retroperitoneum	Longer operative time	
	Increased hospital stay	Difficult in patients with prior abdominal surgery	Difficult in obese patients		
	Increased risk for hernia	Requires patient repositioning for bilateral adrenalectomy	Difficult with larger tumors		
	Risk of iatrogenic injury to intraabdominal organs		Patient must tolerate prone positioning		
	Difficult in patients with prior abdominal surgery				

ACC, Adrenocortical carcinoma; *CO_2,* carbon dioxide; *RP,* retroperitoneum.

made, and the abdomen is examined in similar fashion. The gastrocolic ligament is divided to mobilize the splenic flexure of the colon distally. The spleen and tail of the pancreas are mobilized medially to expose the kidney and adrenal gland (see Fig. 3). For tumors that surround or invade the splenic vessels, a simultaneous splenectomy is performed, dividing the splenic artery at the upper border of the pancreas and the individual gastrosplenic arteries, while preserving the vessels along the greater curvature of the stomach. The tail of the pancreas is usually preserved unless directly invaded. If the left kidney is involved with the adrenal tumor, the kidney is mobilized from lateral to medial from the lower pole and removed en-bloc with the adrenal tumor.

If there is no invasion into surrounding structures, in contrast with a right adrenalectomy, the left adrenal vein is ligated as an earlier step along with the inferior adrenal arteries, to aid in mobilization of the adrenal gland. The superior and inferior arteries are controlled and ligated, and the adrenal gland is dissected along with all surrounding perinephric fat off the superior pole of the kidney to ensure adequate margins.

Open Posterior Adrenalectomy

The patient is placed in the prone position with the patient's arms lifted over his or her head. An incision is made over the 12th rib, and the rib is resected for exposure. The peritoneum is swept inferiorly and laterally, and the retroperitoneal organs are identified and mobilized, with the kidney being retracted inferiorly. The adrenal gland is identified medially and superior to the renal hilum, and adrenalectomy is completed in a similar fashion to the anterior approach. Open posterior adrenalectomy can be complicated by subcostal nerve injury and lumbar hernias.

Open Thoracoabdominal Adrenalectomy

The patient is placed in the supine position, with the upper torso rotated laterally approximately 45 degrees with the help of a bump. The incision is made in either the 8th or 9th intercostal space, and the diaphragm is divided peripherally near the costal margin to avoid injury to the phrenic nerve and to allow for easy reconstruction at the end of the case. Once the abdominal cavity is opened, the adrenal glands are exposed and ultimately resected in the same manner as the anterior approach (Fig. 4).

At the end of the case, the diaphragm should be repaired with interrupted nonabsorbable sutures in a figure-of-8 fashion, and a chest tube is placed to water seal.

Laparoscopic Transabdominal versus Retroperitoneoscopic Adrenalectomy

Patient anatomy, past surgical history, underlying pathology, and the surgeon's expertise should be considered when determining the appropriate minimally invasive surgical approach to adrenalectomy. A summary of such considerations can be found in Table 3. For instance, patients who have had extensive abdominal surgery or require bilateral adrenalectomy will likely benefit from a retroperitoneoscopic approach as this approach avoids the peritoneal cavity and does not require repositioning for bilateral procedures, whereas patients with tumors > 6 cm may benefit from a transabdominal laparoscopic approach given the larger working area. Patients with high body mass index (BMI) or extensive retroperitoneal fat (both are particularly difficult in male patients) may be better suited for the laparoscopic approach.

Laparoscopic Right Transabdominal Adrenalectomy

The patient is placed in the left lateral decubitus position, with the bed flexed just above the waist and the kidney rest elevated, to allow for maximum exposure to the flank. The patient is secured in place with a beanbag, and the right arm is supported on an upper arm rest. A gel roll is placed under the left axilla, and the head is supported.

Four ports are typically used for the right-sided approach (Fig. 5A). The most medial port, placed in the epigastric/subxiphoid

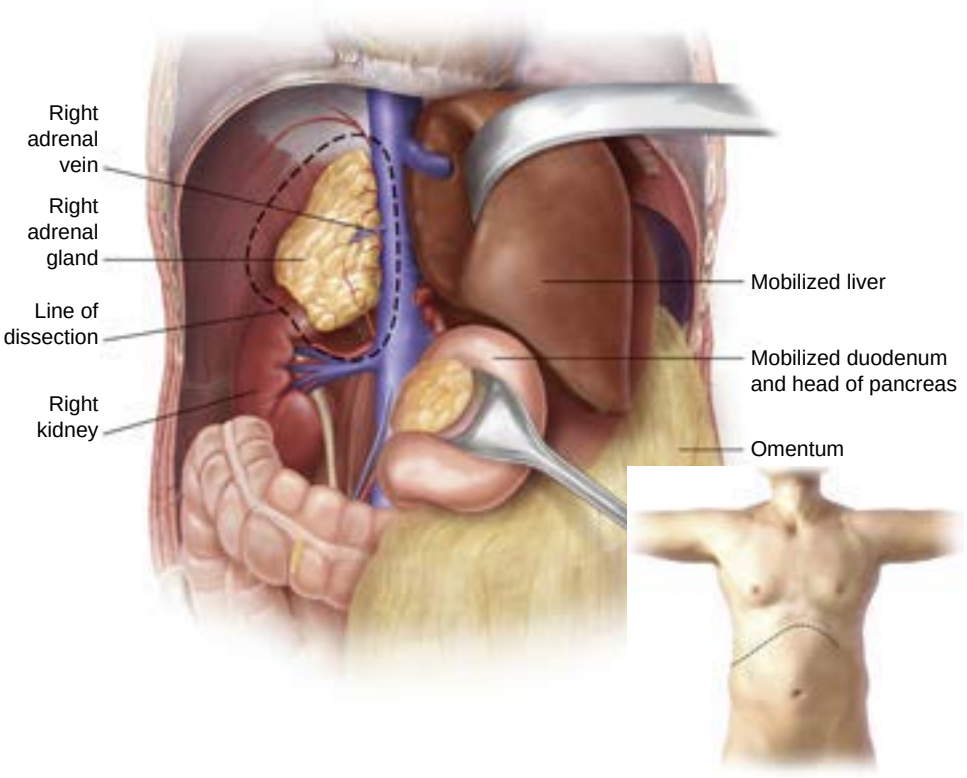


FIG. 3 Exposure of the right and left adrenal glands via an open abdominal approach.

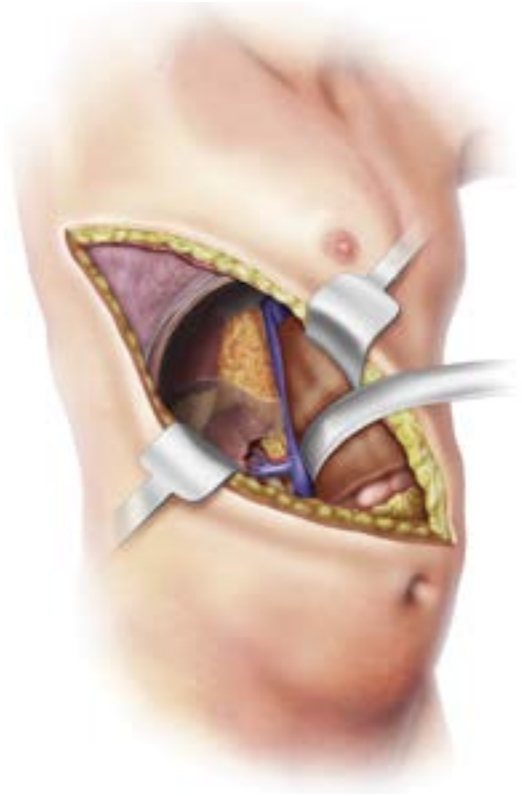


FIG. 4 Exposure of the right adrenal gland via a thoracoabdominal approach.

region, is used to retract the liver superiorly. The two other working ports are placed approximately 6 to 10 cm apart along the subcostal margin, with the most lateral in the midaxillary line, to allow for the unobstructed use of the instruments. The final port, for the camera, is placed in the right upper quadrant. These locations should be marked before insufflation as a guide, but after placing the first port (the camera port via an open technique) and insufflating the abdomen to 15 mm Hg with CO_2, the other ports should be placed under direct visualization. Before placing the most lateral port, the surgeon should examine the hepatic flexure to determine if mobilization is needed (rare). The liver is mobilized by dividing the right triangular ligament, and use of a liver triangular retractor (or fan retractor) through the medial subxiphoid port aids in retracting the liver superiorly and medially. The use of a harmonic scalpel or hook electrocautery allows the opening of the retroperitoneal fascia between the inferior edge of the liver and the superior margin of the adrenal gland. It is helpful to work from medial to lateral and avoid the adrenal vein at the superomedial aspect of the gland. At this point, the surgeon should look for and carefully divide any accessory veins between the adrenal and liver or IVC. In general, for any rotation or movement of the adrenal gland, blunt instruments like a closed grasper or laparoscopic peanut should be used, or, alternatively, grasp the periadrenal fat to avoid disrupting the adrenal capsule. Next, mobilization is performed along the medial edge of the adrenal gland to open the Gerota fascia in a longitudinal fashion from inferior to superior and identify the lateral edge of the IVC. The perinephric fat is dissected off while leaving a small layer on the adrenal gland for margin. The surgeon continues to carefully develop the space between the kidney, adrenal gland, and IVC while working superiorly toward the adrenal vein. The adrenal vein is divided using a harmonic scalpel or clips. The harmonic scalpel is then used to dissect the inferior aspect of the adrenal gland off the superior pole of the kidney, while dividing the small inferior adrenal arteries. At this point, attention is paid to

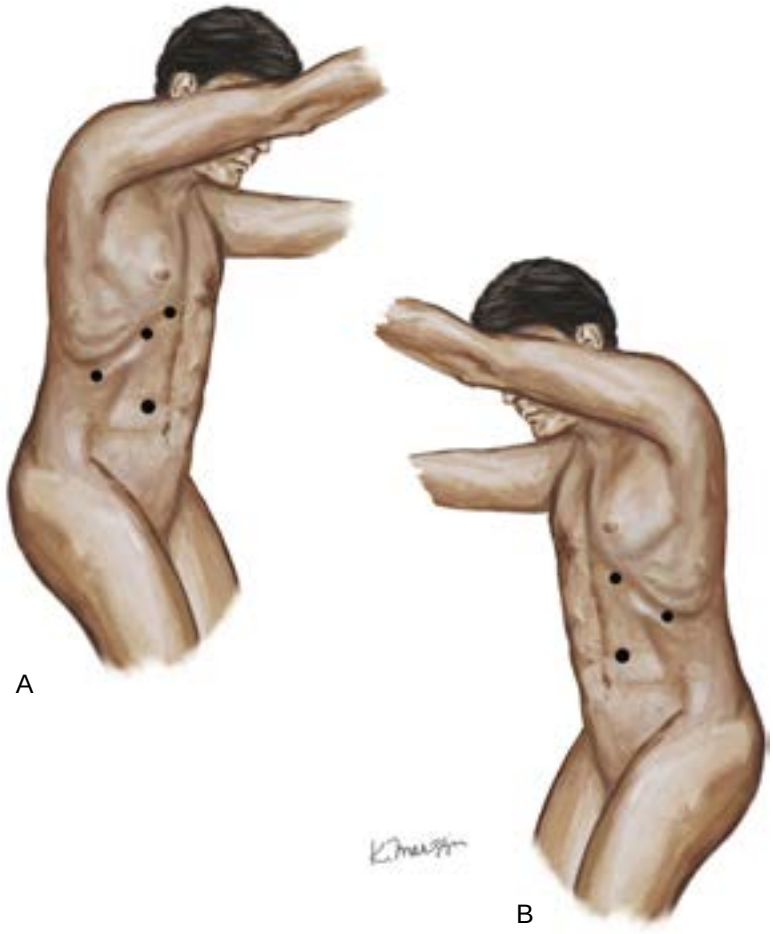


FIG. 5 Patient positioning and port placement for **(A)** right-sided and **(B)** left-sided laparoscopic transabdominal adrenalectomies. Although not indicated in the figure, the subxiphoid port can be used in a left-sided approach to aid with retraction of the spleen and tail of the pancreas. *(Netter illustration from www.netterimages.com. Copyright Elsevier Inc. All rights reserved.)*

protect any accessory renal artery branches. The dissection continues to remove all periadrenal fat with the gland, working from a medial to lateral fashion until the adrenal gland is taken off the diaphragm posteriorly and laterally. The adrenal gland can then be removed in a retrieval bag via the camera port. The port site can be enlarged to remove the tumor in an intact fashion, and then all port sites are closed in the normal fashion.

Laparoscopic Left Transabdominal Adrenalectomy

The patient is positioned and port placements are mirrored to those of a laparoscopic right transabdominal adrenalectomy, with the only difference being that the subxiphoid port can be used if needed to rotate the spleen (see Fig. 5B). The splenocolic ligaments are divided, and the splenic flexure is mobilized while retracting the colon inferiorly. The spleen is then mobilized along its lateral aspect from an inferior to superior dissection, continuing all the way superiorly to the fundus of the stomach. The spleen is then retracted medially with the tail of the pancreas.

The Gerota fascia is then opened medially to identify the kidney and the adrenal gland. The dissection then continues along the superomedial edge of the adrenal gland, sweeping the gland off the diaphragm posteriorly. The phrenic vein is identified and traced down from the diaphragm to the left adrenal vein and then to the location where the left adrenal vein enters the left renal vein. The adrenal vein is then ligated and divided using a harmonic scalpel or clips. The adrenal gland is elevated superiorly, and the small inferior adrenal arteries are then divided while mobilizing all periadrenal fat off the superior medial aspect of the kidney while working from a medial to lateral fashion. The superior attachments are then divided, and the adrenal gland is removed using a retrieval bag placed through the camera port. This port site may be enlarged as necessary to remove the gland intact, and the ports can then be closed in the normal fashion.

Posterior Right Retroperitoneoscopic Adrenalectomy

The patient is placed in the prone position with the abdomen resting in an open rectangular support, and the hips and knees flexed and supported at 90 degrees (Fig. 6). The retroperitoneal space is accessed via a 1.5-cm incision just under the tip of the 12th rib using sharp and blunt dissection. With a finger inserted into the retroperitoneum and lifting up on the 11th rib, a 5-mm trocar is placed just below the tip of the 11th rib. CO_2 insufflation to 20 to 25 mm Hg is initiated through a blunt trocar with an inflatable balloon. A 10-mm trocar is then placed medially under direct vision to avoid the subcostal nerve, about halfway between the spine and the initial incision. The retroperitoneum is then examined with a 30-degree camera, and the area is bluntly dissected to expose the diaphragm, spine, and top of the kidney. Next, the adrenal gland is mobilized inferiorly first, elevating it superiorly away from the kidney. Definitive identification of the vena cava is critical as the pressure from the insufflation may likely cause compression of this structure. The inferior adrenal arteries are divided along the IVC, working clockwise or lateral to medial, from 3:00 to 9:00 superiorly toward the adrenal vein at the superomedial border. Once the adrenal vein is divided, the remainder of the adrenal attachments are dissected free.

Throughout the dissection, be careful not to enter the peritoneal cavity as the hole will lead to loss of pneumoretroperitoneum and exposure. The adrenal gland is extracted through the central incision using a retrieval bag, and the ports are closed in the normal fashion.

Posterior Left Retroperitoneoscopic Adrenalectomy

A similar approach is taken for a left retroperitoneoscopic adrenalectomy. Here, the adrenal gland is often anterior and medial to the superior pole of the kidney, requiring more extensive mobilization of the superior pole to expose it. Dissection of the adrenal gland is again approached from its inferior aspect, working counterclockwise or lateral to medial, from 9:00 to 3:00, to expose the adrenal vein medially. The superior attachments are removed last, and the adrenal gland is extracted as described earlier.

Newer Techniques

Single-Port Adrenalectomy

The single-port approach is a newer technique that has been gaining more traction over the past decade. The initial studies comparing the single-port and the traditional laparoscopic approaches showed no significant difference in complications, but significantly increased operative times, decreased hospital stay, and decreased postoperative pain. However, newer studies have since shown that with continued refinement, all variables showed no significant differences between the two techniques, proving that a single-port adrenalectomy is a

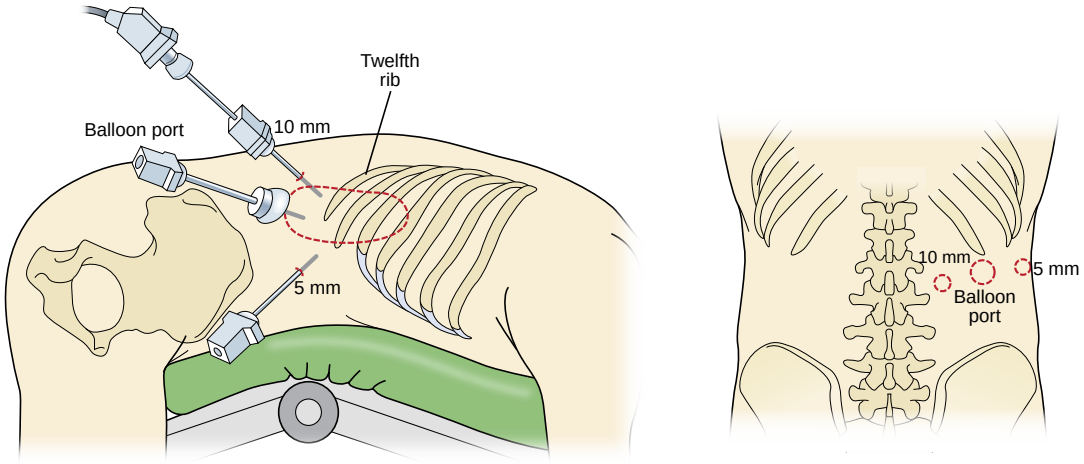


FIG. 6 Patient positioning and port-site placement for a posterior retroperitoneoscopic adrenalectomy. The port sites are mirrored for left- and right-sided adrenalectomies.

feasible option in the skilled surgeon that results in a single incision with excellent cosmesis.

This approach can be done in either a transabdominal or retroperitoneal fashion. A transabdominal approach utilizes a 2- to 3-cm periumbilical incision, a specialty multiport device, and extra-long instruments to reach the adrenal glands. A right-sided adrenalectomy may also utilize an additional 2-mm needlescopic port for liver retraction.

This technique is essentially the same as the retroperitoneoscopic approach; however, a 2- to 3-cm incision below the 12th rib is used in conjunction with a specialty multiport device allowing for a total of three ports. The space is then insufflated to 30 mm Hg, and using a blunt dissector and a LigaSure, the remainder of the operation is similar as noted earlier. The difficulty with this approach is the minimal maneuverability caused by the smaller retroperitoneal space and the close location of the ports to fit into the single 2- to 3-cm incision. An extended mobilization of the upper pole of the kidney may be required compared with the standard retroperitoneoscopic approach.

Studies have shown that this is a safe and feasible approach when done by an experienced surgeon; however, there is no significant advantage in outcomes compared with the standard laparoscopic approaches other than cosmesis.

Robotic Adrenalectomy

A computer-assisted surgical device (robot) can be used in both minimally invasive transabdominal and retroperitoneal approaches. Since the first robotic adrenalectomy was described in 2001, perioperative outcomes and average length of hospitalization are decreased compared with open adrenalectomy and are comparable to laparoscopic adrenalectomy—albeit at an increased cost. Meta-analyses have shown that there are no differences in intraoperative and postoperative morbidity and mortality between the robotic and laparoscopic approaches. Operative times are increased in the robotic approach but appear to decrease as a surgeon's experience moves past the learning curve. Conversely, multiple studies have shown that robotic adrenalectomies actually have shorter operative times in patients with tumors > 6 cm. The main advantages of the robotic approach are the added dexterity in a small working space and the three-dimensional visualization of the operative field.

In placing the robotic trocars, special consideration is needed to avoid having the robotic arms hit each other throughout the case. The optical trocar is inserted first 2 cm beneath the costal margin at the anterior axillary line under direct visualization, and the abdomen is then insufflated. Two 8-mm trocars are placed a few centimeters away, equidistant, on either side of the optical trocar and 2 cm below the costal margin. For a left adrenalectomy, a single 5-mm trocar is placed a few centimeters medial to the most medial robotic trocar for the bedside assistant to utilize, yet still along the same line connecting the other ports to facilitate a fast and easy conversion to an open procedure if needed. For a right adrenalectomy, the same 5-mm port is placed medially, but an additional 10-mm port can be placed inferiorly along between the mid and anterior axillary lines to utilize a fan liver retractor. The robot is then docked, approaching the patient from behind and over his or her shoulder. The reminder of the procedure is performed similar to the laparoscopic approach described earlier.

SPECIAL CONSIDERATIONS

Genetics

As discussed previously, obtaining a family history is crucial in helping to identify a genetic link to adrenocortical tumors. ACCs, for example, are thought to be hereditary in 50% of cases. Some genetic mutations driving sporadic ACC are also found as the driving mutation for some familial tumor syndromes that are characterized by including ACC such as Li Fraumeni syndrome (*TP53* mutation), Beckwith-Wiedemann syndrome (*IGF2* mutation), and Gardner syndrome (*APC* mutation). Mutations in the tumor suppressor gene *ARMC5* have identified families with an autosomal dominant inheritance type of Cushing's syndrome (primary bilateral macronodular adrenal hyperplasia), and activating mutations in *GNAS1* caused adrenocortical tumors in infants with McCune-Albright syndrome via elevated cAMP signaling. While most benign cortisol-producing tumors are related to elevated cAMP signaling, the drug mitotane has been found to inhibit basal and cAMP-induced cortisol secretion in ACC. Additional genetic syndromes that were associated with adrenal neoplasia or hyperplasia include Carney complex *(PRKAR1A)* and MEN 1 *(Menin)* (Table 4). If any of these mutations are identified, further workup is indicated with a referral to the appropriate specialty.

POSTOPERATIVE CONSIDERATIONS

Cortisol-secreting tumors are often associated with diabetes, and blood glucose levels must be monitored closely in the perioperative setting. ACCs commonly secrete cortisol; therefore, like other cortisol-secreting tumors, resection can be associated with perioperative and postoperative adrenal insufficiency (e.g., hypotension, tachycardia, hypoxia, fever). Patients with cortisol-producing tumors often require perioperative stress-dose steroids with a long postoperative taper often managed in conjunction with endocrinology. Additionally, cortisol-producing ACCs have been shown in several studies to be an independent risk factor for poorer prognosis compared with non–cortisol-producing ACCs, and these patients should be closely monitored.

Patients with aldosteronomas are usually managed with different types of hypertension medications such as calcium channel blockers (nifedipine), mineralocorticoid antagonists (spironolactone), ACE inhibitors (lisinopril), and/or angiotensin receptor blockers (losartan). These must be weaned off so as to not cause hypotension in the postoperative period. Spironolactone should be started preoperatively for blood pressure control as it also gives an idea as to the estimated blood pressure the patient will obtain postoperatively. Patients are also generally on potassium supplementation before surgery, and this should be stopped immediately preoperatively.

It is important to note the final pathology for ACC not only to ensure that a complete oncologic resection was achieved, but also to identify the Ki67 Labeling Index (Ki67 LI) status of the tumor. Of all clinicopathologic variables, the Ki67 LI status is the most important prognostic factor in regard to recurrence and survival—even in patients with a complete oncologic resection. Ki67 is a proliferation marker identified in an ACC sample by immunohistochemistry, and tumors that have a lower percent of Ki67 staining (<10%) have decreased risk of recurrence and increased survival compared with patients with higher levels of Ki67. Therefore patients with an ACC that has ≥10% of its cells staining of Ki67, despite an R0 resection, may need additional adjuvant therapies.

Adjuvant Treatment for Adrenocortical Carcinoma

After resection of an ACC, adjuvant treatment with mitotane and/or external-beam radiation therapy may be utilized to potentially improve cure rates and increase survival in high-risk patients for local recurrence. Chemotherapy treatment, with or without mitotane, has not been well studied for treating ACC in the adjuvant setting; however, a cisplatin-based regimen has been suggested with mitotane treatment for high-risk patients. The European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ENS@T) recommend the use of adjuvant mitotane in high-risk patients. Retrospective studies have differed on their results as to if adjuvant mitotane improves overall survival; however, multiple prospective randomized clinical trials are currently in process looking at mitotane with or without additional chemotherapeutic agents in the adjuvant setting, and their results will be crucial for this fatal disease.

TABLE 4 Genetic Syndromes Associated with Adrenal Cortical Tumors

Condition	Gene	Adrenal Disease	Associated Nonadrenal Disease	Important Next Steps
Beckwith-Wiedemann syndrome	*IGF2*	ACC, adrenal hyperfunction, and hyperplasia	Embryonal tumors, macroglossia, omphalocele, renal abnormalities, visceromegaly/hemihypertrophy	Genetic testing
Carney complex	*PRKAR1A*	Primary pigmented nodular adrenocortical disease	Heart and skin myxomas, skin hyperpigmentation	Cardiac evaluation
Gardner syndrome	*APC*	Adrenal adenomas	Desmoid tumors, epidermoid cysts, fibromas, gastrointestinal polyps, lipomas, osteomas, periampullary carcinoma, thyroid cancer	Annual thyroid evaluation, colonic screening, genetic testing, family history
Li Fraumeni syndrome	*TP53*	ACC	Breast cancer, leukemia, sarcoma	Family history, genetic testing, associated cancer screening
McCune-Albright syndrome	*GNAS1*	Bilateral adrenal hyperplasia, Cushing's syndrome	Fibrous dysplasia, skin hyperpigmentation (near midline)	Endocrinology consult, orthopedic consult
Multiple endocrine neoplasia, type 1	*Menin*	Adrenal adenomas, ACC	Pituitary tumors (prolactinomas, growth hormone–secreting), pancreatic tumors (gastrinomas, insulinomas), parathyroid tumors	Endocrinology and endocrine surgery consults
Primary bilateral macronodular adrenal hyperplasia	*ARMC5*	Hyperplasia, Cushing's syndrome	—	Endocrinology and endocrine surgery consults

ACC, Adrenocortical carcinoma.

Suggested Readings

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Management of Pheochromocytoma

Wilson M. Alobuia, MD, MS, and Electron Kebebew, MD

BACKGROUND

Pheochromocytomas and paragangliomas (PPGLs) are rare tumors that arise from chromaffin cells, and they have the potential to produce, accumulate, and/or secrete catecholamines (epinephrine, norepinephrine, dopamine) and metabolites of catecholamines. Approximately 80% to 85% of these tumors arise from the adrenal medulla and are referred to as *pheochromocytomas*. Conversely, paragangliomas make up the remaining 15% to 20% of chromaffin neoplasms that arise from outside the adrenal gland, but along the path of the embryologic neural crest cells as they migrate in the autonomic ganglia. Because of the cranial, vagal, trunk, and sacral locations of the neural crest cells, patients can develop paraganglioma anywhere from the skull base to the perineum. The incidence of PPGL is about 2 to 8 cases per 1 million, with a prevalence between 1 in 2500 and 1 in 6500. The prevalence is higher between the third and fifth decades of life and among patients with hypertension (0.1%–0.6% in adults and 2%–4.5% in the pediatric population). Although the overall prevalence is low, the incidence and prevalence of PPGL

reported at the time of autopsy is higher (about 0.05%–0.1%), which suggests that a good proportion of PPGLs go undiagnosed, and these patients are at risk of premature death resulting from cardiovascular and metabolic complications associated with a functional PPGL. Patients with a functional PPGL may have cardiovascular and metabolic complications such as hypertension, myocarditis, cardiomyopathy, arrhythmias, impaired glucose tolerance, and diabetes. With the increasing use of imaging studies, adrenal incidentalomas are increasingly being discovered. Approximately 10% of all PPGLs are discovered incidentally on imaging performed for other reasons. Recent advancements in genetics and whole-genome sequencing have revealed that about one-third of patients with pheochromocytomas and one-half of patients with paragangliomas have a genetic predisposition to developing these tumors. Although once described as "the rule of 10s tumor" with 10% of tumors described as being familial, bilateral, multiple, extraadrenal, malignant, and in pediatric populations, it is now recognized that the rate of these clinical characteristics is associated with the specific genetic background of PPGL. This information has become particularly important in the workup and management of patients diagnosed with PPGL because knowledge of genetic mutation status has been associated with increased overall disease-free survival and optimal treatment and surveillance. Patients with a genetic predisposition to PPGL have an increased likelihood of developing multiple, bilateral adrenal and/or extraadrenal tumors. This information is essential in determining the optimal surgical treatment for such patients because the preoperative identification of these genes has been shown to affect the surgical approach and the extent of adrenalectomy. For example, patients diagnosed with PPGL who are found to have a mutation in *RET, NF1,* or *VHL* have a low risk of metastatic disease and are therefore good candidates for cortical-sparing adrenalectomy, especially if the tumor is small (<2–3 cm) and there is no family history of metastatic disease. On the other hand, patients with a mutation in the *SDHB, FH,* or *MAX* genes and a large primary tumor are at a much higher risk of metastatic disease and may therefore be better treated with a total adrenalectomy and regional lymphadectomy. Similarly, improvements in functional imaging and tumor localizing studies have made it easier to accurately define the extent of disease in patients with PPGL and has important implications in preoperative and intraoperative decision making.

In this chapter, we highlight the important clinical features, diagnostic tests, syndromic features and susceptibility genes, imaging studies, and key perioperative measures that are essential for the optimal surgical management of patients with PPGL.

CLINICAL PRESENTATION

Some patients with functional PPGL tumors may have a triad of symptoms: paroxysmal headaches, excessive sweating, and palpitations. These symptoms may be provoked by a variety of stimuli including postural changes, exercise, anxiety, trauma, pain, or certain medications. Hypertension among PPGL patients can be sustained, or it can be paroxysmal, with occasional orthostatic hypotension and hypertensive episodes occurring daily, weekly, or even every few months. Patients may also experience other symptoms such as warmth, pallor, tremors, paresthesia, weight loss, anxiety and fear of death, vision changes, dyspnea, chest pain, abdominal pain, nausea, vomiting, and grand mal seizures. Patients who present with these symptoms as well as asymptomatic patients with an incidental finding of an adrenal mass with or without hypertension, those who experience hypertensive episodes during surgery or anesthesia without a previous diagnosis of pheochromocytoma, and those with a genetic predisposition or history of PPGL should all undergo screening for PPGL.

Patients with hereditary forms of PPGL commonly have a familial history, multiple and bilateral lesions, younger age at presentation, and extraadrenal disease. However, patients with apparently sporadic PPGL can have an inherited predisposition in nearly one-third of cases. Von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), and familial paraganglioma/pheochromocytoma syndrome (caused by mutations in succinate dehydrogenase A *[SDHA],* B *[SDHB],* C *[SDHC],* D *[SDHD]* and AF2 *[SDHAF2]* subunits) account for most hereditary PPGL syndromes. Over 15 genes with germline or somatic mutations have been implicated in hereditary PPGL with varying likelihood of disease susceptibility (Table 1), so all patients diagnosed with PPGL

TABLE 1 Clinical Features of Genetic Syndromes or Mutations Associated with Pheochromocytomas and Paragangliomas*

Gene	SDHD	SDHC	SDHB	SDHA	SDHAF2	VHL	RET	NF1	TMEM127	MAX	HIF2α†	PHD1†	PHD2†	FH
Single PCC	+	+/−	++	−	−	++	++	+	+++	++	++	+	+	+
Chest/abdomen/pelvic PGL	++	+	+++	+	−	+	−	−	+/−	−	++	+/−	+/−	+/−
Head and neck PGL	+++	++	++	+	+++	+/−	−	−	+/−	−	+/−	−	−	−
Multiple PGL	+++	+	++	−	++	+	−	−	+/−	−	+	++	++	++
Bilateral PCC	+	−	+	−	−	+++	++	−	++	++	++	+	+	+
Malignant PGL/PCC	+	+/−	+++	+/−	+/−	+	−	+	+/−	+	+	+/−	+/−	+

*Patients who have bilateral or multiple pheochromocytomas/paragangliomas, extra-adrenal paragangliomas, younger than 40 years of age at presentation, or with a family history pheochromocytoma/paraganglioma should undergo genetic testing for *SDHx*, *VHL* and *RET*. Patients with a history of any of the tumors present in MEN2 (medullary thyroid cancer, hyperparathyroidism) and VHL (central nervous system and retinal hemangioblastomas, renal cell carcinoma and cysts, pancreatic tumors and cysts, and epididymal cystadenomas) should also undergo genetic testing.

†Occur as a somatic mutation (or mosaic) and have been associated with polycythemia and require aggressive hydration perioperatively, and most of these patients are on aspirin therapy. Patients with *HIF2α* mutation are also at risk of developing neuroendocrine tumors such as somatostatinomas.

+/−, Not enough data; *FH,* Fumarate Hydratase gene; *HIF2α,* hypoxia-inducible factor 2-alpha gene; *MAX,* MYC Associated Factor X gene; *NF1,* Neurofibromin 1 gene; *PCC,* pheochromocytoma; *PGL,* paraganglioma; *PHD1-2,* Prolyl hydroxylase domain 1-2 gene; *RET,* Ret proto-oncogene; *SDH(A-AF2),* succinate dehydrogenase (A–AF2); *TMEM127,* transmembrane protein 127; *VHL,* Von Hippel-Lindau tumor suppressor gene.

should have genetic counseling and testing. This information is also extremely important to enable the physician to identify syndromic disease (other diseases that may be present), for screening and surveillance of the patient and other at-risk family members, and for surgeons to select the optimal management strategy, surgical approach, and treatment (Table 2).

DIAGNOSIS

Biochemical Testing

Patients with a suspected catecholamine-secreting tumor should undergo biochemical testing. Confirmation of the presence of pheochromocytoma and functional paraganglioma with biochemical

TABLE 2 Inherited Pheochromocytoma/Paraganglioma Syndrome*

Syndrome	Susceptibility Genes	Clinical Features	Surgical Management Considerations
Carney-Stratakis syndrome	*SDHB, SDHC, SDHD*	Dyad of PPGL and GISTs, with risk of RCC	Patients with large tumors and SDHB mutation have a high risk of malignant tumors, so consider open resection and prophylactic lymphadenectomy.
Hereditary PPGL syndrome	*SDHA, SDHB, SDHC, SDHD, SDHAF2*	Most common germline mutations found in hereditary PPGL *SDHB* related with higher morbidity and mortality and higher risk of malignancy GISTs, renal cell carcinoma, pituitary adenomas	Patients with large tumors and SDHB mutation have a high risk of malignant tumors, so consider open resection and prophylactic lymphadenectomy.
HIF-related PPGL	*HIF2α/EPAS1*	PPGL, polycythemia	High-risk for multiple tumors that should be localized preoperatively to avoid persistent disease
MAX-related PPGL	*MAX*	PPGL, renal cell carcinoma, renal oncocytoma	High-risk of malignant tumors; should consider open resection for large tumors and include prophylactic lymphadenectomy
MEN2A/B	*RET*	Recurrent and bilateral PPGL with a relatively low risk of malignancy Pheochromocytoma >>> Paraganglioma • Mutation in codons 918, 833, 634 on exons 16 and 11 associated with ~50% risk of pheochromocytoma • Mutation in codons 609, 611, 618, 620 in exon 10 associated with ~20% risk of pheochromocytoma • Mutation in codons 804 and 891 in exons 13-15 associated with ~5% risk of pheochromocytoma	Consider partial adrenalectomy to avoid need for steroid replacement as low risk of malignant tumors
TMEM-related PPGL	*TMEM127*	Pheochromocytoma > Paraganglioma RCC	
VHL	*VHL*	Pheochromocytoma > Paraganglioma Low risk of malignancy Clear-cell renal cell carcinoma, pancreatic islet cell tumors, lymphatic sac tumors, hemangioblastoma of the kidney, pancreas, cerebellum and retina	Consider partial adrenalectomy to avoid need for steroid replacement as low risk of malignant tumors.
Von Recklinghausen's disease	*NF1*	Relatively later age of presentation Pheochromocytoma > Paraganglioma Neurofibromas, dermal café-au-lait spots, Lisch nodules, bone dysplasia, skinfold freckling, optic gliomas	Consider partial adrenalectomy to avoid need for steroid replacement as low risk of malignant tumors.

*Mutations in the following genes have also been described, but are either very rare, have not been well-studied, or have not been associated with any known genetic syndromes: *FH, SLC25A11, GOT2, MDH2, PHD2, KIF1β, MERTK, MET,* and *H3F3A*.

GIST, Gastrointestinal stromal tumor; *HIF,* hypoxia-inducible factor; *MEN,* multiple endocrine neoplasia; *PPGL,* pheochromocytoma/paraganglioma; *RCC,* renal cell carcinoma; *VHL,* von Hippel-Lindau.

testing is then followed by imaging studies to localize the tumor. The initial biochemical screening tests include 24-hour urinary fractionated metanephrine and normetanephrine as well as plasma-free fractionated metanephrine and normetanephrine. The sensitivities and specificities of these biochemical tests are dependent on the cutoff value used (> two- to fourfold of the upper limit of normal) and whether the patient has a hereditary predisposition for pheochromocytoma. In patients with a hereditary predisposition for pheochromocytoma, plasma metanephrine testing should be used for screening because it has an overall higher sensitivity compared with 24-hour urinary fractionated testing. However, its specificity is lower, and it is associated with a false-positive rate as high as 10%. Plasma metanephrine should therefore be drawn in the supine position and after an overnight fast to reduce the likelihood of false-positive results resulting from increased levels caused by upright posture, caffeine use, or nicotine use. In patients with borderline elevation in metanephrine and normetanephrine levels, checking chromogranin A and urinary-fractionated metanephrine levels in combination or performing a clonidine suppression test have also been proposed to reduce the likelihood of false-positive results. In addition to many food products, several medications, including acetaminophen, labetalol, sotalol, alpha-methyldopa, tricycle antidepressants, buspirone, phenoxybenzamine, monoamine oxidase inhibitors (MAOIs), sympathomimetics, sulphasalazine, and levodopa, can also cause falsely elevated levels of plasma and urinary metanephrine and normetanephrine. Paragangliomas (by virtue of their extraadrenal location) do not secrete epinephrine because of the lack of phenylethanolamine *N*-methyltransferase (PNMT), except when located in the organ of Zuckerkandl.

Imaging

Once biochemical evidence of PPGL is confirmed, the precise location of the tumor(s) must be identified. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging modalities (Fig. 1). Pheochromocytomas are better visualized on adrenal protocol CT scans that use thin-cut and timed

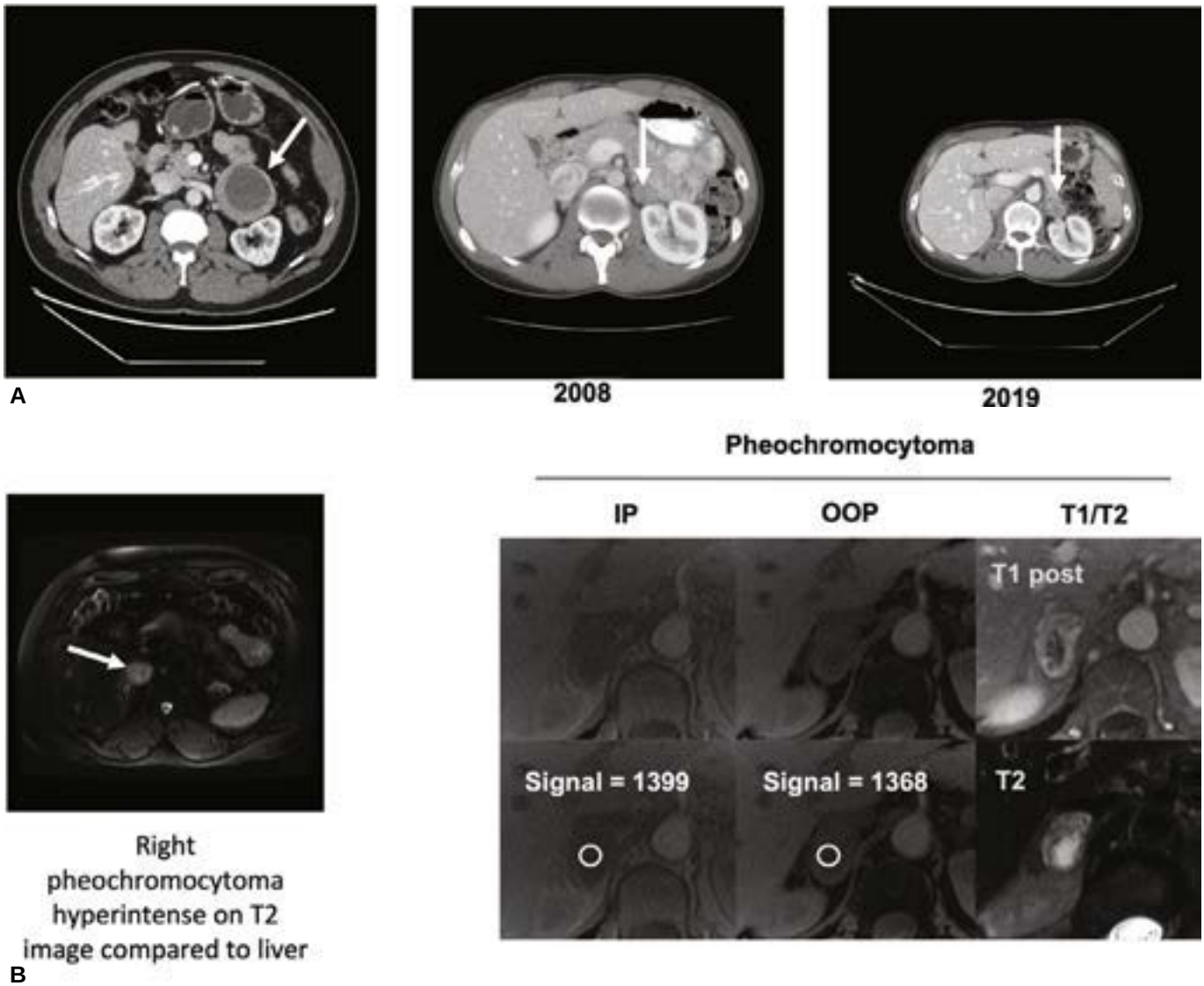


FIG. 1 Anatomic imaging of pheochromocytoma. **(A)** CT scan of the abdomen with intravenous contrast shows a left sided pheochromocytoma that has a central area of necrosis and peripheral enhancement *(left panel, arrow showing mass)*. CT scan of the abdomen in a patient who was found to have an adrenal incidentaloma in 2019 *(right panel, arrow showing mass)* with biochemical testing showing elevated normetanephrine and metanephrine. The tumor is a heterogenous mass, but there was no change in tumor size when compared with an older CT scan in the same patient done in 2008 *(middle panel, arrow showing mass)*. **(B)** MRI of the abdomen on fat-suppressed T2-weighted image shows right-sided pheochromocytoma that is hyperintense *(left panel, arrow showing mass)*. MRI showing a right adrenal pheochromocytoma in phase (IP), out of phase (OOP), and on T1 and T2 *(right panel)*.

intravenous (IV) contrast images to evaluate for tumor enhancement and washout. CT has excellent sensitivity (ranging from 90%–100%) for the detection of both PPGLs. CT findings consistent with a pheochromocytoma include Hounsfield units (HUs) greater than 10 and vigorous tumor enhancement in the early contrast phase, with less than 60% of washout in the venous phase (see Fig. 1A). On noncontrast CT scans, pheochromocytomas commonly have HUs in the range of 40 to 50. PPGLs on CT scan may appear homogenous or heterogeneous, necrotic with some calcification, solid, or cystic. Smaller tumors tend to be more homogenous, while larger tumors are typically more heterogenous and more likely to have necrotic, calcified, and cystic components. CT scans of the neck, chest, abdomen, and pelvis, with and without contrast, should be performed to exclude extraadrenal paragangliomas, using a section thickness of 2 to 2.5 mm in the neck and 5 mm through the chest, abdomen, and pelvis, especially in high-risk patients: young patients (< 40 years) and patients with germline *SDHx* mutations or a family history of PPGLs (see Table 1).

MRI is the imaging test of choice in pediatric and pregnant or lactating patients. Other patient groups that benefit from this modality include patients with documented allergies to CT contrast agents and patients who refuse radiation exposure. Because of their increased vascularity and high water content, PPGLs may have a pathognomonic high signal intensity on T2-weighted MRI (see Fig. 1B). However, this is not always the case, and PPGLs can appear homogenous with intermediate intensity, diffusely heterogeneous with swirl-like areas of high and low signal intensity, and heterogeneous with multiple pockets of high signal intensity (cystic lesions) (see Fig. 1B). MRI has a higher sensitivity for the detection of extraadrenal paraganglioma compared with CT scans, with some studies reporting a sensitivity as high as 100% with MRI.

Although anatomic imaging modalities like CT and MRI have excellent sensitivity, they have very poor specificity. Functional imaging studies, such as nuclear scintigraphy with ^{123}I-metaiodobenzylguanidine (MIBG), ^{18}F-fluorodeoxyglucose (FDG), ^{18}F-3,4-dihydroxyphenylalanine (DOPA), ^{18}F-fluorodopamine (FDA), and ^{68}Ga-DOTA (DOTATATE, DOTATOC, DOTANOC) peptide positron emission tomography (PET)/CT, can be helpful in localizing previously undetected tumors on CT/MRI and for identifying additional tumor sites (Figs. 2 and 3). For ruling out metastatic disease and localizing the primary tumor, ^{18}F-FDG PET/CT and ^{68}Ga-DOTA peptide PET/CT are most accurate (see Figs. 2 and 3). ^{123}I-MIBG scanning is not as sensitive as the other functional imaging modalities and should only be used when planning radiotherapy with ^{131}I-MIBG for patients with metastatic disease.Table 3 summarizes the anatomic and functional imaging studies that can be used to localize PPGLs, with their advantages and disadvantages, and the clinical settings in which their use can facilitate the selection of the optimal surgical management strategy.

PREOPERATIVE MANAGEMENT

The preoperative management of patients with PPGL should focus on the optimization of blood pressure and treatment for tachyarrhythmias. Hypertension and elevated levels of circulating catecholamines predispose patients with PPGL to compromised cardiovascular function, which is commonly manifested as a tachyarrhythmia. These patients may have concomitant, long-standing hypertension, which predisposes them to cardiomyopathy and aseptic myocarditis. A preoperative cardiac evaluation is therefore prudent, regardless of blood pressure levels, to assess cardiac function, optimize perioperative management, and risk-stratify patients for perioperative cardiovascular events.

Preoperative antihypertensive medications to reduce the risk of intraoperative hemodynamic instability are required for all patients with catecholamine-producing PPGLs. Alpha-adrenergic antagonists are usually the first agents of choice because of their ability to lower blood pressure, reverse volume depletion, and reduce peripheral vascular resistance. Patients who are normotensive should be started on alpha blockade to counter any potential activity from dormant tumors that may release catecholamines during intraoperative tumor manipulation. Adrenergic blockade should start 7 to

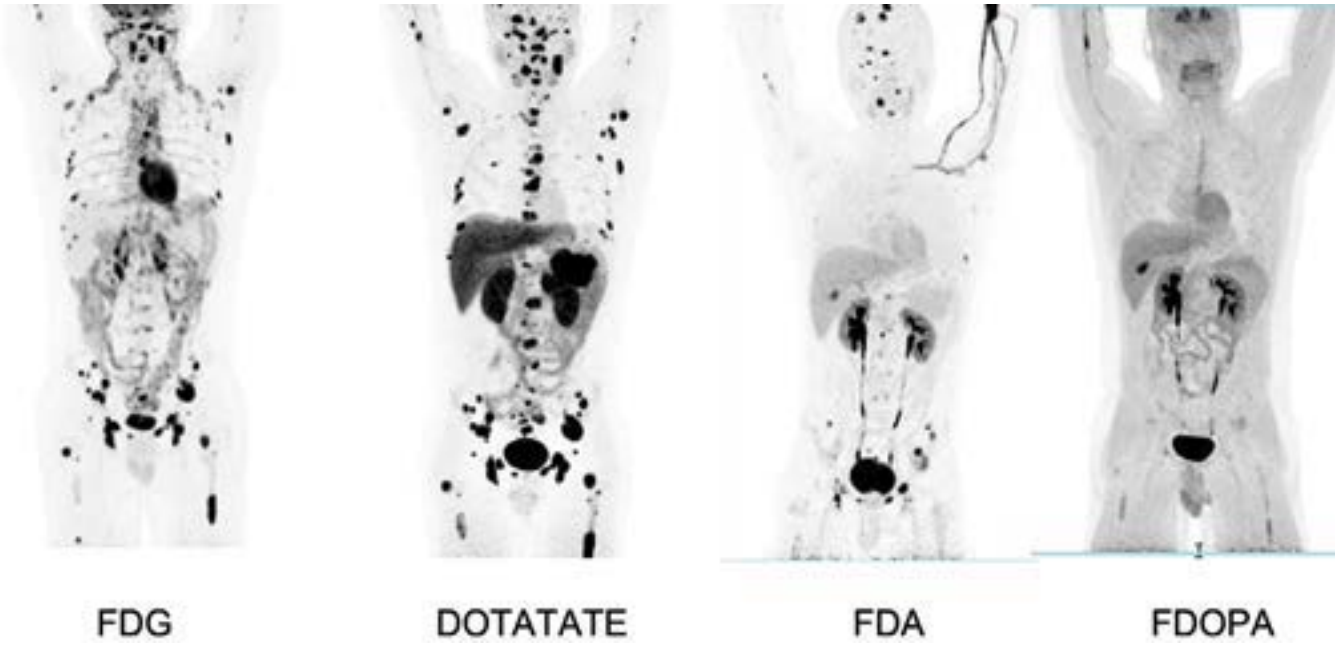


FIG. 2 Functional imaging in a patient with metastatic and recurrent pheochromocytoma. ^{18}F-fluorodeoxyglucose (FDG), ^{68}Ga-DOTATATE, ^{18}F-fluorodopamine (FDA), and ^{18}F-3,4-dihydroxyphenylalanine (FDOPA). The DOTATATE imaging shows the greatest number of metastatic lesions followed by FDG and FDA, and none is seen on FDOPA.

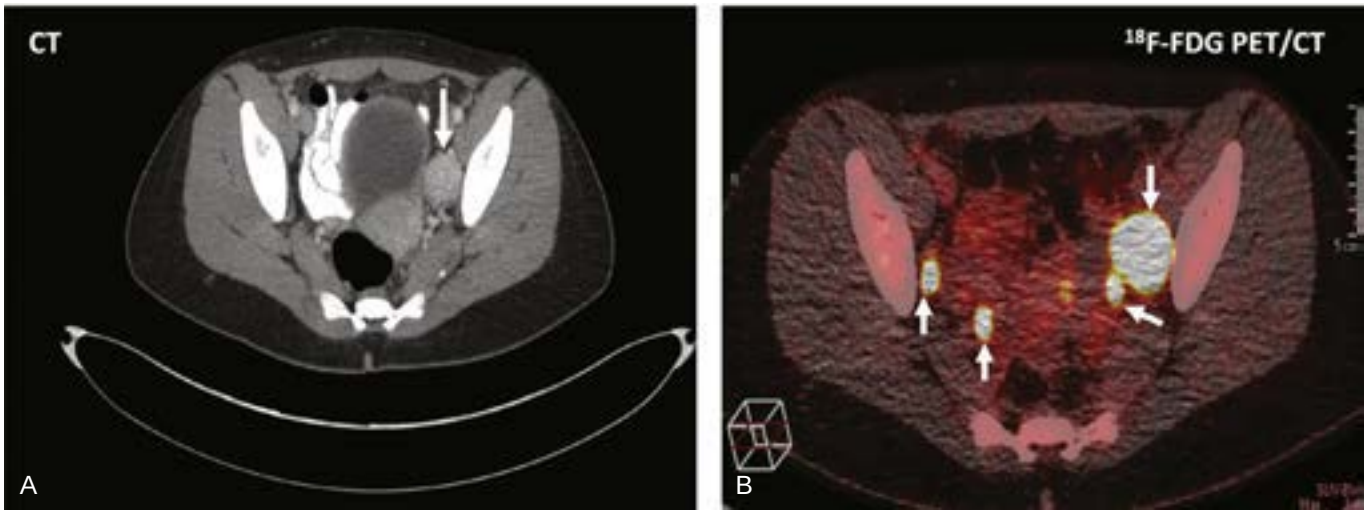


FIG. 3 CT scan **(A)** and ^{18}F-fluorodeoxyglucose (FDG) PET/CT scan **(B)** in a 16-year-old girl with a left functional paraganglioma. CT scan showed only the left paraganglioma *(arrow)*, but ^{18}F-FDG showed additional tumor adjacent to the mass *(arrows)* and on the right side of the pelvis.

TABLE 3 Anatomic and Functional Imaging Studies Used to Localize Pheochromocytomas and Paragangliomas

Imaging Modality	MRI	CT	^{18}F-FDG	^{68}Ga-DOTA Peptide	^{18}F-FDA	^{18}F-DOPA	MIBG
Advantages	Anatomic detail	Anatomic detail	Widely available, preferred functional imaging test	Most sensitive functional imaging study for all sites of disease, potential for therapy with avid disease	Sensitive functional imaging for primary tumor (except skull base and neck)	Most sensitive functional imaging study for skull base and neck paragangliomas	Potential for therapy if disease avid tumor is not resectable
Disadvantages	Lower specificity	Lower specificity	Lower sensitivity and higher false-positive rate compared with other functional imaging studies	Not widely available	Not widely available	Not widely available	Lower sensitivity than other functioning imaging studies
Best clinical setting to use imaging studies	Initial localization of tumor	Initial localization of tumor	Rule out metastatic disease or multiple primary	Rule out metastatic disease or multiple primary; SDHx mutation carriers; when planning treatment with peptide receptor radionuclide therapy	Rule out metastatic disease or multiple primary	Patients with primary skull base and neck paragangliomas; multiple and metastatic disease	When planning treatment with ^{131}I-MIBG

14 days preoperatively to normalize blood volume, blood pressure, and heart rate. We normally initially place patients on phenoxybenzamine (10 mg twice a day). Other alternative agents include a selective alpha antagonist such as doxazosin (2 mg once a day), prazosin (2 mg twice a day), or terazosin (2 mg once a day). The goal should be to achieve a preoperative blood pressure of 130/80 mm Hg or less while sitting and approximately 100 mm Hg while standing. If the patient continues to have high blood pressure, the dose is increased in increments of 10 to 20 mg every 2 to 3 days. In addition, medications are titrated for a heart rate of about 60 to 70 beats per minute (bpm) while sitting and 70 to 80 bpm while standing.

Many patients with PPGL have chronic vasoconstriction secondary to high levels of catecholamines. Preoperative normalization of blood volume reduces the risk of hypotension during or after removal of the tumor. A high-salt diet 3 days after initiation of alpha blockade and 1 to 2 L of normal saline starting the evening before surgery can normalize intravascular volume and reduce the risk of hypotension after removal of the tumor. With appropriate alpha-adrenergic blockade, patients may experience tachyarrhythmias. A beta blocker should be added to control the heart rate 2 to 3 days after initiation of alpha blockade. Most importantly, a beta blocker should never be used in the absence of adequate alpha blockade. The utilization of a beta blocker without alpha blockade leads to unopposed alpha-adrenergic catecholamine stimulation, which will exacerbate vasoconstriction. Beta-selective drugs such as atenolol or metoprolol are started for a target heart rate of 60 to 80 bpm. Labetalol, a nonselective beta blocker, should not be used as first-line therapy because the beta effect is seven times more potent than the alpha effect. For patients with persistent hypertension despite optimal alpha and beta blockade, a calcium channel blocker (30 to 90 mg of nifedipine a day) or metyrosine (1 to 4 grams a day) may be used, although it is important to note that metyrosine has very significant side effects including sedation, fatigue, sexual dysfunction, extrapyramidal symptoms, headache, diarrhea, nausea, and vomiting. Its use should therefore be limited to patients with refractory hypertension and not as a first-line agent.

A diagnosis of PPGL during pregnancy is associated with significant rates of maternal mortality (up to 40%) and fetal mortality (over 50%), resulting largely from the challenges related to preoperative management. Alpha-adrenergic antagonists should be initiated immediately at the time of diagnosis, and plans should be made for an elective third-trimester caesarean delivery. Vaginal delivery is contraindicated in patients with PPGL because of the potential for catastrophic, massive catecholamine release during labor and at the time of delivery. Overall, a combined adrenalectomy at the time of caesarean section versus early postpartum resection is generally preferred. Tumor removal should be avoided during the first trimester because of the high risk of miscarriage. However, adrenalectomy in the second trimester has been reported and may be considered if necessary.

INTRAOPERATIVE CONSIDERATIONS

Successful intraoperative management of PPGL requires collaborative preparation and good communication between the surgery and anesthesiology teams. Despite being adequately blocked by preoperative adrenergic blockade, patients with PPGL may still have hypertensive crises or tachyarrhythmias during manipulation of the tumor. Therefore intraarterial monitoring is required and appropriate venous access, including a central venous catheter for monitoring the volume status, is imperative. Patients may have fluctuations in blood pressure during the operation, so multiple vasoactive medications should be premixed and ready to be administered in anticipation of these labile blood pressures. Hypertensive episodes can be treated with esmolol (500 μg/kg over 1 minute loading dose, followed by a 4-minute maintenance infusion of 50 μg/kg/min) or sodium nitroprusside (0.5 to 3 μg/kg/min), which reduces cardiac preload. Excellent communication between the surgeon and anesthesiology team is required just before ligation of the adrenal vein because this maneuver can lead to abrupt hypotension, which should initially be treated with crystalloids. Once adequate volume resuscitation has been achieved, treatment of persistent hypotension with vasopressors such as norepinephrine, phenylephrine, or vasopressin can be initiated.

OPERATIVE TECHNIQUE

Options for the surgical approach in the resection of PPGL include open and minimally invasive approaches (laparoscopic, robotic), which can all be performed using either a transabdominal or retroperitoneal approach. Minimally invasive surgery for the removal of PPGL is the procedure of choice in most cases and has been shown to be associated with significant advantages compared with open resection: decreased blood loss, decreased blood transfusion requirement, shorter intensive care unit and postoperative hospitalization, decreased analgesic requirements, and faster return to normal patient activity. Furthermore, minimally invasive approaches are associated with fewer catecholamine surges during tumor manipulation and therefore fewer episodes of blood pressure lability. A direct open approach is typically reserved for larger, locally advanced or malignant tumors. Conversion to an open procedure may also be required because of intraoperative suspicion of malignancy or metastatic disease. Robotic-assisted removal of PPGL is also safe and feasible, but it does not appear to afford any significant advantages over laparoscopic resection using either the transabdominal or retroperitoneal approach, especially in light of its higher financial cost.

The surgical approach and extent of resection for pheochromocytoma we use depends on (1) whether the tumor is unilateral or bilateral, (2) whether there are any additional paragangliomas or possible sites of metastatic disease, (3) tumor size, (4) patient body habitus and body mass index, (5) whether the tumor is sporadic or familial relative to the risk of malignancy, and (6) the risk of developing metachronous pheochromocytoma in the contralateral and remnant adrenal gland. We most commonly use a transabdominal laparoscopic approach in patients who have unilateral adrenal tumors and sporadic disease and those who have no evidence of extraadrenal tumors. In patients with bilateral tumors and familial disease with a low risk of malignant pheochromocytoma, such as the MEN2 or VHL syndromes, we perform a cortical-sparing adrenalectomy using a transabdominal or retroperitoneal laparoscopic approach. When patients have unilateral or recurrent tumors, possible site(s) of lymph node metastasis/local invasion, and an *SDHB* germline mutation, we perform a total adrenalectomy and retroperitoneal lymph node dissection with an open approach. Even when the tumor is large, we usually begin the operation using a laparoscopic approach until we encounter evidence of local invasion or features suspicious for malignancy. We believe that a complete resection is most important and, whatever the surgical approach, there should be no fracturing of the tumor or violating the tumor capsule, as there have been reports of pheochromocytomatosis with evidence of higher rates of peritoneal implants, locoregional recurrence, and metastatic disease among patients who underwent laparoscopic resection. For this reason, clinical guidelines recommend open resection for large tumors (>6 cm) and locally invasive PPGLs. Minimally invasive approaches may be used, however, for small, noninvasive paragangliomas in safe and favorable locations.

Transabdominal Laparoscopic Adrenalectomy and Paraganglioma Resection

Transabdominal laparoscopic adrenalectomy is the most common laparoscopic approach used by most surgeons. The main advantage of this approach is a larger working space than that afforded by the retroperitoneal approach. The procedure is performed by placing the patient in the lateral decubitus position, with the operating table flexed. An incision is made one fingerbreadth below the costal margin in the midclavicular line. We use a 0-degree videoscope to enter the peritoneal cavity under direct visualization. Then we use a 30-degree videoscope to place additional trocars and for the dissection. The tumor should not be manipulated, or manipulation should be kept to a minimum, until the venous drainage is divided, as severe hypertension can result otherwise. Clear communication with the anesthesia team is important to anticipate and treat hemodynamic instability during manipulation of the tumor and division of the adrenal vein. The key steps and intraoperative images of a transabdominal laparoscopic adrenalectomy (right and left) are summarized in Figure 4.

For a right adrenalectomy, we use four trocars, from the mid-clavicular line to the mid-axillary line, with a distance of

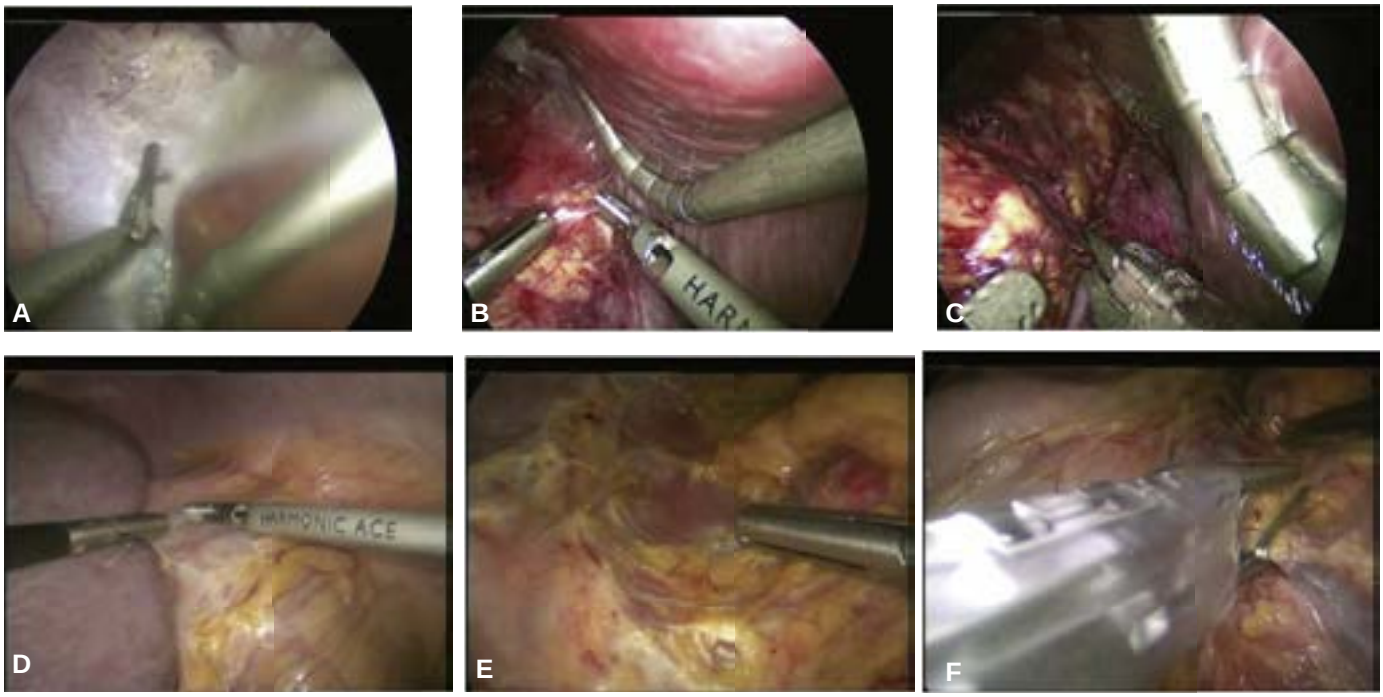


FIG. 4 Key steps in right lateral laparoscopic adrenalectomy. On the right side, **(A)** the triangular ligament is divided to mobilize the right lobe of the liver medially; **(B)** the adrenal gland and tumor are dissected from the top down along the medial edge after opening Gerota's fascia; **(C)** the adrenal arteries (usually small) and the adrenal vein are encountered and the vein is clipped and divided. Adrenal pheochromocytoma may have multiple parasitic vessels. The inferior limb of the gland is carefully dissected free from the renal hilum and the renal vessels. The gland is then mobilized free from the kidney and retroperitoneal fat. The adrenal gland is placed in a bag and removed without morselization. On the left side, **(D)** the splenic flexure of the colon is mobilized free, as well as the lateral attachments of the spleen along the avascular space; **(E)** Gerota's fascia is divided superior and medial to the adrenal gland and the dissection continued inferior; **(F)** often the inferior phrenic vein is identified along the medial aspect of the adrenal gland and can be traced down to the adrenal vein. The vein is clipped and divided. The inferior limb of the gland is carefully dissected free from the renal hilum and the renal vessels. The gland is then mobilized free from the kidney and retroperitoneal fat. The adrenal gland is removed in a bag.

approximately two fingerbreadths between the trocars. The initial dissection consists of dividing the triangular ligament of the liver to mobilize the right lobe of the liver medially and expose the right adrenal gland. Once this has been completed, a fan, paddle, or snake retractor is placed on the right lobe of the liver to maintain the working space. The dissection from the triangular ligament is extended down inferiorly, dividing the peritoneum and Gerota's fascia along the liver down to the infrahepatic inferior vena cava. Commonly, the adrenal vein is encountered during this top-down dissection and is circumferentially dissected, clipped, and divided. Any accessory veins and the three adrenal arteries, which are usually more prominent in patients with pheochromocytoma, are divided by an energy device along this medial dissection. The inferior pole of the gland is then mobilized free from the renal hilum, taking care not to injure the renal artery and vein. The attachment to the superior pole of the kidney and posterior musculature is then divided, and the dissection is extended up to the diaphragm, removing the periadrenal fat along with the gland. We usually detach the attachment to the diaphragm last as it keeps the adrenal gland in place, allowing good visualization of the adrenal hilum and inferior limb of the gland.

For a left adrenalectomy, we usually use three trocars because the spleen and the tail of the pancreas are retracted by gravity. The first subcostal trocar is placed in the midclavicular line at the Palmer point, and the lateral two are placed approximately two fingerbreadths apart and one fingerbreadth from the costal margin. The lateral attachment of the spleen (approximately 1 cm from the lateral edge of the spleen) and the splenic flexure of the colon are released up to the diaphragm until visualization of the cardia of the stomach. This dissection allows the spleen and the tail of the pancreas to be retracted medially by gravity. At the medial aspect, the adrenal gland is dissected top-down along with the periadrenal fat and the adrenal arteries divided with an energy device. Often the inferior phrenic vein is encountered during this medial dissection and can be traced to the left adrenal vein. The adrenal vein is then clipped and divided above the renal vein into which it drains. The inferior pole is carefully dissected free from the renal hilum without injury to the renal vein and artery, and then free from the superior pole of the kidney and from the posterior musculature.

Posterior Retroperitoneal Adrenalectomy

We commonly use the posterior retroperitoneal approach in patients who require bilateral total or partial adrenalectomy and in patients who have undergone previous abdominal operations and have significant intraabdominal adhesions. The key steps of a posterior retroperitoneal adrenalectomy (left and right), including intraoperative images, are outlined in Figure 5. Once there is adequate general anesthesia and intravenous and intraarterial lines are placed and secured, the patient is placed in the prone jackknife position. The hips and knees are flexed at 90 degrees, and all pressure points are padded. Cushions are used to support the hips and lower chest, allowing the anterior abdominal wall to hang unconstrained between

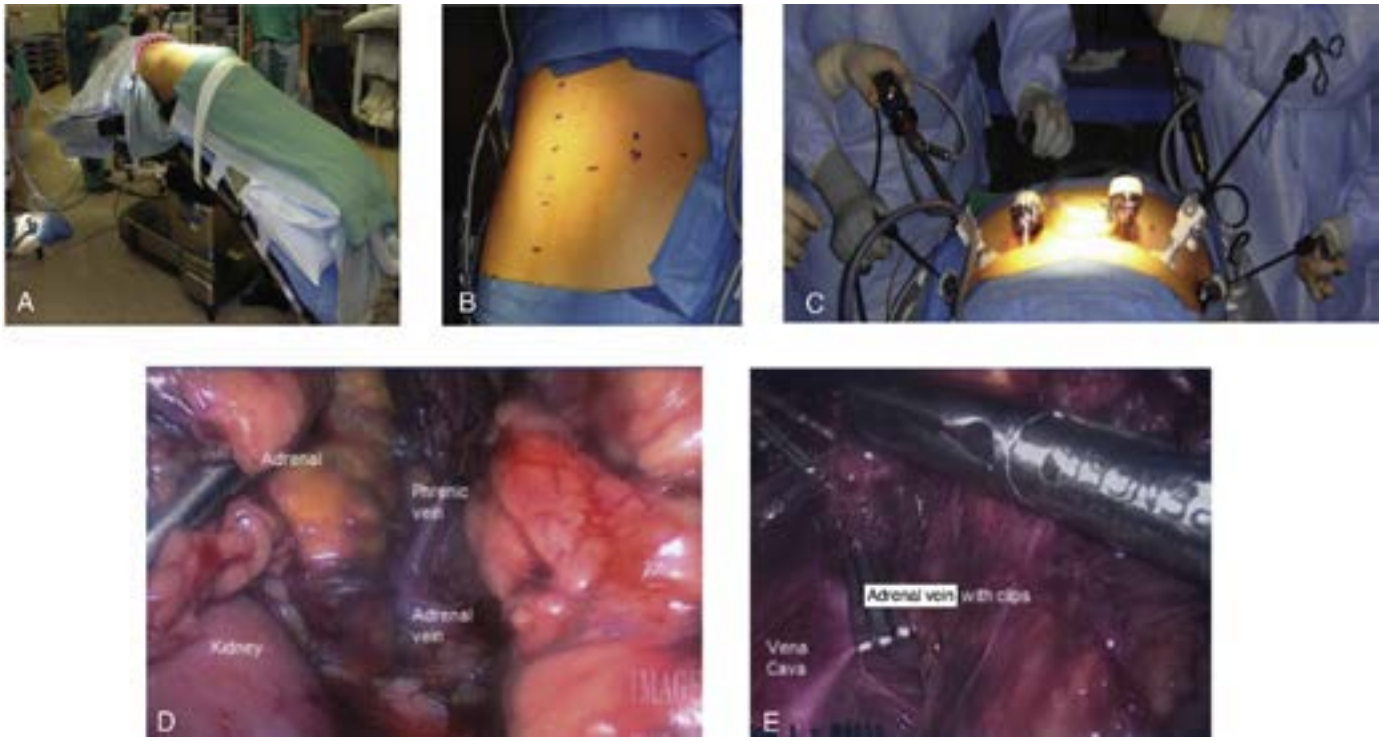


FIG. 5 Retroperitoneal approach for adrenalectomy. **(A–C)** Patient positioning and trocar placement. **(A)** Patient is supported in a modified prone jackknife position. **(B)** Port sites are marked using the 12th rib as a landmark. **(C)** Operative image of simultaneous bilateral adrenalectomy. **(D)** Left adrenal tumor is retracted to expose adrenal vein. **(E)** Operative field after blunt dissection of the retroperitoneal fat down with visualization of the adrenal vein.

the cushions. This helps to expand the retroperitoneal space. The tip of the 12th rib is palpated, and a 1.5-cm transverse incision is made below the tip of the rib and extended into and through the posterior musculature and fascia to enter the retroperitoneum. A working space is initially created by blunt digital separation of the retroperitoneal fat. A lateral 5-mm trocar is inserted 4 to 5 cm from the initial incision, beneath the 11th rib, under finger guidance. Next, a medial 10-mm trocar is inserted 4 to 5 cm medially from the initial incision. Finally, a 10-mm, blunt-tip trocar with an inflatable balloon is inserted and secured in the initial incision, followed by insufflation with carbon dioxide. The pressure should be maintained around 20 mm Hg. The retroperitoneal fat is pushed down and away medially from the posterior musculature and diaphragm. The retroperitoneal fat and the adrenal gland are dissected free from the diaphragm superiorly. The superior pole of the kidney is retracted, and the adrenal gland is mobilized free medially and inferiorly: on the right side, the adrenal vein is identified during this dissection draining into the inferior vena cava; on the left side, it is identified medially and inferiorly along with the phrenic vein in most cases. Once the adrenal vein is clipped and divided, the gland, along with the retroperitoneal fat, is lifted and retracted laterally and superiorly to divide the remaining small vessels and attachments. Hemostasis should be checked after the carbon dioxide pressure is reduced.

Laparoscopic Cortex-Sparing Adrenalectomy

In patients who have MEN2 and VHL and who also have bilateral pheochromocytomas, there is an opportunity to perform cortex-sparing adrenalectomy to avoid the need for long-term steroid replacement and the risk of an Addisonian crisis if a bilateral total adrenalectomy were to be performed. Furthermore, patients with MEN2 and VHL who have unilateral pheochromocytoma may also need to have cortical-sparing adrenalectomy because of the risk of developing a contralateral pheochromocytoma, which would require an adrenalectomy. Laparoscopic cortex-sparing adrenalectomy can be performed in a similar fashion to laparoscopic adrenalectomy in terms of port placement and mobilization of surrounding organs. Intraoperative ultrasound is beneficial in identifying smaller tumors and helping the surgeon identify the margins of resection. The adrenal gland parenchyma can be transected using electrocautery or Harmonic and LigaSure scissors. The remnant adrenal gland is left in situ and not dissected. This is critical, especially if the adrenal vein cannot be spared to maintain adequate blood flow and drainage of the remnant adrenal gland.

Open Adrenalectomy

We use an open adrenalectomy approach in patients who may have malignant tumors, a diagnosis based on a sufficiently large tumor size, the presence of local invasion, or presentation with locoregional recurrence—and for those who have a positive germline *SDHB* mutation or other less-common susceptibility gene mutations, such as *FH* and *HIF2α,* which are associated with a high rate of metastatic disease. We use a subcostal incision for our open adrenalectomies, but a thoracoabdominal incision may be necessary in patients with large, locally invasive tumors. In addition to resecting the primary tumors or site of recurrent disease, we routinely perform a prophylactic retroperitoneal locoregional lymph node dissection. There are several key steps in an open right adrenalectomy for malignant or potentially malignant PPGLs. An extended Kocher maneuver is essential for adequate exposure and to allow vascular control of the infrahepatic inferior vena cava (Fig. 6). The triangular ligament should be routinely divided, and the right lobe of the liver should be fully mobilized medially. When resecting locally invasive tumors, it is essential to gain vascular control over the suprahepatic and infrahepatic inferior vena cava before dissecting the tumor free from the vena cava or dissecting the right adrenal vein. Depending on the extent of local disease, adjacent organs may need to be

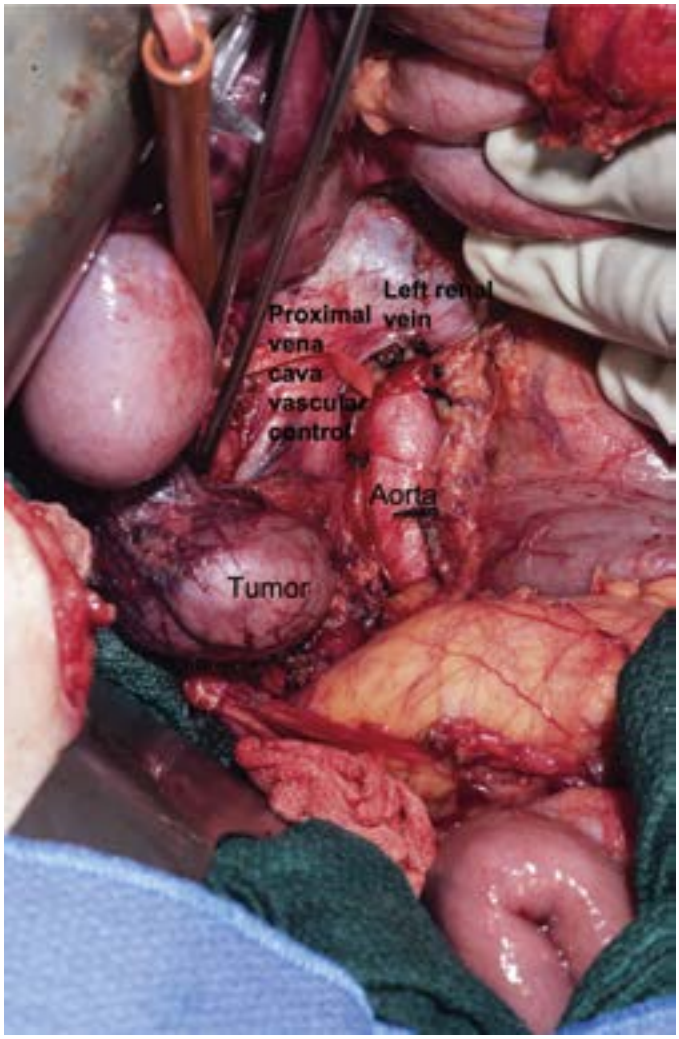


FIG. 6 Open resection of a right infrarenal pericaval paraganglioma after extended Kocher maneuver and proximal vena cava control.

resected (nephrectomy/nonanatomic liver resection/right hepatic lobectomy). For a left open adrenalectomy, division of the gastrocolic ligament and mobilization of the pancreas may be necessary if an en bloc resection of the tail of the pancreas and spleen is planned. If not, the left adrenal gland is exposed by medial rotation of the spleen, pancreas, and left colon. Vascular control of the renal vessels is important for a right or a left open adrenalectomy when removing a locally invasive tumor. For negative margins, a cuff of the posterior musculature or diaphragm, or a full-thickness resection of the diaphragm may be necessary and should be reconstructed primarily or with a Gore-Tex patch graft and an angled chest tube left above the diaphragm. Although it is rare for a patient to require such aggressive surgical treatment for locally advanced PPGLs, most patients who have cardiovascular complications associated with their tumors benefit from such an approach to functioning tumors, especially when an R0 or R1 resection can be performed.

POSTOPERATIVE MANAGEMENT

Postoperatively, patients should be monitored for blood pressure fluctuations in the intensive care unit or a step-down unit for the first 24 hours. Patients may have hypotension caused by the continued effects of alpha-adrenergic blockade or withdrawal of catecholamine and metabolites, and they may require vigorous infusion of intravenous fluids. There have been reports of hypoglycemia caused by rebound secretion of insulin after removal of a pheochromocytoma; therefore blood sugars should be monitored. Plasma metanephrine levels should be evaluated at 6 weeks and at 6 months to confirm the patient's biochemical response.

MALIGNANT PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Currently, there are no histologic, biochemical, or molecular markers that can differentiate patients with benign and malignant PPGLs in the absence of locoregional invasion, distant metastasis, or lymph node metastasis. A metastatic PPGL may be present at the initial time of diagnosis or (commonly) become evident within 5 years of diagnosis. However, there are reports in the literature of recurrences up to 42 years after pheochromocytoma resection, which emphasizes the importance of annual biochemical screening in both sporadic and hereditary PPGLs and imaging surveillance in patients without a functional tumor. Features that have been associated with metastatic PPGLs include a tumor size greater than 5 cm and germline *SDHB* gene mutation.

In patients with metastatic PPGLs, surgical resection of recurrent or metastatic disease is the best treatment option. This is especially true in patients for whom an R0 or R1 resection can be achieved. However, some patients who have widely metastatic disease with elevated catecholamine and metabolites may still benefit from cytoreductive surgery to palliate symptoms or control cardiovascular events associated with the presence of excess catecholamine and their metabolites. The prognosis of patients with metastatic PPGLs is variable, with some patients developing stable disease and others developing rapidly progressive disease, including debilitating symptoms and difficult-to-control cardiovascular complications from the presence of excess catecholamines and metabolites. Overall, the median survival for patients with malignant PPGLs is 7 years, with less than 50% of patients surviving past 5 years.

Patients with unresectable disease may benefit from cytotoxic chemotherapy, such as treatment with a combination of cyclophosphamide, vincristine, and dacarbazine or ^{131}I-MIBG therapy. Unfortunately, only two-thirds of metastases are avid upon MIBG scanning, which can limit the efficacy of this therapy. Up to two-thirds of patients can have an objective response, with complete response, partial response, or stable disease with ^{131}I-MIBG therapy. PPGLs have been localized using newer imaging modalities such as ^{68}Ga-DOTA peptide PET/CT, which shows superior metastatic disease detection rates compared with other anatomic and functional imaging studies. For tumors that are ^{68}Ga-DOTA peptide–avid, peptide receptor radionuclide therapy with ^{177}Lu or ^{90}Y may result in a partial or complete response and symptomatic relief and is currently being studied in clinical trials.

SUMMARY

PPGLs are rare tumors that can occur throughout the body, and they are associated with an increasingly recognized number of genetic mutations. Initial diagnosis of functional PPGLs is by biochemical testing with 24-hour urinary or plasma metanephrines, followed by tumor localization with CT/MRI. Functional imaging studies with ^{18}F-fluorodeoxyglucose (FDG) and ^{68}Ga-DOTA peptide PET/CT are helpful for the evaluation of additional primary tumors and metastatic disease. Genetic testing should be performed in all patients with PPGL. Surgical management of PPGL requires close collaboration and communication with the anesthesiologist. Preoperative alpha blockade and beta blockade is imperative to optimize blood pressure, treat tachyarrhythmia, and restore normal circulating blood volume. Surgical removal is the mainstay of treatment and can be performed via minimally invasive or open approaches with excellent results.

Suggested Readings

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Management of Thyroid Nodules

Quan-Yang Duh, MD, and Sarah S. Sims, MD

INTRODUCTION

There has been a substantial increase in the detection of thyroid nodules and thyroid cancer over the past decades in the United States and other countries, which is attributed to the availability of neck ultrasound. However, deaths from thyroid cancer have remained rare yet relatively constant. Due to increased detection, not accompanied by increased mortality, some are concerned about the overtreatment of thyroid nodules and cancer, and this controversy has been popularized in the mainstream media. It is very important to risk-stratify patients with thyroid nodules to avoid the morbidities of overtreatment that can substantially affect quality of life, while still providing appropriate treatment to achieve optimal outcomes.

Thyroid nodules are very common, affecting as many as half of the population by age 50. Most thyroid nodules are asymptomatic and identified incidentally from imaging studies. Some patients have a palpable neck mass or goiter. The vast majority of thyroid nodules are not cancerous. The rate of cancer, however, is higher in patients with risk factors such as exposure to ionizing radiation at a young age or having a first-degree relative with thyroid cancer. In contrast, thyroid nodules causing hyperthyroidism are rarely cancerous. Patients with suppressed thyroid-stimulating hormone (TSH) (hyperthyroid) and a thyroid nodule are usually first evaluated by scintigraphy to establish the diagnosis (e.g., solitary or multiple hyperfunctioning nodules [Plummer's disease] or hypofunctioning nodules in Graves' disease).

ULTRASONOGRAPHY

Ultrasonography is safe and the most efficient first-line evaluation for thyroid nodules. Multiple large cohort studies have identified ultrasound characteristics of thyroid nodules that are associated with risk of cancer. The high-risk characteristics include nodules that are large, hypoechoic, contain microcalcifications, have irregular borders, or are taller than they are wide. Ultrasound characteristics associated with a low risk of thyroid cancer include nodules with more cystic components and those that have clear borders or are spongiform. Ultrasound characteristics help to stratify the risk of thyroid cancer and are used to determine when fine-needle aspiration (FNA) biopsy is indicated. The 2015 American Thyroid Association guidelines recommend FNA for thyroid nodules larger than 1 to 2 cm depending on their ultrasound characteristics: 1 cm for those classified at highest risk by ultrasound and 2 cm for those classified at the lowest risk (Fig. 1). The American College of Radiology has developed the Thyroid Imaging Reporting and Data Systems (TI-RADS) to provide a point scale option to "quantify" the level of risk for each nodule in addition to guidance for size threshold of when to biopsy based on TI-RADS score (Fig. 2).

NONULTRASOUND THYROID INCIDENTALOMAS

Occasionally, thyroid nodules are found on imaging modalities other than ultrasound, such as computed tomography scans and magnetic resonance imaging. These still should be investigated by ultrasound, and further workup should proceed accordingly. Hypermetabolic thyroid nodules incidentally found on fluorodeoxyglucose-positron emission tomography (PET) scan are at higher risk for cancer, thus FNA is recommended at the lower threshold of more than 1 cm.

OTHER TESTS IN EVALUATION OF THYROID NODULES

Serum levels of thyroglobulin are useful in the follow-up of patients with differentiated thyroid cancer but not in the diagnosis of whether a thyroid nodule is cancerous, because serum thyroglobulin can be elevated in many patients with benign thyroid disease. Although serum calcitonin measurement has been advocated in some European countries as a screening test for medullary thyroid cancer in patients with thyroid nodules, it is not done routinely in the United States. Furthermore, of studies showing that calcitonin screening is helpful, most used pentagastrin stimulation, which is not available in the United States or Canada. Without a known risk factor for medullary thyroid cancer (such as a family history or other manifestation of multiple endocrine neoplasia type 2), routine measurement of serum calcitonin has a low yield, a high false-positive risk, and is not cost effective.

SIZE OF THYROID NODULE

Current guidelines generally recommend further evaluation only for thyroid nodules larger than 1 cm. Nodules smaller than 1 cm in patients with previous radiation exposure, family history of thyroid cancer, or other high-risk clinical findings, such as hoarseness or rapid growth, and those associated with lateral lymphadenopathy may warrant biopsy. Evaluation of multinodular goiters follows similar criteria for biopsy as for solitary thyroid nodules. Rapidly growing goiters or those causing compressive symptoms, such as dysphagia, dysphonia, or dyspnea, have independent indications for thyroidectomy and may not need biopsy unless the results will change the operative plan.

BIOPSY

FNA biopsy can be done by palpation, but ultrasound-guided biopsy is associated with fewer nondiagnostic aspirates. To address variability in the reporting of FNA results for thyroid nodules, the National Cancer Institute developed the *Bethesda Classification* of thyroid cytopathology in 2009, which was updated in 2017. In this system, there are six categories that represent a spectrum for the risk of thyroid cancer. Category I is nondiagnostic, and categories II and VI are benign and malignant, respectively. Benign FNA cytology (category II) has a malignancy rate of up to 3%. A small subset of thyroid nodules with very high-risk ultrasound characteristics will likely have a

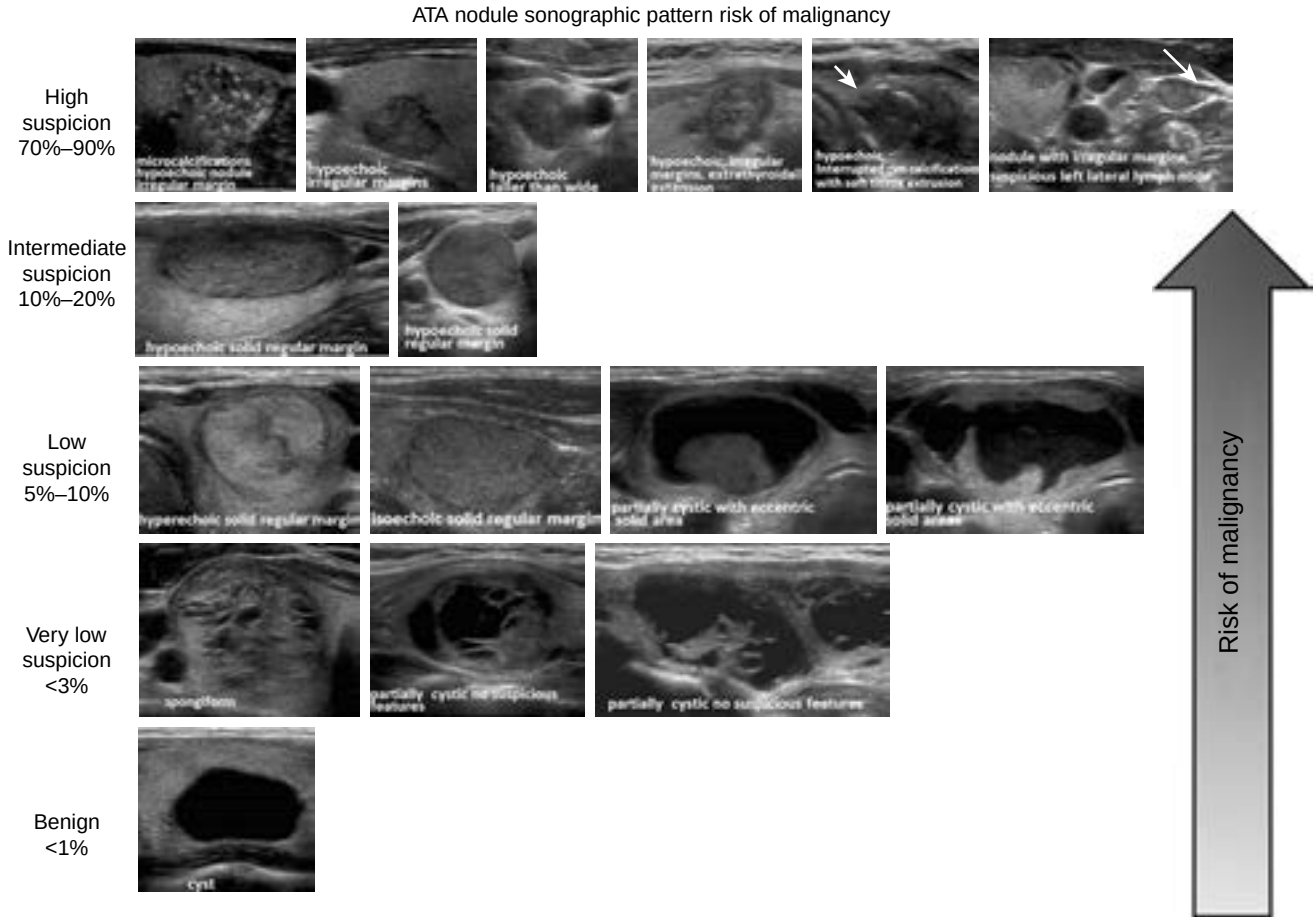


FIG. 1 American Thyroid Association (ATA) nodule sonographic pattern risk of malignancy. *(From Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;14:26, Fig. 2.)*

much higher risk of malignancy even with a benign FNA cytology. Malignant biopsies (category VI) have an accuracy rate of 97% to 99%. Categories III through V nodules have a spectrum of risk that varies by center and depends also on the malignancy rates of the population ("pretest probability"). Category III nodules include nodule with atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS). Category IV nodules include follicular neoplasm (FN)/suspicious for follicular neoplasm. Hurthle cell neoplasms are included in this category. Category V nodules are those suspicious for malignancy. The reported rates of cancer in these categories are 10% to 30% for AUS/FLUS, 25% to 40% for FN, and 50% to 75% for suspicious for malignancy lesions (Table 1).

Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFT-P)

Since the release of the 2015 American Thyroid Association Guidelines, an additional pathologic classification for some thyroid nodules has been created. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFT-P) represents a subset of thyroid nodules with almost no risk of metastatic spread and is therefore no longer considered a malignancy. The diagnosis requires a complete histopathologic review of the entire nodular capsule to ensure no capsular invasion. NIFT-P is indistinguishable from other follicular lesions on FNA, and therefore surgical removal is required to differentiate these lesions from well-differentiated thyroid cancers. As it is no longer considered malignant, Table 1 demonstrates probabilities of malignancy that are lower because a subset of tumors previously defined as malignant are now considered benign.

INDETERMINATE NODULES

For patients with benign or malignant nodules, there is usually a clear treatment plan. For FNA cytology of indeterminate nodules, Bethesda categories III and IV, the decision for operation versus observation is more complex because of the uncertainty for risk of malignancy. Over the past decade, there has been an explosion of research into molecular analysis of these thyroid nodules with indeterminate cytology. Knowing when and whether to use which molecular tests and how to interpret their results has become an important prerequisite for a modern thyroid surgeon.

MOLECULAR TESTING

Molecular testing may be used for patients with indeterminate nodules to help with the decision to operate (or to perform a more aggressive operation) or to observe. It is important to know that molecular testing may not give a simple yes or no answer but usually returns a probability for risk of cancer for the nodule tested.

MUTATIONAL ANALYSIS

ThyroSeq v3

ThyroSeq is a molecular test for indeterminate thyroid nodules based on molecular alterations in cell DNA and RNA. Since its initial introduction in 2007, it has evolved from a 7-gene panel to the most recent ThyroSeq v3 genomic classifier which was launched in 2017 and uses sequencing technology to analyze 112 genes to test for mutations,

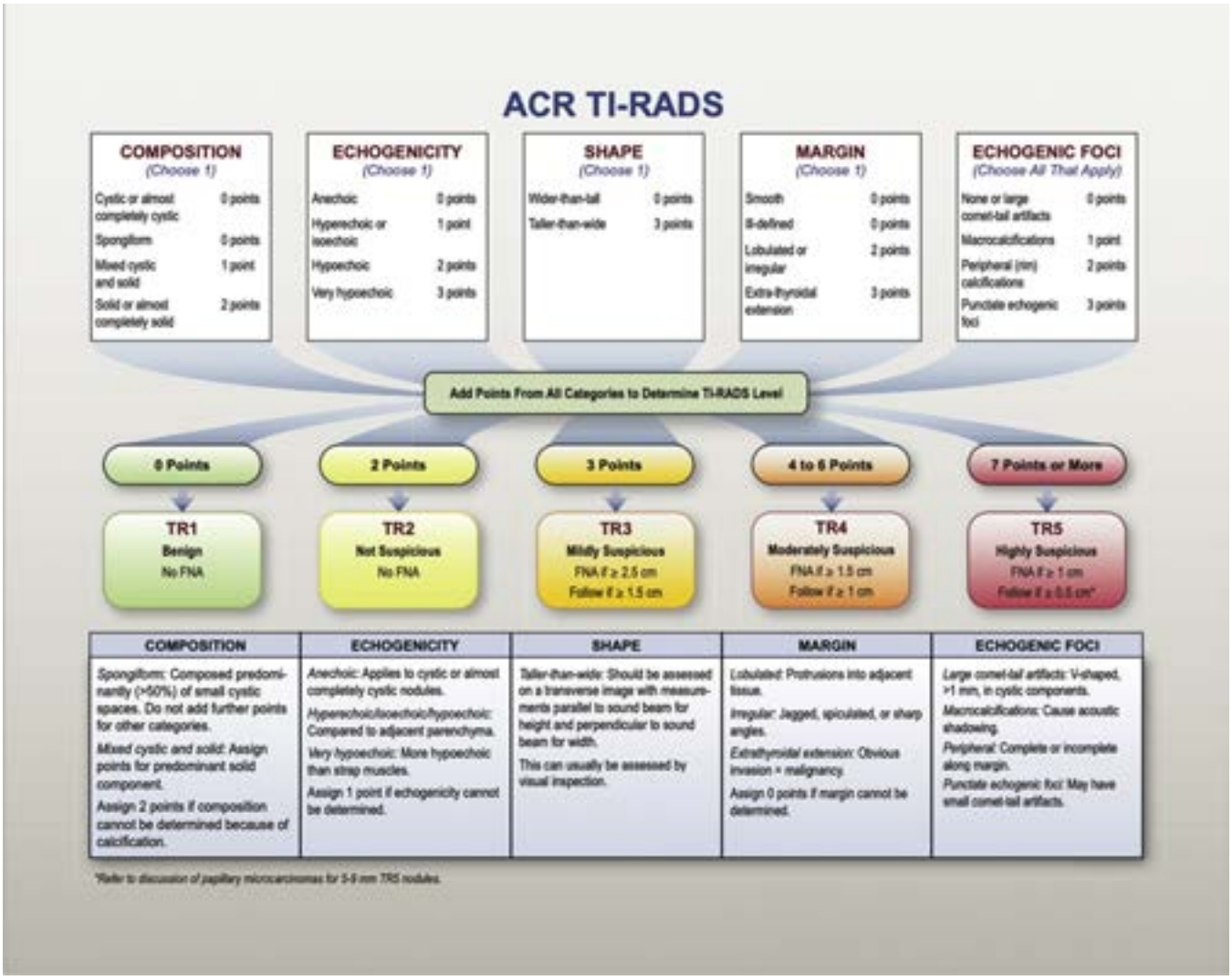


FIG. 2 American College of Radiology Thyroid Imaging: Reporting and Data Systems (ACR TI-RADS. *(From Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J Am Coll Radiol. 2017;14[5]:587–595.)*

TABLE 1 The 2017 Bethesda System

Diagnostic Category	Risk of Malignancy if NIFTP ≠ CA (%)	Risk of Malignancy if NIFTP = CA (%)	Usual Management[†]
Nondiagnostic or unsatisfactory	5–10	5–10	Repeat FNA with ultrasound guidance
Benign	0–3	0–3	Clinical and sonographic follow-up
Atypia of undetermined significance or follicular lesion of undetermined significance	6–18	~10–30	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm or suspicious for a follicular neoplasm	10–40	25–40	Molecular testing, lobectomy
Suspicious for malignancy	45–60	50–75	Near-total thyroidectomy or lobectomy[‡,§]
Malignant	94–96	97–99	Near-total thyroidectomy or lobectomy[§]

CA, Carcinoma; *FNA*, fine needle aspiration; *NIFTP*, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.
[†]Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.
[‡]Estimate extrapolated from histopathologic data from patients with "repeated atypicals."
[§]In the case of "Suspicious for malignancy" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.
From Ali S, Cibas E. *The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria and Explanatory Notes*. Second edition. Springer; 2018.

insertions and deletions, gene fusions, gene expression alterations, and copy number alterations (important for Hurthle cell and follicular carcinomas). A ThyroSeq v3 result provides the clinical team with the genetic alterations, if present, and the respective probability of cancer based on that combination of alterations. The frequency of negative test result in ThyroSeq v3 for Bethesda III/IV nodules is above 60% (benign call rate), and residual cancer risk in these test-negative nodules is approximately 3%, which allows some patients with indeterminate nodules to safely avoid surgery with a negative ThyroSeq v3 result.

Afirma Genomic Sequencing Classifier (GSC)

Afirma Genomic Expression Classifier (GEC) used a microarray measurement of messenger RNA expression of 167 genes in indeterminate nodules to give further guidance on management. It had a great negative predictive value (NPV) of up to 95%; however, it has been replaced by Afirma GSC due to its lower positive predictive value (PPV) of around 38% and specificity of 50%, limiting use in positively predicting malignancy. Afirma GSC evaluates nuclear and mitochondrial RNA transcriptome gene expression, RNA sequencing, and genomic copy number analysis. It has a benign call rate of around 76% and specificity of 94%. This has reduced the number of unnecessary surgeries as compared to Afirma GEC.

SURGICAL MANAGEMENT

Although surgery is not the main focus of this chapter, it is obvious that diagnostic testing for thyroid nodules have significant implications for thyroid surgery. Current guidelines have trended toward more conservative surgery (lobectomy instead of total thyroidectomy with no routine central neck dissection) for smaller, low-risk thyroid cancers. If a diagnostic lobectomy is the definitive treatment for low-risk small cancer, preoperative confirmation of thyroid cancer may not be as important. When determining the extent of surgery such as a thyroid lobectomy versus total thyroidectomy, the probability the nodule is cancer, the type of mutation or cancer the nodule has, and the probability that the cancer would progress should all be considered. Other indications for surgery can include thyroid nodules that are symptomatic or causing local symptoms, including substernal goiters or substernal nodules. In addition, hyperfunctioning nodules can be an indication for resection instead of treatment with radioiodine treatment.

MANAGEMENT OF BENIGN NODULES WITH RADIOFREQUENCY ABLATION

Thyroid radiofrequency ablation (RFA) is an emerging technique that is used to treat benign thyroid nodules without surgery. RFA uses alternating electric current to agitate tissue ions with results in heat production and coagulation necrosis of the tissue. This results in progressive volume reduction over time, 50% reduction within the first few months and 85% reduction beyond 6 months. For appropriately selected patients with nodules showing benign characteristics on imaging, aspiration cytology confirmed benign, and who desire volume shrinkage of their thyroid nodule for symptomatic or cosmetic reasons, this is a newly adopted technique that shows promise. Following RFA, patients require surveillance with ultrasound. On follow-up, if the nodule grows or has other sonographic changes, or if the patient becomes symptomatic, FNA or lobectomy can be offered.

CONCLUSION

As more thyroid nodules are being found, it is important for a thyroid surgeon to have a clear algorithm for their evaluation. Ultrasound is the primary imaging test for a thyroid nodule. Size and ultrasound characteristics are used to determine the need for FNA. Cytology should be reported based on Bethesda classification, which stratifies the risk of cancer. Advances in molecular testing can be useful for surgical decision in patients with Bethesda III and IV indeterminate nodules. Clinical judgment remains paramount in deciding when to use these tests and how to interpret them.

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Nontoxic Goiter

Matthew A. Nehs, MD, and Gerard M. Doherty, MD

OVERVIEW

Goiter is a nonspecific term referring to any enlargement of the thyroid gland. However, in common use, it mainly denotes benign causes of thyroid enlargement, such as toxic multinodular goiter, diffuse toxic goiter (Graves' disease), or nontoxic multinodular goiter. Though malignant enlargement of the thyroid gland can technically be considered a goiter, it is usually referred to as a *mass* or *nodule*.

Nontoxic goiter is a benign condition, even though some specimens may contain small incidental cancers (up to 20% contain microcarcinomas). The predominant decision-making process is based on the benign enlargement and resulting symptoms (e.g., dysphagia, dyspnea, or neck pressure). In some areas of the world, nontoxic goiters are endemic due to iodine deficiency, though public health efforts have reduced this somewhat.

PATHOGENESIS

A nontoxic multinodular goiter is defined as an enlargement of the thyroid gland containing follicles that are morphologically and functionally altered. The pathogenesis is multifactorial and can include

iodine deficiency, goitrogens such as bamboo shoots, maize, and sweet potatoes, genetic factors, and dyshormonogenesis. A family history of nontoxic goiter could implicate the environment, diet, or dyshormonogenesis as causes. Aside from severe iodine deficiency, the cause in an individual is typically not evident nor does it often influence management.

CLINICAL FEATURES

Nontoxic goiters may remain asymptomatic, or they may give rise to compressive features such as dyspnea, dysphagia, or venous congestion/discomfort with certain movements. A change in the voice can occur from direct pressure on the larynx or from stretching of the laryngeal nerves. Direct effects on the nerve causing paresis of the ipsilateral vocal fold are uncommon from benign goiter, as nerve paresis is much more commonly associated with malignant infiltration of the nerve. Sudden changes in the goiter, as from hemorrhage into a nodule, can cause transient, intermittent, or permanent hoarseness. Thyroidectomy can often assuage voice changes due to direct pressure on the larynx, but the benefits for more uncommon changes due to effects on the nerve are inconsistent.

On physical examination, the size of the gland, the features of diffuse enlargement or nodularity, tracheal deviation, and extension of the gland below the sternum or clavicular heads or high up into the neck near the angle of the mandible are all important for treatment planning. Many large goiters are not palpable by physical examination, particularly if they have a predominant substernal or posterior component (Fig. 1). Associated lymphadenopathy should raise suspicion of malignancy.

EVALUATION

Thyroid-stimulating hormone (TSH), free T4, and T3 levels should be assessed to identify subclinical or overt thyrotoxicosis, hypothyroidism, or a euthyroid state. Fine-needle aspiration should be performed with ultrasound guidance for any suspicious thyroid nodule. Ultrasound features that raise the risk of malignancy include hypoechogenicity, microcalcifications, hypervascularity, and solid components of complex (cystic and solid) nodules, as well as regional lymphadenopathy.

Plain chest films can demonstrate tracheal deviation, retrotracheal and retrosternal extension, airway compression, and gross calcifications. However, cross-sectional imaging such as CT or MR is more informative for these findings. In particular, evaluating the extent of airway compression, the precise geometry of goiter position in the chest, and any associated lymphadenopathy that might indicate a clinically significant malignant component is much more effective with CT or MR.

Radioiodine scans, pulmonary function tests, flow volume loops, and barium swallow studies may each be useful in specific situations but are not typically necessary in the era of accurate cross-sectional imaging.

Preoperative assessment of vocal fold movement should be considered for each patient. Deliberate voice assessment is mandatory,

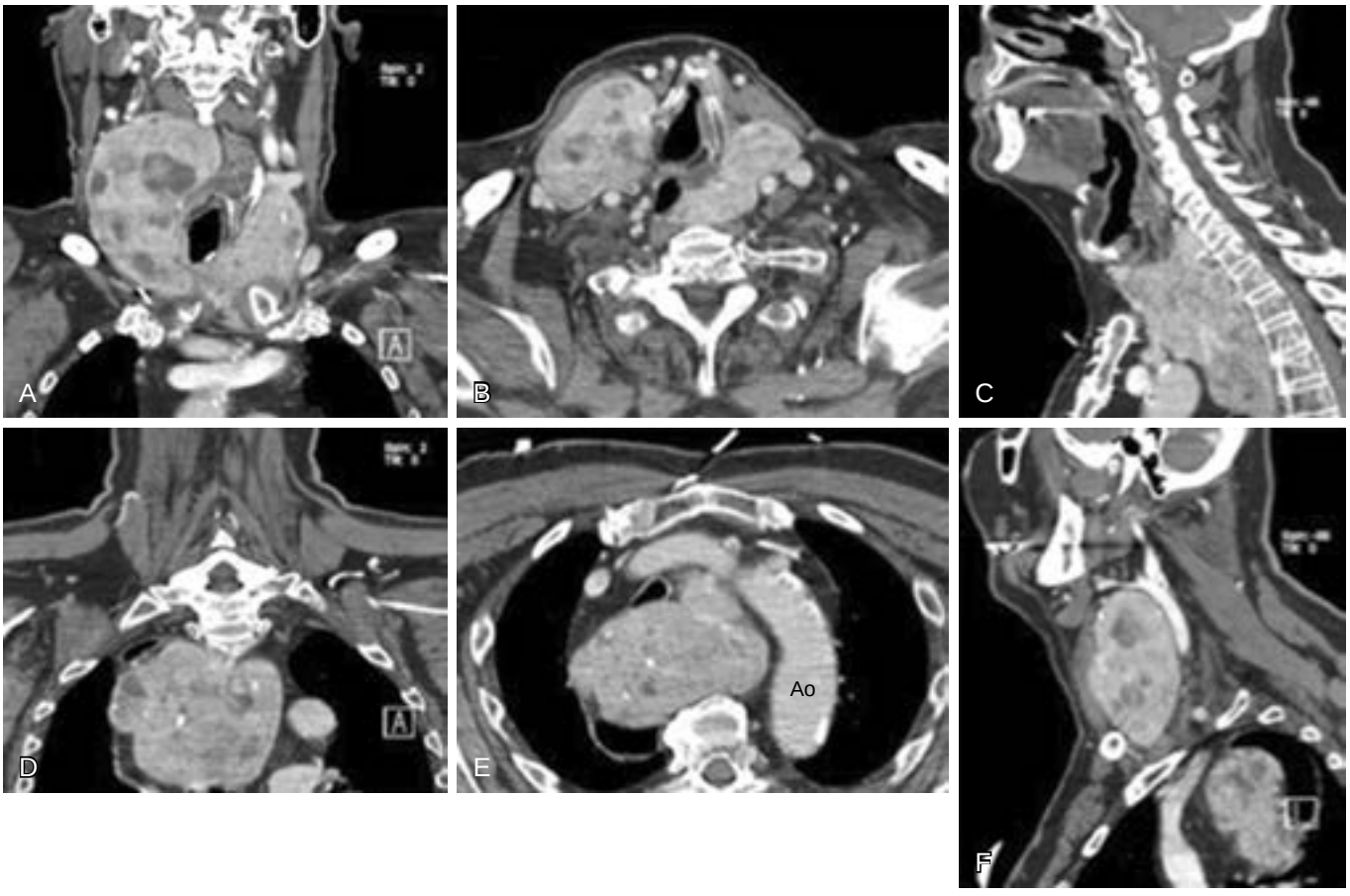


FIG. 1 An 82-year-old man with a palpable right thyroid mass. Cross-sectional imaging revealed a heterogeneous bilateral massive nontoxic multinodular goiter **(A, B)** with a retrosternal left thyroid lobe **(C, D)**. **(E)** Note that the retrosternal component is below the arch of the aorta (Ao) and has grown along the prevertebral fascia. **(F)** The right upper pole has displaced the course of the right common carotid artery. This patient required manubriotomy to deliver the mediastinal component of the gland safely.

and fiber-optic laryngoscopy should be considered for patients with any voice alteration or any prior neck or chest operation that places the vagus or recurrent laryngeal nerves (RLN) at risk of having been injured. It is important to assess for inspiratory stridor, which can be associated with severe narrowing of the tracheal lumen (Fig. 2), and cross-sectional imaging is critical in this situation.

INDICATIONS FOR TREATMENT

Nontoxic goiter that causes local discomfort, such as tightness or a choking sensation, especially with certain movements, or that has caused mechanical partial obstruction of the upper aerodigestive tree should be considered for treatment. Substantial extension of the goiter into the chest, even in the absence of symptoms, should be considered a relative indication for treatment, as further enlargement of the thoracic component can lead to the need for a more disruptive operation to resect it in the future. Cosmesis alone is rarely an isolated concern or indication for therapy because most patients with goiter of sufficient size to be bothersome also have other associated symptoms.

TREATMENT MODALITIES

TSH-suppression therapy with thyroxine has little role in the management of an established goiter. Prospective trials have failed to demonstrate a benefit for management of multinodular goiter. The side effects of TSH-suppression, including bone density loss and atrial arrhythmias, negate the theoretical value, particularly in elderly patients for whom nonoperative therapy might be most attractive.

Radioiodine administration can cause goiter size reduction of 40% to 60% within 2 years, decreasing compressive symptoms. Complications include radiation thyroiditis and hypothyroidism, as well as a temporary enlargement of the gland, which may be important in some clinical situations. Recent experience with the use of exogenous TSH administration to increase the efficiency of radioiodine administration in goiters with limited iodine uptake shows some improvement over radioiodine alone. These approaches may be useful for patients who have comorbidities that affect the safety of operative management, but those same comorbidities must be considered if the patient may become temporarily hyperthyroid from treatment or as the time course of correction of the local pressure symptoms of the goiter is extended. Percutaneous ablation of thyroid tissue shows promise but is currently mainly used for large benign nodules rather than for ablating larger volumes of tissue such as diffuse goiter.

Surgical management is the mainstay of treatment for symptomatic, nontoxic goiter and is generally well-tolerated even in patients with limited physiologic reserve. The operation should typically be a bilateral procedure, removing all, or nearly all, of both thyroid lobes, in addition to any substernal extension. The operation is nearly always limited to a cervical incision, with median sternotomy or posterolateral thoracotomy being necessary only very rarely in previously unoperated patients. In experienced centers, complication rates are low (<2%) with techniques that include careful hemostasis and liberal parathyroid autotransplantation. For patients with significant airway compression or deviation, securing the airway can be the most critical part of the operation and may require conscious fiber-optic intubation under topical anesthesia to begin the procedure.

The thyroid gland should be exposed by a sufficient incision; though many thyroid operations can be done through very limited incisions, the geometry of the large multinodular goiter often requires a long incision to safely expose and remove the gland. Subplatysmal flaps improve the exposure of the limits of the gland, especially superiorly for glands with upper poles that extend high in the neck. The strap muscles can be separated in the midline or divided near the upper pole, as necessary, to expose the thyroid gland. In almost all cases, division of the sternothyroid muscle at the thyroid cartilage is sufficient for this exposure, but the sternohyoid can be divided as well if necessary. The larger the cervical portion of the gland, especially the upper poles, the more likely it is that transverse division of the sternohyoid and sternothyroid muscles will be helpful.

We find it helpful to divide the isthmus early in the case, as this provides a useful anterior landmark, particularly in cases where tracheal deviation distorts the typical course of the trachea and larynx. We then begin the dissection on the side of the larger lobe if the goiter is asymmetric. This ensures that the patient will have the most benefit in case the procedure has to be confined to a unilateral procedure (e.g., intraoperative RLN injury).

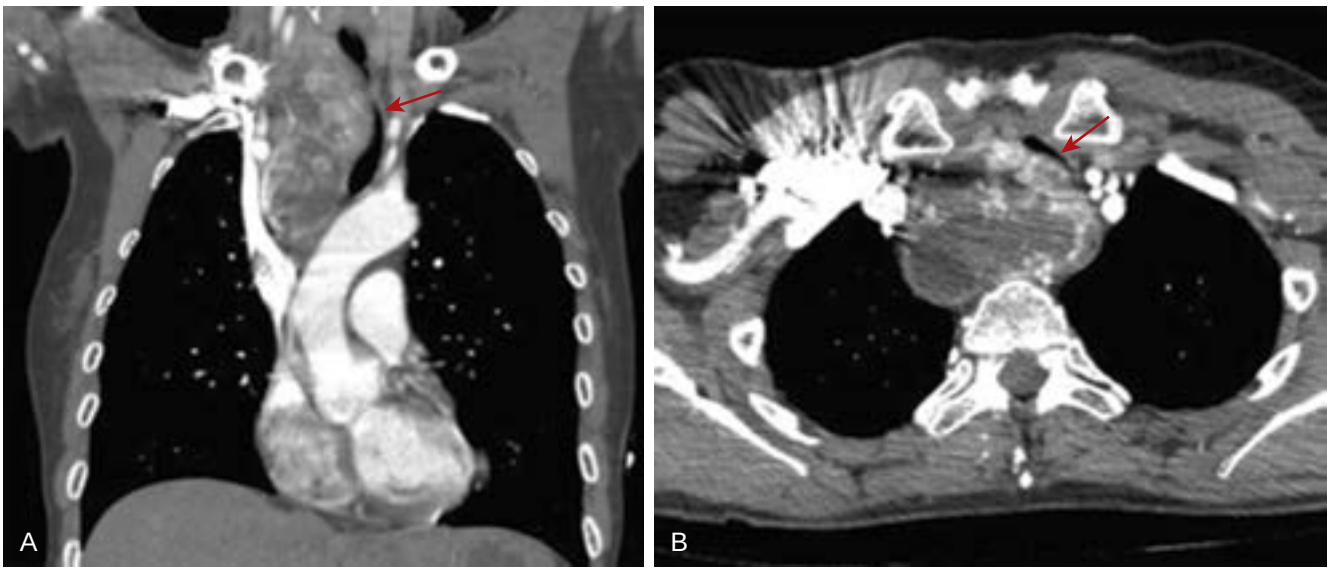


FIG. 2 A 68-year-old woman with an incidental goiter found during workup for dyspnea. On physical examination, the patient had no evidence of a palpable thyroid mass, but she had mild inspiratory stridor. A CT scan revealed a large right-sided substernal thyroid with tracheal deviation to the left **(A)** as well as severe narrowing of the lumen of the trachea **(B)**.

The upper pole of the gland is isolated by first separating the lateral aspect of the upper portion of the thyroid gland from the carotid sheath. If recurrent nerve monitoring is used, then the sheath is opened and the vagus nerve stimulated to establish baseline electromyography (EMG) function. The plane between the larynx and the upper pole of the thyroid gland is then opened, exposing the superior thyroid artery. The external branch of the superior laryngeal nerve (EBSLN) can be identified during some operations by direct inspection or by nerve monitor stimulation, keeping in mind that many EBSLNs run in an intramuscular course. Positive confirmation of the nerve can be determined by seeing a symmetric wave in both the anterior and posterior segments of the ipsilateral cricothyroid muscle in response to nerve stimulation. However, in any case, the delicate fascia over the cricothyroid muscle should be kept intact as the nerve is deep to this. As the plane is followed superiorly, the EBSLN should stay medial and superior to the upper pole of the thyroid and its vessels. The upper pole vessels can then be divided safely using any number of hemostatic strategies, including ligatures, clips, and powered dissection tools. The branches of the superior thyroid artery should be individually controlled immediately adjacent to the thyroid parenchyma to minimize the risk to the EBSLN.

Once the upper pole is fully mobilized, the thyroid is partially rotated anteriorly and medially to continue dissecting the lateral portion of the thyroid gland. The middle thyroid vein, if present, is divided and the thyroid separated from the carotid sheath along its entire extent. The dissection can then be carried posteriorly into the paratracheal space. The ability to rotate the thyroid gland may be limited by a large substernal component. The decision of whether to proceed with the dissection of the tracheoesophageal groove, RLN, and parathyroid glands (our preference), or whether to dissect the substernal portion of the goiter to create the necessary mobility, is dictated by the geometry of the particular patient and goiter. A large substernal component with a narrow thoracic inlet can create venous congestion of the goiter and significant hemorrhage from the capsular veins of the gland. Delivery of the substernal component (either transcervically or by manubriotomy) will often relieve this congestion and allow a more hemostatic dissection.

The tracheoesophageal groove is dissected to identify the RLN. We try to identify the RLN as low in the neck as possible, as this is the area where the nerve is least tethered to surrounding structures and least likely to be stretched during dissection and identification. The nerve is identified by its appearance, anatomic course, and by stimulation if nerve monitoring is used; however, stimulation alone is not sufficient to identify the RLN. In particular, the absence of an EMG signal does not prove that a stimulated structure is not the RLN. Although intraoperative nerve monitoring is used by many experienced thyroid surgeons as an intraoperative adjunct, large trials have failed to show a benefit to patients as measured by RLN injury rates. The use of intraoperative nerve monitoring is a reasonable adjunct at the discretion of the surgeon but is not a required standard of care.

Once the recurrent nerve is identified, it can be separated from the posterior aspect of the thyroid gland, and the intrathoracic portion of the thyroid gland can be safely delivered into the wound. The arterial supply to the thyroid goiter comes entirely from branches in the neck; there is no intrathoracic arterial supply to be concerned with (with the exception of the rare thyroid ima, which can arise from the innominate artery or the aorta). The main risk, then, is traction on the RLN as the substernal or paraesophageal intrathoracic portion of the goiter is delivered into the cervical wound by blunt dissection and gentle traction.

An important note of caution: in posteriorly displaced goiters with a component that extends inferiorly along the esophagus, especially on the right, the RLN may pass anterior to some portion of the goiter and may appear to be buried within the thyroid parenchyma as it has been trapped between nodules. This configuration makes the RLN especially vulnerable to stretch injury if this possibility is not recognized and anticipated early in the dissection.

Once the nerve is identified and the inferior portion of the thyroid gland mobilized, the RLN is traced up to its insertion into the larynx under the inferior border of the cricopharyngeus muscle. The small branches of the inferior thyroid artery are divided along the parenchymal surface of the gland with the RLN always in view and protected. The parathyroid glands typically become evident during this portion of the dissection. Their blood supply from the inferior thyroid artery should be preserved if possible. If not, then the glands should be removed and grafted into the sternocleidomastoid muscle. As the dissection approaches the insertion of the RLN into the larynx, the RLN becomes progressively more fixed by surrounding tissues, including branches of the inferior thyroid artery, the fascial attachments of the thyroid gland to the trachea, and the insertion itself. Great care is necessary to safely dissect the thyroid gland away from the RLN without directly injuring or stretching the RLN. Once the RLN is fully separated from the thyroid gland, the final attachments of the thyroid gland to the trachea can be divided. If intraoperative nerve monitoring was used, then the EMG signal with vagus nerve stimulation should be assessed at the completion of the dissection.

The process is then repeated on the opposite side. If there has been difficulty with the dissection on the initial side, then the contralateral procedure may be modified to reduce the risk of complications. For example, if the RLN lost function as documented by intraoperative nerve monitoring, then the contralateral RLN dissection may be modified to leave the RLN segment near the laryngeal insertion undisturbed by leaving a portion of the thyroid lobe in place at that position.

Devitalized parathyroid tissue should be cut into small (1–2 mm) pieces and grafted into small pockets in the sternocleidomastoid muscle. It is best to close each pocket with a suture to hold the graft in place while it develops a blood supply over the ensuing 6 to 12 weeks. It is not necessary to attempt to mark the site with permanent sutures or clips because subsequent reoperation to remove these remnants is extremely rare and best guided by ultrasound if necessary.

Meticulous hemostasis is important, as bleeding in the confined space of the neck can compromise breathing. The strap muscles are reapproximated in some fashion, depending upon how they were opened or divided, but the closure should not be occlusive. We routinely leave a large gap at the inferior aspect of the strap muscles to allow decompression if a postoperative hematoma should occur. The platysma muscle is reapproximated to align the skin edges and remove tension from the wound. The skin is closed according to the preference of the surgeon; one popular preference is to approximate the skin edges with a running 3-0 polypropylene pull-out subcuticular suture, followed by skin glue. The suture is removed after the glue is dry (about 2 minutes). This provides a cosmetic closure that requires no further attention until after the glue peels away at about postoperative day 14.

POSTOPERATIVE CARE

In our practice, patients remain hospitalized overnight after removal of a nontoxic goiter to manage their limited pain and monitor them for neck hematoma or hypocalcemia. All patients are managed with oral calcium supplements (calcium citrate 950 mg PO QID) and Rocaltrol 0.25 mcg PO daily beginning immediately after the operation. If they are symptomatic with numbness or tingling, or if their calcium on the morning after surgery is below 8 mg/dL, then the dose is doubled. If their symptoms persist, either before or after discharge, or if there is special concern about the immediate parathyroid function (for example, if two or more parathyroid glands were grafted), then we will consider keeping the patient for further observation or facilitating calcium lab draws within a few days of discharge.

Postoperative voice assessment is mandatory in all patients. Most patients have some immediate voice changes, but these nearly all resolve within 2 weeks of operation. Laryngoscopy to document vocal cord motion should be performed for all patients with significant voice changes that persist beyond 2 weeks and for all patients

who have a change in their intraoperative nerve monitoring findings during the procedure if that adjunct has been used. While some have advocated for more broad use of laryngoscopy preoperatively and postoperatively, there is no evidence that this changes patient outcomes, and so most experienced surgeons focus this effort in a more selective way.

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Management of Thyroiditis

Christopher R. McHenry, MD

INTRODUCTION

Thyroiditis refers to inflammation in the thyroid gland that consists of a diverse group of conditions (Box 1) with variable clinical manifestations, which can include neck pain that can radiate to the jaw, chest, or ear; neck tenderness; symptomatic or asymptomatic goiter; subclinical or overt hypothyroidism or hyperthyroidism (Boxes 2 and 3); and rarely fever and chills. Patients with a large goiter may have compressive symptoms including dysphagia, dyspnea, cough, choking, hoarseness, and voice change. Patients with thyroiditis may rarely complain of ear pain.

Thyroiditis can be classified based on whether or not neck pain and tenderness are principal presenting manifestations (Box 4). Patients with subacute thyroiditis, acute suppurative thyroiditis and trauma, or radioiodine-induced thyroiditis have neck pain and tenderness, often occurring in association with thyroid dysfunction. Patients with Hashimoto thyroiditis, painless thyroiditis, and Reidel thyroiditis typically present with a goiter with or without thyroid dysfunction, and neck pain and tenderness are characteristically absent.

The treatment of thyroiditis is dependent on whether or not there are symptoms, thyromegaly, thyroid dysfunction, and/or concern for malignancy. The goal is to achieve a euthyroid state, which in most patients occurs spontaneously and results in resolution of symptoms of hypothyroidism and hyperthyroidism. Thyroid surgery has a role for specific indications (Box 5).

BOX 1 Clinical Variants of Thyroiditis

- Hashimoto thyroiditis (chronic autoimmune thyroiditis, lymphocytic thyroiditis)
- Reidel thyroiditis
- Subacute thyroiditis (granulomatous thyroiditis, De Quervain's thyroiditis)
- Suppurative thyroiditis
- Painless thyroiditis (postpartum thyroiditis, lymphocytic thyroiditis with spontaneously resolving hyperthyroidism)
- Drug-induced thyroiditis
- Radiation-induced thyroiditis

BOX 2 Symptoms of Hypothyroidism

Fatigue
Weight gain
Constipation
Dry skin
Cold intolerance
Muscle cramps
Decreased libido
Menstrual irregularity
Hair loss
Poor exercise tolerance
Depression

BOX 3 Symptoms of Thyrotoxicosis

Increased appetite
Weight loss
Palpitations
Tremor
Heat intolerance
Diaphoresis
Insomnia
Thinning of the hair and hair loss
Anxiety
Irritability
Increased frequency of bowel movements
Menstrual irregularities
Infertility

BOX 4 Thyroiditis Classified Based on the Presence or Absence of Neck Pain and Tenderness

Thyroiditis Manifesting With Neck Pain and Tenderness

- Subacute thyroiditis
- Acute suppurative thyroiditis
- Radioiodine induced thyroiditis
- Traumatic thyroiditis

Thyroiditis Manifesting Without Neck Pain and Tenderness

- Hashimoto thyroiditis
- Painless thyroiditis including postpartum thyroiditis
- Reidel thyroiditis
- Drug-induced thyroiditis

BOX 5 Indications for Surgery

- Associated thyroid nodule and/or suspicion of malignancy
- Thyromegaly with mass effect on the trachea or compressive symptoms
- Hashimoto thyroiditis and persistent autoimmune-related symptoms despite adequate thyroid hormone replacement
- Definitive diagnosis of Reidel thyroiditis and exclusion of anaplastic thyroid cancer
- Suppurative thyroiditis refractory to antibiotic therapy and percutaneous abscess drainage
- Thyrotoxicity refractory to medical therapy in patients with subacute thyroiditis or amiodarone-induced thyrotoxicosis

HASHIMOTO THYROIDITIS

Hashimoto thyroiditis, also known as *chronic autoimmune thyroiditis* or *lymphocytic thyroiditis*, is a T-cell–mediated, chronic autoimmune disease of unknown etiology that progresses to thyroid failure with hypothyroidism in approximately 20% of patients. It is the most prevalent autoimmune disease in the United States and worldwide. It is also the most common cause for diffuse goiter and hypothyroidism in the United States, as opposed to worldwide where iodine deficiency still remains the most common cause for goiter. In iodine-replete populations, the prevalence of hypothyroidism is 1% to 2%, and Hashimoto thyroiditis is the cause in approximately 85% of patients.

Hashimoto thyroiditis tends to cluster in families and can occur in association with Graves' disease and other autoimmune diseases. In general, there are two primary types of Hashimoto thyroiditis, an atrophic form and a goitrogenic form. There is also a fibrosing variant of Hashimoto thyroiditis (Fig. 1), which can sometimes be difficult to distinguish from Reidel thyroiditis.

Hashimoto thyroiditis is associated with elevated antithyroid peroxidase (TPO) antibody (also known as *antimicrosomal antibody*), antithyroglobulin antibody, and inflammatory cytokines. Hashimoto thyroiditis is a common cause for hypothyroidism and less commonly thyrotoxicosis, known as Hashitoxicosis. It is characterized by lymphocytic infiltration of the thyroid gland, lymphoid follicle formation with germinal centers, atrophy of the thyroid parenchyma, fibrosis, and Hurthle cell metaplasia. There may also be associated Hurthle cell nodules.

Patients may present with symptoms of hypothyroidism or hyperthyroidism (see Boxes 2 and 3), which normally resolve with treatment that reestablishes a euthyroid state. They may also present with globus sensation and experience profound fatigue, muscle and joint pain, poor sleep quality, and dry mouth and eyes, which may not resolve with thyroid hormone replacement therapy. Persistent symptoms, despite adequate replacement thyroid hormone therapy, are thought to be autoimmune-related.



FIG. 1 Fibrosing variant of Hashimoto thyroiditis.

Patients with Hashimoto thyroiditis may also present with thyromegaly (Fig. 2), which may cause mass effect in the neck, compressing adjacent structures and causing dyspnea, cough, dysphagia, choking, and hoarseness. Patients may also have neck pain, but this is not typical. The thyroid gland is diffusely firm and may be tender on exam. The thyroid gland is heterogenous in appearance on ultrasound exam (Fig. 3).

Patients with Hashimoto thyroiditis have Hurthle cell metaplasia and may have associated thyroid nodules. Most nodules are benign Hurthle cell nodules. Fine-needle aspiration biopsy (FNAB) reveals follicular epithelial cells, colloid, lymphocytes, and Hurthle cells that are classified as benign (Bethesda category II). FNAB may also reveal a predominance of Hurthle cells, which are cytologically classified either as atypia of undetermined significance (Bethesda category III) or Hurthle cell neoplasm (Bethesda category IV). Hashimoto thyroiditis is also a cause of false-positive FNAB in patients with thyroid nodules interpreted as suspicious for papillary thyroid cancer (Bethesda V). Patients with Hashimoto thyroiditis are known to have a higher incidence of thyroid lymphoma than the general population.

The treatment of Hashimoto thyroiditis is variable. Asymptomatic, euthyroid patients require no treatment. Patients with hypothyroidism are treated with thyroid hormone replacement. Patients are started on a dose of levothyroxine based on weight using a 1.6 ug/kg initial dosage estimate. The dose is adjusted to achieve a normal serum thyrotropin (TSH) level. Surgery is rarely necessary. Indications for surgery include a thyroid nodule with an indeterminate or malignant FNAB (Bethesda III–VI), unilateral or bilateral thyromegaly with mass effect on the trachea or compressive symptoms, and persistent symptoms despite adequate thyroid hormone replacement therapy.

The decision to proceed with thyroid lobectomy and isthmusectomy or total thyroidectomy is based on risk factors for cancer and the extent of the disease, which is determined by physical examination, ultrasound examination, and intraoperative evaluation. Patients with disease limited to one lobe can be treated with lobectomy and isthmusectomy. Most patients are treated with total thyroidectomy.

When thyroidectomy is recommended for persistent symptoms despite adequate thyroid hormone replacement therapy, a total thyroidectomy is performed. Total thyroidectomy removes the target antigens that generate the immunologic response in Hashimoto thyroiditis. Total thyroidectomy is associated with a decrease in the systemic inflammatory response and a reduction in serum antithyroid peroxidase antibody titers and proinflammatory cytokines. The Norwegian Trial on Surgery for Hashimoto Disease, a prospective, randomized clinical trial comparing total thyroidectomy to thyroid hormone therapy alone for persistent symptoms despite adequate thyroid hormone replacement, demonstrated improved health-related quality of life and fatigue and normalization of anti-TPO antibody titers in patients with histologically verified Hashimoto thyroiditis treated surgically compared with no significant change in the control group.

At operation, it is not unusual to have enlarged reactive lymph nodes in the central compartment of the neck. A firm nodule and enlarged lymph nodes associated with Hashimoto thyroiditis can mimic thyroid cancer. Excision of a lymph node and frozen section examination is always an option to exclude metastatic thyroid cancer. The diffusely firm thyroid gland with its associated inflammation in patients with Hashimoto thyroiditis make the thyroid gland difficult to retract anteriorly and medially and can potentially lead to excessive traction on the recurrent laryngeal nerve and paresis. Intraoperative nerve monitoring may be used to help identify transient loss of function related to traction on the recurrent laryngeal nerve.

PAINLESS THYROIDITIS

Painless thyroiditis is also known as silent thyroiditis or lymphocytic thyroiditis with spontaneously resolving hyperthyroidism. Painless thyroiditis is a variant of Hashimoto thyroiditis and is thought to occur as a result of autoimmune-mediated follicular cell destruction. Patients may have a personal or family history of other autoimmune diseases. Postpartum thyroiditis is a specific type of painless thyroiditis that occurs within 1 year of parturition or a spontaneous or induced abortion. It may occur in up to 10% of pregnancies.



FIG. 2 Diffuse goiter removed from a patient with Hashimoto thyroiditis causing compressive symptoms.

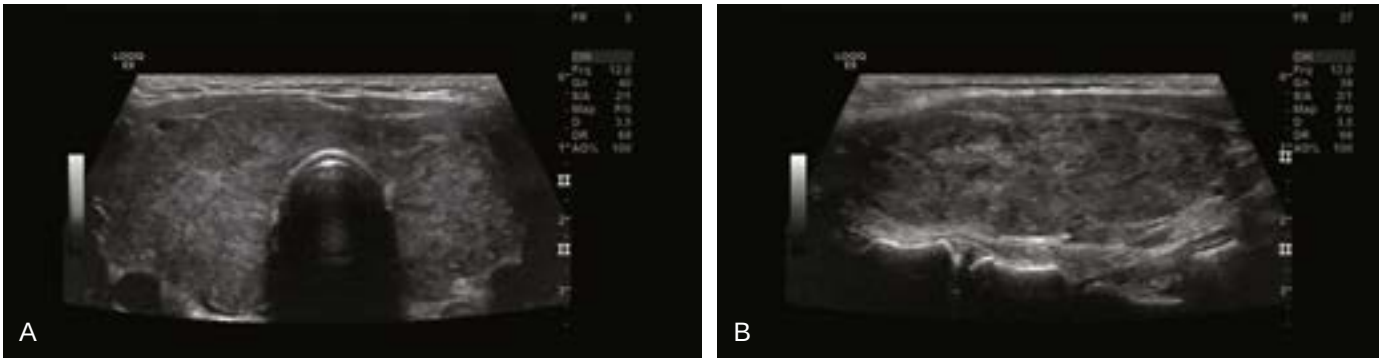


FIG. 3 Diffuse heterogeneity of the thyroid gland characteristic of Hashimoto thyroiditis. **(A)** Transverse view of the trachea and right and left lobes and isthmus of the thyroid gland. **(B)** Sagittal view of the left lobe of the thyroid gland.

However, it may not always be clinically evident and is diagnosed as a result of a low serum TSH level found on routine monitoring of thyroid function tests. Recurrences may occur with subsequent pregnancies.

Painless thyroiditis is characterized by transient thyrotoxicosis resulting from follicular cell destruction and release of thyroid hormone. Patients usually present with symptoms of thyrotoxicosis and diffuse, nontender, firm thyroid enlargement. This may be followed by symptoms of hypothyroidism. The thyrotoxic phase is transient and lasts for 1 to 3 months until thyroid hormone stores have been depleted. It is followed by a euthyroid phase lasting a few months and then a hypothyroid phase that can last up to a year. Most patients recover with normal thyroid function within 12 to 18 months after onset of symptoms, but permanent hypothyroidism may occur in 20% of patients.

During the thyrotoxic phase, patients have an elevated free T4 level and a suppressed TSH level. They may also have an elevated free T3 level. The free T4 and free T3 levels correspond to the normal proportion found in the thyroid gland. The suppressed TSH level inhibits thyroid hormone synthesis. Antithyroglobulin and anti-TPO antibodies are elevated. Radioiodine uptake by the thyroid gland is low, and ultrasound of the neck reveals diffuse hypoechogenicity. Thyroid-stimulating immunoglobulins are negative, distinguishing painless thyroiditis from Graves' disease. During the hypothyroid phase, serum TSH may be elevated and free T4 level normal or low.

Management of patients with painless thyroiditis includes serial monitoring of thyroid function tests as patients may be thyrotoxic, euthyroid, or hypothyroid during the progression of the disease, and some patients will develop permanent hypothyroidism. Many patients are asymptomatic and require no therapy at all because thyroid dysfunction is mild and transient. During the thyrotoxic phase, patients with symptoms of excess sympathetic nervous system activity, such as palpitations, tremor, and diaphoresis, can be treated with a beta-receptor blocking agent. Antithyroid drugs and radioiodine therapy are not effective because the thyrotoxicosis is due to the release of thyroid hormone from damaged follicular cells with suppression of iodine uptake by the thyroid gland and not from increased thyroid hormone synthesis. Levothyroxine can be started during the hypothyroid phase for patients with symptoms or when TSH levels are greater than 10 uIU/mL and may be required lifelong for patients who develop permanent hypothyroidism. Recurrence is common, and patients are followed with a yearly screening serum TSH level.

DRUG-INDUCED THYROIDITIS

Thyroiditis has been reported as a side effect of certain drugs (Box 6). Drug-induced thyroiditis is most often a variant of painless thyroiditis, with follicular cell destruction and thyrotoxicosis secondary to release of free T4 and free T3. This is often followed by transient or persistent hypothyroidism. Many of these drugs can also have additional effects on the thyroid gland.

BOX 6 Drugs That Can Induce Thyroiditis

Interferon alpha
Interleukin-2
Tyrosine kinase inhibitors (sunitinib, vandetanib)
Lithium
Immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab, atezolizumab)
Amiodarone

Before initiation of these drugs, a baseline screening serum TSH level should be obtained and serial monitoring should occur during use of the drug. An abnormal serum TSH level should trigger measurement of free T4 and free T3 levels. Consideration should also be given to measurement of antimicrosomal and antithyroglobulin antibodies. Discontinuation or dosage reduction of the drug is usually not necessary. In most circumstances, however, discontinuation of the offending agent results in return of normal thyroid function. A beta-receptor blocking agent can be used for treatment of thyrotoxicosis symptoms if necessary. Hypothyroidism is managed with thyroid hormone replacement.

Interferon alpha, a recombinant cytokine, was used primarily for treatment of chronic hepatitis C infection. It has also been used for treatment of leukemia, lymphoma, Kaposi's sarcoma, and other malignancies. Interferon alpha can cause both thyrotoxicosis and hypothyroidism. Anti-TPO and antithyroglobulin antibodies are measured before initiation of interferon alpha. Patients with high antithyroid antibodies are at higher risk of developing thyroid dysfunction.

Painless thyroiditis occurs in approximately 2% of patients on interleukin-2, an immunotherapeutic agent often used in combination with other anticancer immunotherapy and chemotherapy to treat metastatic renal cell cancer and melanoma. Sunitinib, vandetanib, and other tyrosine kinase inhibitors can cause hypothyroidism in 50% to 70% of patients. In addition to follicular cell destruction from autoimmune thyroiditis, tyrosine kinase inhibitors also inhibit iodine uptake by the thyroid gland.

Persistent hypothyroidism is also common in patients on other agents. Lithium can cause painless thyroiditis with follicular cell destruction; however, hypothyroidism is most commonly related to inhibition of c-AMP, which results in decreased thyroid hormone synthesis. Immune checkpoint inhibitors, agents targeting the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), and the programmed cell death 1(PD-1) receptor used to treat patients with melanoma and other malignancies are associated with autoimmune-related adverse events in many patients, and endocrinopathies occur in approximately 10% of patients. In addition to painless

thyroiditis, immune checkpoint inhibitors may also cause hypophysitis resulting in hypothyroidism secondary to reduced TSH synthesis by the anterior pituitary. Patients have a decreased FT4 level with a decreased TSH level. Other pituitary hormones are also decreased.

Amiodarone, an antiarrhythmic agent, has a molecular structure similar to T4 and T3, and one-third of its molecular weight is made up of iodine. It is also highly lipid soluble. Amiodarone, because of its large iodine content, is a cause for iodine-induced increase in thyroid hormone synthesis that occurs more often in patients with a multinodular goiter (Type I amiodarone-induced thyrotoxicosis). More commonly, however, amiodarone has a direct toxic effect on the follicular cells of the thyroid gland causing thyroiditis and follicular cell destruction, release of thyroid hormone stores, and thyrotoxicosis (Type II amiodarone-induced thyrotoxicosis). Patients with preexisting Hashimoto thyroiditis are more likely to develop subsequent hypothyroidism, which usually resolves with discontinuation of amiodarone but can be permanent.

Amiodarone can be discontinued and another antiarrhythmic agent started. However, because of its high lipid solubility, the plasma levels of amiodarone decrease very slowly. Type I amiodarone-induced thyrotoxicosis usually responds to thioamide drug therapy, although high doses are more often required. Glucocorticoids are the mainstay of therapy for Type II amiodarone-induced thyrotoxicosis. Total thyroidectomy is indicated for patients with amiodarone-induced thyrotoxicosis refractory to medical therapy.

SUBACUTE (DE QUERVAIN) THYROIDITIS

Subacute thyroiditis, also known as De Quervain thyroiditis, granulomatous thyroiditis, giant cell thyroiditis, and painful thyroiditis, is a transient self-limited inflammatory disease of the thyroid gland, which is thought to be precipitated by a viral upper respiratory infection. Subacute thyroiditis has been described as an extrapulmonary manifestation of SARS-CoV-2 infection. It is an important entity for surgeons to be aware of because the signs and symptoms are similar to acute suppurative thyroiditis.

The inflammatory process in the thyroid gland results in damage to the follicular epithelial cells and proteolysis of thyroglobulin. This results in release of stored thyroid hormone into the circulation causing thyrotoxicosis, which persists until all of the thyroglobulin stores are depleted. Increases in circulating T4 and T3 suppress TSH secretion from the anterior pituitary, inhibiting thyroid hormone synthesis and euthyroidism followed by hypothyroidism ensues. As the inflammatory process resolves, the follicular epithelial cells regenerate and thyroid hormone synthesis resumes leading to complete recovery and a euthyroid state.

Subacute thyroiditis is usually a clinical diagnosis. Patients present with severe neck pain, which often radiates to the jaw, upper chest, and ear. They may also have symptoms of thyrotoxicosis. On examination, they have asymmetric or diffuse thyroid enlargement with significant neck tenderness. At the onset of the disease process, laboratory evaluation reveals a suppressed TSH, an increased free T4 and T3 level, and an increased erythrocyte sedimentation rate and C-reactive protein. Serum anti-TPO and antithyroglobulin antibodies are usually undetectable. Subacute thyroiditis is distinguished from other causes of thyrotoxicosis with iodine-123 imaging that demonstrates low uptake (less than 3%).

Rarely, ultrasound or FNAB may have a role in distinguishing subacute thyroiditis from suppurative thyroiditis, hemorrhage into a thyroid nodule, thyroid cancer, or thyroid lymphoma. Ultrasound exam can exclude nodular disease and abscess, and Doppler sonography shows decreased flow in contrast to Graves' disease, which is characterized by increased flow. Characteristic fine needle biopsy findings in patients with subacute thyroiditis are multinucleated giant cells, granulomas, and mononuclear cell infiltration.

Thyroid function tests will change with time as patients experience predictable changes in thyroid function, initially presenting with thyrotoxicosis, followed by euthyroidism, hypothyroidism, and eventual complete recovery of normal thyroid function in most patients in 3 or 4 months. Long-term hypothyroidism requiring thyroid hormone replacement therapy may occur in 5% to 15% of patients.

Subacute thyroiditis is treated with an antiinflammatory agent. Aspirin or a nonsteroidal antiinflammatory agent is used for most patients. Patients with severe pain or pain refractory to antiinflammatory agents are treated with glucocorticoids. A beta-receptor blocking agent may be used for treatment of symptoms of thyrotoxicosis. Thyroid hormone replacement therapy may be necessary for symptomatic patients during the hypothyroid phase and is necessary for patients who develop long-term hypothyroidism.

REIDEL THYROIDITIS

Reidel thyroiditis is a rare disease characterized by chronic inflammation, dense fibrous tissue infiltration, and follicular cell destruction of the thyroid gland that may also affect surrounding structures in the neck. It is most often an insidious disease with a good prognosis, but it can be rapidly progressive. Patients present with compressive symptoms such as dyspnea, dysphagia, hoarseness, and stridor and have an enlarged, "rock hard", fixed thyroid gland on exam. Patients may present with Horner syndrome secondary to involvement of the sympathetic trunk. Most patients have hypothyroidism and, less commonly, hypoparathyroidism secondary to parathyroid gland involvement. Retroperitoneal, mediastinal and orbital fibrosis, primary sclerosing cholangitis, and Hashimoto thyroiditis may occur in association with Reidel thyroiditis.

Anti-TPO antibodies are positive in most patients with Reidel thyroiditis. Ultrasound of the neck reveals a diffusely hypoechoic and hypovascular thyroid gland with ill-defined borders; on computed tomography (CT), the thyroid gland is hypodense without enhancement after administration of intravenous contrast. CT of the neck is valuable for assessment of involvement of the surrounding structures in the neck including encasement of the carotid artery, mass effect on the trachea and esophagus, and involvement of the neck musculature.

It is important to distinguish Reidel thyroiditis from anaplastic thyroid cancer, thyroid lymphoma, and sarcoma of the thyroid gland. FNAB may show spindle cells and fragments of fibrous tissue but is most often nondiagnostic (Bethesda I), and it cannot reliably exclude anaplastic thyroid cancer. A definitive diagnosis of Reidel thyroiditis usually requires an incisional biopsy, which demonstrates dense fibrous tissue, occlusive phlebitis, and an eosinophilic infiltrate. Giant cells, granulomas, and malignant cells are absent.

The mainstay of treatment of Reidel thyroiditis is glucocorticoid therapy; however, the response to therapy is variable. Early in the disease process when chronic inflammation predominates and fibrous tissue replacement is less prominent, patients may experience a reduction in the size of the thyroid gland and dramatic improvement in symptoms. Late in the disease, when fibrous tissue replacement predominates, there may be no response to glucocorticoids.

Tamoxifen, a selective estrogen receptor modulator, used alone or in combination with glucocorticoids may decrease the size of the thyroid gland in patients with Reidel thyroiditis. The therapeutic effect of tamoxifen on the thyroid gland is thought to be mediated by induction of tumor growth factor beta, a potent growth inhibitor. Alternative therapies have been used in patients without response to glucocorticoids and tamoxifen including mycophenolate mofetil, rituximab, azathioprine, and radiation.

Surgical intervention is usually limited to incisional biopsy for making a definitive diagnosis of Reidel thyroiditis and rarely thyroid resection or tracheostomy to relieve obstruction. The loss of the normal tissue planes related to the chronic inflammation and extrathyroidal fibrosis makes surgery difficult and increases the risk of complications. Thyroid isthmusectomy is the preferred operation to relieve mass effect on the trachea and minimize complications.

ACUTE SUPPURATIVE THYROIDITIS

Acute suppurative thyroiditis is a potentially life-threatening infection of the thyroid gland with a 5% to 10% mortality rate. Infection may extend into the deep spaces of the neck and mediastinum and are a cause for necrotizing soft infection, laryngeal and pharyngeal edema, and septicemia. Infection of the thyroid gland is rare. Factors that may protect the thyroid gland from infection include a high iodine content, rich blood supply and lymphatic drainage, and a thick capsule.

Acute suppurative thyroiditis may occur as a result of direct extension of infection from the pyriform sinus, a thyroglossal duct cyst, or the tonsils; hematogenous spread of infection; traumatic injury; or a complication from a locally invasive esophageal cancer or an esophageal perforation. A pyriform sinus fistula is the most common cause for acute suppurative thyroiditis in children and young adults. In older adults, acute suppurative thyroiditis occurs more often in elderly, immunocompromised, and debilitated patients.

Patients present with neck pain, which often makes it difficult to distinguish from subacute thyroiditis. It may also be difficult to distinguish from anaplastic thyroid cancer, which may present with neck pain and tenderness as a result of rapid growth and necrosis mimicking acute suppurative thyroiditis. Patients with acute suppurative thyroiditis may have dysphagia, odynophagia, and symptoms of thyrotoxicosis. On examination, they appear acutely ill with fever and chills, asymmetric thyroid enlargement, neck tenderness, and erythema. Patients have leukocytosis and may also have thyrotoxicosis with a suppressed serum TSH level and increased free T4 and free T3 levels. Serial thyroid function tests are recommended to detect release of thyroid hormones related to the destruction of thyroid follicles. Ultrasound or CT of the neck with contrast is obtained to help establish a diagnosis and identify an abscess that will need to be drained.

Fine needle aspiration may also help establish a definitive diagnosis of acute suppurative thyroiditis and exclude other causes. Cytologic evaluation reveals follicular epithelial cells, with or without colloid, acute inflammatory cells, and bacteria. Needle aspiration is also important for obtaining material for gram stain, culture, and antibiotic sensitivity testing. This should also include fungal and acid-fast bacteria culture. The most common pathogens are Streptococcus and Staphylococcus species. Other pathogens include *Pneumocystis carinii, Coccidioides* species, *Aspergillus*, and *Mycobacterium tuberculosis*. Mortality is highest in patients with fungal infections.

Management of patients with acute suppurative thyroiditis consists of obtaining blood cultures, administration of empiric broad-spectrum antibiotics, and abscess drainage. Once a specific organism is identified, the antibiotics are adjusted accordingly. In the absence of an abscess, patients may respond to antibiotic therapy alone. Patients who do not respond to antibiotic therapy and abscess drainage should undergo open surgical drainage or thyroidectomy.

After abscess resolution, imaging with a barium swallow or a CT of the neck with oral and intravenous contrast should be performed to assess for a pyriform sinus fistula. A trumpet maneuver may help to enhance visualization of a pyriform sinus fistula on CT. The trumpet maneuver is performed by having a patient blow into a catheter that is attached to a syringe to inflate the syringe. Pyriform sinus fistulae develop from remnants of the third and fourth branchial pouches, which typically form a tract to the left lobe of the thyroid gland. Resection or obliteration of a pyriform sinus fistula may be best accomplished after treatment of infection and resolution of acute inflammation. Flexible fiberoptic laryngoscopy may be helpful in identifying an internal opening of a pyriform sinus tract and for endoscopic cauterization and potentially eliminating the need for resection.

RADIOIODINE–INDUCED THYROIDITIS

Thyroiditis is a rare complication of radioiodine therapy for Graves' disease, occurring in less than 1% of patients. It usually manifests with neck pain and tenderness within the first 10 days following radioiodine administration and may cause acute exacerbation of thyrotoxicosis that is transient. It occurs because of direct radioiodine–induced follicular cell necrosis and destruction. Neck pain and tenderness can be treated with a nonsteroidal antiinflammatory agent or prednisone.

SARS-COV-2–INDUCED THYROIDITIS

Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with an increased frequency of thyrotoxicosis secondary to inflammatory thyroiditis with follicular cell destruction and transient thyrotoxicosis. It has been associated with atrial fibrillation and thromboembolic complications. The thyroiditis is thought to be correlated with SARS-CoV-2–induced increase in proinflammatory cytokines, specifically interleukin-6 and tumor necrosis alpha. Subacute thyroiditis and Hashimoto thyroiditis have also been described in rare patients with COVID-19.

Suggested Readings

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Management of Hyperthyroidism

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INITIAL EVALUATION

Hyperthyroidism refers to a state of inappropriate high hormone production by the thyroid gland and can be overt or subclinical. Patients with overt hyperthyroidism often present with classic symptoms such as weight loss, heat intolerance, palpitations, tremors, and anxiety (Table 1). Physical examination often will reveal a goiter, and they will have low serum TSH with high T3 and T4. On the other hand, patients with subclinical hyperthyroidism generally endorse minimal or limited symptoms; their T3 and T4 may be normal despite a suppressed TSH.

In patients with suspected hyperthyroidism, serum TSH should be measured first, because it has the highest sensitivity and specificity in the diagnosis of thyroid dysfunction. If the TSH is low, serum T3 and T4 levels (free or total) should be obtained to differentiate

TABLE 1 Signs and Symptoms Associated with Thyrotoxicosis

	Signs	Symptoms
General	Weight loss	Increased appetite; heat intolerance; sweating
Cardiovascular	Tachycardia, hypertension, arrhythmia (atrial fibrillation)	Palpitations
Pulmonary	Tachypnea	Dyspnea
Gastrointestinal		Diarrhea, nausea, vomiting
Reproductive	Changes in menstrual cycle	
Ocular	Proptosis, eyelid retraction, periorbital edema	Diplopia, blurry vision, retro-orbital pain, irritated eyes
Dermatologic	Warm and moist ("clammy") skin	
Neuromuscular	Tremors, hyperactivity, hyperreflexia	Nervousness, anxiety, fatigue, weakness, disturbed sleep, poor concentration

between subclinical and overt hyperthyroidism. The ratio of total T3 to total T4 also can be useful in determining the cause of thyrotoxicosis, because T3 will be more elevated in hyperthyroidism, whereas T4 is more elevated in thyrotoxicosis caused by thyroiditis.

Once the diagnosis is established, the cause should be determined. Current American Thyroid Association (ATA) guidelines recommend the following diagnostic strategies, depending on available expertise and resources: measurement of thyrotropin receptor antibodies (TRAb), determination of radioactive iodine (RAI) uptake, or measurement of thyroidal blood flow on ultrasonography (Fig. 1). Elevated TRAb levels are diagnostic for Graves' disease, an autoimmune disease caused by antibodies to the TSH receptor. Normal TRAb levels are suggestive of toxic multinodular goiter or toxic adenoma. An iodine 123 (123-I) scan will demonstrate different patterns of uptake in Graves' disease vs. toxic nodule(s) (Fig. 2). Thyroid ultrasonography should be performed in conjunction with TRAb measurement if nonfunctioning or hypofunctioning nodules are identified on 123-I scans or if a thyroid nodule is noted on physical examination. The evaluation of a cold thyroid nodule with fine-needle aspiration (FNA) biopsy should be guided by existing guidelines for the management of thyroid nodules in euthyroid individuals; thyroid nodules that are functional on radioiodine uptake scans do not need FNA as these are rarely malignant.

Based on the initial evaluation, patients with hyperthyroidism may be ultimately diagnosed with thyroiditis, Graves' disease, toxic multinodular goiter, or toxic adenoma. This chapter focuses on the medical and surgical management of the latter three diagnoses. Selection of the appropriate treatment modality not only depends on the patient's diagnosis and comorbidities but also the patient's preference (Tables 2 and 3). In the end, the patient should make an informed treatment decision in consultation with their medical and surgical teams, as there are different risks and benefits for each option.

MEDICAL MANAGEMENT OF HYPERTHYROIDISM

Although the long-term management of hyperthyroidism can take many routes, initial treatment should be focused on controlling the signs and symptoms of hyperthyroidism. The initial management of patients with symptomatic thyrotoxicosis should include β-adrenergic blockade, particularly in elderly patients and patients with resting heart rates greater than 90 beats/min or coexistent cardiovascular disease. These include a nonselective β-adrenergic receptor blocker such as propranolol (10–40 mg, 3–4 times a day) or those with relative β-1 selectivity, such as atenolol (25–100 mg, 1–2 times daily) or metoprolol (25–50 mg, 2–3 times daily). β-blockers are generally contraindicated in patients with asthma, given that there is insufficient β-1 selectivity at the recommended doses, and they also should be used cautiously in patients with congestive heart failure, bradyarrhythmias, and Raynaud's disease. For patients who do not tolerate β-adrenergic agents, calcium channel blockers have been shown to provide effective rate control.

Antithyroid Medications

Thionamides such as methimazole (MMI) and propylthiouracil (PTU) inhibit thyroid hormone synthesis to control hyperthyroidism, but they are not curative. MMI and PTU are available in the United States, and carbimazole (which is completely metabolized to MMI) is a third option in some countries. These medications can be used as primary treatment for Graves' disease or as a temporizing measure before RAI or thyroidectomy. If thionamides are used, MMI is favored over PTU due to the black box warning added to PTU in 2010, which is described in more detail later.

Thionamides can be used as primary treatment for Graves' disease. In Europe, Latin America, and Japan, there has been greater physician preference for antithyroid medications as first-line therapy. Patients should be treated for 12 to 18 months because results of a randomized clinical trial demonstrated that remission rates are not improved after more than 18 months of treatment. After completion of initial therapy, the medication can be tapered or discontinued among patients where TRAb levels have normalized, based on the clinical symptoms. Remission is defined as biochemical euthyroidism more than 12 months after discontinuation of therapy. Relapse rates are 20% to 30% over 3 to 5 years of follow-up. In patients who relapse, definitive therapy with RAI or thyroidectomy should be considered.

Major adverse effects of thionamides include agranulocytosis, vasculitis, and hepatotoxicity. MMI-induced hepatotoxicity is usually cholestatic, whereas PTU can cause hepatocellular injury and lead to fulminant hepatic failure. In 2010, the Food and Drug Administration added a black box warning to PTU due to reports of associated liver injury and even liver failure. Based on adverse event reports and published case reports, PTU was found to carry a higher risk of liver injury in children, leading to recommendations that PTU be stopped in favor of alternate therapies for children with hyperthyroidism. Now, PTU is used in rare clinical scenarios such as thyroid storm and the first trimester of pregnancy (due to the teratogenic risk of MMI).

In addition to liver injury, PTU at any dose is more likely to cause agranulocytosis than low doses of MMI. If a patient using a thionamide develops fever and/or sore throat, the medication should be discontinued and a complete blood count obtained. The diagnosis is established if the absolute neutrophil count is less than 500/μL in the

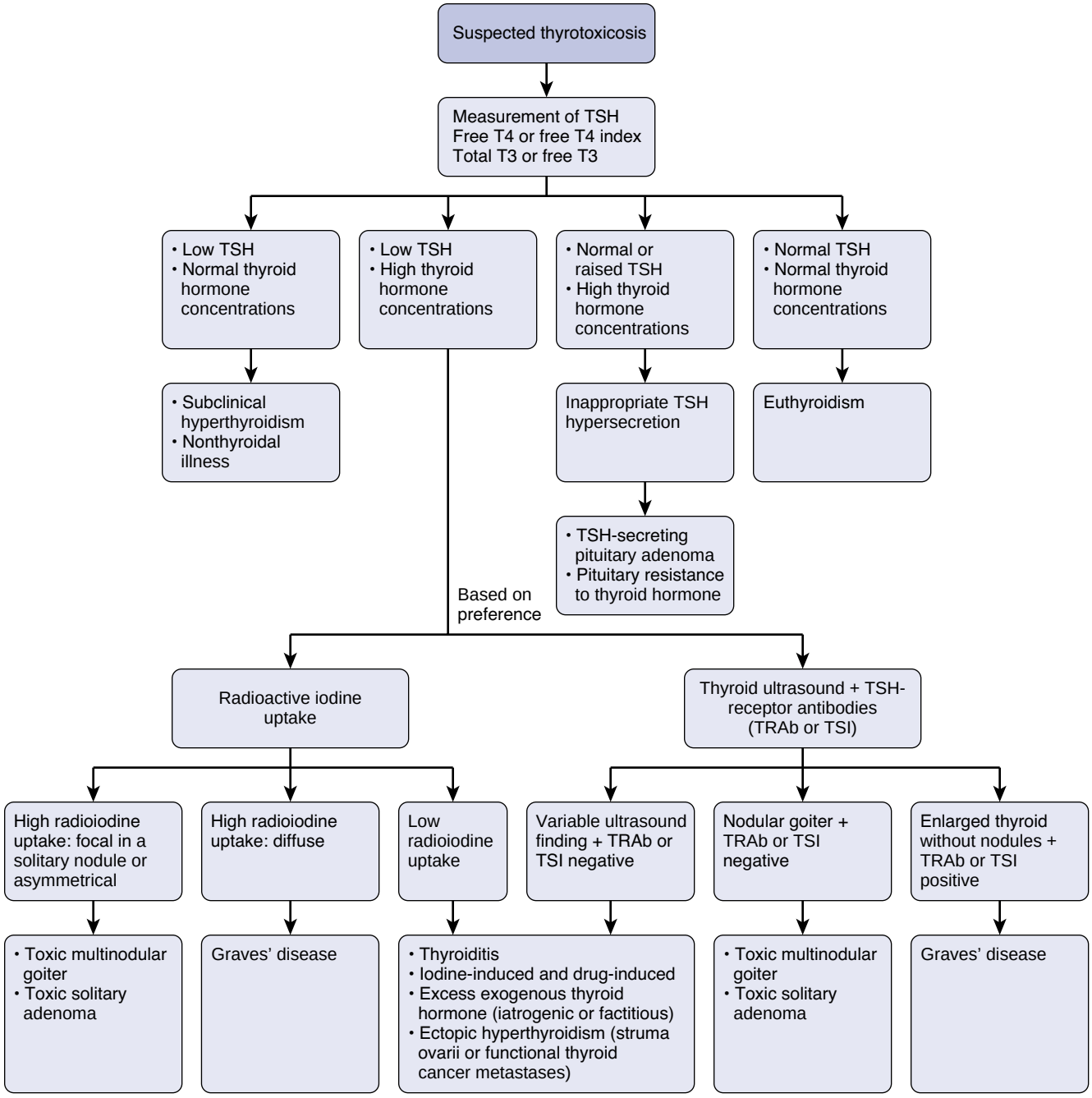


FIG. 1 Algorithm for assessment of thyrotoxicosis. *T3,* Triiodothyronine; *T4,* thyroxine; *TRAb,* TSH-receptor antibodies; *TSH,* thyroid stimulating hormone; *TSI,* thyroid stimulating immunoglobulins. *(From De Leo S, Lee SY, Braverman LE. Hyperthyroidism.* Lancet. *2016;388:906–918.)*

appropriate clinical scenario. Treatment includes discontinuation of the drug, collection of blood and urine cultures, and admission for intravenous broad-spectrum antibiotics. In severe cases, granulocyte colony stimulating factor can be used as adjunctive treatment.

In contrast to patients with hyperthyroidism secondary to Graves' disease, not all patients with toxic thyroid nodules will require pretreatment with antithyroid medications. Current ATA guidelines recommend that any patient at increased risk of complications related to a persistent hyperthyroid state, such as geriatric patients and patients with cardiovascular disease, be pretreated with antithyroidal medications with consideration of β-blockade. However, younger and middle-aged patients may only require β-blockade for symptomatic hyperthyroidism related to toxic nodules.

Adjunctive Therapies

Patients with severe hyperthyroidism or an adverse reaction to thionamides may benefit from alternative medical treatment. Glucocorticoids can be used to inhibit peripheral T4 to T3 conversion; they have been used to treat thyroid storm. Cholestyramine, when given with MMI, can also help lower serum T3/T4 faster than MMI alone. Other infrequently used medications include lithium and rituximab, although utility is limited by associated adverse effects.

Radioactive Iodine Therapy

In the United States, RAI has been the preferred modality of treatment for Graves' disease. In a 2011 survey of clinical endocrinologists,

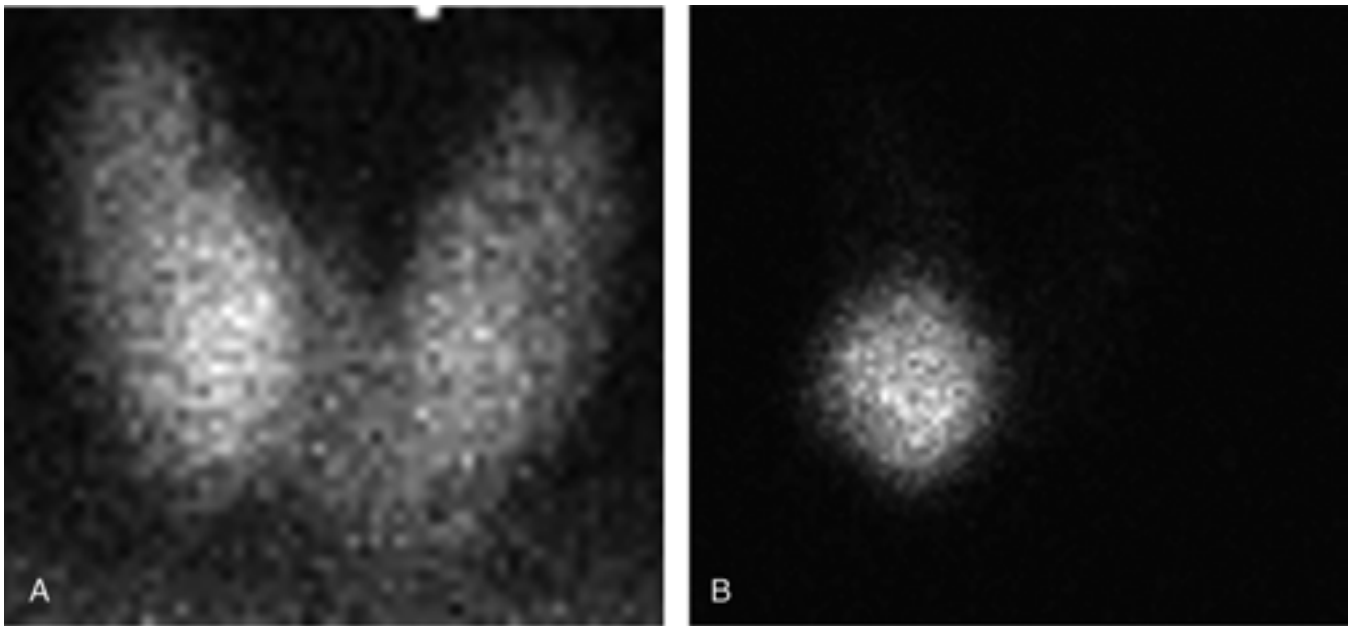


FIG. 2 Iodine 123 thyroid scan can demonstrate different patterns of radioactive iodine uptake in hyperthyroid patients. Diffuse, elevated uptake is consistent with Graves' disease **(A),** while uptake in a single nodule is consistent with toxic adenoma **(B)**.

TABLE 2 Clinical Situations That Favor a Particular Modality as Treatment for Graves' Hyperthyroidism

Clinical Situations	RAI	ATD	Surgery
Pregnancy[a]	—	Preferred, use caution	Acceptable, use caution
Comorbidities with increased surgical risk and/or limited life expectancy	Preferred	Acceptable	Contraindicated
Inactive GO	Acceptable	Acceptable	Acceptable
Active GO	[c]	Preferred	Preferred
Liver disease	Preferred	Use caution	Acceptable
Major adverse reactions to ATDs	Preferred	Contraindicated	Acceptable
Patients with previously operated or externally irradiated necks	Preferred	Acceptable	Use caution
Lack of access to a high-volume thyroid surgeon	Preferred	Acceptable	Use caution
Patients with high likelihood of remission (especially women, with mild disease, small goiters, and negative or low-titer TRAB)	Acceptable	Preferred	Acceptable
Patients with periodic paralysis	Preferred	Acceptable	Preferred
Patients with pulmonary hypertension or congestive heart failure	Preferred	Acceptable	Use caution
Elderly with comorbidities	Acceptable	Acceptable	Use caution
Thyroid malignancy confirmed or suspected	Contraindicated	[b]	Preferred
One or more large thyroid nodules	[b]	Acceptable	Preferred
Coexisting primary hyperparathyroidism requiring surgery	[b]	[b]	Preferred

[a]Women considering a pregnancy within 6 months.
[b]Not first-line therapy but may be acceptable depending on the clinical circumstances.
[c]RAI is not recommended for those with active, moderate/severe GO, but can be considered with or without glucocorticoids in patients with active, mild GO.
ATD, antithyroid drugs; *GO*, Graves' orbitopathy; *RAI*, radioactive iodine
From Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* 2016; 26:1343–1421.

TABLE 3 Clinical Situations That Favor a Particular Modality as Treatment for Toxic Multinodular Goiter or Toxic Adenoma

Clinical Situations	RAI	ATD	Surgery
Pregnancy[a]	Contraindicated	Preferred, use caution	Acceptable, use caution
Advanced age, comorbidities with increased surgical risk and/ or limited life expectancy	Preferred	Acceptable	Contraindicated
Patients with previously operated or externally irradiated necks	Preferred	Acceptable	Use caution
Lack of access to a high-volume thyroid surgeon	Preferred	Acceptable	Use caution
Symptoms or signs of compression within the neck	Acceptable	[b]	Preferred
Thyroid malignancy confirmed or suspected	Contraindicated	[b]	Preferred
Large goiter/nodule	Acceptable	[b]	Preferred
Goiter/nodule with substernal or retrosternal extension	Acceptable	[b]	Preferred
Coexisting hyperparathyroidism requiring surgery	[b]	[b]	Preferred

[a]For women considering a pregnancy within 6 months.
[b]Not first-line therapy but may be acceptable depending on the clinical circumstances.
ATD, Antithyroid drugs; *RAI*, radioactive iodine; *TMNG*, toxic multinodular goiter.
From Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343–1421.

nearly 60% of respondents practicing in North America preferred RAI as primary treatment. The goal of RAI therapy is to render the patient hypothyroid; RAI is incorporated into thyroid hormone, causing ionizing damage to thyroid follicular cells and destruction of the gland. RAI treatment can cause a transient exacerbation of hyperthyroidism; therefore, consideration should be given to initiation of antithyroid medication and for β-adrenergic blockade in symptom-free patients who may be at risk of complications from worsening thyrotoxicosis, such as the elderly or patients with cardiopulmonary comorbidities. Antithyroid medications should be stopped 2 to 3 days before RAI therapy and restarted 3 days later, which allows for RAI incorporation into the thyroid. Most patients will develop hypothyroidism 2 to 3 months after a single dose of 12 to 15 mCi of RAI. Patients should have repeat assessment of TSH, total T3, and free T4 in 1 to 2 months after therapy; biochemical monitoring should occur every 4 to 6 weeks for 6 months or until the patient is hypothyroid and stable on thyroid hormone replacement. Consideration for repeat therapy should not be considered for at least 6 months after initial treatment.

RAI is contraindicated in pregnant or lactating women, those with coexisting thyroid cancer or suspicion of thyroid cancer, and those unable to comply with radiation safety guidelines. Assuming a RAI dose of 10 to 15 mCi, radiation safety precautions include sleeping alone for 3 to 6 days (15–18 days in the case of a pregnant partner) and keeping a distance of 3 feet from adults and 6 feet from pregnant women and children during the day. RAI also should be used with caution among women planning a pregnancy within the first 4 to 6 months after treatment.

The presence of active moderate or severe Graves' orbitopathy also is a contraindication to RAI due to the risk of worsening eye disease. Total thyroidectomy should be the preferred treatment for these patients. Studies have shown thyroidectomy to be associated with stable or improved Graves' orbitopathy. If patients have absent or mild eye disease, RAI, antithyroidal medications, or thyroidectomy are all equally acceptable. Patients with mild Graves' orbitopathy may benefit from corticosteroid prophylaxis if they opt for RAI. Other side effects of RAI include transient worsening of thyrotoxicosis, risks of secondary malignancy, and potential anterior neck pain from radiation thyroiditis, sialadenitis, and dry mouth.

RAI should also be considered with caution in children and young adults with hyperthyroidism due to the risk of secondary malignancy. Since the early 1900s, experiences with physicians exposed to ionizing radiation and Japanese survivors of the atomic bombings have raised a concern of secondary malignancy with RAI. While the exact relationship between RAI and risk of secondary malignancy remains equivocal, a recent cohort study of 180,805 US and UK patients treated for hyperthyroidism found a positive association between greater organ-absorbed doses of RAI and risk of solid cancer death.

SURGICAL MANAGEMENT OF HYPERTHYROIDISM

Surgical management will require total or near-total thyroidectomy for patients with Graves' disease or toxic multinodular goiter and thyroid lobectomy for those with a toxic adenoma. Compared with medical treatments, surgery can achieve rapid correction of the hyperthyroid state and avoid potential long-term sequelae of RAI. These benefits may be most attractive to children and young adults with hyperthyroidism in whom the risk of secondary malignancy from RAI is most significant. Also, patients with local compression symptoms related to a large goiter or concurrent concern for thyroid malignancy may prefer surgery.

Surgery as First-Line Treatment for Graves' Disease

Despite the safety and effectiveness of antithyroid medications and RAI for the long-term treatment of hyperthyroidism secondary to Graves' disease, there may be circumstances that warrant a clinical preference for surgery. Of all preoperative diagnoses that may warrant thyroid surgery, Graves' disease has been associated with the highest risk of hypoparathyroidism and recurrent laryngeal nerve injury. Therefore, thyroidectomy for Graves' disease should be considered with appropriate preoperative preparation and an experienced, high-volume surgeon. Indications for surgical management of Graves' disease include women planning a pregnancy in less than 6 months, patients with other indications for thyroidectomy (presence of large thyroid nodules >4 cm, large goiters with compressive symptoms, suspected or known thyroid malignancy, or concurrent primary hyperparathyroidism requiring parathyroidectomy), and persistent disease despite previous treatment with antithyroid medications or RAI. Also, as mentioned previously, surgery should be the preferred treatment for patients with moderate to severe Graves'

orbitopathy. Surgery is relatively contraindicated in patients who have comorbidities that can shorten their life expectancy or increase the risk of perioperative morbidity, such as severe cardiopulmonary disease or advanced cancer.

Both surgery and RAI aim to render the patient hypothyroid. As recommended by the ATA, surgery should involve total thyroidectomy or near-total thyroidectomy. In a systematic review of published literature between 2001 and 2011, total thyroidectomy was associated with the lowest rate of persistent or recurrent hyperthyroidism. Persistent or recurrent hyperthyroidism was present in 0.3% of patients after total thyroidectomy, compared with 21% of patients who received a single dose of RAI or 10% of patients after subtotal thyroidectomy.

Patients with Graves' disease and associated cardiovascular morbidity also may benefit from total thyroidectomy. In a retrospective comparative cohort study of a Finnish registry, patients treated with RAI had a higher risk of mortality related to cardiovascular disease, hospitalization for cardiovascular disease, and atrial fibrillation compared with those who received thyroidectomy. However, treatment with RAI that resulted in hypothyroidism was not associated with increased cardiovascular comorbidity compared with thyroidectomy. Similarly, in a single institution retrospective US study, patients who underwent total thyroidectomy had higher rates of cardiac arrhythmia resolution than those treated with RAI.

Preoperative Management

Ideally, patients should be euthyroid before undergoing thyroidectomy for hyperthyroidism to minimize the risk of general anesthesia. In hyperthyroid patients, associated cardiovascular comorbidity may cause perioperative hemodynamic instability and require additional anesthetic to manage blood pressure and heart rate. Also, induction of anesthesia may be slower and require higher concentrations of inhaled anesthetics due to higher cardiac output in hyperthyroid patients. Lastly, thyroid storm is a rare perioperative complication that has been reported to occur during surgery and in the immediate postoperative period for hyperthyroid patients, although the incidence is low in patients who receive antithyroid medications.

Specifically for Graves' disease, in addition to thionamides and β-adrenergic blockade, guidelines from both the ATA and the American Association of Endocrine Surgeons (AAES) recommend consideration of potassium iodide-containing compounds in the immediate preoperative period. Potassium iodide (50 mg iodide/drop; 1–2 drops 3 times daily) or Lugol's solution (5% elemental iodine and 10% potassium iodide, 8 mg iodide/drop; 5–7 drops 3 times daily) should be administered for 7 to 10 days before surgery. Potassium iodide-containing compounds inhibit iodine organification in the thyroid to diminish thyroid hormone synthesis and inhibit hormone secretion. In a Turkish prospective clinical trial comparing preoperative treatment with or without Lugol's solution, thyroid mean blood flow and intraoperative blood loss were lower in those treated with Lugol's. However, other studies have shown that use of potassium iodide does not influence immediate postoperative outcomes such as hypoparathyroidism, vocal cord paresis, and hematoma formation. Of note, while the current ATA guidelines recommend using potassium iodide preoperatively for Graves', they discourage use of potassium iodide for toxic nodular disease due to the risk of exacerbating hyperthyroidism.

To optimize post-thyroidectomy outcomes, clinical guidelines from both the AAES and ATA recommend that calcium and 25-hydroxyvitamin D levels be repleted or supplemented preoperatively. One study found that patients treated with oral calcium carbonate 1 g three times daily for 2 weeks before surgery had lower rates of biochemical and symptomatic hypocalcemia. Although not limited to hyperthyroid patients, prospective trials have shown that adding vitamin D supplementation to oral calcium preoperatively is associated with a reduced risk of post-thyroidectomy hypocalcemia. The 2016 ATA guidelines for hyperthyroidism also recommend preoperative calcitriol supplementation in patients at increased risk of hypoparathyroidism, which would include those with Graves' disease or history of Roux-en-Y gastric bypass.

Extent of Surgery

Current ATA guidelines recommend near-total or total thyroidectomy be performed by a high-volume surgeon if surgery is chosen as primary therapy for Graves' disease or toxic multinodular goiter. For toxic adenomas, an ipsilateral thyroid lobectomy can be performed as long as there is no contralateral thyroid lesion that would compel total thyroidectomy.

Total thyroidectomy has been shown to be superior to subtotal thyroidectomy for surgical treatment of Graves' disease and toxic multinodular goiter. Subtotal thyroidectomy preserves a remnant of the thyroid to preserve both the integrity of the recurrent laryngeal nerve as it enters the cricothyroid muscle and the blood supply to the superior parathyroid gland. Subtotal thyroidectomy can be performed in two ways: as a bilateral subtotal (leaving a small amount of thyroid tissue on each side) or as a Hartley-Dunhill procedure (unilateral total lobectomy with contralateral subtotal lobectomy). However, leaving a remnant of thyroid increases the risk of persistent or recurrent hyperthyroidism. In a randomized clinical trial of Graves' disease patients, 9% of patients who underwent subtotal thyroidectomy developed recurrent hyperthyroidism within the 5-year follow-up period compared with 0% of total thyroidectomy patients. There was no difference in rates of transient or permanent hypoparathyroidism or recurrent laryngeal nerve injury. A 2014 systematic review of total thyroidectomy vs. subtotal thyroidectomy for Graves' disease also found that subtotal thyroidectomy was associated with higher risk of recurrent hyperthyroidism. Similarly, for toxic multinodular goiter, a 2015 systematic review of total thyroidectomy vs. subtotal thyroidectomy showed that goiter recurrence was lower with total thyroidectomy, but there was no significant difference in incidence of permanent nerve injury or permanent hypoparathyroidism.

Technical Considerations of Thyroidectomy

Thyroidectomy for hyperthyroidism can be challenging because of the hypervascularity of the gland. A recent US retrospective study of over 200,000 patients undergoing total thyroidectomy found that patients with Graves' disease had higher rates of hypocalcemia and hematoma requiring reoperation compared with patients with multinodular goiter or thyroid cancer. From a technical perspective, hypervascularity of the thyroid in Graves' disease makes identification of the parathyroid glands and recurrent laryngeal nerves more difficult. A few technical aspects that should be considered during thyroidectomy include the following:

1. Although cosmesis is important, particularly for patients with benign disease, the emphasis should be on safe visualization of key structures. Therefore, the incision length should be made with careful consideration of gland size and the expected hypervascularity of the gland.
2. It is often helpful to ligate the superior thyroid vessels first; these are often engorged in patients with hyperthyroidism, and early ligation can facilitate mobilization of the superior pole of the thyroid. This can be done with silk ties or with vessel-sealing devices, but one should be mindful that the maximum vessel size for many devices is 7 mm.
3. The recurrent laryngeal nerve typically lies within the tracheoesophageal groove. Its course can be more variable on the right, and it can lie anterior or posterior to the inferior thyroid artery. In rare cases, a nonrecurrent laryngeal nerve can be present and is typically associated with aberrant subclavian artery anatomy on the right side. If a CT scan of the neck and/or chest is available, aberrant vascular anatomy may raise suspicion for a nonrecurrent laryngeal nerve.

4. Blood supply to both the superior and inferior parathyroid glands is typically derived from the inferior thyroid artery. The inferior parathyroid glands can be more variable in location, and dissection close to the thyroid gland provides the safest plane to avoid inadvertent devascularization of the parathyroid glands.

Intraoperative recurrent laryngeal nerve monitoring is increasingly used during thyroidectomy, although visualization of the nerve remains the gold standard. During surgery, the vocal fold response to nerve stimulation can be measured by an electrode system incorporated in the endotracheal tube, which is positioned at the level of the vocal cords. Auditory or visual electromyographic signals can be obtained from the vagus or recurrent laryngeal nerve by intermittent stimulation using a handheld probe during thyroidectomy and at the time of visualization of the nerve or when dissection is occurring close to the nerve, depending on the system used. Changes in the pattern of the signals may hint at possible nerve irritation and dysfunction. Routine use of intraoperative nerve monitoring has not been shown to decrease rates of recurrent laryngeal nerve injury, and if a surgeon chooses to incorporate it into their practice, routine use allows for familiarity with the system and ability to troubleshoot the technology by all who are involved in the surgical procedure, including the surgeons, anesthesiologists, and nurses.

In current times, technical considerations in thyroidectomy may also include discussion of newer remote access approaches and percutaneous techniques. Remote access approaches such as transoral and bilateral axillary breast approach have been introduced as techniques to perform thyroidectomy while avoiding a cutaneous scar. Transoral endoscopic thyroidectomy vestibular approach, which approaches the thyroid via the oral cavity, has been shown to be a feasible procedure for Graves' disease, although these data derive from a single high-volume center, and operative times were significantly longer compared with open thyroidectomy. For toxic adenomas, physicians have reported successfully applying thermal ablation techniques such as radiofrequency ablation and high-intensity focused ultrasound to render patients euthyroid. These newer techniques currently are only performed at select institutions and require further study before consideration of widespread adoption.

Postoperative Management

After total thyroidectomy for either Graves' disease or a toxic multinodular goiter, thionamides and potassium iodide-containing preparations should be discontinued, while β-blockade can be tapered in patients for whom they are used solely for management of symptoms of hyperthyroidism (rather than preexisting hypertension). Thyroid hormone replacement should be initiated at a dose appropriate to the patient's weight (typically 0.8 μg/lb or 1.5–1.7 μg/kg) and age (typically lower doses in the elderly). TSH levels should be measured 6 to 8 weeks after surgery and then every 1 to 2 months until levels are stable, followed by annual assessment. After lobectomy for a toxic thyroid nodule, TSH and free T4 levels should be obtained 4 to 6 weeks after surgery; thyroid hormone supplementation should be started if there is a persistent rise in TSH levels. Long-term thyroid hormone supplementation may be required in 15% to 20% of patients after thyroid lobectomy.

Complications of Thyroidectomy

The most common complications of thyroidectomy include transient or permanent recurrent laryngeal nerve injury and postoperative hypocalcemia/hypoparathyroidism. Both are uncommon (1%–2% in the hands of experienced thyroid surgeons) but can have a significant effect on the patient's quality of life. Patients who elect to undergo thyroidectomy should have a preoperative voice evaluation, based on any subjective voice changes perceived by the patient and the surgeon's objective assessment of voice quality. Formal vocal cord evaluation should be obtained for any patient with subjective findings of voice change and any patient with previous anterior neck surgery (e.g., parathyroidectomy, thyroidectomy, carotid endarterectomy, or cervical fusion via the anterior approach) or mediastinal/thoracic surgery that places the vagus nerve at risk. Evaluation can include indirect or direct laryngoscopy, videostroboscopy, or transcutaneous vocal cord ultrasonography. Recurrent laryngeal nerve injury can be transient or permanent; subjective changes in voice quality should prompt referral to a voice specialist for evaluation and management.

During total thyroidectomy, manipulation, devascularization, or unintentional resection of the parathyroid glands can result in transient or permanent hypoparathyroidism and associated hypocalcemia. To prevent development of symptomatic hypocalcemia after total thyroidectomy, management options include routine oral calcium supplementation or selective supplementation based on serum calcium or parathyroid hormone levels. Especially in patients with hyperthyroidism, hungry bone syndrome can occur after total thyroidectomy. Hungry bone syndrome is a phenomenon related to the high bone turnover associated with hyperthyroidism; after total thyroidectomy, hyperthyroid patients can experience severe or prolonged hypocalcemia despite normal levels of parathyroid hormone. Other serum electrolyte abnormalities seen with hungry bone syndrome include low phosphate, low magnesium, and high potassium.

SPECIAL CONSIDERATIONS

Thyroid Storm

Thyroid storm (thyrotoxic crisis) is a rare condition that occurs in 1% to 5% of patients admitted to a hospital for thyrotoxicosis and is associated with a high (up to 25%) risk of death. Development of thyroid storm is not dependent on serum TSH levels, and the pathogenesis is not well understood. It can be triggered by cessation of antithyroid medications, acute illness, trauma, or stress. Thyroid storm also can be precipitated by manipulation of the thyroid during surgery, particularly in patients who are not biochemically euthyroid before surgery. The diagnosis is clinical, and in 1993, Burch and Wartofsky introduced a scoring system to assess the severity of the crisis based on temperature, central nervous system manifestations, gastrointestinal-hepatic dysfunction, cardiovascular dysfunction, and any precipitating factors. Treatment of thyroid storm is supportive, and a multidisciplinary approach to management, including definitive therapy with RAI or thyroidectomy, is recommended.

Graves' Disease in Children

Graves' disease is the most common cause of hyperthyroidism in children. Although thionamides, RAI, and thyroidectomy all remain treatment options for children, the choice of initial treatment depends on the patient's age, clinical status, and patient/parent values. If surgery is chosen, the availability of a high-volume thyroid or pediatric surgeon is particularly critical, given the possibility of lifelong hypoparathyroidism or recurrent laryngeal nerve injury. If antithyroid medications are chosen, MMI therapy for 1 to 2 years is considered appropriate initial management, although it is important to recognize that most pediatric patients will not have durable remission on medication alone. MMI should be used and PTU avoided because of the risk of hepatotoxicity.

In patients who are not in remission after initial MMI therapy, consideration for RAI or surgery should be given. The goal of RAI therapy is to induce hypothyroidism in a single treatment, either as an estimated or fixed dose. Smaller doses aimed at euthyroidism result in higher rates of persistent/recurrent hyperthyroidism and exposure of residual thyroid tissue to multiple doses of radiation that may lead to increased risk to the development of thyroid neoplasms. Long-term studies have not yet shown a definitively increased risk of thyroid or nonthyroid malignancies. A 2019 study of US and UK patients with hyperthyroidism found that higher estimated organ-absorbed doses of RAI was associated with higher risk of solid

cancer mortality. Given this theoretical risk, RAI therapy is generally avoided in children younger than 5 years. The European Thyroid Association guidelines recommend thyroidectomy as primary treatment in childhood and consideration of RAI in postpubertal children.

The ATA guidelines prefer surgery for pediatric patients younger than 5 years, those with large thyroid glands >80 g (in which response to RAI may be poor), and those noncompliant or unresponsive to antithyroid medications. Total or near-total thyroidectomy should be performed. Particularly in pediatric patients, access to a high-volume thyroid surgeon is critically important. Multiple analyses of US hospital discharge data have shown that children undergoing thyroid surgery are at higher risk of complications, but outcomes are optimized when surgeries are performed by high-volume surgeons. Current ATA guidelines also strongly recommend total thyroidectomy performed by a high-volume surgeon if surgery is elected for children with Graves' disease.

Graves' Disease in Pregnancy

The diagnosis of hyperthyroidism in pregnancy is challenging because normal pregnancy can alter thyroid function testing. The diagnosis is made with serum TSH values and either total T3 and T4 levels, but reference ranges should increase to 1.5 times above that of the nonpregnant range by the second/third trimester or be trimester-specific. If overt hyperthyroidism is diagnosed during pregnancy, treatment with antithyroid medications should be initiated. PTU should be used during the first trimester, given the teratogenic effects associated with MMI, including aplasia cutis, choanal/esophageal and other intestinal atresias, abdominal wall abnormalities (e.g., omphalocele), and eye, heart, and urinary tract malformations. PTU-associated birth defects have been reported but appear to be less severe than those related to use of MMI. MMI can be used after the first trimester. RAI therapy is contraindicated during pregnancy.

Surgery as definitive therapy should be considered by patients interested in starting families and who require high doses of antithyroid medications for euthyroidism, making spontaneous remission less likely. Surgery for patients diagnosed during pregnancy should be reserved only for those patients for whom medical management is not successful or those who have a contraindication to antithyroid medications. If performed, surgery during the first and third trimesters should be avoided, given the risks for fetal development and preterm labor, respectively.

Amiodarone-Induced Thyrotoxicosis

Amiodarone is an iodine-rich antiarrhythmic drug that can result in amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism in 15% to 20% of patients. AIT may develop at any point during amiodarone treatment, even several months after cessation, secondary to its long half-life (up to 100 days) and storage in fat tissues within the body. There are two forms of AIT, although both forms may occur in a single patient: type 1 develops in patients with underlying thyroid disease (iodine-induced hyperthyroidism), and type 2 develops in patients without underlying thyroid disease (destructive thyroiditis). Thyroid ultrasonography is helpful because it identifies the presence of thyroid nodules and the vascularity of the gland; type 1 AIT is associated with increased vascularity and multinodular goiter, whereas type 2 AIT is characterized by absent vascularity. RAI uptake scans can also be useful, as uptake is very low in patients with type 2 AIT but may be normal or high in type 1 AIT.

For patients with type 1 AIT, the preferred treatment strategy is medical (thionamides), although spontaneous remission is unlikely because of the high levels of iodine present. Therefore, higher doses of thionamides may be needed, and definitive therapy with surgery may be required, particularly given the risks of ongoing thyrotoxicosis in patients with underlying cardiac disease. Type 2 AIT may be self-limited, given that the destructive thyroiditis is caused by the amiodarone. It is best treated with glucocorticoids, at an initial dose of 0.5 to 0.7 mg/kg per day, with an initial course of 3 months. RAI is not feasible in patients with either type of AIT because of the high iodine levels in the thyroid.

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Surgical Management of Thyroid Cancer

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Surgery is a mainstay of thyroid cancer treatment. This chapter summarizes broad categories of thyroid cancer, the basics of staging, and surgical decision making. Surgical anatomy and technical considerations in thyroidectomy and cervical lymph node dissection (CLND) will be addressed.

BACKGROUND

Thyroid nodules are extremely common; roughly half of all adults will develop one or more thyroid nodules during their lifetime. In nonsurgical series, around 5% of thyroid nodules harbor malignancy. However, the incidence of small, asymptomatic thyroid cancers is growing as a result of expansion in diagnostic imaging. By autopsy reports, the prevalence of thyroid cancers is over 10%.

Treatment is broadly dictated by classification into three major categories: differentiated epithelial, undifferentiated (anaplastic), and medullary. Thyroid lymphoma is rarely approached surgically and will not be discussed. Within differentiated epithelial cancers

are papillary carcinomas, follicular carcinomas, and Hürthle cell cancers. Papillary thyroid cancer (PTC) is the most common subtype, accounting for 80% of all thyroid cancers. When localized to the gland, it carries an excellent prognosis (>95% survival at 10 years). Although greater than a third of patients harbor microscopic or macroscopic cervical lymph node metastases, the clinical significance of microscopic lymph node disease is unclear. Follicular thyroid cancer (FTC) accounts for 10% of all thyroid cancers and is more prevalent in the setting of iodine deficiency. Although FTC's natural history remains favorable, it has a higher risk for distant hematogenous spread and disease-specific mortality than PTC. Nodal metastases are comparatively uncommon, at around 10%. Initially considered a subcategory of FTC, Hürthle cell carcinoma is now recognized as a distinct entity. It carries a poorer prognosis than FTC, a higher proclivity for lymph node metastases, and a lower affinity for radioiodine uptake.

In stark contrast with its differentiated counterparts, anaplastic thyroid cancer (ATC) is extremely aggressive, often presents at an advanced stage, and is almost universally fatal. Although it is hypothesized that ATCs arise from more differentiated predecessors because of late, dedifferentiating driver mutations, the exact pathogenesis is unproven. More than 90% of patients present with regional or distant metastases—most commonly to the lung, bone, and/or brain. Mass effect is common, and resection usually serves a palliative—rather than curative—role. The 1-year survival is in the range of 20%. Only in the rare instances that ATC is diagnosed without extrathyroidal extension is the likelihood of long-term survival >75%.

Medullary thyroid cancer (MTC) arises from parafollicular C cells. Well-known for secreting the calcium regulator hormone calcitonin, C cells also secrete to varying degrees adrenocorticotropic hormone, carcinoembryonic antigen, and chromogranin, all of which may occasionally serve as useful tumor markers. Nonelevated calcitonin is usually a marker of dedifferentiation and an aggressive disease course. Prevalence of lymph node metastases is high, ranging from 15% in T1 disease to over 90% in T4 disease. Roughly half of patients with sporadic MTC present with stage III or IV disease, for which 10-year survival is 70% and 20%, respectively. One in four MTCs are hereditary, with germline mutations in the protooncogene *RET* being most commonly identified. Indeed, 50% of sporadic MTCs carry a somatic mutation in *RET*. The natural history of any given MTC is deducible by identifying the specific mutation within *RET*, with M918T and A883F—driver mutations for the MEN2B syndrome—associated with aggressive biology and disease course.

DIAGNOSIS AND STAGING

Thyroid cancers usually present in one of two ways: (1) as a clinically-palpable thyroid nodule, or (2) as an incidental lesion discovered through imaging for an unrelated condition. Following a focused history and physical examination, the basic workup for a new thyroid nodule must include, at minimum, thyroid hormone functional testing and neck ultrasonography. Sonographic suspicion for malignancy is commonly scored using the TI-RADS criteria, and lesions with high-risk features—solid nature, irregular margins, taller-than-wide shape, rim calcifications, or extrathyroidal extension—are recommended for fine needle aspiration (FNA). Cytopathology is then categorized by the Bethesda system into benign (malignancy risk 0%–3%), atypia of undetermined significance or follicular lesion of undetermined significance (5%–15%), follicular neoplasm or suspicious for follicular neoplasm (15%–30%), suspicious for malignancy (60%–75%), or malignant (97%–99%). Results of atypia or follicular neoplasm may prompt repeat FNA, diagnostic lobectomy, or assessment for molecular biomarkers predictive of malignancy to further define the risk window.

Once a diagnosis of thyroid cancer is confirmed, all patients should undergo staging ultrasonography (also known as *lymph node mapping*) of the central and lateral cervical lymph node compartments. For larger tumors and those with extrathyroidal extension, cross-sectional imaging with noncontrast CT or MRI can more accurately assess extent of disease. In advanced cases or those presenting with voice or swallowing complaints, vocal cord mobility should be assessed using ultrasound examination or fiberoptic laryngoscopy. Routine preoperative assessment of thyroglobulin or antithyroglobulin does not affect management and is not indicated. For differentiated epithelial thyroid cancers, cross-sectional imaging to assess for distant metastases is not indicated before resection. Because of a high likelihood of disseminated disease, staging for newly diagnosed ATC should routinely include CT of the chest, abdomen, and pelvis and whole-body FDG PET/CT. Further, any acquired ATC tissue sample should be submitted for DNA testing for actionable mutations.

In patients with newly-diagnosed MTC, basal serum calcitonin and carcinoembryonic antigen provide insight into disease burden. Most patients with calcitonin <20 pg/mL have thyroid-only disease, with 20% to 30% harboring cervical node metastases. Conversely, calcitonin >100 may be indicative of stage IV disease with low likelihood of surgical cure. However, primary resection may be indicated, even in the setting of distant disease because of the highly variable prognosis of stage IV MTC. In addition to cervical ultrasonography, screening for germline mutations in *RET* and concurrent pheochromocytoma should precede thyroid resection given the association of these tumors in the MEN2 syndromes. National Comprehensive Cancer Network (NCCN) guidelines stipulate that patients with a basal calcitonin >400 pg/mL or elevated carcinoembryonic antigen should be considered for cross-sectional staging with ^{68}Ga DOTATATE PET/CT. An alternative staging regimen includes CT of the neck and chest, a triphasic liver CT, and a bone scan. This approach is reflective of MTC's predilection to metastasize to cervical lymph nodes, lungs, liver, and bone.

OVERVIEW OF SURGICAL MANAGEMENT

For patients with differentiated epithelial thyroid cancer, treatment strategies range from active surveillance to total thyroidectomy with adjuvant radioactive iodine (RAI). Papillary thyroid cancers <1 cm in size are categorized as papillary thyroid microcarcinomas (PTMCs). Following resection, disease-specific mortality in this subgroup is <1%, with <5% of patients developing locoregional recurrence. Over two-thirds of patients who develop recurrence harbor mutations in *BRAF*. Most PTMCs are asymptomatic and discovered incidentally following thyroid resection for unrelated pathology. In the uncommon situation that a PTMC is diagnosed *in situ* through needle biopsy, the American Thyroid Association (ATA) recommends either partial thyroidectomy or active surveillance. The safety of active surveillance is supported by several large prospective series from Japan that indicate 10-year primary tumor growth rate of <10%, with lymph node spread in <4%. Overall, 15% of patients on active surveillance undergo resection at 5 years. Although limited by shorter follow-up and smaller numbers of patients studied, Western series have shown similarly low rates of primary tumor progression and metastatic spread. Active surveillance is not recommended for PTMCs located posteriorly in the thyroid gland near the trachea or recurrent laryngeal nerve (RLN), high-grade pathology, or for tumors harboring a *BRAF* mutation. Younger age is also associated with higher rates of primary tumor growth.

For most differentiated thyroid cancers between 1 and 4 cm in size, the ATA recommends thyroid lobectomy or total thyroidectomy. Long-term oncologic outcomes comparing lobectomy versus total thyroidectomy have been assessed by analysis of administrative and clinical databases, rather than prospective trials. Data from the National Cancer Database and Surveillance, Epidemiology, and End Results database indicate equivalent overall survival. Locoregional recurrence after lobectomy for low-risk thyroid cancer is <4%. There are several advantages to thyroid lobectomy. Roughly two-thirds of patients who undergo lobectomy do not require long-term thyroid hormone supplementation. Although complication rates in experienced hands is usually less than 1%, total thyroidectomy is associated with a twofold

higher rate of postoperative hemorrhage, twofold higher rate of permanent RLN injury, and threefold higher rate of persistent hypocalcemia. Less than 10% of patients who appropriately undergo lobectomy will require completion thyroidectomy in the future. Indications include upstaging to high-risk disease, locoregional recurrence, or the development/progression of contralateral nodules. The ATA lists the following indications for up-front total thyroidectomy: size >4 cm, extrathyroidal extension, lymphadenopathy, and need for postoperative RAI. Total thyroidectomy may also be considered for patients with contralateral nodules, prior neck irradiation, preexisting hypothyroidism, and extensive family history of thyroid cancer.

Risk factors for lymph node metastasis in differentiated epithelial thyroid cancer include age <45 years, tumor size >1 cm, multifocality, extrathyroidal extension, lymphovascular invasion, and *BRAF* V600E mutation. However, the prognostic significance of microscopic lymph node metastases is uncertain. As such, there is no role for prophylactic *lateral* cervical lymphadenectomy for clinically node-negative disease. Prophylactic *central* neck dissection (CND) may be considered for patients with tumor size >4 cm, extrathyroidal extension, or if lymph node status will impact recommendations for adjuvant RAI. In most cases, *therapeutic* neck dissection of the central and lateral cervical node basins is indicated for clinically evident lymph node metastases. Even in the setting of low-volume distant metastases, therapeutic neck dissection can reduce macroscopic disease burden, thereby improving the efficacy of high-dose RAI ablation.

Unlike papillary and follicular thyroid cancers, the natural history of sporadic MTC is dictated by stage, while that of hereditary MTC is determined by mutation status. Lymph node metastases, categorized as stage III disease, is present in 10% to 15% of patients with a T1 primary tumor (≤2 cm), and in >90% of patients with a T4 primary tumor (extrathyroidal extension). Lymph node micrometastasis is prognostic for sporadic MTC: 10-year survival of stage I and II cancer is >90%, while that of stage III cancer is roughly 70%. Thus all surgically suitable patients with bilateral and unilateral MTC >1 cm and many patients with unilateral MTC <1 cm should undergo a total thyroidectomy and CND. Management of the clinically negative lateral neck is controversial. More than two-thirds of patients with basal calcitonin >30 pg/mL possess ipsilateral lateral cervical node metastases. Thus some advocate prophylactic ipsilateral modified radical neck dissection (MRND) among these patients. On the other hand, for patients without central neck nodal disease, the likelihood of lateral lymph node metastases is <10%. Thus it is also reasonable to perform a two-stage operation, with total thyroidectomy and central neck nodal dissection in the first operation. Node-positive patients may then be considered for ipsilateral MRND. Although patients with basal calcitonin >100 have a >75% likelihood of *bilateral* cervical node metastases, these patients are also at high risk for synchronous distant metastases, and thus the therapeutic benefit of bilateral MRND may be limited.

The majority of patients with ATC are not surgically curable. The American Joint Committee on Cancer categorizes all ATC as stage IV, regardless of extent of disease. Stage IVa patients—those without extrathyroidal extension—are potentially curable, with a 1-year survival rate of 75%. However, >90% of patients present with stage IVb (extrathyroidal extension) or IVc (distant metastases) disease, and 1-year survival among these patients is well below 25%. Standard treatment for the uncommon stage IVa patient with resectable disease is total thyroidectomy and CND followed by adjuvant radiation with or without concurrent chemotherapy (typically doxorubicin). More than half present with esophageal and/or tracheal invasion, and en bloc resection of adjacent structures should be anticipated for patients with gross stage IVb disease. Although systemic agents can induce objective response in some patients (particularly BRAF/MEK inhibition for *BRAF* V600E–mutant tumors), none have shown consistent impact on survival. Nevertheless, neoadjuvant chemoradiation may be indicated for locally advanced disease without distant spread. Because most patients die of distant metastases within 2 to 5 months, there is no compelling evidence that an R0 resection is superior to R1. Further, because ATC typically does not exhibit radioactive iodine uptake, there is no reason to aggressively "debulk" locoregional disease with the hope of enriching systemic therapy. Many patients with ATC present with unilateral vocal cord palsy resulting from involvement of the RLN. In these patients, a subtotal thyroidectomy may be favored to preserve the contralateral nerve. Palliation is a key goal for stages IVb and IVc ATC. Palliative care and hospice care should be consulted early, and focusing on airway protection with tracheal stenting or tracheostomy in the setting of stage IVb unresectable or IVc disease may be indicated to improve quality of life.

TOTAL THYROIDECTOMY

Anatomy

Proficiency with thyroidectomy begins with an intimate knowledge of surgical anatomy. The thyroid gland is situated anterior to the cricoid cartilage and inferior to the thyroid cartilage. The superior pole on each side may extend several centimeters superiorly, and a surgeon-performed ultrasound can optimize placement of the transverse neck incision. The two lobes of the thyroid gland are joined at the midline by the thyroid isthmus. In one of four patients, the congenital thyroglossal duct remnant retains thyroid tissue, which takes the form of a midline pyramidal lobe extending cephalad. From superficial to deep, the major tissue layers overlying the thyroid include dermis, platysma, the sternohyoid muscle and superior belly of the omohyoid muscle, the sternothyroid muscle, and pretracheal fascia. Each lobe of the thyroid gland is fed by two named arteries (superior and inferior) and drained by three named veins (superior, middle, and inferior). However, inferior venous drainage is often via a plexus of veins rather than a single dominant vessel.

Two named nerves are near each thyroid lobe. The external branch of the superior laryngeal nerve (EBSLN), which innervates the cricothyroid and controls high-pitch voice projection, lies close to the superior thyroid artery. It travels from cephalad to caudad lateral to the vascular pedicle, crossing the superior thyroid artery in a medial direction to enter the cricothyroid. The anatomic relationship between the EBSLN and the superior pole of the thyroid gland is described using the Cernea classification. Type 1 nerves cross more than 1 cm above the superior pole of the thyroid gland, type 2A nerves cross within 1 cm above the superior pole, and type 2B nerves cross below the superior border of the superior pole (Fig. 1).

The recurrent laryngeal nerve (RLN) on the left descends from the vagus nerve, loops around the arch of the aorta, and ascends in the tracheoesophageal groove, ultimately innervating the remaining intrinsic laryngeal muscles. On the right, the RLN loops around the subclavian artery and ascends more laterally than its left-side counterpart, a few millimeters away from the tracheoesophageal groove. It is prudent to establish normal carotid artery anatomy on the right using ultrasound or cross-sectional imaging in the preoperative setting. A carotid artery that originates directly from the aortic arch (rather than the innominate artery) indicates an aberrant, retroesophageal right subclavian artery with an associated *non*-recurrent inferior laryngeal nerve. The prevalence of this anatomy is roughly 0.5%, and in such cases the nerve lies in a near-transverse trajectory behind the thyroid gland (Fig. 2).

Classically, two parathyroid glands (superior and inferior) lie posterior to the thyroid gland on each side. However, innumerable variations in gland number and position have been reported. Superior glands generally lie posterior to the plane of the RLN, while inferior glands lie anterior to this plane. Superior glands are more anatomically predictable, with the right and left superior parathyroid glands on average lying within 2 to 5 mm of the nerve. Inferior glands are more variable, lying on average 7 to 10 mm away from the nerve (Fig. 3). Ectopic parathyroid glands are reported in 15% of patients. Common ectopic locations include retroesophageal,

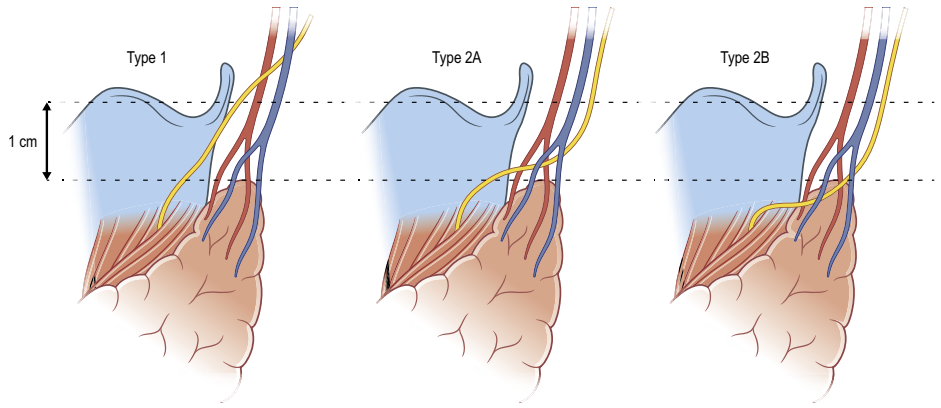


FIG. 1 Cernea classification of the external branch of the superior laryngeal nerve. A type 1 nerve crosses greater than 1 cm above the superior pole of the thyroid. A type 2A nerve crosses within 1 cm of the superior pole. A type 2B nerve crosses below the border of the superior pole. Type 2A and 2B nerves are more prone to injury during superior pole mobilization. *(From Brennan P, Standring S,* Wiseman S: Gray's Surgical Anatomy. *Philadelphia: Elsevier; 2020.)*

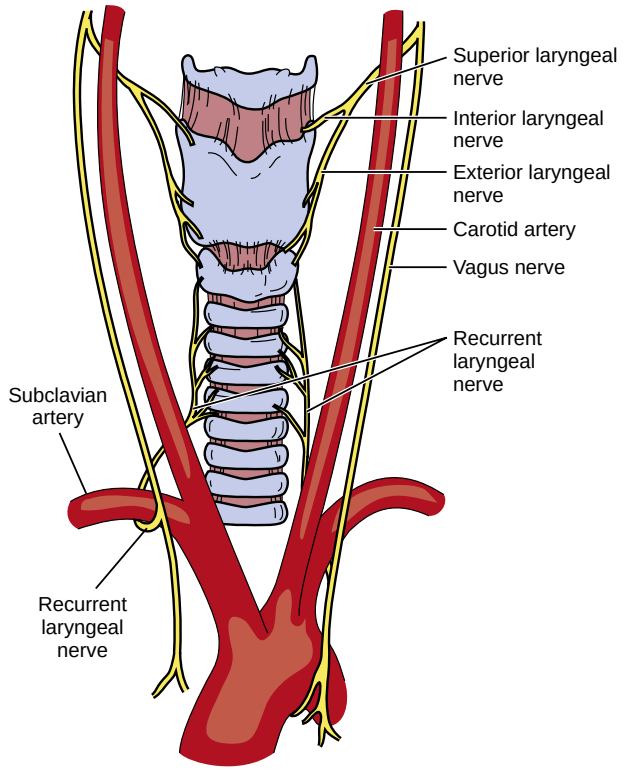


FIG. 2 Anatomy of the recurrent laryngeal nerves. The right nerve takes a more oblique course posterior to the thyroid gland than the left nerve. *(From Phillips N, Hornacky A.* Berry & Kohn's Operating Room Technique. *14th ed. Philadelphia: Elsevier; 2021: F41.14.)*

intrathyroidal, or along the carotid sheath. Inferior glands are also frequently located within the thyro-thymic ligament or even in the mediastinum. Although knowledge of ectopic positions is key to successful parathyroidectomy, parathyroid tissue in these locations seems protective from unintended resection or devascularization during thyroidectomy. Importantly, up to 25% of superior parathyroid glands derive blood supply from the superior thyroid artery rather than the inferior thyroid artery, placing them at risk for devascularization if the superior thyroid artery is ligated and divided away from the upper pole thyroid tissue.

Technique Overview

The fundamental technique of thyroidectomy has not changed in decades. Addition of ultrasonic and bipolar energy devices has reduced operative time but has not changed the broad steps of resection. Minimally invasive approaches such as transaxillary and transoral thyroidectomy offer cosmetic advantages. In this section, a classic open thyroidectomy will be described, along with tenets that facilitate exposure and safe dissection.

Exposure

The patient is positioned supine, with the head raised roughly 15 degrees and the neck extended by way of a posterior shoulder roll. Excessive extension is uncomfortable postoperatively, while inadequate extension crowds the surgical field. A collar incision is made along Langer's lines or within an existing neck crease, typically 2 to 3 cm above the clavicular heads. The incision is carried through the platysma, and the subplatysmal flaps are raised inferiorly to the clavicular heads and superiorly to the thyroid cartilage through a combination of sharp and blunt dissection. The strap muscles are lifted off the thyroid capsule at midline and separated from the thyroid capsule posteriorly along avascular planes. The middle thyroid vein is then exposed and ligated between the thyroid and internal jugular vein (IJV). For very large or firm glands, it may be helpful to transect the sternothyroid muscle either medially or entirely for added lateral exposure. In these cases, the muscle should be divided high, near the insertion into the thyroid cartilage, as innervation from the ansa cervicalis (which may be exposed by laterally retracting the SCM) enters inferiorly. The ansa cervicalis should be preserved along its length in the unlikely event it is needed for reconstruction of the recurrent laryngeal nerve if divided intentionally or unintentionally during the thyroidectomy.

Retraction and Mobilization

We usually begin the thyroidectomy by isolating draining veins of the isthmus and pyramidal lobe. If a lobectomy is planned, early division of the isthmus can facilitate mobilization and delivery of the gland through small (<4 cm) incisions. Development of the isthmus is then followed by dissection of the superior pole of the diseased lobe, which is approached first by developing the avascular cricothyroid space (space of Reeve) between the superior pole and cricothyroid muscle. The superior thyroid artery is isolated

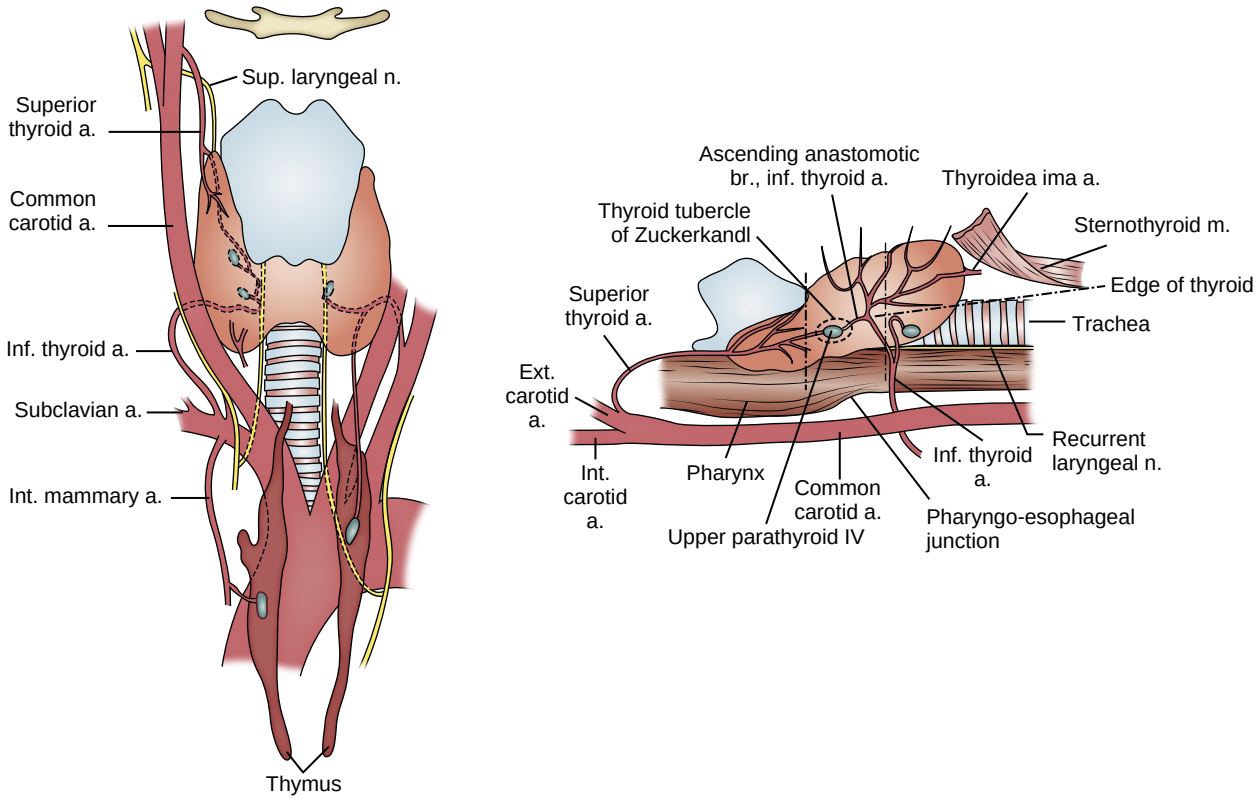


FIG. 3 Parathyroid anatomy. Most common locations for parathyroid glands are along the tracheoesophageal groove, close to the recurrent laryngeal nerves. Ectopic locations include retroesophageal, intrathyroidal, or along the carotid sheath. Inferior glands are also frequently located within the thyro-thymic ligament or even in the mediastinum. *(From Kaplan EL. Thyroid and parathyroid. In Schwartz SI, ed.* Principles of Surgery. *5th ed. New York: McGraw-Hill; 1989: 1613–1685.)*

through blunt, closed-tip dissection. Excessive spreading will cause bleeding and obscure visualization. The EBSLN should be identified (either visually or with the aid of a nerve monitor) before superior pedicle ligation, and the pedicle should be divided as close to the gland as possible to minimize the risk of nerve injury. At this point, the inferior pole can be retracted superiorly, exposing the inferior thyroid vein branches. These are ligated close to the thyroid gland, as straying deep and lateral to the inferior pole risks injury to the recurrent laryngeal nerve and devascularization and removal of the lower parathyroid gland.

Preservation of Parathyroid Glands

With the venous drainage divided, the thyroid lobe is rotated medially and elevated out of the surgical field. Maneuvers for gland retraction include manual retraction, hemostatic clamps, Allis clamps, suction catheter, or Kittner sponge. If clamps are used, repositioning should be limited as repeated gland trauma can cause fracture or bleeding. Medial retraction exposes the tracheoesophageal groove and the carotid sheath. This is a convenient time to test RLN functional integrity by stimulating the vagus nerve. Posterior dissection reveals the inferior thyroid artery and recurrent laryngeal nerve. This posterior exposure also reveals the parathyroid glands in their standard positions. In 80% of cases, both the superior and inferior parathyroid glands are supplied by branches of the inferior thyroid artery. In the remaining cases, the superior gland is supplied by a branch of the superior thyroid artery. Identification of the glands on one side facilitates dissection on the contralateral side, as symmetry in gland position is present in 80% of superior glands and 70% of inferior glands. Dissection immediately along the thyroid capsule to individually divide the tertiary branches of the inferior thyroid artery usually preserves parathyroid blood flow. For parathyroid glands located within the thyroid capsule, the capsule may be entered focally to liberate the gland. This usually preserves the gland's vascular pedicle. The decision to do so must account for the position of the malignant nodule. If the cancer is close to an intrathyroidal parathyroid gland, that gland is removed en bloc with the thyroid gland. Truncal ligation of the inferior thyroid artery without identification and preservation of the parathyroid glands is discouraged; doing so significantly increases the probability of postoperative hypocalcemia due to hypoparathyroidism. If a parathyroid gland is clearly devascularized or unintentionally explanted, it should be preserved in iced saline until the end of the operation (<120 minutes), at which point it is sharply divided into 1- to 3-mm pieces. One or more avascular pockets are then developed in the SCM, and the piecemeal parathyroid tissue is reimplanted. A permanent suture may be placed to mark the implanted location. Hemorrhage must be avoided, as a muscle pocket hematoma prevents parathyroid revascularization.

Preservation of the Recurrent Laryngeal Nerve

From the mediastinum, the course of the RLN is typically anterior or lateral to the tracheoesophageal groove. The right nerve, which is positioned more laterally in the chest than the left, has a more oblique course. As the nerve ascends, dozens of anatomic variations between the RLN and inferior thyroid artery have been described. The most common scenario places the nerve deep to the inferior thyroid artery. However, the nerve can also be found anterior to or coursing between the branches of the artery. Nerves located anterior to the inferior thyroid artery are at particularly high risk of injury as they are drawn

anteriorly with medial retraction of the thyroid lobe. Anatomic variations are more common on the right. In the vast majority of cases, the nerve courses within a few millimeters of the artery and the ligament of Berry before diving deep to the cricothyroid muscle to enter the larynx. At its terminus, the nerve often divides into abductor and adductor branches, and this branching may occur significantly proximal to the cricothyroid muscle, such that two RLNs may be identified within the surgical field. The three most common locations for inadvertent nerve injury are posterior to the inferior pole of the thyroid gland, at the intersection with the inferior thyroid artery, and behind the ligament of Berry. The RLN is also vulnerable to pinching behind the ligament of Berry during medial retraction of the thyroid gland at late stages of the thyroidectomy before dividing the ligament. To safely isolate the nerve, it is prudent to spread perpendicular to the nerve axis through the fatty and nodal tissue posterior to the thyroid gland to initially expose the nerve. Once identified, the nerve is exposed by using a blunt hemostatic clamp with the tip upward to separate the nerve from superficial structures along its course. This protects the nerve and facilitates the safe division of the ligament of Berry. Frequently, cephalad nerve exposure will encounter a posterior, thickened projection of thyroid tissue called the *tubercle of Zuckerkandl.* This projection must be mobilized laterally and lifted anteromedially to expose the nerve course within a fissure between the tubercle and remaining thyroid gland. In cases anticipated to require adjuvant RAI ablation, these maneuvers not only preserve the RLN but also maximize the completeness of thyroidectomy. Although direct visualization of the nerve is advantageous during dissection of the tubercle and the ligament of Berry, we seldomly expose the entire nerve throughout its course in the tracheoesophageal groove during thyroidectomy for benign disease. We do routinely do so during thyroidectomy for cancer when pathologic adenopathy is present and when performing elective CND.

Intraoperative Neuromonitoring

Intraoperative neuromonitoring (IONM) has expanded in popularity over the past 15 years as a useful adjunct that facilitates identification of the RLN. In part because of the low incidence of permanent RLN injury (<0.5% in most series), nearly all studies—randomized and retrospective alike—have been underpowered to show a difference in nerve injury rate. The most common approach to IONM involves a receiving electrode on the endotracheal tube to sense vocal cord signaling and a grounding electrode on the skin. Not surprisingly, effectiveness of IONM is contingent on optimal endotracheal tube positioning and other factors that influence circuit completeness. For this reason, while the negative predictive value of IONM to rule out nerve injury approaches 100%, positive predictive value (i.e., the rate of true nerve injury upon signal loss) is <50% in most large series. Thus an experienced thyroid surgeon who chooses to routinely implement IONM must be familiar with troubleshooting and verification techniques. Even in experienced hands, IONM has not been shown to *prevent* nerve injury but may facilitate nerve identification and alter surgical decision making if injury is suspected. This is particularly true for the reoperative neck, large nodules, and immunogenic goiters. We do not use the monitor to "find" the nerve, rather, we routinely use nerve monitoring during thyroidectomy to confirm visual assignment and map the RLN branching pattern, ensure preservation of signal while retracting the gland at the ligament of Berry, and to reinforce visual identification of the entire nerve during central neck dissection. Our practice is to confirm signal at the vagus and tracheoesophageal groove at the beginning, intermittently throughout, and at the end of the procedure.

Closure

There is no role for routine drainage following thyroidectomy, nor is there compelling evidence for routine placement of synthetic hemostatic agents. Thorough irrigation and meticulous hemostasis are vital. The Valsalva maneuver can assist in inspecting the surgical field for sources of hemorrhage. The strap muscles are reapproximated in the midline using absorbable suture, leaving at least a 1-cm gap at the inferior aspect to prevent fluid or blood accumulation that might compress the trachea. The platysma is similarly approximated with absorbable suture, and skin is closed in a subcuticular layer. Techniques aimed at improving cosmesis vary across institution and may include: (1) not reapproximating the platysma, (2) using a permanent subcuticular suture that is removed in the early postoperative setting, (3) injecting a dilute steroid solution in the subcutaneous layer, and (4) routine prescription of a topical scar-reducing agent.

SELECTIVE CERVICAL LYMPH NODE DISSECTION

Although differentiated epithelial thyroid cancers carry an overall excellent prognosis, over 30% of patients harbor lymph node metastases. Clinically evident synchronous or metachronous nodal disease is common and is generally treated with therapeutic node dissection. Unlike thyroidectomy, compartment-oriented selective CLND can be approached in many ways, all of which require intimate and detailed knowledge of cervical anatomy. Regardless of the specific surgical approach, meticulous technique with attention to staying in native tissue planes is a requirement for safe and thorough lateral neck dissection.

Anatomy

Boundaries of the lateral cervical node stations dictate a thorough CLND. For thyroid cancer, most draining lymph nodes are located in stations IIa and III to V, the boundaries of which are listed in Figure 4. Anatomic descriptions of the vital structures within each station will be described in the following sections.

Technique Overview

Exposure

From the aforementioned position for a total thyroidectomy, the patient's head is turned away gently from the side of dissection while maintaining neck extension. Excessive turning or extension is unnecessary and heightens the risk of postoperative pain. Two types of

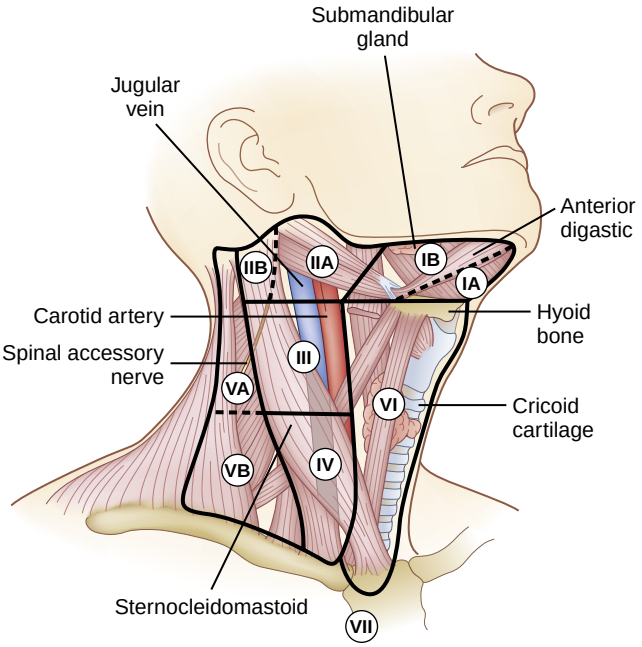


FIG. 4 Boundaries of cervical lymph node compartments. *(From Townsend, et al.* Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice. *21st ed.; Philadelphia: Elsevier; 2022: F37.3.)*

incisions are commonly used. First, a traditional collar incision may be extended superiorly along the anterior border of the SCM to form a "hockey stick" configuration. We find this incision infrequently needed and prefer to usually extend the thyroidectomy collar incision posterolaterally along Langer's lines into level V. This approach yields superior cosmetic results but requires a more extensive subplatysmal flap elevation for adequate cephalad exposure. If needed, a second parallel incision can be made in a higher skin crease to allow exposure to level II cervical nodes, which still yields a cosmetically better result than the hockey stick incision. The subplatysmal flap should be developed from the clavicle inferiorly up to two fingerbreadths from the body of the mandible. Here great care must be taken to avoid the marginal mandibular branch of the facial nerve that courses superficial to the submandibular gland and can be seen at the superior extent of the field. Care should be taken to preserve the nerve as injury results in an asymmetric smile. Flap mobilization over the lateral SCM will expose the greater auricular nerve, which provides sensory innervation to the skin overlying the parotid and external ear and should be preserved. The spinal accessory can be identified at Erb's point located 1 cm superior, lateral, and deep to the greater auricular nerve (Fig. 5). Beneath the submandibular gland is located a packet of lymph nodes overlying the facial vein and its neighboring branches. This packet is mobilized from these veins and submitted separately from the remaining node packet. Medial to the SCM, the IJV is identified and dissected on its lateral extent until the spinal accessory nerve is identified and defines the upper extent of the node dissection.

Lateral Mobilization

We take an extrafascial approach to en bloc dissection of lateral cervical nodes. This is accomplished by first lifting the medial investing fascia off the SCM near its anterior border. Branch vessels between the fascia and the muscle are divided by bipolar cautery. At the superior aspect of this mobilization, along the anterior edge of the SCM, lies the spinal accessory nerve (CN XI). A neurostimulator can elicit trapezius contraction to verify nerve anatomy. Blunt dissection along either side of the nerve will allow circumferential mobilization and elevation. The anterior fascia overlying CN XI should be left in situ, as this contains the nerve's microcirculation. With the nerve separated from the node packet, the fascial layer surrounding the packet is retracted medially from behind the SCM while the muscle is elevated and retracted laterally. The superior extent of this mobilization is the posterior belly of the digastric muscle, beyond which is level IB. The node packet and overlying fascia can be followed deep and posteriorly to pull level V nodal tissue anteromedially into the surgical field. Separating the fascia from the deep border of the SCM will expose the omohyoid muscle belly, delineating the border between levels III and IV. This muscle may be divided for exposure.

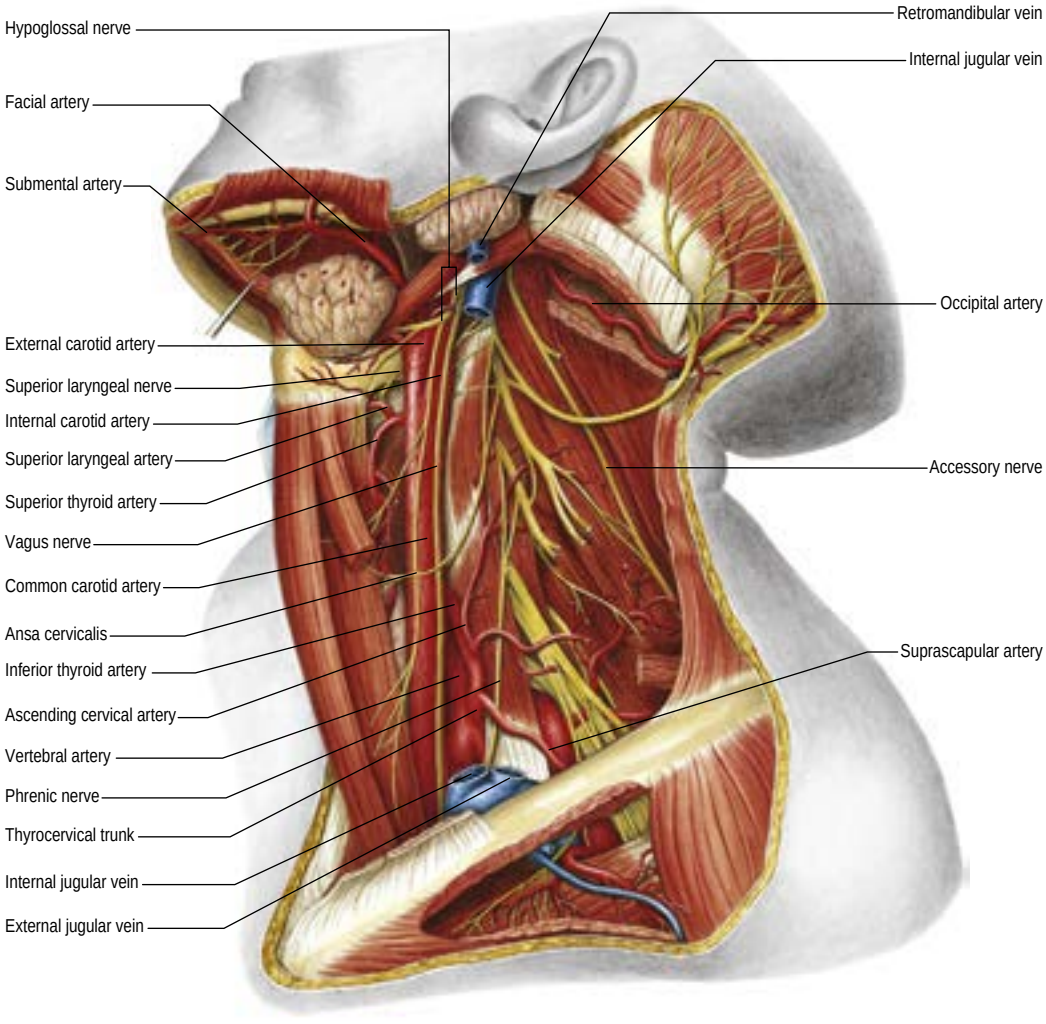


FIG. 5 **Lateral neck neurovascular anatomy.** *(From Waschke J, Paulsen F, eds.* Sobotta Atlas of Human Anatomy. *15th ed. Philadelphia: Elsevier; 2013.)*

The angle of dissection is then altered toward the floor, dividing the fascial plane and ultimately exposing the scalene fascia. At the correct depth, the cervical plexus is exposed. Nodal tissue between the plexus rootlets is mobilized and lifted off of the scalene fascia. Along this floor of dissection, the phrenic nerve travels lateral to the IJV.

Inferior Mobilization

At the inferior aspect of the deep dissection, the transverse cervical artery is encountered and preserved. On the left, the thoracic duct and lymphatic drainage from the head and neck converge near the level of the transverse cervical artery. It is customary to avoid sharp or cautery dissection at this level and instead mobilize the inferior aspect with suture tie ligation to minimize risk of lymphatic or thoracic duct leak.

Medial Mobilization

With the nodal tissue fully mobilized inferiorly and laterally, the packet is retracted medially, exposing its posteromedial attachments to the IJV. The fascia is incised over the IJV, and the vein is retracted laterally while the node packet is elevated off the IJV just anterior to the vein. Mobilization along the IJV will encounter the facial vein superiorly, which may be preserved or ligated as necessary. Once the medial edge of the IJV is fully dissected away from the node packet, the fascia investing the node packet is incised to release it from the carotid sheath. This dissection approach respects the fascial planes of the carotid sheath and does not expose the vagus nerve for potential injury. Finally, the node packet in its entirety is retracted laterally, demonstrating its remaining medial attachments to the strap muscles. The strap muscles are separated from the node packet superiorly to the hyoid bone and inferiorly to the clavicle. This anterior plane is then joined to the posterior dissection to fully separate the node packet along its medial edge. If the level IIA dissection is incomplete, this node packet can be retracted inferiorly to facilitate separation from the posterior belly of the digastric muscle. Dissection deep to the digastric muscle is unnecessary and places the hypoglossal nerve at risk of injury.

Closure

It is our practice to routinely place one drain along the dissection bed behind the SCM, lying along the inferior lymphatic-rich tissues. A second drain is occasionally placed in the central neck if an extensive central and mediastinal node dissection is performed. Special attention is paid to the level IV area behind the clavicle to ensure that no thoracic duct leak is present, reflected by excessive lymph fluid. If present, tissues are re-ligated and fibrin glue or similar can be placed. Platysma is approximated with interrupted absorbable suture, and the skin is closed in a subcuticular fashion. Surgical drains in the lateral neck are typically removed as an outpatient, depending on quality and quantity of output.

Suggested Readings

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Primary Hyperparathyroidism

Shkala Karzai, MD, and Jason D. Prescott, MD, PhD

BACKGROUND

Normocalcemia is critical to physiologic function, and adaptive feedback mechanisms have thus evolved to maintain normal body calcium levels. The most specific of these is mediated by the parathyroid glands, which are four small (20–40 mg) organs situated in the neck, adjacent to the thyroid gland (Fig. 1). The function of these glands is to actively maintain normocalcemia by producing parathyroid hormone, an 84–amino acid polypeptide that acts to increase body calcium levels. Under normal circumstances, parathyroid hormone production and thus parathyroid gland activity is actively titrated to blood calcium concentration.

The most common pathology involving the parathyroid glands is primary hyperparathyroidism, which is characterized by adenomatous, hyperplastic, or, rarely, malignant parathyroid gland growth, with concomitant loss of gland regulatory control. This results in chronic blood parathyroid hormone level elevation and, consequently, hypercalcemia, both of which can disrupt normal physiologic function and produce end organ damage.

DIAGNOSIS

The diagnosis of primary hyperparathyroidism is biochemical, depending on coincident frank or inappropriately elevated blood calcium and parathyroid hormone levels. Although parathyroid imaging plays an important role in preoperative planning and intraoperative decision making, imaging is not used to establish diagnosis. Physical examination may reveal an associated neck mass, especially in cases of parathyroid carcinoma, although neck inspection/palpation is unremarkable in the majority of cases. It is critical to distinguish primary hyperparathyroidism (intrinsic parathyroid dysfunction) from secondary hyperparathyroidism (physiologic blood parathyroid hormone elevation) (Box 1). This distinction is not always straightforward, as associated biochemical testing may be equivocal. Physiologically, blood calcium and parathyroid hormone levels are inversely related, with low blood calcium levels inducing compensatory blood parathyroid hormone level elevation (secondary hyperparathyroidism) and vice versa. Apart from some cases of renal failure–related disease, secondary hyperparathyroidism should be managed medically. Relative loss of this inverted relationship, however, represents primary disease (Table 1). Testing the 24-hour urine calcium level may also reveal hypercalciuria, although normal urine calcium levels do not rule out primary hyperparathyroidism. In contrast, hypocalciuria (24-hour urine calcium levels <100 mg) in the context of normal dietary calcium intake is suggestive of familial hypercalcemic hypocalciuria (FHH), an autosomal dominant condition that does not require surgery.

Indications for Surgery

Parathyroidectomy is the standard of care for management of primary hyperparathyroidism, although not all patients require definitive management. As such, well-established guidelines based on the presence of associated signs and symptoms as well as the potential

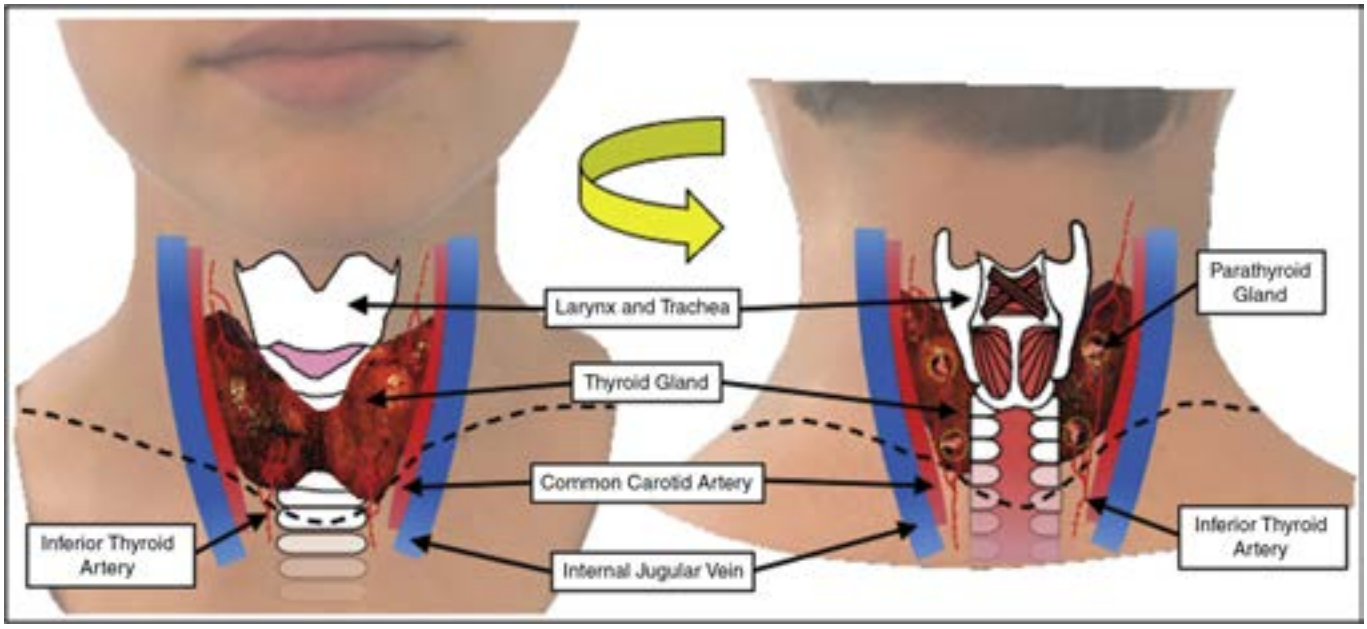


FIG. 1 Normal parathyroid gland localization. The normal anatomic location of the thyroid gland is shown, anterior *(left)* and posterior *(right)*, with associated laryngeal and major vascular structures included, respectively. The four parathyroid glands are shown *(dashed yellow circles)* in their most typical locations, situated adjacent to the posterior surface of the thyroid gland. It is important to note that parathyroid gland localization may be highly variable. The *dashed black line* indicates the position of the clavicle and sternal notch.

BOX 1 Indications for Parathyroidectomy Among Asymptomatic Patients

Estimated glomerular filtration rate <60 mL/minute
Hypercalciuria (24-hour urine calcium level >400 mg)
Nephrolithiasis
Osteoporosis, fragility fracture
Vertebral compression fracture
Blood total calcium level >1 mg/mL above the normal high range value
Age <50 years
Inability to participate in serial follow-up monitoring
Patient preference for surgical management

*Modified from the 2013 Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism Guidelines (see Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014;99[10]:3561–3569).

sequalae of chronic hypercalcemia have been developed (see Box 1). Symptoms of hyperparathyroidism are divided into neurocognitive, musculoskeletal, and gastrointestinal categories and include memory deficits, difficulty concentrating, muscle and joint pain, abdominal pain, heartburn, depressed mood, irritability, and fatigue. Signs of hyperparathyroidism include osteoporosis, pathologic fractures, hypertension, insomnia, nephrolithiasis, kidney dysfunction, constipation, urinary frequency, and pancreatitis. These signs and symptoms are nonspecific, however, and not all patients with this diagnosis develop signs and/or symptoms. Moreover, the severity of signs and symptoms, if present, varies among patients and may not be related to the degree of hypercalcemia/hyperparathyroidism. For these reasons, alternative etiologies for potentially associated signs and symptoms should be carefully considered.

Patients having symptoms attributable to primary hyperparathyroidism should be offered parathyroidectomy as these symptoms usually improve following surgery. Parathyroidectomy is also indicated among asymptomatic patients if any of the following are identified: renal dysfunction (estimated glomerular filtration rate <60 mL/minute), hypercalciuria, nephrolithiasis, osteoporosis, vertebral fracture, blood total calcium >1 mg/mL above the normal high range value, age <50 years, inability to participate in regular follow-up, and patient preference for surgical management (see Box 1). Otherwise, serial monitoring for development of surgical indications is reasonable. Medical intervention for primary hyperparathyroidism, including treatment with calcium-sensing receptor agonists such as cinacalcet (Sensipar), should be reserved for patients who are not operative candidates as current medical interventions are inferior to parathyroidectomy. Parathyroidectomy is curative in up to 98% of primary hyperparathyroidism patients.

Preoperative Considerations

Preoperative planning plays a critical role in successful parathyroidectomy. In particular, localization imaging to identify causative gland(s) facilitates focused surgical exploration, minimizing operative time and the extent of neck exploration, and thus associated complication risk. All preoperative imaging studies should be reviewed collaboratively by the operating surgeon and interpreting radiologist as this facilitates anatomic correlation during surgery. In addition, preoperative assessment for concomitant surgical thyroid disease is critical, as such disease should be addressed at the time of parathyroidectomy. Finally, careful preoperative assessment for an underlying syndromic etiology (e.g., MEN1, MEN2A, jaw tumor syndrome, familial primary hyperparathyroidism) is critical as such syndromic disease requires additional workup for concomitant diagnoses potentially affecting management (in particular, coexistent pheochromocytoma and/or medullary thyroid cancer in cases of MEN2A.) In such cases, appropriate preoperative workup is greatly facilitated by an experienced endocrinologist and/or

TABLE 1 Approximate Biochemical Features of Hyperparathyroidism Subtypes

Blood Total Calcium (Normal 8.5–10.5 mg/dL)	Parathyroid Hormone	25-OH Vitamin D	Diagnosis
>10.5 mg/dL	Elevated or unsuppressed	Normal	Primary hyperparathyroidism
10–10.5 mg/dL	Elevated or unsuppressed	Normal	Probable primary hyperparathyroidism (normocalcemic or normohormonal)
9.5–10 mg/dL	Elevated	Normal	Possible normocalcemic primary hyperparathyroidism
9–9.5 mg/dL	Elevated	Normal or low	Probable secondary hyperparathyroidism
<9 mg/dL	Elevated	Normal or low	Secondary hyperparathyroidism

medical geneticist. We therefore strongly encourage a multidisciplinary approach to parathyroid disease management.

Preoperative Imaging

Neck Ultrasound

All patients for whom parathyroidectomy is planned should undergo formal neck ultrasonography (Fig. 2). Ultrasound is ~80% sensitive for single parathyroid adenoma identification. Sensitivity is dependent on the skill and experience of the operator, however, and decreases for multigland disease. Disease localization also depends on the anatomic domain involved, as ultrasound cannot visualize parathyroid glands located posterior to bony structures, such the clavicles, or air-filled structures, such as the trachea. Parathyroid adenomas generally appear solid, homogenous, hypoechoic, smooth, and, in contrast with cervical lymph nodes, tend to demonstrate internal vascularity when imaged using color Doppler ultrasound. Any thyroid nodules identified by preoperative ultrasound should be categorized using primary malignancy risk criteria (e.g., those established by the Thyroid Imaging Reporting and Data System [TI-RADS] or the American Thyroid Association), and fine-needle aspiration should be performed if indicated. Patients diagnosed with coexistent surgical thyroid disease should undergo thyroid surgery at the time of parathyroidectomy.

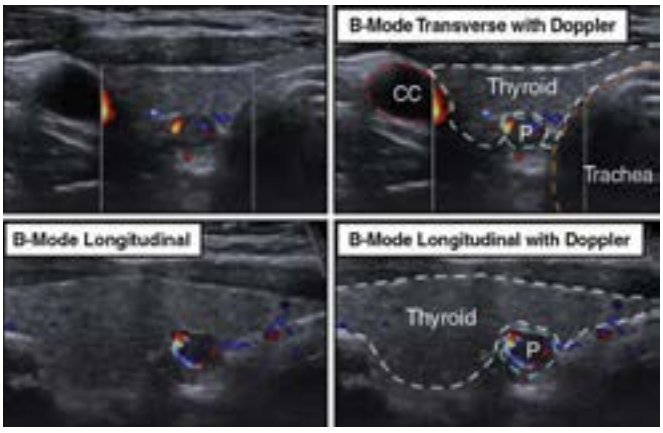


FIG. 2 Thyroid/parathyroid B-mode ultrasound with Doppler enhancement. Transverse *(top row)* and longitudinal *(bottom row)* images are shown. An enlarged parathyroid gland *(P, dashed blue line)* is shown abutting the posterior thyroid surface *(dashed white line)* in the tracheoesophageal groove. The *dashed orange line* shows the trachea. *CC,* Common carotid artery.

Nuclear Scintigraphy/Sestamibi Scanning

Nuclear scintigraphy for parathyroid gland localization is performed with intravenous (IV) technetium-99m (Tc-99m) sestamibi radiotracer (Fig. 3). Both parathyroid and thyroid tissue absorb this tracer, although tracer washout for the thyroid is more rapid than for parathyroid tissue. Thus sequential timed imaging for persistent radiotracer retention (representing parathyroid tissue) is necessary. This includes immediate (5-minute) and delayed (2- to 4-hour) planar imaging, relative to the time of Tc-99m administration. Single photon emission computed tomography (SPECT) imaging can be performed concurrently to allow superimposition of anatomic structures, thus improving localization sensitivity. The sensitivity of nuclear scintigraphic disease localization is similar to that of neck ultrasound. In particular, this modality may be useful in identifying ectopic parathyroid adenomas inaccessible by ultrasound, including ectopic mediastinal/chest and high cervical disease. The quality of nuclear scintigraphy is highly variable, depending on precise image acquisition timing relative to radiotracer administration and on the experience of the interpreting radiologist.

Four-Dimensional Computed Tomography

Four-dimensional computed tomography (4D CT) involves fine-cut four-phase scanning of the neck and upper chest (including noncontrast, arterial, venous, and delayed/washout series in the axial, coronal, and sagittal orientations; Fig. 4). 4D CT is the most sensitive (90%) modality for parathyroid localization and is particularly useful in cases of failed prior exploration or recurrent disease. CT also provides superior anatomic structural information, defining peri-parathyroidal structures, including the thyroid gland, trachea/larynx, esophagus, ipsilateral common carotid artery, ipsilateral internal jugular vein, clavicles, and lung apices. Parathyroid adenomas frequently show early arterial contrast enhancement and early

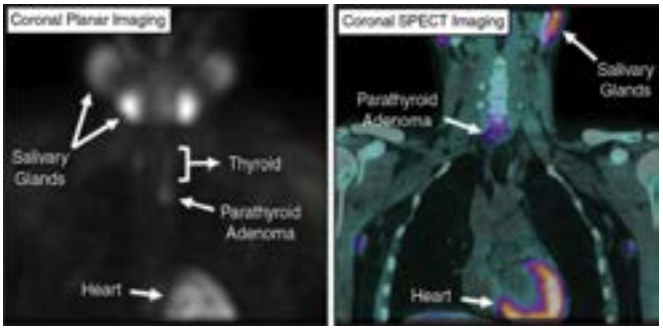


FIG. 3 Nuclear scintigraphy for parathyroid disease localization. Planar *(left)* and SPECT *(right)* examples are shown, each representing a different case. Artifactual tracer uptake is prototypically seen in the salivary glands and heart, as shown.

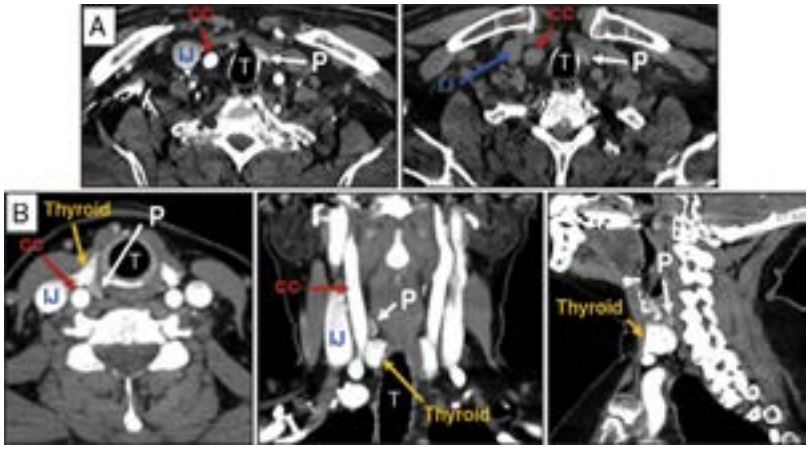


FIG. 4 Four-dimensional CT scan for parathyroid disease localization. Axial arterial and noncontrast images are shown for case A *(top)*. Axial, coronal, and sagittal washout images are shown for case B *(bottom)*. *White arrows* indicate enlarged parathyroid glands *(P)*. The common carotid artery *(CC)*, internal jugular vein *(IJ)*, and trachea *(T)* are shown, where relevant.

contrast washout during the venous phase. On unenhanced images, parathyroid glands appear hypodense relative to the thyroid gland. Despite these imaging features, enlarged parathyroid glands may be difficult to distinguish from benign cervical lymph nodes, which are common and may localize similarly. A small arterial branch of the inferior thyroid artery (see Fig. 1) may be seen supplying a parathyroid adenoma, helping to distinguish a parathyroid gland from a lymph node.

Other Imaging Modalities

Magnetic resonance imaging (MRI), selective venous blood parathyroid hormone level sampling/catheter angiography, and image-guided fine-needle aspiration biopsy with parathyroid hormone washout are additional options for preoperative parathyroid disease localization. In general, these modalities are less sensitive, more expensive, more invasive, and/or require special expertise relative to the first-line studies discussed previously.

We recommend preoperative neck ultrasound and 4D CT scanning for all primary hyperparathyroidism patients planning surgery as we have found this imaging combination to be most predictive of parathyroid disease localization, especially for single gland disease. We have abandoned routine preoperative nuclear scintigraphy-SPECT scanning as progressive improvement in 4D CT scanning protocols has allowed more sensitive and accurate disease localization. We limit MRI, catheter angiography/venous sampling, and image-guided fine-needle aspiration biopsy to special circumstances, including pregnancy (MRI), and to cases for which first-line localization modalities have failed.

PARATHYROIDECTOMY

Surgical Approach

Parathyroidectomy should be performed using as small an incision as possible, generally 3 cm or less (especially if single gland disease is expected). General or regional anesthesia (cervical nerve block) may be employed. Regional anesthesia affords faster recovery in the immediate postoperative period and thus shorter time to hospital discharge as well as improved postoperative nausea. These features reduce overall associated cost and promote efficient clinical workflow. Drawbacks include the need for an experienced anesthesiology team and the potential need for intraprocedural conversion to general anesthesia if unexpected disease complexity/multigland disease, airway concerns, and/or intraoperative patient intolerance is encountered. In addition, traditional technology for intraoperative recurrent laryngeal nerve monitoring cannot be used in the context of regional anesthesia as the associated monitoring circuit requires a specialized endotracheal tube electrode. Given these factors, with particular emphasis on regular use of real-time intraoperative recurrent laryngeal nerve monitoring and our experience of relatively high multigland disease rates (~35%), we use general anesthesia whenever possible. Long- and intermediate-acting neuromuscular blockers/paralytics commonly used for general anesthesia (e.g., rocuronium, vecuronium) must be avoided as such agents will interfere with recurrent laryngeal nerve monitoring. Induction doses of short-acting neuromuscular blockers like succinylcholine (paralytic effect 4–6 minutes) may be used during intubation without such interference. Parathyroidectomy is a "clean" surgery (does not access inherently unsterile body compartments); thus perioperative antibiotic administration is contraindicated. Whenever possible, preoperative therapeutic dose anticoagulation and antiplatelet therapy should be suspended preoperatively to minimize the potential risk of postoperative expanding neck hematoma.

The overwhelming majority of expert parathyroid surgeons use intraoperative blood parathyroid hormone level testing to guide intraoperative decision making, and this testing is standard for all parathyroid surgeries performed by our group. Following anesthesia induction, large-bore intravenous access may be established for blood sample acquisition. Alternatively, samples may be obtained from the surgical field, most commonly from the internal or external jugular veins or from accessible individual peripheral veins (we usually prefer superficial foot veins). A baseline blood parathyroid hormone level should be obtained preoperatively on the day of surgery. The arms are then tucked to facilitate operative field access, and the patient is positioned in the semi-Fowler position. The patient's head is then gently extended by placing a shoulder roll behind the neck, assuming this maneuver is not precluded by concomitant cervical spine disease. Wide sterile skin prepping is then performed to include the upper chest, the bilateral anterior and lateral neck, and the chin, mandibles, and earlobes. Sterile drapes are placed, leaving these anatomic zones visible during surgery (Fig. 5A).

A transverse Kocher incision is then made in the anterior neck. To facilitate favorable cosmetic outcomes, this incision should be as small as possible, should lie within a preexisting skin crease, and should be symmetric and made as inferiorly as possible (to blend with the natural neck irregularity created by the clavicles and be readily hidden by clothing). The superficial subcutaneous tissues, including the platysma, are then divided using electrocautery, and subplatysmal flaps are raised. The superior flap is dissected to the level of the cricoid cartilage, and the inferior flap is raised to the

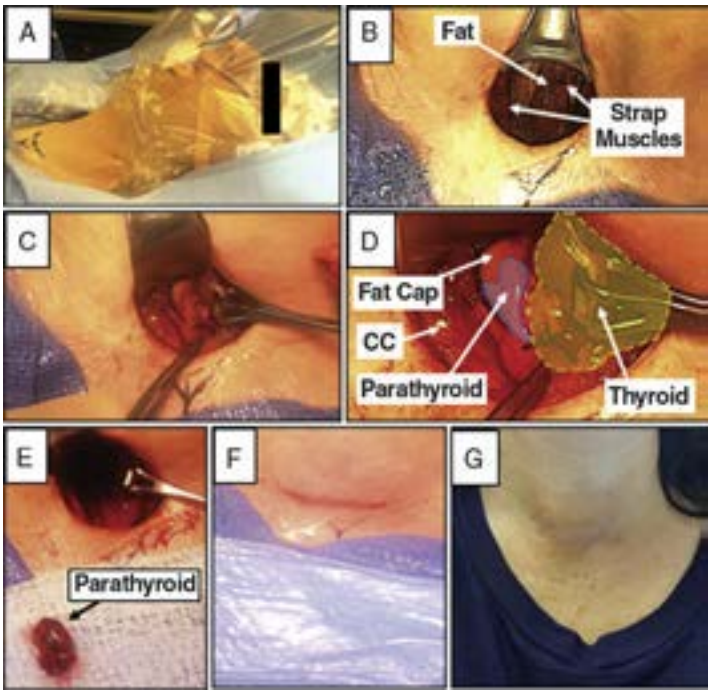


FIG. 5 Parathyroidectomy operative sequence. **(A)** Pre-incision positioning following sterile prepping and draping. **(B)** Operative field view following subplatysmal flap creation. The longitudinally coursing strap muscles are shown (the sternohyoid anteriorly), with interposed fat between these muscles in the midline, anterior to the underlying thyroid gland. (**C** and **D)** Magnified view of tracheoesophageal groove exploration. The strap muscle is retracted laterally to expose the right thyroid lobe *(area outlined in yellow),* which is retracted medially using a Babcock clamp. This exposes the posterior adjacent parathyroid adenoma *(area outlined in blue)* and associated fat cap, which are rotated anteromedially with the right thyroid lobe. The right recurrent laryngeal nerve is not visualized. **(E)** Resected parathyroid adenoma. **(F)**Closed incision. **(G)** Healed incision 17 days postoperatively.

level of the sternal notch. The associated external jugular veins are generally preserved during flap creation, although these may be ligated if significant bleeding is encountered. The midline raphe between the exposed strap muscles (coursing longitudinally, Fig. 5B) is then incised, and the strap muscle ipsilateral to the expected causative gland is dissected from the underlying thyroid lobe. This allows lateral retraction of the strap muscle and sequential thyroid lobe exposure. Associated thyroidal blood supply should be ligated mechanically and/or with vessel-sealing technology to minimize the risk of postoperative bleeding. The dissection plane should be maintained at the thyroid capsule to facilitate identification and preservation of normal parathyroid tissue and the ipsilateral recurrent laryngeal nerve. As dissection proceeds, the thyroid gland is rotated medially and anteriorly using a finger or an atraumatic clamp (Fig. 5C, D), which allows progressive exposure of the tracheoesophageal groove.

The tracheoesophageal groove is then carefully explored. All dissected tissue is carefully assessed for the presence of the recurrent laryngeal nerve and for normal parathyroid tissue, both of which must be assiduously preserved. A detailed understanding of this anatomy is thus critical. Once identified, the enlarged parathyroid gland (Fig. 5C, D) is carefully dissected away from the surrounding tissue. This dissection should be performed at the level of the parathyroid capsule, with care taken to identify the recurrent laryngeal nerve, which may be in close proximity to the enlarged gland. The surgeon should also avoid damaging the abnormal parathyroid gland capsule as this may result in spillage of parathyroid cells into the operative field, with subsequent implantation and recurrence (parathyromatosis). We also request routine intraoperative specimen frozen-section analysis to verify specimen tissue identity and gland enlargement by weight.

Following excision of a single enlarged parathyroid gland (Fig. 5E), we pause our dissection for intraoperative blood parathyroid hormone level testing (although deferring such testing in favor of exploring the remaining parathyroid glands remains an alternative option if preoperative localization imaging is negative or if four-gland disease is anticipated). This intraoperative testing uses sequential decrement in blood parathyroid hormone level to estimate probability of surgical cure on the basis of in vivo parathyroid hormone metabolism kinetics (blood hormone half-life 3–5 minutes). In our practice, we use a modified version of the standard Miami criteria to estimate surgical cure on the basis of intraoperative blood parathyroid hormone level testing. Specifically, this involves blood sampling before incision on the day of surgery ("baseline"), at the time of abnormal gland excision ("time zero"), and 10 minutes, 20 minutes and 30 minutes later. We have found surgical cure rates to be near 100% when: (1) intraoperative blood parathyroid hormone levels fall by at least 50% relative to the baseline or time zero value (whichever is higher) at 10 minutes following abnormal gland excision and (2) the remaining parathyroid gland function is suppressed (blood parathyroid hormone trends down to <35 pg/mL). Failure to meet these criteria indicates additional parathyroid disease, and exploration is consequently continued, with repeat intraoperative blood testing performed sequentially following each subsequent enlarged parathyroid gland excision. Normal parathyroid glands identified during sequential dissection should be left in situ on their native vascular pedicles. If the identity of a parathyroid gland is unclear, a small fragment of this tissue may be sharpy resected (with care taken to avoid compromising the gland's blood supply) for intraoperative frozen-section analysis.

When four-gland disease is encountered or expected (as in familial forms of primary hyperparathyroidism), subtotal parathyroidectomy or total parathyroidectomy with autotransplantation should be performed. Subtotal parathyroidectomy involves resecting all but a normal volume of viable parathyroid tissue, which is left in situ on the tissue's native vascular pedicle. Associated bilateral neck

exploration may require a longer surgical incision, although we are often able to accomplish this using the same incision length planned for single-gland disease. After resecting three enlarged parathyroid glands, we place a large titanium hemoclip across the width of the remaining unresected enlarged gland, leaving a normal volume of parathyroid tissue proximal to the clip on an intact vascular pedicle. The tissue distal to the clip is then sharply resected, leaving the clip, a normal volume of parathyroid tissue, and the associated vascular supply intact. We prefer subtotal parathyroidectomy to total parathyroidectomy with autotransplantation, as parathyroid tissue left in situ is more likely to be viable when supplied by its native vascular pedicle, which translates into lower rates of postoperative permanent hypoparathyroidism.

When performing a total parathyroidectomy with autotransplantation, we transplant into the anterior surface of the ipsilateral sternocleidomastoid muscle as this area is readily accessed via the existing cervical incision. In addition, we have not experienced increased technical difficulty or complication rates when reaccessing this site in the rare circumstance of associated disease recurrence. Autotransplantation into the nondominant brachioradialis muscle is an alternative option, although this requires creating a separate operative field. Autotransplantation involves resecting an approximately normal volume of parathyroid tissue, confirmed by frozen-section analysis, and then sharply mincing this tissue into a fine slurry (1- to 2-mm fragments). The ipsilateral sternocleidomastoid muscle is then exposed, and three to four pockets are bluntly dissected into the anterior muscle surface. Equal volumes of parathyroid slurry are then passed into each muscle pocket, which are then closed using nonabsorbable suture. The suture ends are left long to facilitate future reoperative localization, when needed. Autotransplanted parathyroid tissue will survive initially via imbibition but will eventually recruit an independent blood supply. Autotransplanted tissue will not produce adequate parathyroid hormone for the first 2 to 12 weeks postoperatively, and aggressive supplementation with calcium and activated vitamin D such as calcitriol (Rocaltrol) will generally be required to avoid symptomatic hypocalcemia. In some cases, this may require postoperative hospitalization for intravenous calcium gluconate infusion.

Rarely, intraoperative parathyroid hormone levels will not decrease adequately following excision of all identified enlarged glands. This scenario indicates additional disease, representing either unidentified ectopic causative gland(s) or hyperfunctional supernumerary gland(s). Under this circumstance, a thorough sequential bilateral neck exploration is indicated, including exploration of the carotid sheaths, exploration of the paraesophageal and retroesophageal tissues, and, because ectopic parathyroid tissue commonly localizes to the thymus, bilateral transcervical thymectomy. Except in cases of supernumerary disease, laterality will be apparent if both parathyroid glands on the contralateral side have been identified. Otherwise, direct comparison of blood intact parathyroid hormone levels from each internal jugular vein may facilitate lateralization. Finally, intraoperative failure to identify all but one parathyroid gland, despite thorough bilateral neck exploration, may indicate intrathyroidal localization of the remaining abnormal gland. This may be misidentified as a thyroid nodule by preoperative ultrasonography. In this case, we perform a thyroid lobectomy on the side for which the remaining parathyroid gland has not been identified. For this reason, the potential need for thymectomy and/or thyroid lobectomy should be discussed preoperatively with all patients.

Failure of blood parathyroid hormone levels to decrease appropriately is uncommon. When this occurs, however, additional exploration is unlikely to be fruitful. In such cases, we stop our operation, with the understanding that future attempts at disease localization, followed by reoperation, will be necessary. Sternotomy and/or thoracotomy are not indicated without clear preoperative mediastinal disease localization.

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism and is generally associated with very high preoperative blood parathyroid hormone and calcium levels. Intraoperatively, the causative gland is hard/firm in consistency and may be fixed to adjacent tissues, especially the ipsilateral thyroid lobe. Treatment requires en bloc resection of the tumor with neighboring associated tissues, including the ipsilateral thyroid lobe, as well as ipsilateral comprehensive central neck dissection. Preservation of the parathyroid tumor capsule is of paramount importance during dissection as tumor capsule violation may allow seeding of liberated cancer cells in the surgical field, with subsequent development of incurable parathyromatosis.

The operation concludes with careful wound bed inspection for hemostasis, which must be verified to minimize the potential for development of postoperative expanding neck hematoma. Hemostatic agents may be applied for this purpose as well (we coat the operative field with a small volume of fibrinogen-thrombin sealant). Identified normal parathyroid glands should also be assessed for viability. The recurrent laryngeal nerve(s), if identified, should be evaluated for anatomic integrity and, if nerve monitoring is used, for functionality. The strap muscles are then closed vertically, with subsequent transverse closure of the platysma, using absorbable 3-0 suture. The skin is then closured with a 4-0 running absorbable monofilament suture (see Fig. 5F). Care should be taken to appose the dermal edges of the incision to maximize the chance of good cosmetic healing (see Fig. 5G).

Intraoperative Adjuncts and Alternative Surgical Approaches

Recurrent Laryngeal Nerve Monitoring

The recurrent laryngeal nerve on each side of the neck courses in the immediate vicinity of the ipsilateral parathyroid glands, and these nerves are often encountered during parathyroidectomy. Because each nerve innervates all but one of the ipsilateral intrinsic laryngeal muscles, inadvertent injury to these delicate structures results in ipsilateral vocal cord paresis. Depending on the position of the paralyzed cord, associated morbidity may be asymptomatic or may be significant, including hoarseness, subjective shortness of breath, thin liquid aspiration, and, in cases of bilateral nerve injury, possible airway compromise requiring emergent tracheostomy. Recurrent laryngeal nerve monitoring allows real-time intraoperative assessment of nerve function, which translates into improved recognition of nerve injury. This may, in turn, facilitate intraoperative decision making, especially if exploration of the side contralateral to known nerve dysfunction is entertained. In addition, this technology can facilitate intraoperative nerve identification, thus theoretically diminishing nerve injury risk. Specialized equipment (including an endotracheal tube electrode) and surgeon expertise are required for intraoperative nerve monitoring, however. Use of this technology therefore requires general anesthesia and incurs both additional cost and operative complexity.

Gamma Probe–Facilitated Intraoperative Parathyroid Disease Localization

As is the case for preoperative parathyroid disease localization by nuclear scintigraphy, technetium (^{99}TC) sestamibi may also be employed for intraoperative identification of hyperfunctional parathyroid glands. Specifically, a handheld radioisotope (gamma) probe can be used during surgery to guide intraoperative parathyroid exploration following preoperative ^{99}TC sestamibi injection. This technique has largely been abandoned, however, as the associated specificity is often confounded by background signal originating from normal thyroid tissue, which also absorbs technetium.

Parathyroid Autofluorescence Detection

Parathyroid tissue is known to produce autofluorescence when exposed to excitation wavelengths in the near-infrared range. This has led to recent development of technology for detection of this autofluorescence, with one potential application being improvement in

identification of hyperfunctional parathyroid glands during parathyroidectomy. Intraoperative autofluorescence detection necessitates specialized equipment, however, and currently requires operative exposure, or near exposure, of the autofluorescing gland(s). For these reasons, this new technology has not yet demonstrated incremental value during parathyroid surgery relative to traditional disease localization strategies, and it has not been generally adopted by expert parathyroid surgeons.

Alternative Surgical Approaches to the Parathyroid Glands

In the context of ongoing interest in surgical technology/technique development and the relative importance of optimal postoperative cosmesis (complete avoidance of a surgical scar) for some patients, surgical approaches to parathyroidectomy that avoid a neck incision have been developed. These include transaxillo-breast, postauricular (facelift), and, most recently, transoral vestibular parathyroidectomy approaches, all of which allow complete avoidance of a neck scar. In general, these techniques do not afford the same potential for neck exploration inherent to the traditional approach and thus should be limited to cases of well-localized single-gland disease. In addition, these techniques are associated with potential complications not otherwise encountered during parathyroidectomy, including brachial plexus (transaxillo-breast), marginal mandibular nerve (facelift), and mental nerve (transoral) injuries. For these reasons, alternative approach parathyroid surgery should be reserved for patients who are highly motivated to avoid a neck incision scar and should be performed by surgeons with experience in one or more of these techniques.

OPERATIVE COMPLICATIONS

Significant complications associated with parathyroid surgery include recurrent laryngeal nerve injury, described earlier, permanent hypoparathyroidism, and expanding neck hematoma. Overall, risk is related to extent of neck exploration, with complication rates of approximately 4% for bilateral neck surgery and between 1% and 3% for focused/unilateral exploration. Permanent hypoparathyroidism and airway compromise potentially requiring emergent tracheostomy are only associated with bilateral neck exploration as these morbidities require injury to bilateral structures (all four parathyroid glands or both recurrent laryngeal nerves, respectively).

Recurrent laryngeal nerve dysfunction and associated symptoms related to nerve compression, traction, or minor thermal injury are usually self-limited, with spontaneous nerve recovery usually within 6 months of surgery. Vocal fold paresis resulting from recurrent laryngeal nerve transection is permanent, however, and cannot be restored by nerve reconstruction (although end-to-end nerve reconstruction should be performed whenever possible to minimize subsequent laryngeal muscle atrophy). Formal laryngeal evaluation should be performed postoperatively if the recurrent laryngeal nerve is injured or if injury is suspected.

Temporary hypoparathyroidism is common after parathyroidectomy (20%–30% of cases) as resumption of normal synthetic function by remaining normal parathyroid tissue may take several days. In contrast, inadvertent damage to or resection of all parathyroid tissue or a failed autotransplantation following total parathyroidectomy results in permanent hypoparathyroidism. Related signs and symptoms include perioral and/or distal extremity paresthesias and muscle spasms/cramps. Tetany and/or seizures may occur in cases of severe hypocalcemia, usually in the context of severe permanent hypoparathyroidism. Blood calcium levels should be assessed if symptoms develop, and oral calcium carbonate supplementation should be titrated to improve associated symptoms/blood calcium levels. Calcium citrate should be used in cases of previous gastric surgery or low stomach acidity as calcium carbonate is not readily absorbed in this context. Vitamin D plays a crucial role in calcium homeostasis and is required for normal intestinal calcium absorption. Supplementation with oral vitamin D should be initiated in combination with calcium supplementation if blood levels are low. Intravenous calcium gluconate is required if severe hypocalcemia is encountered (blood total calcium <7 mg/dL).

Postoperative expanding neck hematoma is a rare but serious complication of parathyroid surgery. This is generally characterized by rapid neck swelling followed by tachypnea, anxiety, and progressive airway compromise. Any evidence of expanding neck hematoma postoperatively should be interpreted as a surgical emergency. This should prompt immediate opening of the surgical wound at the bedside/in the emergency department for clot evacuation followed by surgical wound bed exploration for hemostasis in the operating room.

POSTOPERATIVE CONSIDERATIONS

We assess blood parathyroid hormone, total calcium levels, and vitamin D levels during the routine postoperative office visit, usually 2 to 4 weeks following surgery. The blood parathyroid hormone levels may be mildly elevated at this time in the context of normal or low normal blood total calcium levels. This is almost always the result of vitamin D deficiency and relative postoperative hypocalcemia, and it resolves with oral vitamin D and calcium supplementation. We reassess these blood values again at 6 months postsurgery to verify surgical cure. Recurrent primary hyperparathyroidism will develop in up to 2% of these patients, and for this reason, blood total calcium levels should be assessed annually.

SUGGESTED READINGS

Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3561–3569.

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Persistent and Recurrent Hyperparathyroidism

Aditya S. Shirali, MD, and Nancy D. Perrier, MD

Persistent hyperparathyroidism (HPT) is defined by elevation of serum calcium (and parathyroid hormone [PTH] in the event of eucalcemic hyperparathyroidism) within 6 months after parathyroidectomy. Recurrent hyperparathyroidism is defined as the existence of eucalcemia at 6 months and then the development of hypercalcemia and/or elevated PTH afterward. This chapter will address management in the reoperative setting. The etiology of persistent and recurrent HPT, diagnosis and surgical indications for reoperation, preoperative evaluation, and surgical techniques will be discussed.

ETIOLOGY

Persistent HPT occurs at a rate of 1% to 6% and recurrent HPT from 2.5% to 15%. The most common causes of persistent disease are a missed gland or unrecognized multigland disease. Other less common causes include incomplete resection (i.e., a dumbbell-shaped gland), implantation of disease from a ruptured parathyroid cyst (parathyromatosis), or parathyroid carcinoma (Fig. 1). In cases of a missed gland, it is not uncommon to have removal of a gland, albeit not the autonomous hyperactive gland. Anatomically, missed hyperfunctional glands are most commonly located deep in the tracheoesophageal groove or posterior to the thyroid gland tethered within the capsule. Glands deep within the tracheoesophageal groove are superior glands that fall from a vascular pedicle lateral to the recurrent laryngeal nerve (RLN). On a more rare occasion, superior glands can be located in the retropharyngeal space. Alternatively, large inferior glands may fall into the thymus or superior mediastinum. Inferior glands can be undescended and in the high submandibular region or even within the thyroid parenchyma. Because most missed abnormal parathyroid glands, however, are found in the usual anatomic locations, the surgeon should have a thorough knowledge and understanding of the anatomy and embryology of the cervical and mediastinal regions.

The most common cause of recurrent HPT is multigland disease. Multigland disease may occur sporadically or in patients with familial disease, such as Multiple Endocrine Neoplasia (MEN) Types 1, 2A, and 4. Recognizing familial disease preoperatively informs the correct operation, which is not single gland removal, and management of future endocrinopathies.

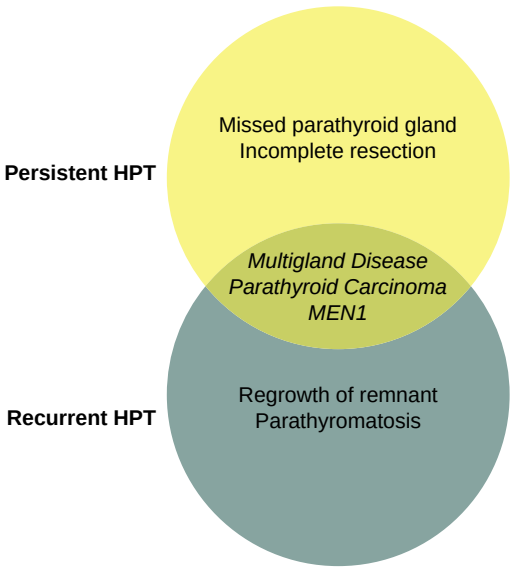


FIG. 1 Causes of persistent and recurrent hyperparathyroidism (HPT). Patients with suspected multigland disease or parathyroid carcinoma may present with either persistent or recurrent hyperparathyroidism. *MEN1*, Multiple endocrine neoplasia, type 1.

DIAGNOSIS AND INDICATIONS FOR REOPERATIVE PARATHYROIDECTOMY

The evaluation of suspected persistent or recurrent HPT is initiated with confirming the biochemical diagnosis of HPT with serum calcium, PTH, 25-hydroxy vitamin D, creatinine, and phosphorus. Hypercalcemia with a concomitant inappropriately elevated PTH confirms the diagnosis. Eucalcemia with only elevated PTH may be due to hungry bone syndrome, vitamin D deficiency, or renal failure. It is imperative to rule these out as potential confounders. In addition, thiazide diuretics, sarcoidosis, hypercortisolism, multiple myeloma, and other causes of hypercalcemia should be reconsidered when an elevation in PTH is not identified. A 24-hour urinary calcium level measurement also should be performed to exclude familial hypocalciuric hypercalcemia (FHH) to avoid unnecessary reoperation. A young patient should raise the suspicion of MEN syndromes and familial endocrinopathies, such as familial isolated HPT, and one should have a low threshold for referral to genetic counseling in the reoperative setting.

The decision to reoperate should consider the risks and benefits, symptoms and disease severity, the etiology of persistent or recurrent disease, and the likelihood of achieving cure and relief of the patient's symptoms. In general, reoperative parathyroidectomy should be considered for patients with a failed initial operation, for symptomatic HPT patients, and those with progressive decline in end organ disease (i.e., osteoporosis or worsening kidney function).

EVALUATION

After the diagnosis of persistent or recurrent HPT is rendered, the most important next step is determination of single or multigland disease. This can be deciphered through a thorough review of biochemical trends and prior operative and pathology reports.

Review of prior pathology reports is the most important aspect of care. Gross and histologic review of all tissue removed, number of specimens, degree of hypercellularity, size and weight of the glands, and the presence of thyroid parenchyma, lymph nodes, and fat should be performed. Preferably, or if there is any uncertainty about the histopathologic diagnosis, the slides from the initial operation should be reviewed. Next, operative reports should be meticulously read to determine the number of glands visualized and the reported appearance and number of glands presumed to have been resected. Deciphering whether clips were placed or biopsies performed and the identification of the RLN are critical. Correlating the operative reports with pathologic confirmation of hypercellular parathyroid tissue is critical to discern single-gland versus multigland disease. For example, a pathology report that shows no evidence of hypercellular parathyroid tissue in the resected specimen(s) is more likely to suggest missed single-gland disease than the operation that involved resection of two parathyroid glands found to be hypercellular upon histologic review.

Once the reoperative surgeon has a better understanding of the cause of persistent or recurrent HPT, repeat localization studies

should be performed. For reoperative parathyroidectomy for a suspected missed single gland, a minimum of two concordant imaging studies is required for proper operative planning. This allows for planning of a directed and targeted operation. Cervical ultrasonography, technetium (^{99}Tc) sestamibi-single photon emission computed tomography/computed tomography (sestamibi-SPECT/CT), and four-dimensional multidetector computed tomography (4D-CT) are the preferred initial imaging modalities for reoperative cases. Growing evidence in Europe has identified ^{11}C-choline and ^{18}F-fluorocholine positron emission tomography (PET)/CT as attractive second-line imaging studies for localization.

The most important aspect of imaging is that the surgeon understands the techniques and strengths and weaknesses of each study at their institution. Although nuclear medicine and anatomic cross-sectional imaging can be combined, having a well-synchronized team of collaborating radiologists and nuclear medicine experts working together is the most important aspect of care. In addition, interpretation of negative studies can be as helpful as positive studies. For example, if a missed gland is in the thymus, one would expect the ultrasound to be negative because that modality cannot adequately visualize behind the sternum.

For suspected multigland disease requiring reoperation, we do not routinely advocate for multiple imaging modalities in patients because a bilateral approach is warranted, and intraoperative inspection should identify enlarged glands. Nuclear medicine studies are not reliable in multigland disease because radiotracer uptake may not be seen in all hyperfunctioning glands. Furthermore, asymmetric enlargement of glands is common in multigland disease, and anatomic imaging is frequently less sensitive in identifying small glands and thus adds little benefit to operative planning.

LOCALIZATION STUDIES

A review of several common localization studies follows:

Ultrasonography plays a key role because of its cost effectiveness and added benefit of identifying any concomitant thyroid pathology. Imaging from the submandibular region cephalad to the clavicles caudally is completed with Doppler imaging to assess the vascularity of any suspicious lesions and inform the surgeon of the location of the vascular pedicle. A fine-needle aspiration (FNA) biopsy of a suspicious lesion, whether extra- or intrathyroidal, can be obtained at the time of ultrasound and sent for both cytologic confirmation and PTH biochemical assay. Cytologic assessment of intrathyroidal parathyroid lesions may inaccurately be read as indeterminate follicular lesions, highlighting the importance of the PTH biochemical assay to cytologic interpretation. The combination of cytologic and biochemical confirmation improves the accuracy of ultrasonography alone from 65% to more than 80% and the sensitivity from 75% to 90%.

4D-CT is a powerful modality for identifying missed parathyroid glands, especially those in undescended positions (Fig. 2). The

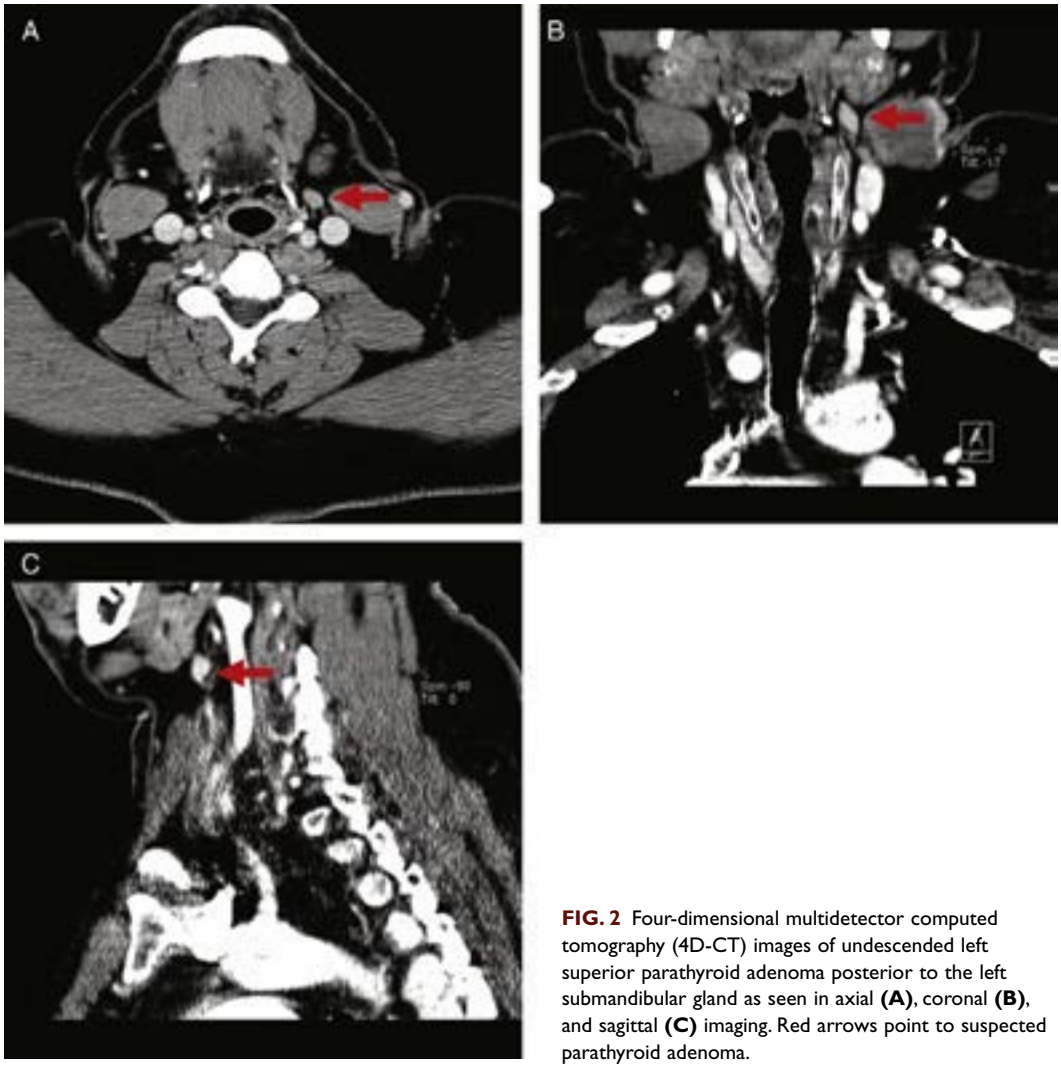


FIG. 2 Four-dimensional multidetector computed tomography (4D-CT) images of undescended left superior parathyroid adenoma posterior to the left submandibular gland as seen in axial **(A)**, coronal **(B)**, and sagittal **(C)** imaging. Red arrows point to suspected parathyroid adenoma.

study should include multiple views from the jaw to the aortic arch and with arterial and delayed enhancement phases. 4D-CT allows visualization of differences in perfusion characteristics between hyperfunctioning parathyroid glands (i.e., rapid uptake and quick washout) and normal parathyroid glands and other structures in the neck. This single study provides both anatomic information and a correlation for function (perfusion). 4D-CT has a sensitivity of over 90% in identifying single-gland disease initially with recent studies showing a sensitivity greater than 75% in recurrent or persistent HPT compared with less than 50% for sestamibi and ultrasound alone. Having experienced radiologists engaged and using common terminology in these interpretations is pivotal to the success of the reoperative parathyroid surgeon.

The use of ^{11}C-choline and ^{18}F-fluorocholine PET/CT, previously used for detection of recurrent prostate cancer, has shown promise in providing parathyroid adenoma localization. The study combines the use of these specific radiotracer injections and PET from the skull base to the upper thighs with dedicated arterial-enhanced CT of the neck to provide the true functional component missing in 4D-CT imaging. Several small studies have shown sensitivity and specificity for parathyroid localization greater than 90%. One recent study by Christakis et al. examined its use in persistent/recurrent primary hyperparathyroidism (PHPT) with negative first-line localization studies and identified cure in 58% of patients. Further studies examining its utility in persistent/recurrent PHPT are necessary.

Historically, invasive methods to differentiate laterality based on the discrepancy of PTH drawn from the cervical veins were previously a modality of discussion. In the era of enhanced imaging, this practice has gone out of favor. It serves as mere lateralization, is less specific, and fails to provide sufficient information for directed resections. Selective venous sampling (SVS) involves catheterization of the internal jugular and multiple veins in the neck and mediastinum. We do not advocate routine use of this invasive study due to alteration of the venous drainage pattern from previous neck operations or thyroid lobectomy that may obscure localization, high risk of technical failure, and rare operative complications (such as bleeding, infection, pseudoaneurysm, and arteriovenous fistula). More importantly, the use of new imaging modalities, such as PET/CT with ^{11}C-choline or ^{18}F-fluorocholine, and FNA of suspicious targets with PTH aspirate, may actually be more specific.

PLANNING AND RISK ASSESSMENT

After diagnosis of persistent or recurrent HPT, appropriate indications for surgery are met, the etiology of persistent or recurrent HPT is identified, and localization is attempted by preoperative imaging, the surgeon must next consider the patient's functional status, comorbidities, any sequelae of previous neck operations, and anesthetic risks when weighing the risks and benefits of reoperative parathyroidectomy (Fig. 3; Box 1). Compared with initial surgery, reoperative surgery is associated with more operative complications due to scarring and fibrosis from the previous operation as well as potential devascularization and inadvertent removal of remaining parathyroid glands.

Preoperative planning for a reoperation should involve reviewing previous operative imaging, operative reports, and pathology reports. Surgeons should identify whether a unilateral or bilateral exploration was performed, the location and number of parathyroid glands that were identified, whether biopsies or clips were placed by suspicious parathyroid glands, and whether resection of the thyrothymic tract was performed. Furthermore, the operative report should be reviewed for concerning thyroid pathology, such as Hashimoto's thyroiditis or multinodular goiter, that may further complicate the dissection and/or necessitate concomitant thyroidectomy.

Reoperations are associated with a greater incidence of vocal cord paralysis, with a RLN injury rate of approximately 2% to 15% (compared with 0.5% to 1% in initial operations). The patient should be considered to undergo videostroboscopy to assess function of their vocal cords and the RLN integrity before consideration for reoperation. Unilateral RLN paralysis may already be present yet unnoticed, especially if the length of time between the initial operation and recurrence has been extensive. This information may influence use of intraoperative adjuncts. If there is a documented unilateral RLN injury, the risks and benefits of reoperation on the contralateral side must be considered and the implications of possible bilateral RLN palsy should be explicitly discussed with the patient.

The surgeon must have a clear understanding of the viability of the remaining parathyroid glands. Prior knowledge of which parathyroid glands were explored, and thus potentially devascularized, and which glands were biopsied and/or clipped will help the surgeon develop a strategy to prevent postoperative hypoparathyroidism, which may be permanent in 10% to 16% of patients. This is especially important in patients undergoing subtotal parathyroidectomy, as leaving a devascularized remnant will place the patient at high risk for permanent hypoparathyroidism. If the suspected diseased gland is the only viable parathyroid gland, autotransplantation should be considered. Patients should be counseled about the risks of future repeat hyperfunction of autotransplanted tissue and need for future debulking of the autograft. Patients must also be counseled about the risk for aparathyroidism, particularly in the setting of previous four-gland exploration with resection or devascularization of multiple glands. The exact number of functioning parathyroid glands is impossible to know preoperatively, and thus the surgeon should always keep immediate or delayed autotransplantation in their armamentarium during reoperative parathyroidectomy.

Cryopreservation involves removing confirmed parathyroid tissue from the neck at the time of surgery, dicing of tissue to increase surface area, preservation with Tis-U-Sol solution, and freezing at −80°C for later autotransplantation. Cryopreservation of parathyroid tissue is a tedious process that requires adequate planning and appropriate storage techniques for the possibility, but low probability, of future autotransplantation. Furthermore, this practice may have legal and ethical ramifications involving the storage, destruction, or use of tissue for research purposes. In addition, there is a significant cost to processing and storage of cryopreserved tissue. Most institutions have abandoned the practice of routine cryopreservation as the utilization of cryopreserved tissue is low and delayed autografts were found to be functional in only 50% to 60% of patients. In contrast, the success rate for fresh parathyroid autografts has been reported to exceed 80%. For this reason, in patients who have already had multiple glands removed, autotransplantation at the time of gland removal is an ideal option. Transplantation into the ipsilateral pectoralis major muscle (already in the surgical field and without overlying fat) or the nondominant brachioradialis muscle at the time of reoperative surgery are both good options. These sites are preferred over the sternocleidomastoid to avoid reoperative neck surgery in the event the patient experiences persistent or recurrent disease due to the autotransplanted tissue. The brachioradialis position also affords future discernment of the source of PTH because comparative venous samples can be obtained in each arm, denoting large gradients from systemic versus local production.

Intrathyroidal and retroesophageal parathyroid glands are rarely encountered. However, patients found with these lesions may require thyroid lobectomy or retroesophageal dissection, respectively. Patients should be counseled regarding the potential development of hypothyroidism, especially in the setting of preexisting Hashimoto's thyroiditis, and requirement of lifelong thyroid supplementation. Patients requiring retroesophageal dissection in a reoperative field should be counseled regarding risks of postoperative dysphagia and the small, but present, risk of esophageal injury and leak.

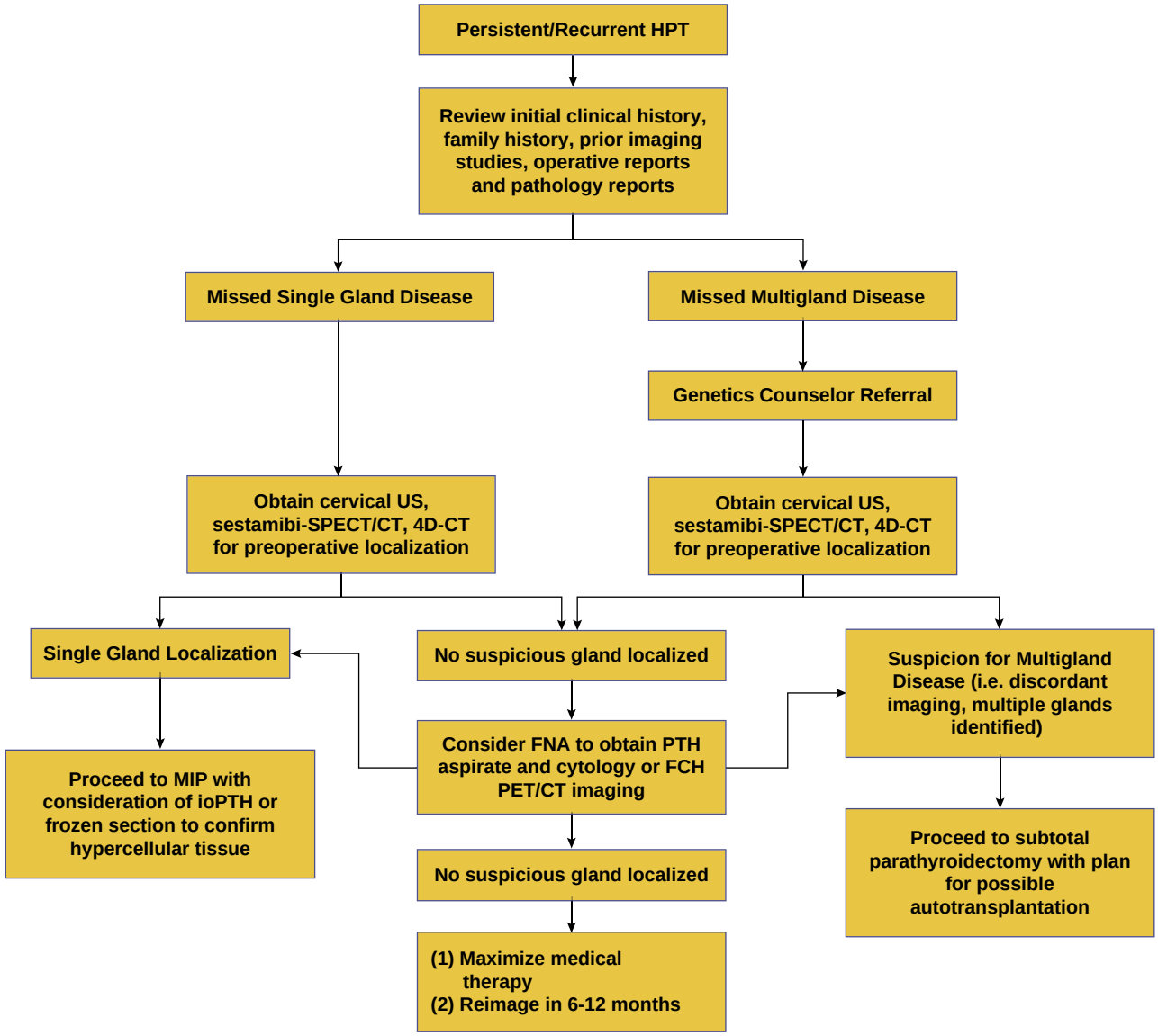


FIG. 3 Algorithm for managing persistent or recurrent hyperparathyroidism (HPT). *4D-CT,* four-dimensional multidetector computed tomography; *FCH PET/CT*, ^{18}F-fluorocholine positron emission tomography/computed tomography; *FNA*, fine-needle aspiration; *MIP*, minimally invasive parathyroidectomy; *sestamibi-SPECT/CT,* sestamibi-single photon emission computed tomography/computed tomography; *US*, ultrasonography.

BOX 1 Indications for Reoperative Parathyroidectomy in Persistent or Recurrent PHPT

- Worsening hypercalcemia refractory of medical management
- Worsening bone mass
- Ongoing nephrolithiasis
- Progressive renal dysfunction
- Associated neuromuscular and neurocognitive symptoms

OPERATIVE TECHNIQUE

Reoperation for persistent or recurrent HPT can be hindered significantly by fibrosis, loss of normal anatomic planes, and anatomic modifications that resulted from the initial operation. Thus, the endocrine surgeon must have a clear operative plan to avoid risks of hypoparathyroidism or injury to the RLN and surrounding structures. The surgeon must use their understanding of the etiology of disease (i.e., missed single-gland disease versus multigland disease), preoperative localization studies, prior operative reports, and documentation of vocal cord mobility to guide decision making. If parathyroid carcinoma is suspected, a metastatic workup for distant disease should be obtained before operative intervention and the operative plan should include en bloc resection with ipsilateral thyroid lobectomy. If parathyromatosis is the cause, the surgeon should expect multiple implants of tissue in the prior cervical region. Intraoperative ultrasound can help to localize and guide complete resection, which can be tedious as the parathyroid tissue implants into muscle and fat.

Critical to the technical success of reoperative parathyroidectomy for benign etiology is a thorough knowledge of the embryology and anatomy of parathyroid disease. This knowledge combined with preoperative localization studies and descriptions of parathyroid location in previous operative reports can help guide operative approach. A nomenclature system proposed by Perrier and colleagues (2009) classifies parathyroid glands as types A through G, with the recent

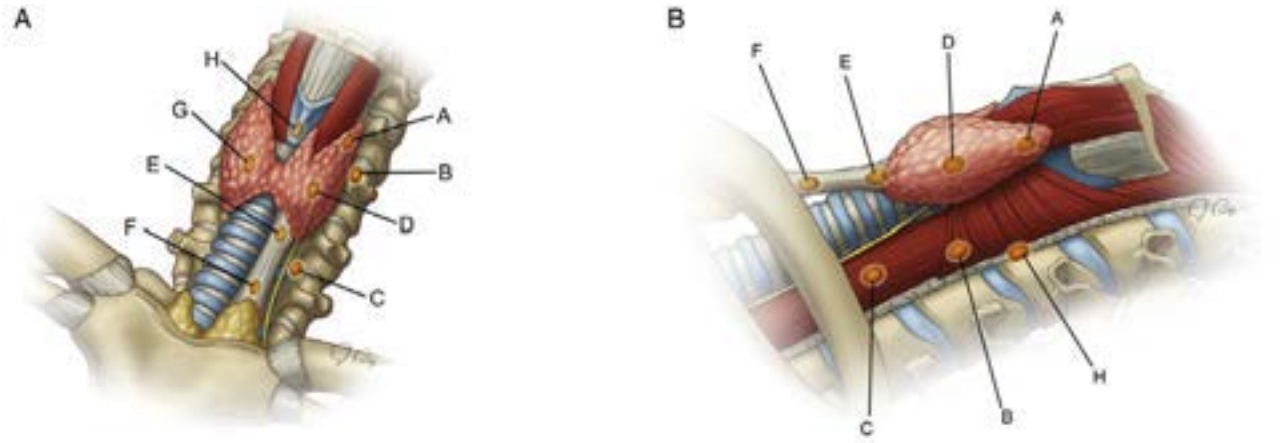


FIG. 4 The position of type A to H glands in the nomenclature system of Perrier and colleagues. Types A, B, C, and H glands are superior glands, and types E, F, and G glands are inferior glands. Type D glands may be either superior or inferior glands with determination made intraoperatively based on the location of the vascular pedicle in relation to the recurrent laryngeal nerve. Illustrations of coronal **(A)** and sagittal **(B)** views.

addition of type H glands in the retroesophageal position (Fig. 4). This nomenclature system emphasizes the anterior-posterior location of enlarged parathyroid glands in relation to the thyroid parenchyma, trachea, and esophagus. Types A, B, and C represent superior parathyroid glands that are usually found on a vascular pedicle that is lateral and posterior to the RLN; when adenomatous, these glands may fall posterior to the thyroid tissue (A) or into the tracheoesophageal groove (B and C). Glands that are derived embryologically from the inferior pedicle are classified as type E or F glands; the pedicles of these glands are medial and slightly more anterior to the RLN. Type D glands are found overlying the RLN. Types G and H are infrequently encountered and are found either intrathyroidal or posterior to the esophagus in the midline, respectively. A thorough understanding of these positions in relation to adequate localization may help the parathyroid surgeon determine an operative approach.

The focused lateral approach is a good option for missed single-gland disease (adenomas) located in a superior or posterior position, or A, B, C, D, or H types of Perrier's nomenclature. This approach is an excellent option in reoperative cases to avoid scar tissue in the central compartment of the neck if the initial operation used a central approach. A 2- to 3-cm horizontal incision is made at the level of the adenoma, extending from the midline to the anterior border of the sternocleidomastoid muscle. The plane between the sternocleidomastoid and the strap muscles is entered with blunt dissection, the carotid sheath is visualized and carefully retracted laterally, while the thyroid lobe and the strap muscles are retracted medially (Fig. 5), exposing posterior to the thyroid, the tracheoesophageal groove and the retroesophageal position.

The focused central anterior approach is ideal for missed single inferior parathyroid glands (types E, F, and G) that may require excision of the thyrothymic tract or thyroid lobectomy. This approach, which requires a cervical collar incision, involves separation (not division) of the strap muscles in the median raphe and a midline-initiated approach. It has obvious disadvantages if previously used in the initial operation but nevertheless provides a direct route to inferior parathyroid glands without having to "cross" the RLN. Furthermore, this approach is ideally suited for patients with suspected multigland disease who require bilateral cervical exploration and subtotal parathyroidectomy. These patients, in particular, are at risk for hypoparathyroidism given concern for devascularization during their initial operation. Every effort should be made to avoid aggressive dissection, clip application, and biopsy of normal-appearing glands to prevent inadvertent devascularization.

Most parathyroid glands located in the superior mediastinum can be removed via a transcervical approach by gentle manipulation and retraction of the ipsilateral thymic tissue with the help of digital dissection and the use of a right-angle instrument. In rare cases in which the parathyroid gland is located inferiorly in the mediastinum, the use of video-assisted thoracoscopy in combination with a thoracic surgical colleague can prevent the need for a sternotomy to excise the gland. This procedure should only be performed in the presence of concordant preoperative localization studies.

In patients undergoing reoperative parathyroidectomy with concern for devascularization of multiple glands, consideration should be made for immediate autotransplantation into the ipsilateral pectoralis major muscle. We prefer to use the pectoralis major muscle just inferior to the clavicle as a site for autotransplantation in patients without a familial endocrinopathy. Patients with familial endocrinopathies may undergo autotransplantation in the nondominant brachioradialis muscle to help guide localization of recurrence by laboratory assessment. Creating a single pocket in the region immediately below the clavicle where there is the least amount of subcutaneous fat allows for easy access (Fig. 6). The area is on the surgical field and, if contained with a clip, the pocket can be opened on the morning after the operation and tissue easily evacuated after confirmation of detectable and robust PTH, confirming viable tissue elsewhere. This is an easy but important "insurance policy" to prevent against aparathyroidism. If on the morning after the operation the PTH is undetectable, suggestive of no viable intact parathyroid tissue, the autotransplanted tissue can be left in place to grow and vascularize. It usually requires 4 to 6 months for the tissue to be robust enough for detectable PTH to become apparent on blood draws and for the patient to be weaned from calcium supplementation.

The following operative adjuncts may be used in the reoperative setting:

1. **Intraoperative Neurophysiological Monitoring**
   Intraoperative neurophysiologic monitoring (IONM) in reoperative parathyroid surgery may be useful to confirm nerve function during dissection in the event of contralateral nerve injury confirmed by videostroboscopy. Surgeons must be well-versed in the use of IONM before its use for this indication to avoid false positives or negatives that may result in further unnecessary dissection.
2. **Intraoperative PTH Aspirate**
   Frozen section analysis is always used to confirm the identity of abnormal removed parathyroid glands before cessation of

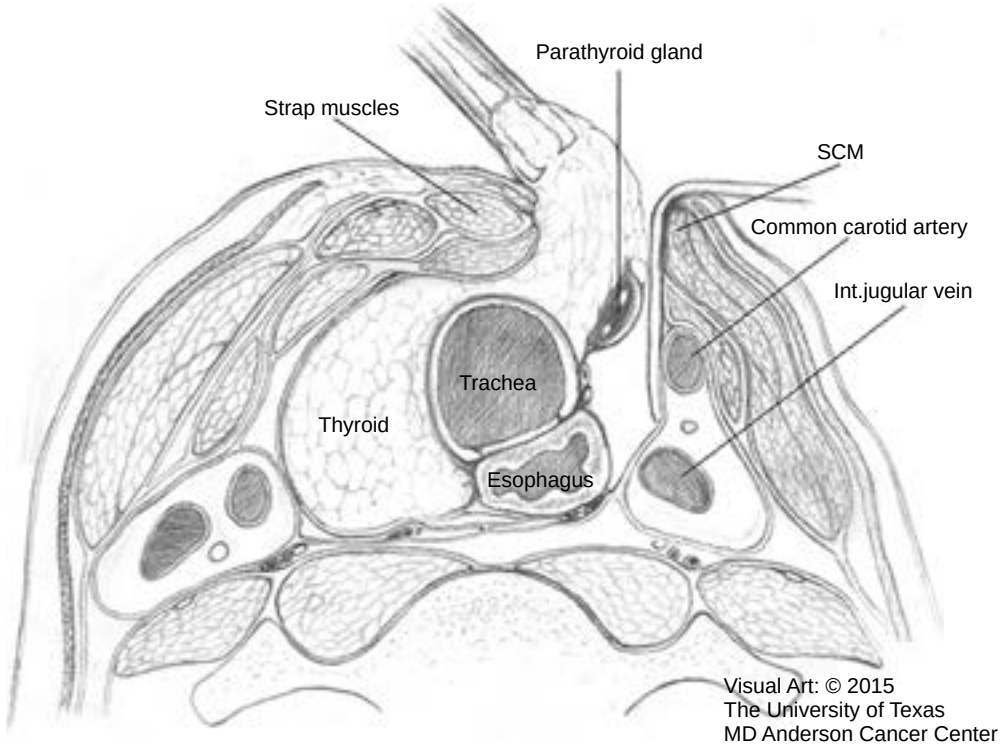


FIG. 5 Cross-sectional drawing of the cervical region undergoing a focused lateral approach. Dissection is performed lateral to the strap muscles for a minimally invasive parathyroidectomy. Retracting the thyroid lobe superiorly and medially allows the identification of a left type A gland attached to the undersurface of the left thyroid parenchyma. *Int. jugular vein*, internal jugular vein; *SCM*, sternocleidomastoid muscle.

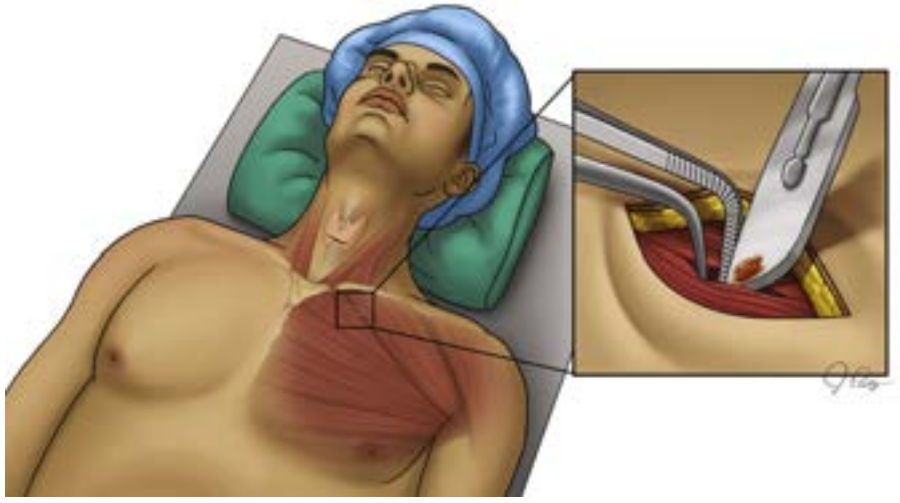


FIG. 6 Illustration of pectoralis major muscle autotransplantation. The transplanted gland is placed in a small pocket of the pectoralis major muscle through a mini-incision.

surgery. In addition to histologic confirmation, direct aspiration of the suspected gland may be useful for biochemical confirmation. PTH values greater than the upper limit of normal (1900 pg/mL with the Roche assay) confirm that the tissue is of parathyroid origin, although this does not confirm cellularity; hence aspiration of the gland for PTH measurement can be a useful tool to complement histologic evaluation.

3. **Intraoperative Ultrasonography**
Intraoperative ultrasonography can facilitate incision placement in patients with ectopic glands. After the patient is anesthetized and in position, an on-the-table ultrasonographic examination is performed to identify and confirm the location of the gland.

POSTOPERATIVE MANAGEMENT

The postoperative management for reoperative parathyroidectomy is similar to that of initial parathyroidectomy. In general, serum calcium and PTH levels are obtained on the evening of the procedure and the morning of the first postoperative day to detect hypocalcemia. A detectable PTH level ensures viability of residual parathyroid gland function. In our practice, prophylactic calcium supplementation is not routinely performed. Oral calcium and vitamin D supplementation is given in the presence of clinical symptoms of hypocalcemia, if the serum calcium levels falls below 7.5 mg/dL, or the PTH level falls below 5 pg/mL. If the serum calcium level is lower than 7.0 mg/dL, we administer intravenous calcium gluconate and bridge to oral supplementation of calcium and possible calcitriol until calcium levels have normalized. Interpretation of the biochemistry along with the clinical status of the patient should drive the decisions regarding hospital discharge. Before discharge, patients are thoroughly educated regarding signs and symptoms of hypocalcemia and are sent home with appropriate calcium supplementation, if indicated.

Patients who undergo pectoralis muscle autotransplantation, as discussed earlier, will undergo removal of the autograft in the event of a detectable and normal PTH on postoperative day one. Patients who undergo brachioradialis autotransplantation should be educated regarding future venous blood draws for assessment of PTH and should undergo bilateral venous blood draws to determine function of the autograft.

After discharge, the patient returns for laboratory analysis including serum calcium and PTH at 2 weeks postoperatively and again at 6 months postoperatively to ensure cure. If the indication for surgery was osteopenia or osteoporosis, a repeat bone mineral density study is obtained 18 months following successful cure. Given the reoperative nature, patients are thoroughly educated and screened for potential voice changes and referred for videostroboscopy if there is any concern for RLN palsy.

CONCLUSION

Reoperative parathyroidectomy is complex. Before considering reoperative surgery, the surgeon must determine the etiology of persistent or recurrent HPT and indications for reoperation, and then must weigh these against the risks of reoperation. The focused lateral approach offers an attractive operative strategy for missed single-gland disease to avoid a previous scarred cervical incision. Patients with missed multigland disease require safe subtotal parathyroidectomy with creation of a healthy viable remnant.

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Surgical Management of Secondary and Tertiary Hyperparathyroidism

Zeyad T. Sahli, MD, and Martha A. Zeiger, MD

INTRODUCTION

Hyperparathyroidism (HPT) is defined as the hypersecretion of parathyroid hormone (PTH) from one or more parathyroid glands. This results in an imbalance in serum calcium levels that are maintained through a regulatory axis consisting of the parathyroid glands, PTH, membrane calcium receptors, kidneys, the gastrointestinal tract, and bone. **Secondary HPT** is defined as a compensatory increase in PTH secretion due to a nonparathyroid cause of calcium dysregulation and **hypocalcemia** (Box 1). This occurs most commonly or "secondary" to chronic kidney disease (CKD) with up to 90% of renal failure patients developing the disease by the time hemodialysis is required. Secondary HPT can also be caused by decreased calcium intake, decreased calcium absorption, renal calcium losses, or secondary to phosphate replacement therapy in bone metabolism disorders. Decreased calcium absorption can be due to vitamin D deficiency or gastrointestinal malabsorption due to chronic pancreatitis, small bowel disease, or malabsorption-dependent bariatric surgery. Other causes include long-term lithium therapy and bone metabolism disorders.

Tertiary HPT refers to the autonomous hypersecretion of PTH after successful correction of the primary reason for secondary HPT (e.g., CKD). Up to 30% of renal transplant recipients with secondary HPT are at risk of developing tertiary HPT. In contrast to secondary HPT, the patients are **hypercalcemic**.

PATHOPHYSIOLOGY

Secondary HPT develops after chronic parathyroid gland stimulation from hypocalcemia, hyperphosphatemia, and reduced renal production of 1,25-dehydroxy vitamin D. This constellation of factors results in PTH hypersecretion and parathyroid cell proliferation among all four glands. The pathophysiology of secondary HPT due to CKD is summarized in Figure 1. CKD patients have been shown to have an increase in fibroblast growth factor 23 (FGF23) due to hyperphosphatemia. FGF23, secreted by osteocytes, and alpha Klotho, its obligate coreceptor, induce phosphaturia and inhibit renal production of 1,25-dehydroxy vitamin D. Moreover, CKD patients also exhibit decreased expression of calcium-sensing receptor (CaSR) in parathyroid cells as well as bone resistance to PTH due to diminished expression of the PTH receptor in osteoblasts. In turn, these events lead to hypocalcemia and resulting stimulation of the parathyroid glands. When left untreated, changes such as decreased extracellular calcium-sensing and monoclonal expansion of parathyroid cells may cause further derangement in calcium metabolism, leading to tertiary HPT.

Classically, tertiary HPT develops among end-stage renal disease (ESRD) patients with chronic secondary HPT after renal transplantation. Within 1 year of successful renal transplantation, PTH hypersecretion, hypercalcemia, and hypophosphatemia will resolve in the majority of patients with secondary HPT. In tertiary HPT, the hypertrophied parathyroid glands will continue to autonomously hypersecrete PTH resulting in hypercalcemia, even after correction of the primary disorder.

BOX 1 Signs and Symptoms of Hyperparathyroidism

- Fatigue/mental status changes
- Renal calculi
- Proximal muscle pain
- Bone pain
  - Due to osteitis fibrosa cystica, mainly affecting weight-bearing joints including hips, knees, ankles, and lower back
- Joint pain
  - Joint inflammation due to periarticular calcium deposits
- Bone fracture
  - Atraumatic fractures or nonhealing of fractures
- Pruritus
- Calciphylaxis
  - Results in expanding, painful, cutaneous, purpuric lesions that cause tissue calcification and ischemic necrosis, which lead to dry gangrene if untreated

CLINICAL PRESENTATION

Physicians should maintain a high level of suspicion for the diagnosis of HPT when evaluating patients with renal failure (see Box 1). Patient symptoms include fatigue, changes in mental status, nephrolithiasis, proximal muscle pain, skeletal abnormalities, bone and joint pain, pathologic fractures, pruritis, and calciphylaxis. Skeletal abnormalities and bone pain are due to renal osteodystrophy, hyperphosphatemia, and hypercalcemia. More severe symptoms due to HPT occur at PTH levels greater than 1000 pg/mL. Calciphylaxis or calcific uremic arteriolopathy, wherein calcium accumulates in small vessels of fat and skin, can be found in patients with renal failure involving subcutaneous vascular calcification and cutaneous necrosis (Fig. 2). This sign is indicative of severe HPT and its often-fatal sequelae. Parathyroidectomy (PTX) should be offered as it can enhance wound healing.

DIAGNOSIS

The diagnosis of secondary and tertiary HPT is made biochemically (Table 1). Because the vast majority of CKD patients have some degree of HPT, there is no unique presentation for secondary HPT, and most diagnoses are made during routine laboratory testing to monitor CKD patients. Serum levels of PTH, calcium, phosphorus, and 25-hydroxyvitamin D should be measured. Patients with secondary HPT exhibit low to normal calcium levels and elevated PTH. Serum phosphorus level is dependent on the secondary HPT etiology. CKD patients will tend to have hyperphosphatemia, whereas patients with secondary HPT due to vitamin D deficiency will have hypophosphatemia. Levels of bone metabolic markers, including total alkaline phosphatase and osteocalcin, will be elevated. Unlike secondary HPT associated with hypocalcemia, in addition to hypercalcemia, patients with tertiary HPT also exhibit hypophosphatemia.

MEDICAL MANAGEMENT

Although no global consensus for treatment has been established, the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease Mineral Bone Disease (CKD-MBD) guideline is considered the leading resource for the treatment of secondary and tertiary HPT in the United States. Medical management is the mainstay of mild secondary HPT, whereas tertiary HPT is treated surgically. Primarily, calcium and vitamin D or vitamin D analogues supplementation can be used to slow the progression of secondary HPT until the patient can undergo a renal transplant. Other treatment options include calcimimetics and phosphate binders. Currently, there are two FDA-approved calcimimetics: cinacalcet and etelcalcetide.

Approved by the FDA in March 2004, cinacalcet is an oral calcimimetic that functions by allosteric activation of the calcium-sensing surface receptor expressed by parathyroid gland chief

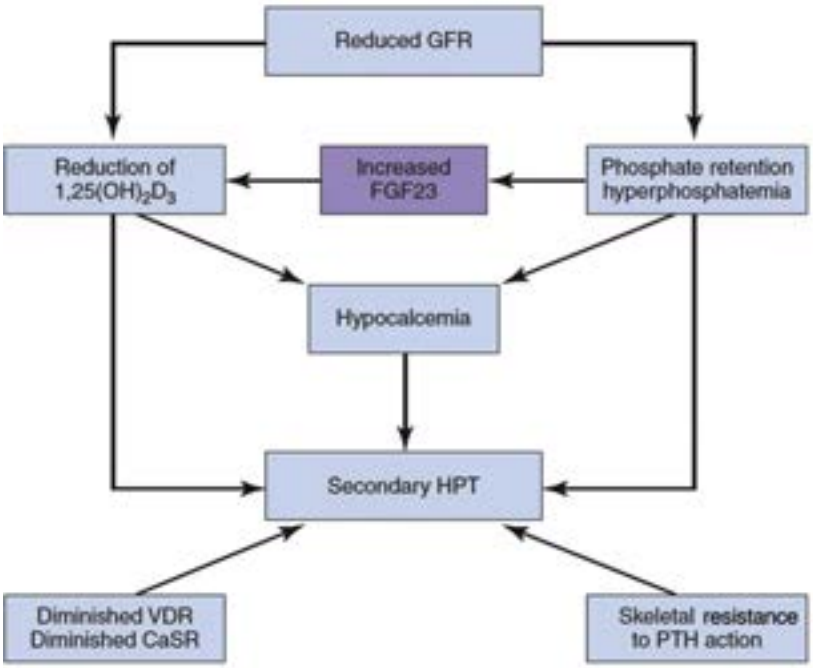


FIG. 1 Pathogenesis of secondary hyperparathyroidism due to chronic kidney disease. *GFR*, Glomerular filtration rate; *FGF*, fibroblast growth factor; *HPT*, hyperparathyroidism; *VDR*, vitamin D receptor; *CaSR*, calcium-sensing receptor; *PTH*, parathyroid hormone. *(From Tominaga, Y. Surgery of the Thyroid and Parathyroid Glands, 3rd ed, Philadelphia: Elsevier; 2021.)*



FIG. 2 **(A)** Calciphylaxis showing cutaneous purpuritic lesions and ischemic necrosis on the leg. **(B)** Calciphylaxis of the lower abdomen in a patient with chronic renal failure demonstrating skin necrosis. *(A from Bolognia, J. Dermatology, 4th ed, Philadelphia: Elsevier; 2018. B courtesy Fitzsimons Army Medical Center teaching files.)*

TABLE 1 Secondary versus Tertiary HPT Biochemical Profile

	Secondary HPT	Tertiary HPT
Calcium	Low to normal	Elevated
PTH	Elevated	Elevated
Serum Phosphorus	Elevated	Elevated
Vitamin D	Low	Low to normal

cells, resulting in reduced PTH production. The randomized trial Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) found that CKD patients treated with cinacalcet were less likely to develop severe progression of secondary HPT, although cinacalcet did not reduce the risk of all-cause and cardiovascular mortality. Cinacalcet treatment has also been reported to be associated with a significant reduction in the risk of needing PTX, fracture, and cardiovascular hospitalization compared with placebo. Moreover, its long-term effect on patients or allograft survival appears to be safe and effective for the treatment of post-transplant HPT, though no randomized clinical trials examining this have been performed.

In 2017, the FDA approved etelcalcetide, an intravenous calcimimetic, for the management of secondary HPT in hemodialysis patients. Etelcalcetide is administered intravenously three times per week at the end of each dialysis session. A double-blind, randomized clinical phase III trial by Block et al. found that etelcalcetide was superior to cinacalcet in achieving a more than 30% reduction in mean predialysis PTH concentrations. Further studies are needed to evaluate the effect of etelcalcetide on the progression of HPT and need for surgery.

PARATHYROIDECTOMY

Despite the initial medical management of secondary HPT, PTX is required in approximately 20% of patients after 3 to 10 years of dialysis and up to 40% after 20 years. The goals of parathyroid surgery include the immediate reduction in PTH levels, long-term symptomatic relief, and end organ improvement. Due to the lack of randomized clinical trial data, indications for and timing of PTX vary greatly among experts.

ANATOMY

A thorough understanding of the anatomy is essential to safely perform the surgery (Fig. 3). The four parathyroid glands descend from the third and fourth pharyngeal pouches. The two inferior parathyroid glands and thymus originate from the third pharyngeal pouch, while the two superior parathyroid glands originate from the fourth pharyngeal pouch. Due to the longer descent of the inferior parathyroid glands, their anatomical location is more variable compared with the superior parathyroid glands. It should be noted that the inferior parathyroid glands lie ventral to the recurrent laryngeal nerve (RLN), while the superior glands lie dorsal to the RLN (Fig. 4). The four glands are vascularized by the left and right inferior thyroid arteries. There are usually four parathyroid glands. However, it has been reported that 1% to 3% of patients have only three identifiable glands, and 2% to 13% of individuals have supernumerary parathyroid glands. Parathyroid glands are yellow-brown, flat, and oval-shaped tissue that normally weigh approximately 30 to 35 mg each.

INDICATIONS FOR SURGERY

Secondary HPT

Recommendations regarding the guidelines for PTX in secondary HPT patients differ geographically and lack a clear consensus. As a general rule, all symptomatic HPT patients or those who failed medical management should be considered surgical candidates (Box 2). The National Kidney Foundation recommends PTX in patients with a PTH greater than 800 pg/mL associated with hypercalcemia and/or hyperphosphatemia refractory to medical therapy as an indication for surgery. However, the Kidney Disease: Improving Global Outcomes Group recommends a PTH target threshold for treatment nine times above the upper limit of normal for the PTH assay (585 pg/mL).

Among asymptomatic patients, consensus among experts regarding indications for PTX is also inconsistent. PTX patient selection must be individualized based on age, comorbidities, and risk-benefit evaluation. Younger patients (<65 years) with little comorbidity are more likely to tolerate surgery and benefit over the long term. The benefits of PTX have been documented in observational studies and

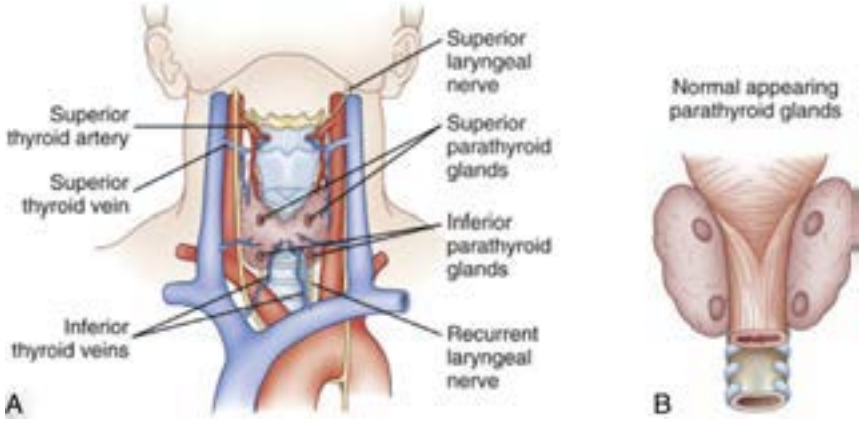


FIG. 3 Anatomy of parathyroid glands. *(From Miller FR, Netterville JL. Surgical management of thyroid and parathyroid disorders.* Med Clin North Am. *1999;83[1]:247, Fig. 1.)*

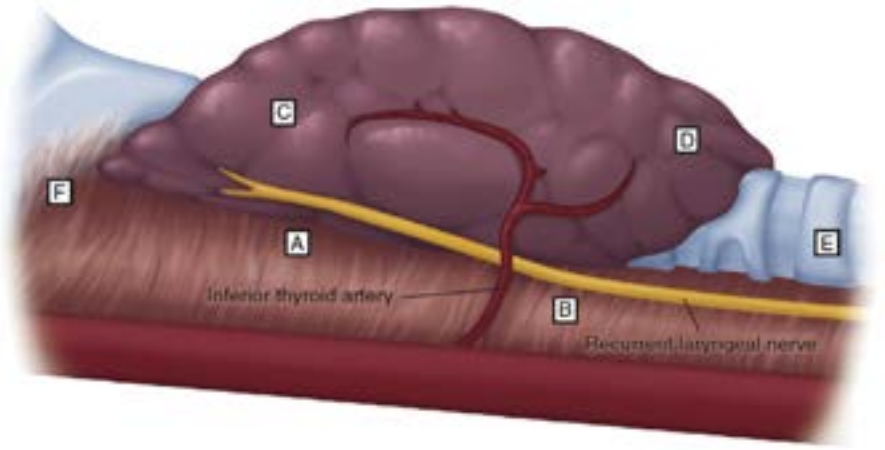


FIG. 4 Location of parathyroid glands. *A,* The superior glands are most frequently located superior to crossing point of the inferior thyroid artery and recurrent laryngeal nerve (RLN) and dorsal to the RLN. *B,* The inferior parathyroid gland most frequently is located inferior to the artery-nerve crossing point and lies ventral relative to the RLN. *(From Tominaga, Y.* Surgery of the Thyroid and Parathyroid Glands, *3rd ed, Philadephia: Elsevier; 2021.)*

include a reduction of 10% to 37% in mortality, 33% to 41% in cardiovascular risk, and 32% in fracture risk, as well as improvements in peripheral arterial disease, quality of life, erythropoietin-resistant anemia, nutritional status, and humoral and cellular immunity.

Tertiary HPT

Despite the potentially high incidence of tertiary HPT, PTX is performed in less than 10% of renal transplant recipients who harbor this disorder after 1 year of surgery but should be considered the standard of care and recommended to all. Indications for surgical management among patients with tertiary HPT include those who are symptomatic, have persistent or severe hypercalcemia, or osteoporosis (see Box 2).

PREOPERATIVE MANAGEMENT

Patient risk assessment and counseling is recommended before operative management for the selection of appropriate surgical candidates. Risk assessment is especially important among ESRD patients who may have comorbidities, such as coronary artery disease, heart failure, myocardial infarction, hypertension, stroke, anemia, uremic coagulopathy, pulmonary disease, and general debility, which may prevent safe surgery. Moreover, patients with calciphylaxis may develop unique complications including peripheral vascular disease and wound sepsis, potentially requiring revascularization procedures or wound debridement, respectively. When scheduling surgery, the surgeon should coordinate with the patient's nephrologist or dialysis center to arrange for dialysis one day before surgery and to avoid unnecessary delay on the day of surgery caused by conditions such as hyperkalemia. Although renal transplant patients are commonly healthier than patients with ESRD, their immune system is medically suppressed, which may increase the risk of postoperative complications.

Despite the involvement of all four parathyroid glands in secondary and tertiary HPT, the authors still recommend preoperative localization studies to localize ectopic glands. The importance of preoperative imaging among secondary/tertiary HPT patients is highlighted because 32% of recurrent or persistent cases are due to supernumerary glands. We recommend the use of ^{99}Tc-Sestamibi scans or 4D scans. Similar to any patient undergoing parathyroid surgery, a thyroid ultrasound should also be performed to exclude any concerning thyroid nodules. There is, however, a lack of consensus among experts for the use of preoperative localization imaging before initial surgery in patients with secondary or tertiary HPT. Opponents of preoperative imaging have argued that preoperative imaging is not sensitive in localizing ectopic glands and that imaging

BOX 2 Adult Parathyroidectomy Indications for Secondary versus Tertiary HPT

Secondary HPT Indications

- Calciphylaxis
- Patient preference
- Medical observation not possible
- Symptoms due to hyperparathyroidism
- Failure of maximal medical management with:
  - Hypercalcemia
  - Hypercalcuria
  - PTH >800 pg/mL
  - Hyperphosphatemia (with calcium × phosphorus >70)

Tertiary HPT

- Severe hypercalcemia (serum calcium >12.5 mg/dL)
- Persistent hypercalcemia
  - Serum calcium >10.2 mg/dL more than 3 months after surgery
- Osteoporosis
- Symptomatic hyperparathyroidism

will not change operative management since a bilateral exploration is warranted. On the other hand, advocates of preoperative imaging argue that ultrasound examination may identify concurrent abnormalities in the thyroid gland that may require further evaluation or simultaneous surgical management. Furthermore, preoperative imaging may localize an ectopic gland within the chest that may require a different surgical approach.

Before reoperation, vocal cord visualization should be performed by laryngoscopy among patients with a history of thyroidectomy, PTX, carotid endarterectomy, or cervical spine surgery to exclude prior RLN injury. In secondary or tertiary HPT patients undergoing reexploration, preoperative imaging is strongly recommended among experts.

EXTENT OF SURGERY

Surgical options for secondary and tertiary HPT patients include sub- or near-total PTX and total PTX with or without heterotopic autotransplantation. Subtotal PTX is the resection of three (or more, if supernumerary glands are present) glands and subtotal resection of a fourth gland, with preservation of a viable, histologically confirmed remnant, approximately the size of a normal gland. A total PTX with a heterotopic autotransplantation removes all parathyroid glands, including supernumerary if present, that can be identified and autotransplants a small portion of a gland to a new, nonanatomic site such as the neck, chest, or forearm.

Published literature regarding the recommended extent of surgery in both secondary and tertiary HPT is inconsistent. For this reason, the decision regarding extent of surgery is largely dependent on surgeon preference in addition to several other factors, including whether the surgery is primary or reoperative and whether the patient has an existing or planned renal transplant. The extent of surgery should be weighed according to the advantages and disadvantages of each procedure. A 2019 meta-analysis of 3656 patients comparing subtotal PTX with total PTX with autotransplantation found no significant differences between symptomatic improvement, hypocalcemia rate, persistence rate, time to recurrence, recurrence rate, and reoperation rate. Significantly longer operative time and patient length of stay (LOS) were observed in patients who underwent total PTX with autotransplantation compared with those who underwent subtotal PTX. However, patients with a relative contraindication for future neck surgery due to prior history of repeated neck surgery, known RLN injury, or significant medical comorbidities should undergo a total PTX with autotransplantation to facilitate access to the gland in case of recurrent HPT.

Total PTX without autotransplantation has been reported to prevent recurrence more effectively than with autotransplantation. However, it also has the highest risk of hypoparathyroidism postoperatively among the three procedures. Patients anticipating a kidney transplant should avoid undergoing total PTX without autotransplantation.

Targeted PTX is not commonly performed among patients with secondary or tertiary HPT but can be considered in patients with recurrent HPT or in post–renal-transplant patients with single or double adenomas, reported in up to 29% among post–renal-transplant patients. However, this may be associated with an increased risk of recurrence. Currently, debate exists regarding the need for a prophylactic thymectomy. Thymectomy should be performed, however, during the search for a missing inferior parathyroid gland or supernumerary glands.

SURGICAL TECHNIQUE

The common steps of these procedures are detailed in Box 3 and Figure 2. General anesthesia is used for most patients undergoing PTX with bilateral neck exploration. However, local or regional anesthesia has also been described in patients deemed too high risk for general anesthesia. The RLN should be identified and preserved during the entire course of the procedure. After identification of the parathyroid glands, care should be taken to avoid biopsy, capsular rupture, or fragmentation of the glands to prevent parathyromatosis.

If the surgeon fails to identify four parathyroid glands on bilateral exploration, then a search for the missing gland is warranted. Ectopic parathyroid glands are shown in Figure 3 and can be found in the tracheoesophageal groove, retroesophageal, paratracheal, carotid sheath, intrathyroidal, mediastinal, and thymus. All suspected parathyroid glands resected should be confirmed on frozen section.

Intraoperative PTH Monitoring

The PTH half-life in patients with normal renal function is 2.2 minutes, whereas that of ESRD patients is 6.6 minutes. Due to the partial

BOX 3 Parathyroidectomy Steps

1. The patient is placed in a supine position with the neck hyperextended by placing a head ring under the patient's head. Potential sites of auto transplantation should be exposed and prepped.
2. A standard Kocher incision measuring 3 to 5 cm should be made through skin and platysma.
3. Superior and inferior flaps should be created in usual fashion to thyroid cartilage superiorly, sternal notch inferiorly.
4. Strap muscles are divided longitudinally in the midline and retracted.
5. All four parathyroid glands should be exposed after a bilateral neck exploration.
6. If four parathyroid glands cannot be identified, then a search for the ectopic gland is warranted in the tracheoesophageal groove, retroesophageal, undescended paratracheal, carotid sheath, intrathyroidal, mediastinal, or thymus.
7. If indicated, create an autograft to implant in neck, chest, or forearm.

renal metabolism of PTH, an intraoperative PTH monitoring protocol, such as the Miami criteria in cases of primary HPT, to confirm treatment has not been established in patients with secondary or tertiary HPT. Despite this, intraoperative PTH level measurements are commonly used. Multiple studies in the literature have used various time periods, PTH thresholds, or PTH level decline from baseline to predict cure in these patients. A lack of consensus remains regarding how to monitor PTH intraoperatively, but its use has been shown to be beneficial. These include a recommended range of decline of 50% to 90% at anywhere between 10 to 30 minutes after PTX as a reliable predictor of postoperative cure.

Creating a Parathyroid Remnant

During subtotal PTX, the parathyroid remnant should be created before resection of other glands to monitor its viability throughout the operation. The parathyroid remnant should be approximately 50 to 100 mg and preferably an inferior parathyroid gland remnant. This would leave the remnant in a relatively easily accessible position and away from the RLN should the patient require reoperation. Marking the remnant with a titanium clip or nonabsorbable suture facilitates its localization in the event of a reoperation.

Creating an Autograft

The process of creating an autograft is described in Box 4. A recent technique includes injecting a suspension of parathyroid tissue fragments into a muscle with a syringe. There is no consensus regarding the optimal site for grafting. Potential autotransplantation sites include the neck, chest, or forearm subcutaneously or intramuscularly. Implantation and resection of subcutaneous parathyroid autografts is simpler to perform than intramuscular procedures. Regardless of implantation sites, parathyroid fragments often infiltrate surrounding tissues, which may make resection of all foci challenging. In cases of recurrent HPT among patients with a history of total PTX with autotransplantation, the surgeon must have a high level of suspicion about the presence of an additional cervical gland, complicating the picture of recurrent HPT.

We recommend implanting the autograft in the nondominant forearm brachioradialis muscle or subcutaneously due to its relatively easy access under local anesthesia for reexploration. We also recommend that the implanted arm not have an arteriovenous fistula. Furthermore, determination of autograft function can be performed by differential PTH measurements. A twofold increase in PTH from a sample drawn above the autograft compared with measurement in the contralateral arm denotes a hyperfunctioning autograft. Patients with a forearm autograft may require several reoperations to completely remove autografts from the forearm because of regrowth causing recurrent HPT. For this reason, during reexploration procedures, it may be appropriate to excise all visible autograft tissue.

The sternocleidomastoid muscle is another convenient location for autotransplantation as it is within the operative field. A third possible location for autotransplantation is in the middle to lower third of the presternal area subcutaneously. The autograft can be easily located and excised under local anesthesia in the event of a recurrence. Autografts are rarely placed intramuscularly in the chest.

BOX 4 Creation of a Parathyroid Autograft

1. Resected parathyroid tissue is preserved in cold saline until transplantation.
2. Use frozen section to confirm parathyroid tissue.
3. Using a scalpel, divide a portion of the excised parathyroid gland into a total of 10 to 20 pieces measuring approximately 1 to 2 mm. The aim is to implant approximately 50 to 100 mg of parathyroid tissue.
4. Insert one or separate pockets subcutaneously or intramuscularly in the neck, chest, or forearm.
5. Mark the autograft site with nonabsorbable silk suture and a hemoclip to facilitate localizing site in case of recurrent HPT.

Cryopreservation

Cryopreservation of parathyroid tissue is available in less than 30% of healthcare centers. When possible, cryopreservation of parathyroid tissue in patients undergoing subtotal or total PTX is recommended in patients at higher risk of hypo-PTH. However, the low utilization combined with the high associated costs of storing cryopreserved tissue for later use has raised concerns regarding the cost effectiveness of the procedure. The cryopreserved tissue can be used for delayed autotransplantation in case of parathyroid remnant ischemic necrosis or autograft failure. Variable success rates have been reported ranging from 17% to 83%. The duration of cryopreservation has been reported to be a significant indicator of graft failure, with preservation beyond 22 months failing to yield a functional autograft.

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

ESRD patients have a 17% unplanned admission rate. Half of those readmitted are due to postoperative hypocalcemia and hungry bone syndrome—the hyperdynamic reabsorption of calcium into bones. Moreover, PTX patients experience a 39% higher hospitalization rate in the first year after surgery compared with the prior year. In addition, 5% to 20% of patients experience persistent disease, which is defined as hypercalcemia or PTH level above the recommended target range according to CKD stage after PTX. ESRD patients are at high risk for transient postoperative hypocalcemia due to delayed autograft or remnant function. For this reason, protocols must be in place to prevent postoperative hypocalcemia including administration of calcitriol as well as oral calcium, or intravenous calcium gluconate during the immediate postoperative period, and oral medication when discharged home.

Patients typically do not require pain medications stronger than acetaminophen. Patients may resume dialysis after surgery in the hospital; however, the minimum amount of heparin should be used during the first few dialysis sessions to minimize the risk of neck hematoma.

After hospital discharge, patients should be followed up with a baseline laboratory profile of serum and ionized calcium, magnesium, and serum PTH at 1 to 4 weeks after surgery and vitamin D levels at 3 and 6 months. Long-term follow-up, with serum calcium and serum PTH measurements at least annually, is important to monitor for potential persistent or recurrent HPT.

SUMMARY

Surgical management of secondary and tertiary HPT is complex due to the lack of specific guideline consensus. From 2015 to 2018, the incidence and prevalence of ESRD increased 3.19% and 0.93% annually, respectively. This is due to a decline in mortality rate among these patients according to the United States Renal Data System. During this time period, patients with a severe HPT (PTH >600 pg/mL) increased from 21.8% to 28.0%. For these reasons, it is important to understand how to effectively manage these patients. A well-developed prospective multiinstitutional randomized controlled clinical trial comparing the three procedures (subtotal *versus* total with autotransplantation *versus* total without autotransplantation) is needed.

Subtotal PTX and total PTX with autotransplantation are acceptable surgical approaches. Total PTX without autotransplantation should be used only in select patients due to its high risk for permanent hypoparathyroidism. However, all three procedures are effective at treating HPT and its associated metabolic disturbances. The creation of multidisciplinary consensus guidelines is needed regarding the ideal surgical management of these patients.

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Metabolic Changes Following Bariatric Surgery

Patrick Crosby, MD, Thomas H. Magnuson, MD, and Michael A. Schweitzer, MD

METABOLIC CONSEQUENCES OF OBESITY

Morbid obesity is a syndrome resulting from an excess accumulation of body fat that has been shown in multiple studies to be severely detrimental to overall health. There are numerous ways to define obesity, each with benefits and limitations. Body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of the height in meters (kg/m^2), is the most commonly used measurement of obesity, especially in the world of medicine and biostatistics. It is easy to calculate and a reproducible and accurate population-level indicator. A BMI of more than 30 kg/m^2 indicates obesity. The main limitation of BMI, however, is that it does not differentiate between fat and lean muscle mass. A world-class athlete, who would otherwise be considered fit, could be classified as overweight or obese. An alternative method to avoid this is defining obesity according to the percentage of body fat: more than 32% in women and 25% in men. The problem is that body fat calculations require specialized measurements or devices such as calipers or body composition, making them less reproducible, especially in unskilled hands. More importantly, neither of these two methods addresses the regional distribution of fat or weight, which is critical because the metabolic consequences of obesity are determined by both the amount and distribution of body fat. Central or visceral obesity (also referred to as android or abdominal obesity) is more common in men and is associated with increased risk of insulin resistance, hyperlipidemia, hypertension, cardiovascular disease (CVD), and stroke. Visceral fat is a highly active endocrine organ, which may lead to a chronic inflammatory state caused in part by the release of free fatty acids and cytokines from this adipose tissue. The gynecoid pattern of obesity, on the other hand, is characterized by an excess accumulation of subcutaneous fat in the hips and thighs, typically seen in women. Gynecoid obesity is less frequently associated with adverse metabolic effects. The importance of central obesity is again highlighted in populations who, despite relatively low BMI, have high levels of visceral obesity (e.g., Asians) and are prone to adverse effects of obesity at a lower BMI. A simple measurement of waist circumference or waist-to-hip ratio can address visceral obesity but does not accurately address height and fat content. A waist circumference of more than 35 in. in women or 40 in. in men indicates higher risk of metabolic syndrome and obesity-related comorbidities, and a waist–hip ratio above 0.85 for females or 0.90 for males can be used to classify obesity.

The current global obesity epidemic is a well-documented and worsening public health crisis. According to the CDC, US obesity prevalence was 42.4% in 2017 to 2018. From 1999 to 2000 through 2017 to 2018, US obesity prevalence increased from 30.5% to 42.4%. During the same time, the prevalence of severe obesity increased from 4.7% to 9.2%. Similar rates are described in several western countries The World Health Organization indicates that, in 2016, more than 1.9 billion adults were overweight (39% of the world population). Of these, more than 650 million (13%) were obese. Worldwide obesity has nearly tripled between 1975 and 2016, and now most of the world's population live in countries where overweight and obesity kills more people than underweight. The obesity epidemic also extends to children as 39 million children under the age of 5 were overweight or obese in 2020. With all the health consequences that come with obesity, it has quickly become a significant public health crisis worldwide.

Adipose tissue was initially thought to be a quiescent storage medium for excess calories. However, recent studies have shown it to be metabolically and hormonally active. In severe obesity, excess lipid accumulates in adipocytes, hepatocytes, and muscle cells. Excess accumulation of nutrients, especially fat, within these cells leads to increased secretion of adipocyte-derived peptides (e.g., leptin, adiponectin, resistin) and cytokines (e.g., tumor necrosis factor-a [TNF-a], interleukin-6 [IL-6]), collectively referred to as adipokines. The paracrine and endocrine actions of these adipokines contribute to a state of chronic low-grade inflammation, which in turn interferes with many physiologic cellular processes (e.g., insulin signaling) and leads to the metabolic derangements seen in obesity (e.g., insulin resistance and type 2 diabetes mellitus [T2D]). Our center has conducted the first studies showing the relevance of C1q/TNF-Related Protein (CTRP) family, a family of novel adipokines, in humans as it relates to obesity, metabolic syndrome, insulin resistance, and T2D.

The obesity-induced inflammatory state adversely affects organ systems in the body and contributes to a shortened life expectancy. Each 5-unit increase in BMI is associated with a 30% increase in all-cause mortality, with BMIs of more than 40 associated with a reduced life expectancy of 8 to 10 years, similar to that of regular cigarette smoking. Obesity is characterized by poor quality of life, with increased risk of many life-threatening conditions including cancers, heart disease, T2D, hypertension, stroke, gastroesophageal reflux disease (GERD), hyperlipidemia, and sleep apnea. The prevalence of these comorbidities often increases with the severity of obesity (Table 1). This is most evident with T2D. At age 18 years, women with a BMI of 30 to 35 have a 54.6% lifetime risk of development of diabetes, which is increased to 74.4% for those with BMI of more than 35.

Although modest weight loss (5%–10% excess weight) can lead to reductions in the risk of these chronic diseases, nonsurgical weight loss is often unsuccessful or short-lived in 90% to 95% of patients. As a result, bariatric surgery (weight loss surgery) has become the standard of care in the treatment of medically complicated or severe obesity.

METABOLIC IMPROVEMENTS AFTER WEIGHT LOSS SURGERY

Weight Loss

The term excess body weight loss (EWL), calculated by subtracting ideal body weight from current weight, is commonly used to describe weight loss. Not surprisingly, the degree of EWL varies between procedures. At 2 years postprocedure, mean EWL is 70% to 80% for biliopancreatic diversion (BPD) with or without a duodenal switch, 60% to 70% for Roux-en-Y gastric bypass (RYGB), 50% to 60% for sleeve gastrectomy (SG), and 40% to 45% for laparoscopic adjustable gastric banding (LAGB). In general, procedures with higher EWL are also associated with increased short-term and long-term complications. The balance between the desired weight loss and surgical risk influences both the patient and surgeon when deciding upon the optimal procedure.

The mechanisms underlying postprocedure weight loss are multifactorial and vary by procedure. There is no single mechanism that explains the change but instead a combination of them. The proposed mechanisms have been summarized in Table 2. Some of them are still controversial and being studied. Of critical importance are long-term changes in hunger signals and food preference after surgery. In contrast, nonsurgical weight loss leads to increased hunger and reduced energy expenditure, which presumably contributes to the ultimate failure of dieting in achieving long-term weight reduction. Weight loss surgery prevents such physiologic responses and maintains hunger control despite limited calorie intake.

Long-term follow-up studies such as the Swedish Obesity Study show significant long-term weight loss in surgical patients compared with control subjects, with up to 20 years of follow-up. The durability of postsurgical weight loss is a concern for patients and clinicians. The definition of successful weight loss after bariatric surgery varies depending on the procedure; for RYGB, success often is described as losing and maintaining 50% or more EWL. Most patients regain some weight after reaching their nadir weight, with pathologic weight regain (>20% of the maximal weight loss) reported in 15% to 20% of patients. This observation highlights the fact that bariatric surgery is not a replacement for long-term lifestyle changes,

TABLE 1 Risks of Cardiovascular and Metabolic Disorders Associated with Obesity

Life expectancy	30% increase in mortality rate for each 5-unit increase in BMI. At BMI >40, life expectancy is reduced by 8 years.
Cardiovascular disease	There is a 9% increase in cardiovascular mortality with each unit increase in BMI. A BMI >25 increases the risk of CVD by 32%. A BMI >30 increases the risk of CVD by 81%.
Hypertension	Fivefold risk of hypertension in obesity. 85% of patients with hypertension have a BMI >25.
Stroke	A BMI >25 increases the risk of stroke by 22%. A BMI >30 increases the risk of stroke by 64%.
Type 2 diabetes	Men with BMIs of 30 or higher have a sevenfold higher risk of developing type 2 diabetes. Women with BMIs of 30 or higher have a twelvefold higher risk. At BMI >35, patients have a 74% lifetime risk of type 2 diabetes.
Cancer	There is a confirmed direct association between obesity and cancers of the breast, colon and rectum, endometrium, esophagus, kidney, ovary, and pancreas.

TABLE 2 Proposed Mechanisms for Weight Loss After Bariatric Procedures

Caloric restriction	Immediate effect in RYGB and SG due to anatomical changes. In the perioperative period of bariatric surgeries, the caloric intake is dramatically reduced to 200–300 kcal/day.
Malabsorption	Although a degree of this occurs after BPD, little malabsorption is seen after LAGB, SG, or RYGB as measured with stool calorimetry and nitrogen balance.
Decreased hunger signals	This is true for all bariatric procedures secondary to neuroendocrine changes. There is an altered hormonal expression (leptin, ghrelin, GLP-1, PYY, etc.) along the gut-brain axis after surgery that decreases hunger signals.
Vagus nerve stimulation	Vagal nerve endings sense the increased gastric distention and nutrients in the Roux limb leading to activation of anorexigenic mechanisms.
Increased energy expenditure	There is controversial evidence on this matter, and no definite conclusions on the role of energy expenditure can be drawn at this time.
Changes in food preference	Several studies have shown the predilection for lower-fat foods after RYGB. Options to explain such behaviors include postoperative enhanced taste acuity and altered craves for food.
Changes in gut microbiota	Animal studies show a potential role for the gut microbiome in obesity and diabetes. Definitive human data are currently lacking, but this is an area of significant scientific interest.

which are needed to help maintain weight loss. A commitment to changes in diet and exercise are critical for long-term success. The importance of such lifestyle changes and the need for regular (at least annual) postoperative follow-up with the bariatric team should be emphasized with patients before surgery.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of clinical disease that ranges from simple accumulation of liver fat (steatosis) with resultant inflammation to nonalcoholic steatohepatitis (NASH), eventually leading to fibrosis and cirrhosis. Hepatic steatosis and NASH, markers of central adiposity, are thought to be important in the pathogenesis of obesity-related metabolic disorders, often referred to as the metabolic syndrome (visceral adiposity, insulin resistance, hyperinsulinemia, hypertension, and hyperlipidemia). NASH is now a leading cause of cirrhosis in the United States and thus one of the main indications for liver transplantation. In patients undergoing bariatric surgery, the prevalence of simple steatosis may be greater than 95%, NASH is often reported from 20% to 30% (prospective data from our center shows a prevalence of NASH of 54.5%), and fibrosis between 10% and 14%. Therefore, the improvement and sometimes resolution of NAFLD is a significant endpoint for bariatric surgery.

Bariatric surgery leads to a near-universal improvement in the severity of hepatic steatosis with most studies reporting more than 75% of patients with no evidence of steatosis after weight loss. Yung Lee et al performed a systematic review and meta-analysis to determine the overall effects of bariatric surgery on histologic features of NAFLD (steatosis, inflammation, ballooning degeneration, and fibrosis). They analyzed data from 32 cohort studies (15 retrospective, 17 prospective cohort studies, no randomized controlled studies) including 3,093 biopsy specimens. Bariatric surgery resulted in biopsy-confirmed resolution of steatosis in 66% of patients, inflammation in 50%, ballooning degeneration in 76%, and fibrosis in 40%. Other studies show that overall RYGB has greater improvement in liver disease compared with primarily restrictive procedures such as SG.

Lipid Profiles

Dyslipidemia is seen in up to 50% of patients who undergo bariatric surgery. The STAMPEDE trial 5-year outcome data, comparing intensive medical therapy to RYGB and SG, showed that the decrease from baseline in triglyceride levels (−39.8 mg/dL for RYGB and −29.4 mg/dL for SG; $P = 0.03/0.04$) and the increase from baseline in high-density lipoprotein (HDL) cholesterol levels (+31.9 mg/dL for RYGB and +29.6 mg/dL for SG; $P = 0.012/0.016$) were significantly greater at 5 years after RYGB and SG than after intensive medical therapy. By contrast, no significant change in low-density lipoprotein levels was observed among the three study groups. Overall, RYGB has a greater effect than primarily restrictive procedures, and significant changes in lipid profiles can be seen as early as 1-month postoperation.

Hypertension

Hypertension (HTN) is common in obese individuals and is increasingly prevalent in patients with increasing BMI. In the normal weight population (BMI <25), HTN is present in 15% to 20% of the population, rising to 30% to 40% in the obese population (BMI >30). When compared with normal-weight controls, the odds ratio for HTN is 1.7 for BMI 25 to 29.9 kg/m^2, 2.6 for BMI 30 to 34.9 kg/m^2, 3.7 for BMI 35 to 39.9 kg/m^2, and 4.8 for BMI 40 kg/m^2 or more. Furthermore, a 10 kg (22 lb) higher body weight is associated with 3.0 mm Hg higher systolic and 2.3 mm Hg higher diastolic blood pressure.

The mechanism that links obesity with HTN is not fully understood. It is thought to involve a combination of enhanced renal reabsorption of sodium (possibly resulting from insulin resistance), expansion of intravascular volume, activation of the renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, and release of angiotensinogen from adipose tissue. The chronically increased intraabdominal pressure seen with central obesity has been shown to significantly upregulate the hormonal output of the renin-angiotensin-aldosterone system and may play an important role in obesity-induced hypertension. Weight loss has been shown to be associated with a reduction in vascular resistance, total blood volume, and cardiac output, an improvement in insulin resistance, a reduction in sympathetic nervous system activity, and suppression of the activity of the renin-angiotensin-aldosterone system.

HTN is seen in up to 50% of patients who undergo bariatric surgery. Of these, 50% to 60% have remission, and 60% to 70% show improvement after bariatric surgery. One study of patients undergoing RYGB versus intensive medical therapy showed that the rate of hypertension remission was 49% for the surgical group versus 23% for the medical therapy group. BPD has also been shown to resolve hypertension in 60% to 80% of patients.

Cardiovascular Risk and Mortality

CVD remains the leading cause of mortality in the United States. The Framingham Heart Study (FHS) is a long-running prospective cohort study, initiated in 1948, that has contributed to our understanding of obesity, its associated diseases, and to how these conditions relate to overall and cardiovascular-related mortality. These long-term data show a relative risk for CVD of 1.38 in obesity compared with normal weight. The FHS was also used to create the Framingham Risk Score (FRS), which combines several parameters and allows one to calculate an individual's risk of having a cardiovascular event. Bariatric surgery has been shown to reduce the FRS and the 10-year risk of a cardiac event by 40%. Serum and laboratory risk predictors, such as C-reactive protein (CRP), have also been shown to decline after surgery by about 60%.

At 10 years, the Swedish Obesity Study showed a 23.7% unadjusted (30.7% adjusted) overall reduction in overall mortality in well-matched patients who underwent weight-loss surgery when compared with those who did not. Another propensity score-matched cohort study from Canada, including 2638 patients with previous ischemic heart disease or heart failure who received bariatric surgery, showed a significant difference in the incidence of major cardiovascular events when compared with the control population (11.5% vs. 19.6%—adjusted hazard ratio 0.58 [95% CI, 0.48–0.71]; P <0.001).

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of unknown etiology characterized by menstrual abnormalities with hyperandrogenism. It is a common cause of infertility in women, especially in severe obesity. Up to 50% of those with PCOS are overweight or obese, and the phenotypic severity of PCOS is reported to correlate with the severity of insulin resistance and to worsen with increased weight. A meta-analysis of 13 studies involving 2130 female patients who underwent bariatric surgery gathered evidence of the effects of bariatric surgery on PCOS. Out of all the patients, 45.6% had PCOS before their operation. At 12-month follow-up after surgery, only 6.8% of the patient still had PCOS. A total of 56.2% of the patients had irregular menstrual cycles; 12 months after their surgical procedure, only 7.7% still had this irregularity. Before surgery, 67% of the patients had hirsutism. At 12-month follow-up, the incidence of hirsutism had decreased to 38.6% and to 32% at the study end. Furthermore, the incidence of preoperative infertility was 18.2%, which significantly decreased to 4.3% at the study end.

Fertility

The mechanism by which obesity leads to decreased fertility in women is multifactorial and complex. Excess adipose tissue leads to increased aromatization of androgens to estrogen, as well as an overproduction of leptin. Furthermore, insulin resistance and

hyperinsulinemia, resulting from obesity, lead to hyperandrogenemia, which in part leads to a decrease in sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP). All these changes affect the neuroregulation of the hypothalamic-pituitary-gonadal axis leading to impaired ovulatory function and thus reproductive health. When it comes to men, obesity leads to decreased levels of testosterone. This together with the decreased levels of SHBG and increased levels of estrogen (also seen in women) leads to reduced sperm counts and subfertility. Other hormones involved in the regulation of Sertoli cell function and spermatogenesis, such as FSH/LH ratios and inhibin B, have also all been observed to be decreased in males with increased BMI.

One study in Canada included 783 women after bariatric surgery, 251 of which had postoperative pregnancies. Of patients who were unable to become pregnant preoperatively, 47.0% were successful postoperatively. Ninety out of 109 women (82.6%) reported an appropriate weight gain (9.1 ± 5.9 kg) during postoperative pregnancies. The incidence of fetal macrosomia decreased from 34.8% to 7.7%, with a concomitant increase in normal-weight babies from 62.1% to 82.7%.

Several studies have also examined the effects of bariatric surgery on pregnancy complications compared with matched controlled subjects. Collectively, they suggest that the risk of gestational diabetes and large-for-gestational-age infants during pregnancy are decreased after bariatric surgery. Although preterm birth, stillbirth, and congenital malformations were not impacted, the risk of small-for-gestational-age babies appears to be increased after bariatric surgery. Other recent studies suggest that surgical weight loss before pregnancy has the potential to reduce the risk of obesity and metabolic risk factors in offspring by epigenetic mechanisms involving DNA methylation.

Type 2 Diabetes

The metabolic changes after bariatric surgery associated with glucose homeostasis have been one of the most studied overall. Diabetes is a significant public health problem worldwide, with persistently increasing prevalence. Over the last 25 years, the prevalence of diabetes has doubled in the United States and multiplied by three to five times in India, Indonesia, China, Korea, and Thailand. In 2014, 8.5% of adults worldwide aged 18 years and older had diabetes. Between 2000 and 2016, there was a 5% increase in premature mortality from diabetes with more than 1.5 million deaths in total attributed directly to diabetes. It represents a substantial economic burden as reflected by diabetes and obesity consuming 14% and 5.7% of the total US health expenditure, respectively. Unfortunately, new pharmacologic therapies like glucagon-like-peptide-1 (GLP-1) analogs and dipeptyl-peptidase IV inhibitors have been disappointing in the morbidly obese, and many diabetic patients on maximal medical therapy fail to reach the therapeutic goal of HbA1c <7% set by the American Diabetes Association. For this reason, bariatric surgery has quickly been pushed to the forefront when it comes to the treatment of diabetes in obese patients.

Improvements in glycemic control after gastrointestinal surgery were originally reported in the 1960s. This was followed by studies showing the durable effect of bariatric surgery in improving glucose homeostasis in T2D patients as early as 1995. Since then, several meta-analyses have confirmed that all bariatric procedures lead to significant improvements in glucose control and diabetes remission, although success does vary among the different surgeries (Table 3).

Naturally, the next step was comparing bariatric surgery to intensive medical therapy. By 2021, most studies conclude that bariatric surgery leads to better glycemic control and diabetes remission when compared with intensive medical therapy in obese patients. The Swedish Obese Subjects data shows that, of the patients who underwent bariatric surgery with T2D at baseline, 72% were in remission at 2 years postoperation compared with 21% in the medical treatment group. At 10 years, this decreased to 36% in the surgery group and 13% in the control group. Additionally, bariatric surgery reduced the risk of developing T2D by 96%, 84%, and 78% after 2, 10, and 15 years, respectively, when compared with medical management. The recently published 5-year STAMPEDE trial, which compared rates of diabetes remission (defined as HbA1c <6%) after intensive medical therapy versus RYGB and SG, showed similar results with a 29% remission rate in the RYGP group and 23% in the SG group, compared with only 5% in the medical therapy group. Another large cohort of more than 400 patients who had RYGB, showed that the remission rate after 12 years of follow-up (with a 90% follow-up rate) was 51%.

These data have prompted many diabetes societies to alter their treatment guidelines for the management of diabetes. They now recommend bariatric surgery as an early treatment of eligible patients who have T2D and a BMI ≥35 kg/m^2, or with a BMI between 30 and 35 kg/m^2 when diabetes cannot be adequately controlled by an optimal medical regimen, especially in the presence of other major CVD risk factors.

The exact mechanisms by which bariatric surgery leads to improved glucose homeostasis in diabetic patients is an area that has received significant scientific attention lately. Initially, it was thought that such a profound response was the result of caloric restriction and weight loss. However, it is now known that there are several mechanisms behind this change, with gastrointestinal hormones leading the way (Table 4).

METABOLIC SURGERY AND FUTURE DIRECTIONS

Low BMI Metabolic Surgery

The current National Institute of Health (NIH) consensus statement in agreement with the Diabetes Surgery Summit II recommends bariatric surgery in patients with a BMI of more than 40 kg/m^2; a BMI of more than 35 kg/m^2 with concomitant comorbidities like diabetes, coronary artery disease, or sleep apnea; or a BMI between 30 and 35 kg/m^2 when T2D cannot be adequately controlled by an optimal medical regimen. Unfortunately, despite the consensus and current existing data, surgery is still rarely used in the lower BMI patient group (30–35) and is not covered by most insurance providers in the United States. With the increasing prevalence of T2D, the slow progress in finding new effective medical therapies, and the significant rate of diabetes remission and safety of bariatric surgery, there should be a progressively strong push to encourage surgical intervention in patients with diabetes to 30 kg/m^2 or even lower.

TABLE 3 Weight Changes and Metabolic Improvements After Bariatric Procedures

	TBWL (%)	Hypertriglyceridemia Remission	Hypertension Remission	Type 2 Diabetes Remission
RYGB	30%–35%	90%–95%	40%–70%	70%–80%
SG	20%–25%	50%–60%	30%–60%	50%–70%
LAGB	10%–15%	60%–70%	20%–30%	30%–40%

TABLE 4 Proposed Mechanisms of Antidiabetic Effect of RYGB

Caloric restriction and weight loss	Unlikely to be a major mechanism. Improvement if glucose homeostasis typically begins within days of surgery before significant weight loss.
Malabsorption	There is no clear evidence that RYGB leads to enough nutrient malabsorption to account for the improvement of diabetes as early as postoperative day 2.
Hindgut hypothesis and changes in incretin levels (GLP-1)	Rapid delivery of nutrients to the distal small bowel stimulates L cells leading to increase GLP-1 secretion. Increased GLP-1 levels enhance glucose-stimulated insulin secretion and improve insulin sensitivity and beta-cell proliferation and function.
Foregut hypothesis	Rat models have shown that isolating the duodenum and proximal jejunum results in a decreased release of an unknown anti-incretin leading to improved glucose homeostasis. Ghrelin secretion is also reduced.
Intestinal adaptation	The alimentary limb undergoes compensatory hyperplasia and hypertrophy, with increased expression of glucose transporters and thus glucose absorption into the epithelial cells. There is a reprogramming of intestinal metabolism to use this glucose to support tissue growth.
Changes in circulating bile acids	Human and rodent studies have shown increased levels of circulating bile acids (reduced in diabetic patients) after RYGB. Bile acids have been linked to receptor signaling on incretin-secreting L-cells.

One of the main issues in the matter is that currently there is no clear consensus on the best surgical procedure for this patient group. In a randomized study from Taiwan, including diabetic patients with BMI from 25 to 34, RYGB was shown to be more effective than SG in achieving diabetes remission, with a 93% remission compared with 47%. Importantly, the mean postoperative BMI was 22.8 for RYGB and 24.4 for SG, showing that these lower BMI patients did not lose excessive weight following surgery. Unfortunately, more studies need to be performed for a final consensus on which bariatric surgery to recommend.

Adolescent Bariatric and Metabolic Surgery

The use of BMI as a measure for childhood obesity is more problematic than its use in adults because of the additional complications of growth patterns, age, and sex in a growing child. Special BMI growth charts have been devised to correct for these variables and are used when assessing the pediatric population. These define the BMI range of 85th to 94th percentile as overweight, and 95th percentile or higher as obese. This has been further clarified by the American Academy of Pediatrics who proposes a BMI of 30 to 32 kg/m^2 for youths 10 to 12 years old and 34 kg/m^2 for youths 14 to 16 years old as the 99th percentile. The Bogalusa Heart Study showed that 84% of children with a BMI in the 95th to 98th percentile had a BMI greater than 30 kg/m^2 as adults, showing that childhood BMI was strongly associated with adult BMI in this BMI range.

Childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years. The percentage of obesity in children aged 6 to 11 years in the United States increased from 7% in 1980 to 21.2% in 2018. Similarly, the percentage of obesity in adolescents aged 12 to 19 years increased from 5% to 21% over the same period. Several studies have shown that childhood obesity is strongly associated with adult obesity, as well as a higher incidence of risk factors for CVD, such as high cholesterol or hypertension. In a population-based sample of 5- to 17-year-olds, 70% of obese youth had at least one risk factor for CVD. Current estimates predict a decrease in life expectancy in obese adolescents of 5 to 20 years depending on additional risk factors such as race and sex.

Although studies are limited, current data suggests that bariatric surgery is at least as safe in adolescents as it is in adults, having similar success in both weight reduction and resolution of metabolic derangement. The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study is the largest ongoing observational cohort study of youth undergoing metabolic and bariatric surgery to date. There were 242 patients (12–28 years of age) enrolled at five US centers (2007–2011) undergoing RYGB (n = 161), VSG (n = 67), or LAGB (n = 14). Although the study is still underway, the RYGB and SG groups experienced a mean weight reduction of 27% and resolution of comorbidities at 3 years, including T2D (95%), hypertension (74%), and dyslipidemia (66%), with a reduction of overall prevalence of multiple concurrent CVD risk factors. The FABS-5+, another important study with the longest-term follow-up data in adolescents to date, showed that, after RYGB, adolescents demonstrated a 29% reduction in BMI and significant improvements in blood pressure, dyslipidemia, and T2D at 8 years. Despite all these data, there is hesitancy on the part of pediatricians and pediatric specialists to consider surgery, even for adolescents with life-threatening comorbidities; of polled pediatricians, half of the respondents would not refer their patients for bariatric surgery before 18 years of age.

Alternative Surgical Procedures

Research of the mechanisms for the antidiabetic effects of current bariatric procedures is of particular interest because it also leads to the opportunity of developing less invasive interventions. As explained earlier, the isolation of the duodenum and proximal bowel from nutrient exposure and early exposure of distal bowel and ileum to undigested food are thought to be critical to the metabolic success of bariatric surgical procedures. New surgical procedures such as duodenal-jejunal bypass and ileal interposition with or without SG may offer less invasive options for metabolic surgery targets, especially in patients with low BMI. These procedures, however, are still complex and not without risk, and it is still not clear whether they offer any major advantages in terms of long-term effectiveness and safety over RYGB or SG. More studies are required at the time.

Endosurgical Options and Devices

An area of heavy development at this time, in part, because it is the least invasive option, is endoscopically delivered gastrointestinal manipulation. The goal of these endoscopic procedures is to replicate the metabolic or weight loss success of bariatric surgery without an abdominal incision, making for a less invasive procedure. These options range from implantable neurostimulators to modify vagal or gastric tone, to barrier devices that stent through the proximal bowel and block nutrient contact or intragastric balloons designed for gastric volume restriction and increased satiety. The efficacy of these minimally invasive options needs to be further studied, but endoscopic procedures will, most likely, be an ongoing target for development in the near future.

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Cardiovascular Disease Risk Reduction After Bariatric Surgery

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Despite significant advances in medical and surgical treatment over the past several decades, cardiovascular disease (CVD) persists as the leading cause of morbidity and mortality in the United States. The Centers for Disease Control and Prevention estimates that 49.2% of adults 20 years of age and older are affected by CVD, which includes coronary artery disease, heart failure, cardiomyopathy, hypertension, and stroke. Although the mortality rate resulting from the different CVD entities vary, collectively these entities are responsible for more deaths than cancer and trauma. The American Heart Association lists CVD as the most common underlying cause of death in the United States, outpacing cancer and chronic lower respiratory disease combined, and it remains the leading cause of death globally. Coronary heart disease is the most common (42.1%) cause of CVD-related death, followed by stroke (17%), hypertension (11%), and heart failure (9.6%).

In addition to morbidity and mortality, CVD places significant economic costs on the community and utilizes substantial resources within the healthcare system. From 2016 to 2017, CVD cost the United States an estimated $363.4 billion per year. The Healthcare Cost and Utilization Project found that CVD was associated with 11.6% of 30-day hospital readmissions in 2018. CVD is among the leading conditions filed for disability in the United States. The American Heart Association has projected a $1.1 trillion price tag for treatment of CVD by 2035.

Obesity, diabetes mellitus, and multiple additional risk factors leading to CVD are well established. Controlling these risk factors accounts for up to 75% of the possible reduction in CVD mortality in highly developed countries. Obesity, particularly central obesity, is an independent risk factor. This chapter will explore the relationship between central obesity and CVD and will discuss the effect of bariatric and metabolic surgery on CVD risk factors and outcomes.

CARDIOVASCULAR DISEASE RISK FACTORS

Overview

CVD risk factors can be divided into traditional modifiable, traditional nonmodifiable, and nontraditional (Table 1). Population-based studies have revealed that most CVD results from modifiable risk factors such as poor diet, low level of physical activity, and tobacco smoking. Other modifiable risk factors include high systolic blood pressure, triglyceride cholesterol levels, fasting plasma glucose levels, and body mass index (BMI). Approximately half (47.3%) of the United States adult population has hypertension, just one of the many risk factors for CVD. Black patients experience higher BMI, hemoglobin A1c, and systolic blood pressure on average than white patients, but have lower average total cholesterol and are less likely to be current smokers.

Traditional nonmodifiable risk factors for CVD are increasing age, sex, race, and family history of premature coronary heart disease. Males are at higher risk of CVD. Black patients are at a higher 10-year risk for CVD than their white or Hispanic counterparts when adjusting for age, sex, and social determinants of health.

Metabolic Syndrome

Metabolic syndrome, formerly known as *syndrome X,* comprises a group of conditions that lead to CVD and type 2 diabetes mellitus (T2DM). The International Diabetes Federation (IDF) defines metabolic syndrome by the presence of central obesity plus ≥2 metabolic risk factors, including increased blood pressure, high triglyceride levels, elevated fasting plasma glucose, and low high-density lipoprotein (HDL) cholesterol (Table 2). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) uses the presence of any three of the aforementioned five factors to define metabolic syndrome (Table 3). The prevalence of metabolic

TABLE 1 Cardiovascular Disease Risk Factors

TRADITIONAL NONMODIFIABLE
Age (men ≥45 years; women ≥55 years)*
Sex*
Race
History of premature CHD in first-degree relative (male <55 years; female <65 years)
TRADITIONAL MODIFIABLE
Smoking*
High systolic blood pressure (≥140/90 mm Hg)*
Blood pressure treated with medication*
High total or LDL cholesterol or low HDL cholesterol*
Diabetes
Prediabetes
EMERGING NONTRADITIONAL CARDIOVASCULAR DISEASE RISK FACTORS
Insulin resistance/hyperinsulinemia
Dyslipidemia with elevated triglycerides, low HDL cholesterol, and increased apolipoprotein-B serum concentrations
Procoagulation and abnormal fibrinolysis with increased serum fibrinogen concentrations and increased production of plasminogen activator inhibitor
Inflammation with increased serum levels of C-reactive protein, tumor necrosis factor, and interleukin-6
Endothelial dysfunction
Premature atherosclerosis
Microalbuminuria

*Included in the current version of the Framingham Risk Score (FRS), a common algorithm used to estimate 10-year cardiovascular risk in an individual patient.
CHD, Coronary heart disease; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein.

TABLE 2 International Diabetes Federation Criteria for Metabolic Syndrome

Central obesity* or BMI ≥30 kg/m² plus presence or treatment of two of the following:	
1. Raised triglycerides	≥150 mg/dL (1.7 mmol/L)
2. Reduced HDL cholesterol	<40 mg/dL (1.03 mmol/L) in males <50 mg/dL (1.29 mmol/L) in females
3. Raised blood pressure	Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg
4. Raised fasting plasma glucose	≥100 mg/dL (5.6 mmol/L)** or previous diagnosis of type 2 diabetes

*If BMI is >30 kg/m², central obesity can be assumed, and waist circumference does not need to be measured.
**If positive, an oral glucose tolerance test is strongly recommended but is not required for diagnosis.*BP,* Blood pressure; *HDL,* high-density lipoprotein.

TABLE 3 Diagnostic Criteria for the Metabolic Syndrome as Defined by the National Cholesterol Education Program Adult Treatment Panel III

Having or on treatment for three or more of the following:	
1. Abdominal obesity	Waist circumference ≥40 inches (102 cm) in males; ≥35 inches (88 cm) in females
2. Hypertriglyceridemia	≥150 mg/dL (≥1.7 mmol/L)
3. Low HDL cholesterol	<40 mg/dL (1.03 mmol/L) in males; <50 mg/dL (1.29 mmol/L) in females
4. Systemic hypertension	≥130/85 mm Hg
5. Elevated fasting plasma glucose	≥100 mg/dL (≥5.5 mmol/L)

HDL, high-density lipoprotein.

syndrome in the United States is estimated to be 34.7%. This number increases with age, affecting only 19.5% of individuals between 20 and 39 years of age and 48.6% of those ≥60 years of age. Metabolic syndrome substantially increases the risk for CVD (RR 1.78, 95% CI 1.58–2.00). Furthermore, all-cause mortality is higher in patients with CVD in the presence of metabolic syndrome (RR 1.58, 95% CI 1.39–1.78). Each additional component of metabolic syndrome that a patient exhibits further increases their risk of major cardiovascular events (RR 1.22, 95% CI 1.09–1.36).

Diabetes Mellitus

Diabetes mellitus is an endocrine disorder in which blood glucose level is dysregulated and is subclassified by the pathogenesis of this dysregulation. In the United States, 1 in 10 individuals has diabetes, and T2DM accounts for more than 90% of these diagnoses. In T2DM, insulin resistance in bodily tissue causes abnormal glucose levels despite continued pancreatic insulin production. Despite previously being considered an adult-onset disease, there has been a concerning increase in the number of youths 10 to 19 years of age diagnosed with T2DM, almost doubling from 0.34 per 1000 youths in 2001 to 0.67 per 1000 in 2017. T2DM is associated with microvascular and macrovascular pathology that increases risk of CVD. Data from the National Health Interview Survey has shown that patients with diabetes have higher CVD-related and all-cause mortality when compared with patients without diabetes.

Obesity

Central obesity is determined by the measurement of the waist circumference and is sex- and ethnic group–specific. Patients with a BMI ≥30 kg/m² are assumed to have central obesity and do not require waist circumference measurement. The prevalence of obesity in US adults increased from 30.5% in 1999 to 2000 to 42.4% in 2017 to 2018. Severe obesity, or BMI ≥40 kg/m², increased from 4.7% to 9.2% over the same period.

Obesity is associated with many other risk factors for CVD (Table 4) and independently increases lifetime risk for CVD, T2DM, hypertension, sleep apnea, and venous thromboembolism. Obesity has been shown to increase all-cause mortality (HR 1.18, 95% CI 1.12–1.25). BMI has an overall *J*-shaped relationship with all causes

TABLE 4 Cardiovascular Conditions Associated with Obesity

- Early and accelerated atherosclerosis
- Hypertension
- Myocardial infarction or acute coronary syndrome
- Structural heart changes and congestive heart failure
- Atrial fibrillation
- Sudden cardiac death
- Stroke

of mortality, with the lowest risk of mortality from most causes between BMI of 21 to 25 kg/m^2. Every 5 kg/m^2 increase in BMI >25 equates to a higher hazard ratio (HR) for mortality and decreased life expectancy. Overweight, obesity, and extreme obesity have an HR of 1.07 (95% CI 0.91–1.26), 1.41 (95% CI 1.16–1.73), and 2.46 (95% CI 1.91–3.16), respectively.

Effect of Weight Loss on Risk for Cardiovascular Disease

Lifestyle-Induced Weight Loss

Weight loss in patients with obesity has been linked to reduced risk of developing CVD. Intentional weight loss improves systolic blood pressure, triglyceride levels, and fasting blood glucose. Lifestyle-induced weight loss has been the target of multiple studies. The Look AHEAD trial, one of the largest randomized controlled trials on lifestyle-induced weight loss, aimed to test the long-term health effects of intensive lifestyle interventions versus standard support and education in patients with both T2DM and overweight/obesity. Patients who lost 5% to 10% of their excess body weight had improved CVD risk factors, including BMI, blood pressure, HDL, and triglycerides (Table 5). Although the Intensive Lifestyle Intervention group was able to achieve significant weight loss of 8.5% at 1 year compared with 0.6% in the support and education group, they had significant weight regain and at year 8 had lost 4.7% and 2.1% of excess body weight, respectively. The two groups had no significant difference in CVD morbidity or mortality, the study's original primary outcome, or in cognitive function or cancer rates.

TABLE 5 Mean Changes in Weight and Risk Factors for Cardiovascular Disease in the Intensive Lifestyle Intervention and Diabetes Support and Education Groups and the Difference Between Groups*

Measure	DSE	ILI	Between-Group Mean Difference	*P*-value
Weight, %initial weight	−0.88	−6.15	−5.7	<0.001
HbA_{1c} level	−0.09	−0.36	−0.27	<0.001
SBP	−2.97	−5.33	−2.36	<0.001
DBP	−2.48	−2.92	−0.43	0.01
HDL	1.97	3.67	1.70	<0.001
TG	−19.75	−25.56	−5.81	<0.001
LDL (adjusted for medication use)	−9.22	−8.75	0.47	0.42

*Averaged over 4 years as reported in 2010 by the Look AHEAD group.
DBP, Diastolic blood pressure; *HbA1c,* hemoglobin A1c; *ILI,* intensive lifestyle intervention; *HDL,* high-density lipoprotein cholesterol; *LDL,* low-density lipoprotein cholesterol; *SBP,* systolic blood pressure; *TG,* triglycerides.

Drug-Induced Weight Loss

Pharmaceutical interventions to target weight loss are on the rise. Multiple drugs developed over the past several decades have had limited use as a result of cardiovascular and neurologic adverse effects, leading to a limited number of medications approved by the US Food and Drug Administration (FDA) for chronic weight management. Orlistat, approved in 2007, is a lipase inhibitor and works by preventing around 30% of dietary fat from being absorbed. Mean body weight loss with orlistat ranges from 4.6% to 10.2%, with average weight regain of 32.5% of initial weight loss. Phentermine/topiramate, a combination of sympathomimetic and antiepileptic medications approved in 2012, has demonstrated 9.3% to 10.5% weight loss over 2 years. Naltrexone/bupropion, a combination of an opioid antagonist and a dopamine/norepinephrine reuptake inhibitor, was approved in 2014. The drug is associated with a variable 3.7% to 8.1% weight loss and has been shown to transiently increase blood pressure, although with no significant difference in cardiovascular events.

Liraglutide is a glucose-like peptide-1 (GLP-1) receptor agonist daily injection that was approved in 2014. It has shown 4.9% to 7.4% mean reductions in body weight in obese patients without diabetes. It has been shown to decrease CVD risk in patients with diabetes, but this reduced risk has not been shown to be weight dependent. Lorcaserin, a serotonin receptor activator initially approved in 2012, has recently been withdrawn as a result of concerns for adverse events including increased occurrence of cancer.

A once-weekly injection with semaglutide 2.4 mg has demonstrated significant weight reduction improvement over prior weight-loss medications. In a double-blind, randomized controlled trial of 1961 obese adults (or BMI ≥27 with obesity-related comorbid conditions), semaglutide demonstrated a 12.4% body weight loss over placebo at 68 weeks. Follow-up studies will help determine whether this weight loss is sustainable longer-term, but initial data are promising. Additional studies on the combination of surgical and medical weight loss may shed light on the optimal strategy to decrease CVD risk in overweight and obese populations.

Metabolic and Bariatric Surgery: Overview of Common Procedures

Metabolic and bariatric surgery is the most effective intervention for significant and sustained weight loss. The common bariatric procedures—sleeve gastrectomy, gastric bypass, gastric banding, and biliopancreatic diversion or duodenal switch—are illustrated in Figure 1. These procedures differ in their effects on the magnitude and durability of weight loss as well as the degree of metabolic disease resolution (Table 6). The benefit of metabolic and bariatric surgery for reduction of cardiovascular risk and metabolic disease has been repeatedly demonstrated in longitudinal studies. This benefit has also been translated to improved quality of life and overall survival, although randomized controlled trials assessing cardiovascular outcome have yet to be conducted. Bariatric and metabolic surgery is believed to improve cardiovascular risk profile primarily through weight loss and possibly through additional mechanisms such as reduced inflammation. The safety of metabolic and bariatric procedures has been well established and has improved with advances in laparoscopic surgery. The risk profiles differ between types of bariatric and metabolic surgery and should be discussed with the patient during the informed consent process (Table 7).

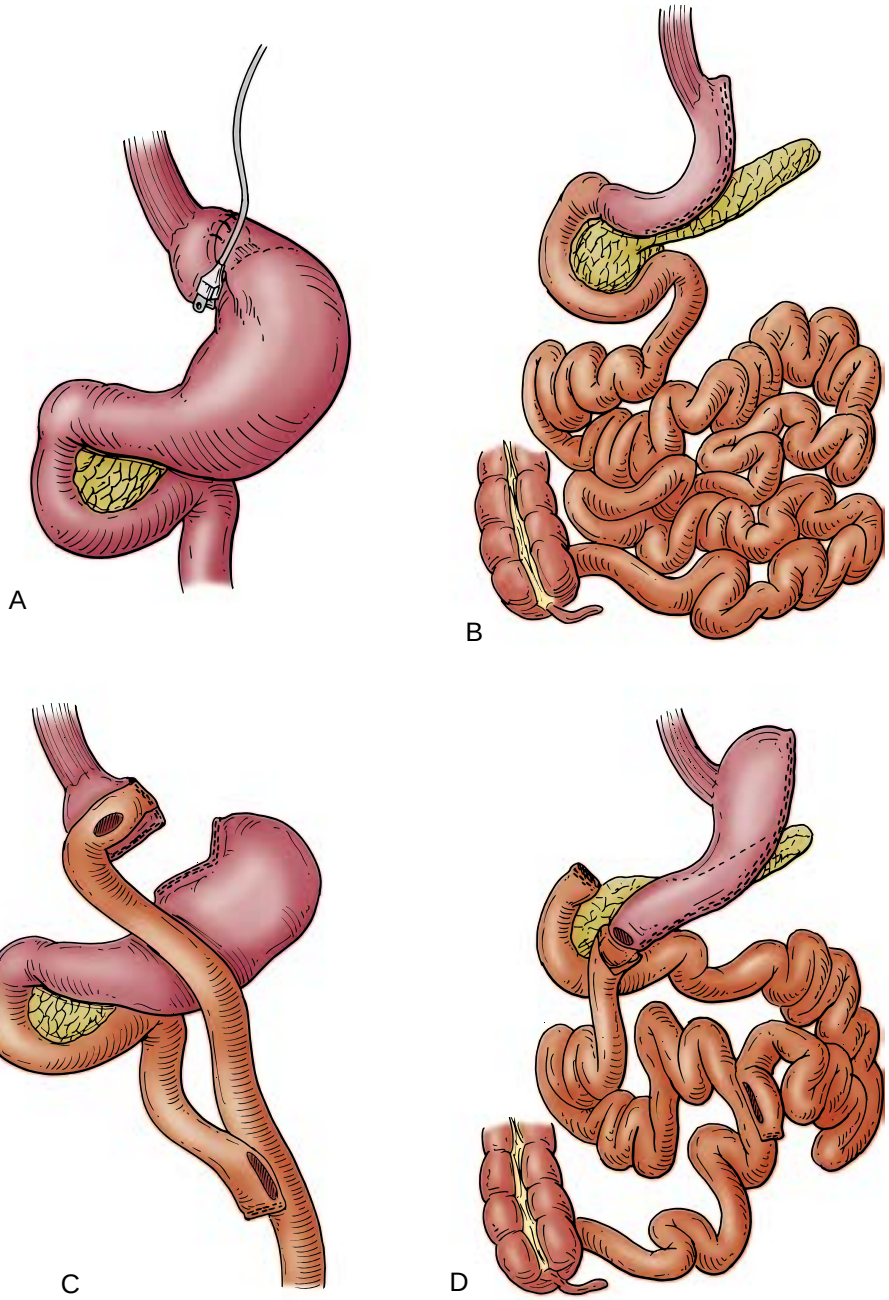


FIG. 1 Commonly performed bariatric procedures. **(A)** Adjustable gastric banding. **(B)** Sleeve gastrectomy. **(C)** Roux-en-Y gastric bypass. **(D)** Biliopancreatic diversion (illustrated with duodenal switch).

Effect of Bariatric Surgery on Cardiovascular Disease Risk Factors

Surgically induced weight loss and associated blood pressure improvement contribute significantly to decreasing CVD risk. Independent of weight loss, bariatric surgery reduces CVD risk by improving glucose and lipid metabolism and reducing systemic inflammation.

Glycemic Control

Bariatric surgery has been known as the most effective therapy to improve insulin resistance and T2DM since the landmark paper by Pories et al. described the durable effect on diabetes control and the safety of bariatric surgery in 1995. Multiple studies have since confirmed the therapeutic effect of the various bariatric procedures in patients with prediabetes and T2DM.

The mechanisms for postoperative improvement in diabetes and glucose metabolism remain an active area of research. Clinically, however, improved glycemic control is evident within days after surgery when the amount of weight loss is insufficient to explain the observed improvement. Schauer et al. reported that 30% of patients who were on oral hypoglycemic agents exhibited immediate postoperative independence from these medications after RYGB. Prolonged remission of diabetes after bariatric surgery has also been described. In a study published by Pories et al, 83% of 146 patients with non–insulin-dependent diabetes mellitus maintained normal blood glucose and HbA1c after RYGB. A randomized controlled

TABLE 6 Weight Loss and Resolution Rates of Obesity-Associated Comorbidities After Weight-Loss Surgery According to Procedure

	Gastric Banding	Gastric Bypass	BPD ± DS**	Sleeve Gastrectomy	Total
Excess weight loss	46%[1]	57%[1]	74%[1]	58%[1]	61%[2]
Resolution of type 2 diabetes	57%[3]	80%[3]	95%[3]	85%[4]	78%[3]
Resolution of hyperlipidemia	59%[2]	97%[2]	99%[2]	50%[4]	79%[2]
Resolution of hypertension	43%[2]	68%[2]	83%[2]	62%[5]	62%[2]
Resolution of sleep apnea	95%[2]	81%[6]	92%[2]	89%[6]	86%[2]

[1]O'Brien PE, Hindle A, Brennan L, et al. Long-term outcomes after bariatric surgery: a systematic review and meta-analysis of weight loss at 10 or more years for all bariatric procedures and a single-centre review of 20-year outcomes after adjustable gastric banding. *Obes Surg*. 2019;29(1):3–14.
[2]Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: A systematic review and meta-analysis. [published correction appears in *JAMA*. 2005;293(14):1728]. *JAMA*. 2004;292(14):1724–1737.
[3]Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122(3):248–256.e5.
[4]Perathoner A, Weißenbacher A, Sucher R, et al. Significant weight loss and rapid resolution of diabetes and dyslipidemia during short-term follow-up after laparoscopic sleeve gastrectomy. *Obes Surg*. 2013;23(12):1966–1972.
[5]Graham C, Switzer N, Reso A, et al. Sleeve gastrectomy and hypertension: a systematic review of long-term outcomes. *Surg Endosc*. 2019;33(9):3001–3007.
[6]Hariri K, Kini SU, Herron DM, Fernandez-Ranvier G. Resolution of symptomatic obstructive sleep apnea not impacted by preoperative body mass index, choice of operation between sleeve gastrectomy and Roux-en-Y gastric bypass surgery, or severity. *Obes Surg*. 2018;28(5):1402–1407.
***BPD,* Biliopancreatic diversion; *DS,* biliopancreatic diversion with duodenal switch.

trial by Mingrone et al. comparing metabolic surgery to conventional medical therapy on T2DM demonstrated an 82% remission rate in surgical patients at 2 years. At 10-year follow-up, the surgical arm maintained a 37.5% remission rate compared with 5.5% in the medical therapy arm.

Long-term durability of remission of T2DM has been shown in the Swedish Obese Subjects (SOS) project, a nonrandomized, matched, prospective observational study that enrolled more than 4000 obese patients and followed them over time. This study showed reversal of diabetes in 72.3% of the surgical group as compared with just 16.4% of the control group at 2 years of follow-up (OR 40.5, 95% CI 21.0–78.2; $P < 0.001$). Weight gain after surgery was associated with a relapse of diabetes. At 10 years, 50% of those patients who had previous T2DM remission had relapsed. At 15 years, diabetes remission rates had decreased to 30% in the surgical group, which was still a substantial improvement over 6.5% in the control group (OR 6.3, 95% CI 2.1–18.9; $P < 0.001$). Although bariatric surgery has been associated with hypoglycemic events in patients without diabetes, patients with baseline diabetes were at no increased risk of hypoglycemic episodes after undergoing bariatric surgery.

Meta-analyses of smaller randomized controlled trials have supported the durability of diabetes remission after bariatric surgery. A 2021 meta-analysis by Carmona et al. reviewed the results of 11 primary trials with a minimum of 5-year follow up. The analysis compared the efficacy of different bariatric surgeries and medical treatment on T2DM remission in patients with T2DM and BMI ≥25 kg/m^2. Compared with standard medical treatment, laparoscopic one anastomosis gastric bypass (RR 0.14, 95% CI 0.04–0.49), duodenal switch (RR 0.17, 95% CI 0.05–0.55), RYGB (RR 0.21, 95% CI 0.07–0.63), and vertical sleeve gastrectomy (VSG) (RR 0.26, 95% CI 0.08–0.79) were all significantly more likely to result in full diabetes remission at 5 years.

Randomized controlled trials, as shown earlier, have begun to provide the strongest evidence for the superiority of bariatric and metabolic surgery to medical therapy alone in improving glycemic control and diabetes remission. Initial results from the Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial were released in 2012. This randomized controlled trial enrolled 150 patients with T2DM (mean HbA1c 9.2%) into intensive medical therapy versus RYGB or VSG plus medical therapy. This 1-year follow-up showed an HbA1c <6% in 42% in the RYGB group, 37% in the VSG group, and 12% in the medical therapy alone group. In 2017, the group published 5-year follow-up results with HbA1c <6% in 22.4% in the RYGB group, 16.9% in the VSG group, and none in the medical therapy alone group. In 2022, Kirwan et al. reported data on 316 patients with T2DM previously enrolled in the STAMPEDE trial and three other ongoing trials (TRIABETES, SLIMM-T2D, and CROSSROADS) to further understand diabetes remission and bariatric surgery. The 3-year data from 160 patients assigned to bariatric surgery were compared with 76 patients assigned to medical and lifestyle therapy. Remission of T2DM (defined as HbA1c ≤6.5% for 3 months without glucose-lowering therapy) at 3-year follow-up was achieved in 37.5% of the surgical group and only 2.6% of the medical/lifestyle treatment group ($P < 0.001$). HbA1c decreased by an average of 1.9 (± 2.0) in the surgery group versus only 0.1 (± 2.0) in the medical/lifestyle group ($P < 0.001$). The decrease in fasting plasma glucose and BMI was also greater in the surgical group.

Another randomized controlled trial by Mingrone et al. reported their initial 2-year follow-up data on bariatric surgery versus medical therapy in patients with T2DM >5 years and BMI ≥35 kg/m^2 in 2012. Diabetes remission was defined as fasting plasma glucose <5.55 mmol/L and HbA1c <6.5% without glucose-lowering medications. Two operations, RYGB and biliopancreatic diversion (BPD), were grouped separately. Diabetes remission at 2 years was 95% in the BPD group, 75% in the RYGB group, and did not occur in any patients in the medical therapy alone group. Post hoc analysis showed that preoperative BMI and postoperative weight loss were not predictive of the degree of improvement in glycemic control in surgical groups. The 5-year follow-up showed a continued 63% remission of T2DM in the BPD group and 37% in the RYGB group,

TABLE 7 Postoperative Complications Associated with Bariatric Procedures

	Complications	
Procedure	**Early Postoperative Period (<30 Days)**	**Late**
RYGB	Anastomotic leak with peritonitis Abdominal abscess Pulmonary embolism Bleeding Pulmonary complications Acute distal gastric dilation Roux limb obstruction Wound infection	Stomal stenosis Marginal ulcer Dumping syndrome Intestinal obstruction Internal hernia Incisional hernia Cholecystitis Vitamin and mineral deficiencies Weight regain Hypoglycemia
BPD ± DS	Same as RYGB	Same as laparoscopic RYGB with the following being more common in the BPD procedure than in RYGB if aggressive prophylactic measures are not followed postoperatively: Anemia Protein-calorie malnutrition Vitamin B_{12} deficiency Hypocalcemia Osteoporosis Fat-soluble vitamin deficiency Night blindness
SG	Staple line leak Abscess Hemorrhage Sleeve stricture Wound infection	Intractable nausea +/– vomiting Reflux symptoms Gastric dilation Weight-loss failure Weight regain
AGB	Hemorrhage Wound infection Food intolerance Reflux Nausea +/– vomiting Band migration Wound infection	Reflux symptoms Erosive esophagitis Esophageal dilation Pouch enlargement Band migration Gastric prolapse Vomiting Tubing-related problems Reservoir leakage Band erosion Weight-loss failure Lower average weight loss

AGB, Adjustable gastric banding; *BPD,* biliopancreatic diversion; *BPD ± DS,* biliopancreatic diversion with or without duodenal switch; *RYGB,* Roux-en-Y gastric bypass; *SG,* sleeve gastrectomy.

with none of the medical therapy patients achieving remission. In 2021, the group published 10-year follow-up data demonstrating continued efficacy of surgery on T2DM. Remission rates were 50% for the BPD group and 25% for the RYGB group. The only participant in the medical therapy group who achieved remission at 10 years did so after crossover to undergo bariatric surgery.

Bariatric surgery for patients with T2DM has been widely considered an acceptable therapy in patients with BMI ≥35 kg/m^2; surgical treatment of class 1 obesity (BMI 30–35 kg/m^2) and lower has been controversial. In 2011, the IDF recognized the role of bariatric surgery in the treatment of class 1 obesity patients whose diabetes cannot be adequately controlled by optimal medical regimens, especially in the presence of other major CVD risk factors. Since 2017, the American Diabetes Association has recommended bariatric surgery in class 1 obesity for patients unable to achieve adequate HbA1c with medical therapy. The American Society for Metabolic and Bariatric surgery (ASMBS) currently recommends bariatric surgery as a safe option for patients with BMI ≥30 kg/m^2 who have not been able to achieve durable weight and comorbidity control with nonsurgical methods.

Lipid Metabolism

Bariatric surgery improves dyslipidemia, a significant component of CVD risk characterized by low HDL cholesterol, hypertriglyceridemia, and elevated LDL cholesterol. In 2021, Liu et al. reported the results of a meta-analysis of 35 randomized controlled trials evaluating the effect of bariatric surgery versus medical therapy on dyslipidemia. Bariatric surgery was found to significantly reduce total cholesterol, triglycerides, and LDL cholesterol and increase

HDL cholesterol. These changes were seen more often after procedures with malabsorptive components, such as RYGB and BPD. A meta-analysis of bariatric surgery outcomes the same year by Lee et al. compared resolution of dyslipidemia between sleeve gastrectomy and RYGB, the two most common bariatric surgical procedures. RYGB was found to result in resolution more often than sleeve gastrectomy at 1 year (RR 0.58, 95% CI 0.46–0.73, $P < 0.001$) and at 5 years (RR 0.68, 95% CI 0.46–0.99, $P = 0.04$).

Inflammatory State

Adipose tissue, once considered an inert energy storage tissue, has been appreciated as an endocrine organ since the early 2000s. It produces an array of adipokines with inflammatory and immune functions, and researchers have begun to describe how bariatric surgery alters these important factors. Chronic systemic inflammation, often seen in central obesity, causes endothelial dysfunction and accelerates atherosclerosis, leading to increased CVD risk.

A 2019 meta-analysis of 116 studies aimed to describe the effect of bariatric surgery on inflammatory markers. C-reactive protein, a key acute-phase reactant of inflammation, was shown to decrease by 5.30 mg/L (95% CI −5.46 to −5.15, $P < 0.001$). IL-6, a proinflammatory cytokine in blood vessels, also produced by adipocytes, was found to decrease by 0.58 pg/mL (95% CI −0.64 to −0.53, $P < 0.001$). Tumor necrosis factor alpha (TNFα), which is involved in vasodilation, leukocyte adhesion to epithelium, blood coagulation, and oxidative stress, was found to decrease by 0.20 pg/mL (95% CI −0.39 to −0.02, $P = 0.031$). A study of 40 patients with significant weight regain after bariatric surgery showed lower levels of IL-6 than their matched counterparts who had not undergone surgery, suggesting that these patients may have maintained decreased levels of IL-6, even after regaining weight. Bariatric surgery may have lasting effects not related to weight-loss maintenance that reduce CVD risk.

Effect of Bariatric Surgery on Cardiovascular Disease and Mortality

Multiple observational studies have shown bariatric surgery to be a safe procedure associated with a reduction in overall mortality (Table 8). In a retrospective case control study in 2004, the McGill Bariatric Cohort Study was among the first to report the association of reduced mortality with excess weight loss. Comparing over 1000 patients who underwent bariatric surgery to over 5700 control patients with normal BMI, they showed that a 67% excess weight loss at 5 years decreased risk of overall mortality by 89%. More recently in 2021, Syn et al. reported a meta-analysis involving 174,772 patients showing that metabolic and bariatric surgery was associated with an increased median life expectancy of 6.1 years (95% CI 5.2–6.9) when compared with usual medical treatment.

Although initial studies focused on improved CVD risk profile and overall mortality after bariatric surgery, newer studies have shed light on the translation of risk-profile improvement to a decrease in CVD morbidity and mortality. The SOS study is the longest running prospective study of bariatric surgery outcomes to date. The SOS study compares 2007 obese individuals (BMI ≥34 kg/m^2 in men; BMI ≥38 kg/m^2 in women) who underwent bariatric surgery (gastric bypass 13.2%, gastric banding 18.7%, or vertical banded gastroplasty 68.1%), 2040 well-matched controls, and 1135 participants in a reference population. Mortality within 90 days of surgery was 0.2%, and 2.9% of patients in the surgical group required repeat surgery. A recent update in 2020 of over 20-year follow-up reported 22.8% mortality in the surgical group and 26.4% mortality in the control group (HR 0.77, 95% CI 0.68–0.87, $P < 0.001$). CVD-specific mortality was also reported with an HR of 0.70 (95% CI 0.57–0.85). The median life expectancy in bariatric surgery patients was 5.5 years shorter than the general population reference group, but 3 years longer than the nonsurgical control group. CVD incidence after controlling for risk profile at baseline was significantly lower in the surgical group

TABLE 8 Observational Studies Reflecting the Mortality Risk Reduction with Bariatric Surgery Compared with Control Groups

Serial	Study	Publication Year	Sample Size		Mortality Risk Reduction (%)	Procedures
			Control (*n*)	Surgery (*n*)		
1	MacDonald KG et al. (J Gastrointest Surg)	1997	78	154	68	Open RYGB
2	Christou NV et al. (Ann Surg)	2004	5746	1035	89	79.2% Open RYGB 2.2% Lap RYGB 18.7% VBG
3	Flum DR et al. (J Am Coll Surg)	2004	62,781	3328	33	RYGB
4	Adams TD et al. (N Engl J Med)	2007	7925	7925	40	RYGB
5	Busetto L et al. (Surg Obes Relat Dis)	2007	821	821	60	AGB
6	Peeters A et al. (Ann Surg)	2007	2119	966	72	AGB
7	Sjostrom L et al. (N Engl J Med)	2007	2037	4047	29	18.7% ABG 13.2% RYGB 68.1% VBG
8	Sowemimo OA et al. (Surg Obes Relat Dis)	2007	112	908	82	RYGB

TABLE 8 Observational Studies Reflecting the Mortality Risk Reduction with Bariatric Surgery Compared with Control Groups —cont'd

Serial	Study	Publication Year	Sample Size		Mortality Risk Reduction (%)	Procedures
			Control (*n*)	Surgery (*n*)		
9	Perry CD et al. (Ann Surg)	2008	11,903	11,903	50	0.3% AGB 67% Open RYGB 28.5% Lap SG or RYGB 1.8% VBG 2.4% Revision
10	Marsk R et al. (Br J Surg)	2010	5327	2765	30	25.5% AGB 31.7% RYGB 6.3% Jejunoilieal Bypass 36.5% VBG
11	Maciejewski MK et al. (JAMA)	2011	41,244	850	36	AGB VBG RYGB SG
12	Johnson RJ et al. (Am Surg)	2012	903	349	40	AGB RYGB
13	Scott JD et al. (Surg Obes Relat Dis)	2013	1327*	4747	25-50	AGB RYGB SG
14	Arterburn DE et al. (JAMA)	2015	7462	2752	53	10% AGB 74% RYGB 15% SG 1% Other
15	Eliasson B et al. (Lancet Diabetes Endocrinol)	2015	6132	6132	58	RYGB
16	Guidry CA et al. (Am J Surg)	2015	802	802	52	RYGB
17	Pontiroli AE et al. (Cardiovasc Diabetol)	2016	681	385	59	AGB
18	Lent MR et al. (Diabetes Care)	2017	2428	3242	56	RYGB
19	Reges O et al. (JAMA)	2018	25,155	8385	50	43% AGB 17% RYGB 40% SG
20	Fisher DP et al. (JAMA)	2018	14,934	5301	67	7% AGB 76% RYGB 17% SG
21	Moussa OM et al. (Ann Surg)	2019	179,375	3842	51	All
22	Doumouras et al. (Ann Intern Med)	2020	13,679	13,679	32	87% RYGB 13% SG
23	Moussa et al. (Eur Heart J)	2020	3701	3701	75	All
24	Stenberg et al. (PLoS Med)	2020	26,199	11,863	16	90% RYGB 10% SG
25	Carlsson et al. (N Engl J Med)	2020	2040	2007	23	69% VGB 18% AGB 13% RYGB
26	Courcoulas et al. (Ann Surg)	2021	87,965	31,158	57 (RYGB) 72 (SG)	45% SG 55% RYGB

*The control group assigned in this study comprised patients undergoing nonbariatric gastrointestinal surgery.
AGB, Adjustable gastric banding; *RYGB,* Roux-en-Y gastric bypass; *SG,* sleeve gastrectomy; *VBG,* vertical gastric banding.

(HR 0.70, 95% CI 0.57–0.85). Compared with controls, the adjusted HR of bariatric surgery for myocardial infarction was 0.51 (95% CI 0.33–0.79), for heart failure was 0.52 (95% CI 0.31–0.88), and for stroke was 0.45 (95% CI 0.24–0.84). Despite significant improvement in cardiovascular outcomes over controls, when compared with the reference population group, HR for CVD-related mortality in the surgical group was 2.64 (95% CI 1.78–3.91). Bariatric surgery mitigates cardiovascular morbidity and mortality in obese patients, but this risk is still elevated compared with that of the general population (Fig. 2). Benefits of bariatric surgery were even when analyzed by subgroups of BMI and cardiovascular risk factors, suggesting limited usefulness of these factors in estimating potential benefits to patients.

In patients with obesity and T2DM who are at significant risk of CVD, bariatric surgery has been associated with significantly lower risk of major adverse cardiovascular events (MACE) when compared with usual care. A retrospective cohort study of patients with diabetes and obesity in the Cleveland Clinic Health System matched 2287 patients who underwent metabolic surgery 1:5 with nonsurgical controls. Cumulative incidence of MACE at 8 years was 30.8% in the surgical group and 47.7% in the nonsurgical group (absolute 8-year risk difference 16.9% [95% CI 13.1–20.4], $P < 0.001$) (Fig. 3).

Nonalcoholic steatohepatitis (NASH), a form of hepatic injury resulting from metabolic syndrome, is strongly linked to CVD. Previously, no therapy was shown to reduce the risk of MACE in these patients. The Surgical Procedures and Long-term Effectiveness in NASH Disease and Obesity Risk (SPLENDOR) study, a prospective controlled cohort study, has revealed that patients with NASH who undergo bariatric surgery are at significantly reduced risk of developing MACE. This study included 650 patients who underwent bariatric surgery and 508 patients in the control group. The 10-year cumulative incidence of MACE was 8.5% in the surgical group and 15.7% in the control group (adjusted absolute risk difference: 13.9% (95% CI 5.9–21.9).

Recent insight to the role of bariatric surgery in obese patients who already have CVD has come from a retrospective cohort based on database information in Ontario, Canada. In 2021, Doumouras et al. reported on MACE in 2638 patients with previous ischemic heart disease or heart failure (1319 bariatric surgery patients and

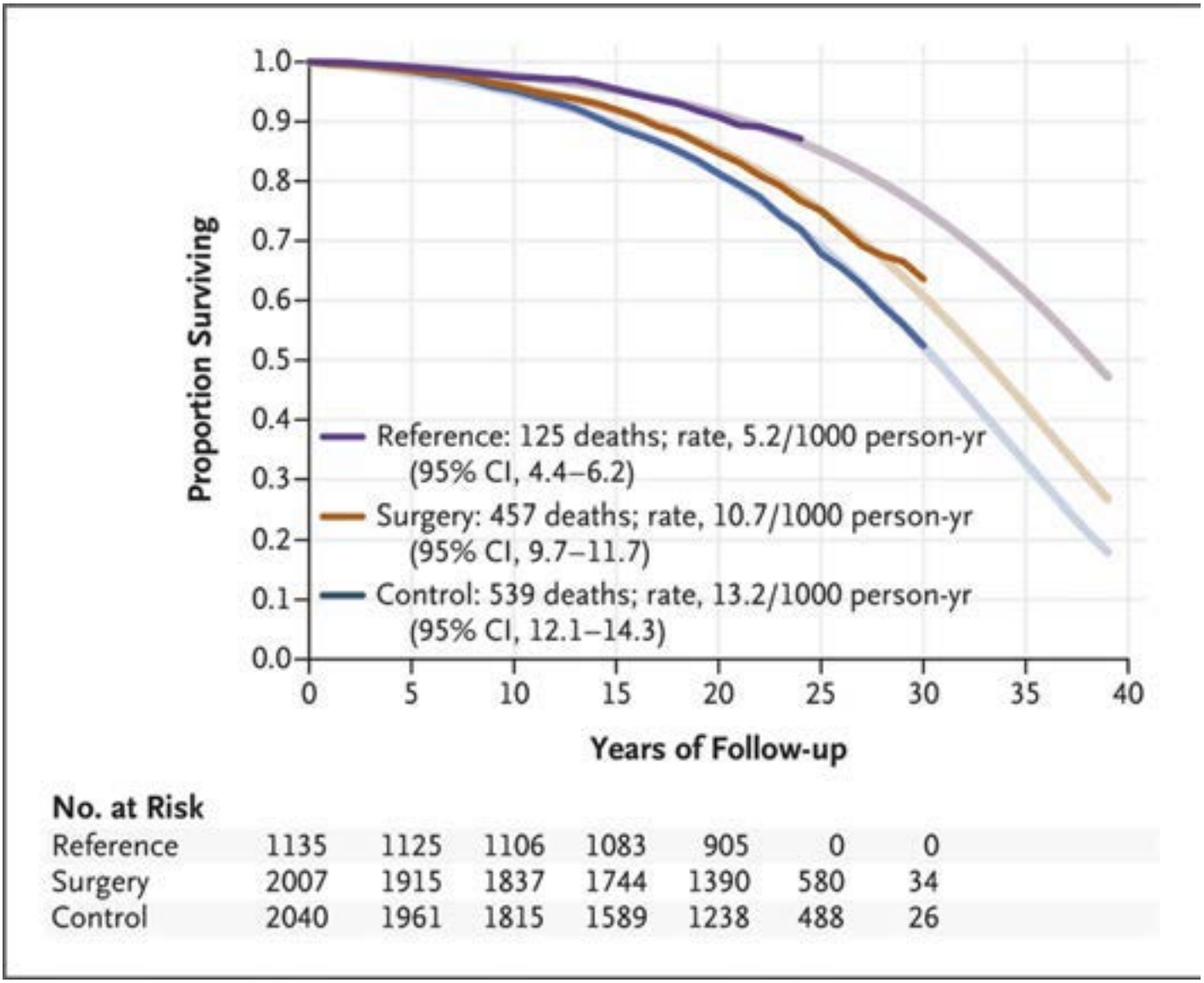


FIG. 2 Survival in the surgery and control groups and in the reference cohort. *(From Carlsson LMS, Sjöholm K, Jacobson P, et al. Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study.* N Engl J Med. *2020;383[16]:1535–1543.)*

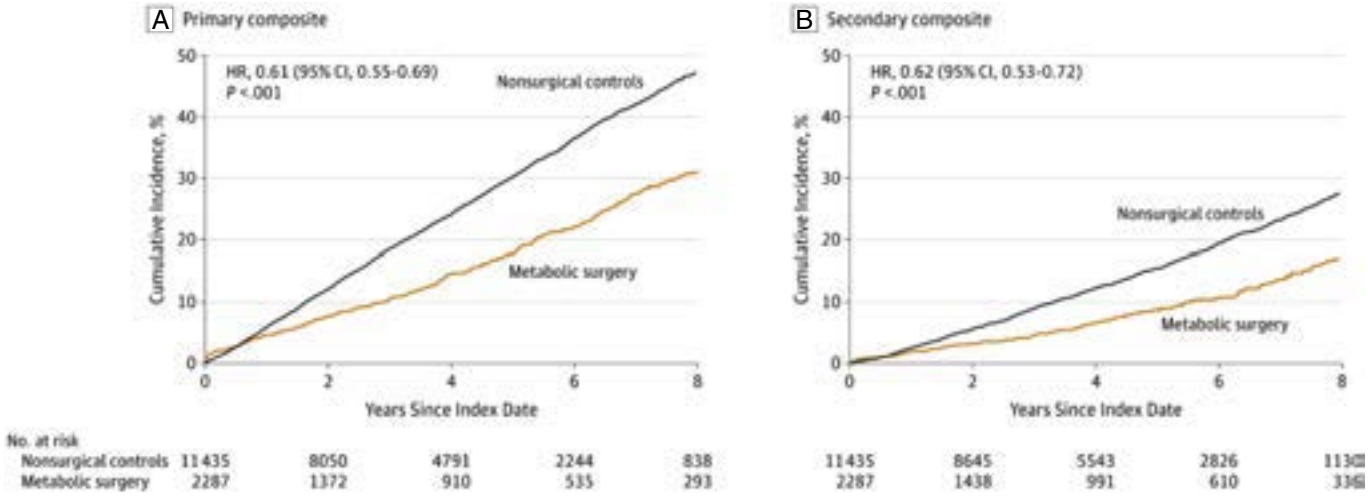


FIG. 3 Eight-year cumulative incidence estimates for two composite end points. The primary end point was the incidence of extended major adverse cardiovascular events (MACE; composite of 6 outcomes), defined as first occurrence of coronary artery events, cerebrovascular events, heart failure, atrial fibrillation, nephropathy, and all-cause mortality, recording the first occurrence after the index date as the event date. The secondary composite end points included the three-component MACE (all-cause mortality, myocardial infarction, and ischemic stroke), recording the first occurrence after the index date as the event date. For both end points, the median observation time was 4.0 years (interquartile range [IQR] 2.1–6.1) for nonsurgical patients and 3.3 years (IQR 1.2–6.3) for surgical patients. *HR,* Hazard ratio. *(From Aminian A, Zajichek A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA. 2019;322[13]:1271–1282.)*

1319 matched controls) at a median follow-up of 4.6 years. MACE occurred in 11.5% of the surgery group and in 19.6% of the control group (adjusted HR 0.58 [95% CI 0.48–0.71]). Cardiovascular mortality in the surgical group was significantly lower, with an HR of 0.35 (95% CI 0.15–0.80).

Bariatric surgery may decrease CVD risk through direct end-organ effects on the heart. A recent study of echocardiographic changes in ventricular systolic function in patients with obesity who underwent bariatric surgery showed that patients with heart failure before surgery had a significant improvement in left ventricular ejection fraction (LVEF) from 38.79% ± 13.26 preoperatively to 48.47% ± 14.57% ($P = 0.039$) 18 months after surgery. There was no significant change in LVEF in patients without prior heart failure.

CONCLUSION

The pandemics of obesity, diabetes, and CVD have a multifaceted impact on both individuals and societies. The surgeon's role in reversing and mitigating the damage of these pandemics cannot be understated as research into advancing bariatric therapies and understanding mechanisms of bariatric surgery continues. Bariatric and metabolic surgery is no longer simply beneficial in weight loss but is proving to have remarkable metabolic and cardiovascular effects in the short and long term, and its safety profile continues to improve. National and international societies have begun to understand the potential role of bariatric surgery in patients with any level of obesity and poorly controlled T2DM, especially in the presence of other CVD risk factors. Results of large-scale systematic reviews and important long-term prospective studies, like the SOS study, all point to the important role of bariatric surgery in improving cardiovascular risk profile and decreasing long-term cardiovascular morbidity and mortality in patients with obesity. However, many clinicians and investigators alike argue that clear and convincing evidence of cardiovascular risk reduction after bariatric surgery remains elusive until such time that a well-conducted randomized controlled trial provides definitive supporting evidence. Regardless of the reality of conducting such a definitive trial, surgeons and scientists will continue to find innovative ways to study and serve patients with obesity and CVD.

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Nonmelanoma Skin Cancers

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Common nonmelanoma skin cancers (NMSCs) include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The common forms of skin cancer arise, respectively, from the upper layers (epidermis) of the skin:

- Basal cell: arises from the basal layer of the epidermis
- Squamous cell: arises from the superficial layer of the epidermis
- Melanoma: arises from the basal pigmented cells of the epidermis

Surgeons are often called upon to evaluate cutaneous lesions and malignancy. This chapter reviews cutaneous nonmelanoma malignancies and provides suggestions for evaluation, planning, and treatment.

BACKGROUND

NMSCs are the most common human malignancies, occurring more frequently than all other solid tumors combined. There are over 80 different NMSCs. The most common of these tumors are BCC and SCC, although several other types exist and will be discussed briefly. The frequency of these cancers is such that almost everyone living in the United States to 80 years of age will have one; as the life span increases, these malignancies become more common as the effects of sun exposure and other causative factors become more important. These are as follows:

- Reduction of protective factors in the atmosphere
- Reduction with aging in previously very effective local skin immune mechanisms responsible for tumor surveillance
- Increased sun exposure and the general reduction of immunity with progressive aging

These factors and the constantly increasing life span keep the incidence of these common malignancies increasing rapidly. Progress in the past 40 years has produced vast improvements in the classification, diagnosis, and treatment of NMSCs. Accurately identifying lesions early in their course allows classification and directed differential treatment for improved outcomes. Not infrequently, patients ignore their initial lesions, permitting development of large tumors. Disfigurement may result as not only skin tissue structures are involved but also muscle, nerves, cartilage, and bone.

Recent figures indicate that the annual cost of treating basal and squamous cell cutaneous cancer in the United States will exceed over $8.1 billion dollars. Although most of these skin lesions have a rather benign behavior as far as cancers are concerned, certain more aggressive subtypes must be identified and treated differently with wider excisions, margin evaluation, possible sentinel lymph node biopsies, and continued periodic observation for regional and distant metastatic spread. Specifically, these subtypes need complete negative peripheral and deep margin confirmation before reconstruction and, subsequently, consideration for frequent postoperative observation. Less commonly, some of these patients will need radiation and medical oncologic treatment, in addition to surgery. Although cutaneous SCC is curable with local excision for the most part, tumor recurrence, metastasis, morbidity, and even disease-specific death does occur. It is estimated that 5600 to 12,600 US patients with cutaneous SCC will develop nodal metastasis, and 4000 to 8800 will die from the disease. Although few surgeons would recognize it initially, these numbers of disease-specific death are similar to deaths from melanoma, leukemia, non-Hodgkin's lymphoma, and renal and bladder cancers.

RISK FACTORS AND PRECURSOR LESIONS

Risk factors for BCC and SCC include a number of carcinogens. The most agreed on is sunlight. Cumulative exposure to sun, especially tropical sun without protection, in fair-skinned individuals who burn rather than tan, is the most generally discussed and accepted risk. Tumors are more common on sun-exposed surfaces such as the face, scalp, and neck. Sun lamp or ultraviolet light treatment for psoriasis is a risk factor for squamous cell skin cancers. Microtrauma to the skin contributes to the etiology of basal cell skin cancers. Radiation exposure, such as historically commonly delivered for acne in teenagers, also predisposes to skin cancer and thyroid cancer.

Because sun exposure has been implicated in the predisposition to these lesions, there has been considerable attention to programs aimed toward preventing excess exposure, especially sunburns. Two guides to this prevention are "Safe Sun Guidelines" and "Skin Protection from Ultraviolet Light Exposure" (available from the Skin Cancer Foundation). The exact effectiveness of prophylaxis is not known but is under extensive study. Sun-protective clothing is also offered.

Genetics and hereditary conditions such as basal cell nevus syndrome predispose to the development of hundreds of multiple cutaneous basal cell skin cancers. Northern Europeans, such as those of Irish and English heritage, also seem more prone to the development of skin cancer. Mutations in the *RIS* and *DOS* oncogenes have been implicated as well as the sonic hedgehog-signaling pathway for basal cell skin cancer. The *PTCH* (patched) gene on chromosome 9Q has been suggested in the genesis of these lesions.

A very significant factor in the development of NMSC is associated with the advances in solid organ transplantation and the medical immunosuppression management for the maintenance of those organs. This progress has rendered longer life spans for these



FIG. 1 Cutaneous malignancies in organ transplant recipients are common and can behave more aggressively than in a similar, immunocompetent patient. This patient, who had a history of kidney transplantation, presented with two large, rapidly growing cutaneous tumors.

patients but is associated with a high risk of NMSC development as well as poor disease prognosis. We have also seen an increase of immunomodulating drugs for many medical conditions such as IBD, rheumatoid arthritis, and several others.

Fifty percent to 70% of OTR patients are affected by NMSC, and posttransplant BCC risk linearly increases, whereas SCC incidence rises exponentially (Fig. 1). This is reflected in the switch from a usual 4:1 ratio of BCC to SCC. SCC is the predominant OTR NMSC observed (although BCC is still highly prevalent). Merkel cell carcinoma occurs in OTRs at 5 to 10 times greater rates compared with the general population. Functional immunosuppression via HIV, lymphoma, and leukemia is a risk factor for NMSC and portends poor disease prognosis.

INITIAL EVALUATION OF SUSPECTED CUTANEOUS MALIGNANCY

Clinical Evaluation

History and physical examination remain the mainstay of initial diagnostic workup in cases of suspected cutaneous malignancy, noting identification of relevant risk factors, especially as they relate to prior carcinogen exposure, genetic cancer syndromes, or immunosuppression. A generalized skin and physical examination must include several key elements: (1) comprehensive skin evaluation of the surrounding area; (2) for lesions in the head and neck region, suspicion should be raised for those in the hair-bearing scalp or behind the ears. A complete regional examination of the skin and lymph nodes, and a complete, careful skin examination is performed because of the frequency of additional lesions. Attention should be directed particularly to sun-exposed skin sites. Patients with BCC and SCC are at increased risk for developing melanoma as well as additional NMSCs.

The clinical appearance of lesions such as squamous cell and basal cell are characteristic. They include color change, nodularity, and ulceration. Scaling and telangiectasia are frequent. Generally, the skin is reddened and thickened. Flaking or keratoses may be present, and both types of lesions frequently demonstrate surrounding premalignant lesions, such as keratoses. Frequently, squamous cells arise in areas of actinic keratoses, known *precursor lesions*.

The physical examination and evaluation of BCCs and SCCs first includes an analysis of tumor location and size. The tumor should be characterized by its apparent appearance as a particular skin cancer type. This evaluation should map the borders of the tumor, the entire local and regional area, and examine local lymph nodes. The lesion is classified as primary, recurrent, or one with less common features. The general health of the patient may dictate treatment considerations. Certain locations have been known to predispose to recurrence (such as fusion planes, which are areas where the primitive parts of the face come together in the fetus) in head and neck BCC, the areas of the nasal labial fold, and the groove between the nose and the cheeks. Certain areas such as the ear, mucosal surfaces, genitalia, and lip, tend to produce squamous cell skin cancers that possess a greater capacity for metastasis (Table 1). The "mask area" of the face has been known to have deeper skin cancers that are prone to incomplete resection and therefore have a higher risk for recurrence or persistence. Those lesions greater than 2 cm in diameter or more than 2 mm in thickness present more risk of persistence and recurrence than do smaller lesions.

In general, all lesions that have higher risk should have surgical complete margin assessment, preferably at the time of resection. Enlarged nodes must be carefully documented and warrant further diagnostic workup. Contrast-enhanced CT or MRI can be used for evaluation of clinically suspicious lymphadenopathy. Soft tissue disease including nerve invasion is best discerned by the use of MRI. Bone or cartilage invasion is best evaluated with CT. Ultrasound-guided fine-needle aspiration biopsy can be used to evaluate suspicious lymphadenopathy.

BASAL CELL CARCINOMA

BCC is the most common malignancy observed in adults. There are at least 5.5 million new BCC cases diagnosed each year in the United States alone; the risk of developing a BCC is more than 20% over the course of an entire lifetime, and its incidence more than 4 times that of SCC. The predominant risk factor for the development of BCC is ultraviolet light exposure, primarily UVB. The strength of

TABLE 1 High-Risk Clinical NMSC Parameters That Predict Incomplete Excision and/or Metastasis per the National Comprehensive Committee on Cancer

Anatomic location
- Mask areas of the face ≥6 mm are considered high risk
  - Central face: nose, lips
  - Eyelids, eyebrows, and periorbital skin
  - Ear, preauricular, and postauricular skin including postauricular sulcus
  - Temple
  - Genitalia
  - Hands, feet
- Nonmask areas of the face, head, and neck ≥10 mm
  - Cheeks
  - Forehead
  - Neck
  - Scalp
- Tumor size ≥2 cm on the trunk or extremities

Immunosuppression: seemingly low-risk tumors can be aggressive and metastatic
- Organ transplant recipients, particularly kidney and heart
- HIV
- Lymphoma and leukemia
- Long-term immunosuppression

Recurrence or chronic conditions
- Chronic inflammation (such as burn scar or other chronic wounds for SCC only)
- Prior radiation therapy

the causal relationship is not as clear as in the case of SCC. UV light induces inflammation of the skin that clinically results in visible erythema. On the molecular level, prostaglandin synthesis is markedly increased through the induction of cyclo-oxygenase-2 (COX-2). COX-2 is induced by inflammation. COX-2 inhibitors markedly decrease the incidence of cutaneous SCC and BCC. Other important risk factors include individuals with fairer skin, freckling, or blonde or red hair coloring. Genetic syndromes such as basal cell nevus syndrome and xeroderma pigmentosum are less common but strong risk factors. Finally, a history of immunosuppression, especially in the context of solid organ transplantation, poses a substantial risk for the development of BCC.

BCC is a mostly indolent entity from the perspective of metastatic or mortality risk. Untreated BCC is most concerning for local tissue destruction as opposed to systemic involvement or death. As a result, the goal of treatment is complete elimination of the primary lesion, sparing of as much healthy tissue as is reasonably achievable. Surgery is typically the preferred treatment and will be discussed in detail later. Less commonly, in circumstances such as very large tumors, cosmetically challenging areas, patients who cannot tolerate surgery, or for palliative treatment of BCC, radiotherapy can be employed with an expected success rate of 90% or more. The problem arises with identification of recurrence in the irradiated bed. There is no pathologic margin status to review and no specimen for microstaging. Medical therapies with topical 5-fluorouracil (5FU), topical imiquimod cream, and intralesional injection of interferon-α-2b have been studied and show some success. More recently, the novel hedgehog pathway inhibitor, vismodegib, has become an option for treatment of challenging or metastatic disease.

The majority (80%) of BCCs will manifest as lesions of the sun-exposed areas of the head and neck. Although it is tempting to treat the subtypes of BCC as superfluous minutiae, knowledge of the different pathologic entities that exist under the umbrella of BCC is essential to prognostication and appropriate treatment.

The most common subtype of BCC is the nodular type, comprising about 50% of all BCC tumors. This entity often presents with a shiny, pearly papule or nodule with a smooth surface and surrounding telangiectasias. Over time, lesions enlarge, ulcerate, and develop a more prominent rolled edge. The most likely location is the face, but other hair-bearing skin areas can also develop nodular BCC; non–hair bearing areas rarely develop these lesions.

Superficial BCC is the second most common, accounting for approximately 20% of all BCC tumors. Masses of this type are most often well-circumscribed, erythematous, and either truly flat macules/patches versus thin papules/plaques. An atrophic quality with associated hypopigmentation is common.

Nonaggressive subtypes of basal cell skin cancers include the keratotic, infundibulocystic, and nodular types and superficial types. Primary lesions in this group may generally be managed with 5-mm resection margins. It is very unusual for BCCs to exhibit lymph node or systemic metastasis. Lesions that do exhibit these aggressive traits have frequently been neglected, previously radiated, or multiply recurrent lesions.

Aggressive subtypes possessing more risk have more aggressive growth. These include the micronodular, infiltrative, sclerosing, morpheaform, and desmoplastic types and "basosquamous" carcinoma.

Some basal cells are pigmented and are easily confused with melanoma by appearance. The difference is often only established pathologically. Micronodular, infiltrative, and sclerosing tumors are notorious for a subclinical component that spreads laterally, leading to a high recurrence rate compared with other BCC subtypes. The final two subtypes worthy of a brief discussion are the basosquamous and morpheaform BCCs. The basosquamous family of tumors exhibit the worst features of BCC and SCC, most notably with tendencies for aggressive local growth, recurrence despite treatment, and metastasis in nearly 10% of cases. Morpheaform lesions have an indurated quality that is usually light pink to white in color with ill-defined borders and areas of regression. Aggressive local tissue destruction is the rule as opposed to the exception.

Basal Cell Nevus Syndrome

Basal cell nevus or Gorlin syndrome or nevoid BCC syndrome is an inherited disorder that presents with multiple cutaneous basal cells, multiple odontogenic keratocysts of the jaws, musculoskeletal and neurologic abnormalities, and pitting of the palmar and plantar surfaces of the skin. The disease is autosomal dominant. The lesions behave as basal cell skin cancers and are usually managed with surgical excision.

Usually, patients will have hundreds of basal cell skin cancers over the course of their lifetime, and many eventually succumb to the disease as sheer numbers overwhelm treatment. Topical chemotherapy agents have been used in an attempt to eradicate early superficial nonfacial basal cells, but surgical excisions are the treatment of choice.

SQUAMOUS CELL CARCINOMA

SCC of the skin is the second most common malignancy, with more than 3.3 million new cases diagnosed per year in the United States alone. Similar to BCC, cumulative UV radiation exposure is considered the strongest risk factor for the development of SCC. In addition to the mentioned risk factors for BCC, which also augment risk for SCC, tobacco smoking, human papillomavirus infection, and chronic/nonhealing wounds are other notable risk factors for SCC. There are many histologic features of these tumors that can affect prognosis (Table 2). Originally, squamous cell skin cancers were divided into several grades; however most pathologists presently feel that two general groups of behavior, can be identified for squamous cell cancers: (1) well-differentiated lesions and (2) moderately differentiated, poorly differentiated, and undifferentiated lesions.

Although the prognosis within the latter groups becomes dramatically worse in the poor and undifferentiated categories (which, like melanomas, are capable of in-transit, lymphatic, and systemic metastasis) the tendency is to treat these high-risk lesions with wider and deeper resection margins. Sentinel lymph node biopsies in the latter group may be considered if the lesion is greater than 2 cm area or greater than 2 mm thickness (Fig. 2). Histologic confirmation of negative peripheral and deep margins before defect closure or flap reconstruction must be routinely accomplished.

SCC carries a risk of metastasis (about 5%) in patients with less differentiated lesions and in certain anatomic areas, such as the lip and genital region. The frequency is also increased for immunoincompetent individuals, who tend to have less differentiated lesions. The mainstay of treatment for most lesions is surgical excision.

Radiotherapy has a role in the treatment of BCC for patients who are poor surgical candidates, those receiving palliative treatment, or those in whom the sheer volume or anatomy of the surgical resection would challenge appearance or function. Of course, radiation is used in the adjuvant setting for patients with aggressive disease and or metastasis to regional nodal beds. There is a subset of SCC lesions that manifest with perineural invasion (as evidenced by the

TABLE 2 High-Risk Histologic Features of Squamous Cell Carcinoma

- Differentiation (moderate or poor)
- Perineural involvement
- Desmoplasia or desmoplastic
- Adenoid, adenosquamous
- Tumor thickness/level of invasion ≥6 mm or involvement of subcutaneous fat
- Lymphovascular involvement

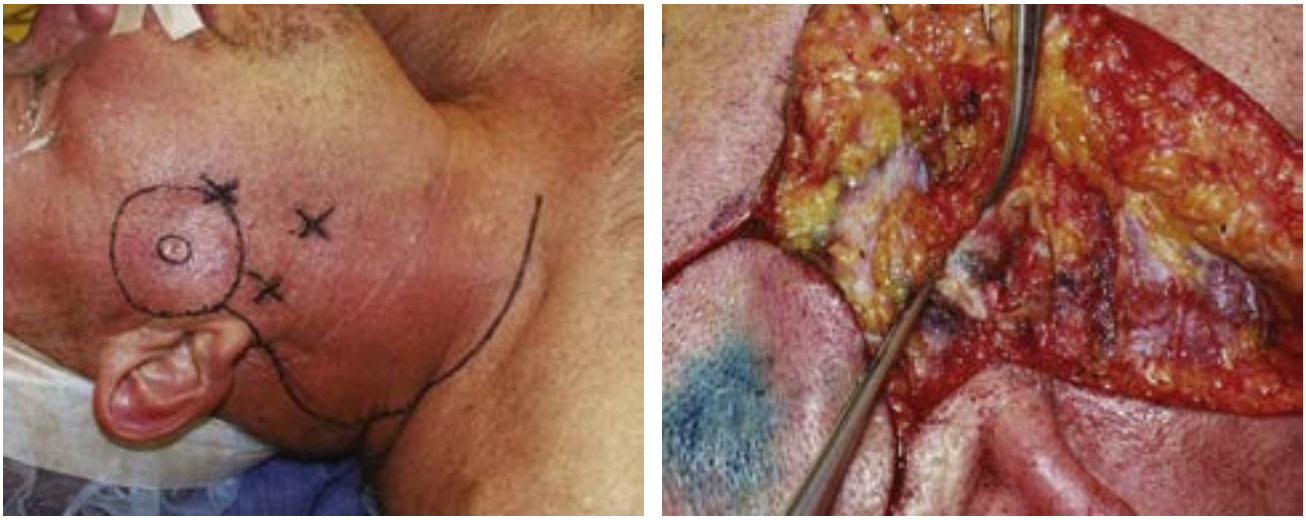


FIG. 2 Sentinel lymph node biopsy has a limited, though important, role in prognostication for squamous cell carcinoma. Particularly high-risk lesions can prompt evaluation of the sentinel node. In this patient with a high-risk lesion, the sentinel lymph node can be seen as the blue tinged tissue at the tip of the instrument, indicating a positive node.

development of neuropathic symptoms or on pathology). These lesions are at higher risk when named rather than unnamed nerves are involved, and contrast MRI will assist in defining the extent of involvement.

Any discussion of SCC requires mentioning important precancerous lesions and in situ malignancies that are both direct precursors to the frankly malignant lesions of SCC. Actinic keratoses are exceedingly common and represent disordered keratinocyte growth that is limited to the epidermis. The growth occurs as a direct result of photodamage, which explains the predilection for the head, neck, upper trunk, and extremities. Although the morphology of these lesions can be quite variable, they classically present as a rough erythematous papule with prominent white to yellow scaling. Associated tenderness portends a higher probability of associated squamous carcinoma.

Keratoacanthoma Squamous Cell Variant

Keratoacanthomas comprise a group of cutaneous neoplasms that share many features of SCC but are unique enough to merit individual discussion at a genetic level. Keratoacanthoma lesions may double in size quite rapidly. The more rapidly growing lesions should be removed for diagnosis as soon as feasible because most of these lesions are malignant. Keratoacanthomas most often manifest as a solitary lesion that grows rapidly over several weeks into a sharply circumscribed nodule with a cratered, keratotic core. The lesions are characteristically sensitive or painful when touched, and sensory nerve symptoms such as numbness, pain, burning, and paresthesia are concerning and should raise suspicion of SCC. Motor nerve involvement is much less frequent and occurs in extensive or deeply penetrating lesions that exhibit paralysis, weakness, or double vision, placing treatment of the tumor in a high-risk category. A contrast MRI is the best modality to document major nerve invasion.

Most lesions occur on the head and neck or in sun-exposed areas of the extremities. Occasionally, the lesion will spontaneously resolve over several months, leaving behind an inconspicuous atrophic scar. Because 95% of these lesions will continue to grow and not involute, creating a much larger lesion which is difficult to treat, it is our recommendation to excise them as growth is frequently alarmingly rapid (doubling every few weeks), and complete removal is always more challenging when larger. They should be treated identically to SCC as even pathologic differentiation from the benign variant is difficult. Recently, syndromes of elderly individuals with multiple keratoacanthoma squamous cells have occurred (frequently on the legs in severely sun-damaged skin), coming back frequently, even in resected squamous cell cancer scars, challenging treatment. Some have postulated a viral etiology. Injections of 5FU have been utilized with success in some patients, especially when multiple lesions appear almost simultaneously in elderly patients or if patients are not good candidates for operative resection.

Subtypes of squamous cell variants, such as the adenoid cystic type or adenosquamous carcinoma, are tumors whose more aggressive behavior characteristics increase the risk of incomplete resection, recurrence, and metastasis.

Desmoplastic cutaneous squamous cell carcinoma has a higher risk of recurrence as a result of incomplete resection because of subtle deeper extensions along fascial planes with failure to achieve clear margins. Some have suggested that invasion of a tumor into the fat or invasion deep enough to penetrate lymphatics constitutes more potential for recurrence and metastasis, as is known with melanoma.

Squamous Cell Carcinoma in Situ

Squamous cell carcinoma in situ represents full-thickness atypia of the upper skin layer (epidermis). Because the lesions are noninvasive, they are treated by simple complete excision because metastasis is not possible. As a pathologic entity, SCC in situ involves the abutment of neoplastic cells onto the epidermis but not into the dermis. Clinically, these lesions resemble eczema or psoriasis and have a characteristic pink to red color with scaling and sharply demarcated borders. Patients who have had development of SCC from SCC in situ are thought to have a roughly twofold to threefold higher chance of metastasis, especially in cases of mucosal, lip, or perineal SCC in situ. Topical chemotherapy agents such as 5FU, imiquimod, or cryotherapy can be utilized for SCC in situ; however, excision with margin confirmation is preferred for recurrence, persistence, or previous treatment failures. It is difficult to predict the cure rate of these treatments because they are not predicated on complete biopsies, and follow-up is generally incomplete and lacking biopsy proof of eradication. Immune modulators can also be offered for extensive disease or for patients who are not candidates for surgical treatment, and success has been described with vismodegib.

Certain precursor lesions, such as actinic keratoses, are precancerous. Actinic keratoses are red, crusty lesions that weep and

sometimes develop cutaneous horn proliferation or thick layers of flaky skin. They have an incidence of in-situ and invasive squamous cell skin cancer development of at least 10% (0.1%/year); therefore, treatment of these lesions with liquid nitrogen, a topical chemotherapy, or excision seems reasonable. However, recurrence should be a marker for progression to SCC and should be treated accordingly. Actinic keratoses may regress and reappear. SCC may be preceded by SCC in situ. Two syndromes are Bowen's disease and Paget's disease, which are types of SCC in situ that affect the breast and perineal areas and may progress to invasive SCC.

Bowen's Disease

Bowen's disease is an erythematous, plaquelike lesion that represents a low-grade, slow-growing intraepithelial variant of SCC. Essentially, the growth of this tumor is intraepidermal, and its history and progression are similar to other intradermal carcinomas such as erythroplasia of Queyrat or Paget's squamous cell disease. It is a less common malignancy that appears as a circumscribed, red or pink patch that can weep and present a scaly appearance. Many lesions occur on the trunk, lower extremities, and genitalia, but the lesions can involve the head and neck region. The progression of the lesion is slow and limited and extends normally over years. Invasive SCC can arise in these lesions, and if so, metastasis is possible. Excision to clear the margins with an initial 5-mm margin is recommended, and Mohs excisions with margin evaluation are favored. Larger lesions may require flap coverage or skin grafting. In the head and neck, cosmetically sensitive flap reconstructive techniques are preferred when primary closure is not possible.

SURGICAL EVALUATION AND TREATMENT

Biopsy

The gold standard in diagnosis of cutaneous lesions is full-thickness skin biopsy to at least the reticular dermis (infiltrative histology, deeper penetration, higher-risk lesions). Pathologic information that results from this biopsy depth includes lesion type, differentiation, histology, histopathologic subtype (for SCC and BCC), ulceration, perineural involvement, vascular involvement, degree of differentiation (SCC), tumor depth (SCC), and tumor thickness (SCC). A shave biopsy of a squamous cell skin cancer will frequently be read as SCC in situ and not confirm any invasive component.

Recall that SCCs with poorly or undifferentiated histologic characteristics and those greater than 2 cm in area or more than 2 mm thick (tumor can invade lymph vessels in the dermis) are at higher risk for infiltrative spread and lymph node involvement. Based on the histologic confirmation of aggressive characteristics, a sentinel lymph node examination or more aggressive resection may be considered. Clinically enlarged nodes should be evaluated with an ultrasound-guided fine-needle aspiration biopsy. The use of the ultrasound guidance allows for a more accurate biopsy, focusing on the most suspicious area of the node based on vascularity and echo texture. This process will help avoid the problem of false-negative biopsies.

RISK PROGNOSTICATION

Appropriate management of NMSC depends on formulating an appropriate risk estimate. A small, slowly growing SCC found in an immunocompetent patient is an entirely different entity than a large, rapidly growing, painful SCC located in the amputation stump of an immunocompromised patient. The workup and treatment for these lesions would be different and is influenced by the risk stratification of a lesion. This includes advanced imaging or diagnostic procedures, different surgical margins, need for lymph node biopsy, consideration for referral to medical or radiation oncology, and follow-up (see Table 1).

Area L: trunk, extremities; Area M: cheeks, forehead, neck, scalp; Area H: "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, ear, temple), genitalia, hands, and feet.

SURGICAL MANAGEMENT OF NONMELANOMA SKIN CANCER

Once a diagnosis is made, (either clinical diagnosis with a high degree of certainty or pathologic diagnosis), a surgical plan may be formulated. All surgical plans have a few commonalities, including expected margins, plan for margin evaluation and amount of resection desired, and type of wound closure or reconstruction.

Markings and Margin Considerations

A systematic approach to marking begins with first tracing the extent of the lesion itself. In straightforward cases, there will be stark differentiation between the abnormal tissue and the normal tissue with an obvious border. Commonly, confounding factors such as marginal erythema, telangiectasias, or dyspigmentation may add confusion in determining which areas of skin constitute the lesion.

Next, an uninvolved segment of tissue is added: the *surgical margin.* There are published and widely circulated national guidelines for resection margins for both BCC and SCC that are confirmed by high-level clinical data from expert national group consensus. Our practice is to follow recommendations from the National Comprehensive Cancer Network (NCCN) in the United States listed in Table 3, which are intelligent, comprehensive, and pragmatic.

Evaluation of Margins and Confirmation of Negative Margins

Marginal evaluation is the most critical aspect of tumor extirpation. An operation that removes some tumor but not all introduces the morbidity of surgery without the benefit of cure. With this in mind, surgeons must be well equipped to fully understand that both all peripheral and deep margins are evaluated. Guidelines exist for peripheral margin distance, as listed earlier, but deep margins are often determined by the surgeon's decision making or, in the case of Mohs micrographic surgery, real-time pathologic evaluation.

Techniques for rapid or intraoperative evaluation of margins include frozen-section assessment and Mohs micrographic surgery. Frozen-section assessment is done by laboratory-based pathologists and considers representative "breadloaf" or interval margin samples. The Mohs technique produces an immediate determination of the full length of the cutaneous margin as well as the deep margin. In

TABLE 3 Recommendations from the National Comprehensive Cancer Network

Tumor Type and Risk	Recommended Margin
Local, low-risk SCC	4–6 mm
Local, high-risk SCC	10–15 mm
Local, low-risk BCC	4 mm
Local, high-risk BCC	3 mm followed by 3 mm if first margin positive; consider Mohs surgery
Dermatofibrosarcoma protuberans	3–5 cm and down to investing fascia; consider Mohs surgery
Merkel cell carcinoma	1–2 cm; include sentinel node biopsy

BCC, Basal cell carcinoma; *SCC*, squamous cell carcinoma.

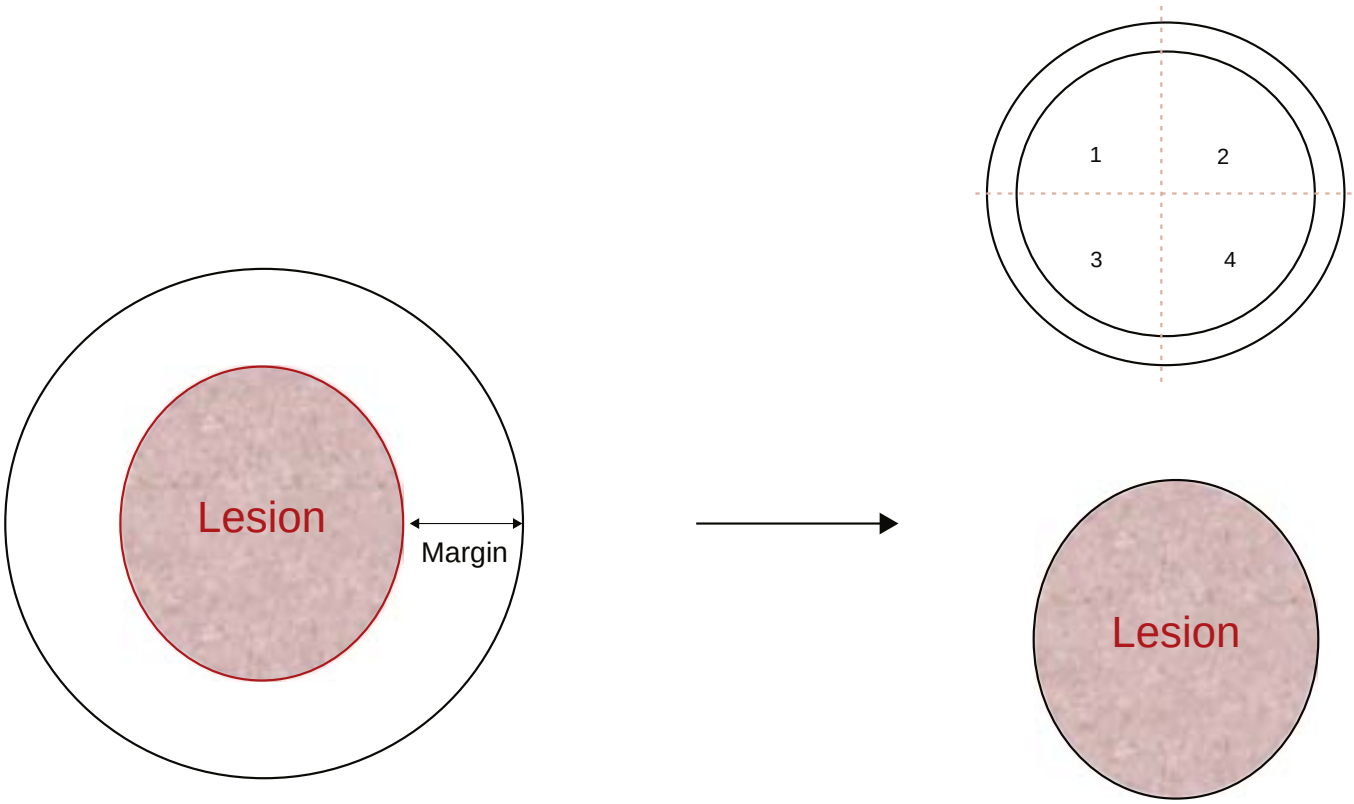


FIG. 3 The authors' preferred method of excisional biopsy and margin evaluation. The appropriate margin should be measured, and this annulus of tissue is excised. It is recommended to section this into four pieces, which can each be viewed by the pathologists as a linear specimen; it is important to make note of which segments came from which portion of the wound. The lesion itself is then sent as well as its own specimen for pathologic review.

either case, the surgeon may request permanent sectioning when unclear. In the case of equivocal margin status, the wound should be temporized with allograft or dressings until final permanent margins are available.

An alternative approach to rapid margin evaluation is to excise a thin rim of tissue from all quadrants at the estimated periphery of the lesion. Each skin section from each quadrant is then labeled and sent individually for analysis guaranteeing identification, and each thin defect is closed primarily (Fig. 3).

The situation of a patient being referred for reconstruction following resection by an outside physician is worth a brief discussion. One course of action is re-resection of a thin margin around the initial resection bed, regardless of the outside pathology report, which serves to even and square the edge, trim a contaminated or devascularized edge, and provide an additional clean margin for further pathologic confirmation. It has been our experience that the rate of residual tumor identified on such secondary marginal examinations may reach 10%.

Considerations for Enlarged Lymph Nodes

If an enlarged node is identified or the lesion is high risk, lymph node sampling is suggested. Sentinel node biopsy or fine-needle aspiration biopsy with ultrasound guidance would be the first options for nodal interrogation. If these modalities are not available, directed, open biopsy may be considered. The author prefers at least consideration of sentinel node evaluation in poorly differentiated or undifferentiated high-risk squamous cell skin cancer; however, the benefit of routine lymph node evaluation in less differentiated squamous cell cancers has *not* been proven. In the event of nodal disease, surgical resection or consultation with medical and radiation oncology should proceed. Many institutions have multidisciplinary conferences in which these discussions occur weekly.

NONSURGICAL MANAGEMENT OF NONMELANOMA SKIN CANCER

Surgical excision is most often the preferred therapy for cutaneous nonmelanoma malignancies. There are a small number of patients who are not candidates for surgery. The most common reason for this is substantial medical morbidity that limits the safe administration of anesthesia. Other patients are resolutely against surgical excision for a variety of reasons. Finally, certain lesions may not be well treated with surgery, such as diffuse lesions of Bowen's disease or those in anatomically sensitive areas that are functional and difficult to reconstruct.

Also, it must be understood that small, noninvasive in situ and precancerous lesions may be treated very effectively with nonsurgical modalities.

Imiquimod is a topical immunomodulator that now provides two different formulations (1% and 3%) that are approved by the US Food and Drug Administration (FDA) for precancerous actinic keratosis, actinic cheilitis, and small truncal superficial BCC lesions; dosing frequency and duration depends on the indication and formulation. Imiquimod functions by inducing local antitumoral cytokines that produce a striking inflammatory breakdown of areas involving superficial BCC and precancerous actinic keratoses. Erosions can be quite extensive depending on the treated area; erosions are predisposed to infection and may require antibiotic treatment during imiquimod therapy. It is important to note that many practitioners

now use imiquimod for off-label, non–FDA-approved uses, such as low-risk BCC (other than superficial) histology or anatomic sites other than the trunk (such as the face).

Liquid nitrogen is very effective for precancerous actinic keratoses and low-risk BCC. Actinic keratoses can be treated with a few seconds of exposure, while BCC requires successive rounds of tissue freezing.

5FU is topical chemotherapy, a derivative of the deoxyribonucleic acid uracil, that intercalates into DNA; rapidly dividing cells (such as NMSC and precancerous actinic keratosis) take up more 5FU, inducing necrosis. Similar to imiquimod, it can cause extensive erosions, and superinfection is common. 5FU has generally fallen out of favor because it is mutagenic on normal tissue and predisposes treated patients to cancer, which makes it a less appealing option compared to nonmutagenic imiquimod.

Electrodessication and curettage effectively treats truncal or extremity low-risk BCC, whereby the tumor is aggressively debulked with a curette, and then a broad-tipped curette tip is used under the electrodessication setting to ablate the bed of the tumor. This is repeated two additional times. Advantages are that it is quick, simple, has a good cure rate, and has favorable healing (a small circular white scar). Disadvantages include wound care required sometimes for weeks, which may be inconvenient if a patient does not have anybody assisting them at home.

Radiation as Primary or Adjunctive Treatment

Radiation therapy in cases of primary straightforward NMSC of the basal or squamous type can often produce good cure rates (90%) and excellent cosmetic results. Multiple treatments are required over a period of weeks, and there is no confirmation of negative margins, nor is there complete examination of the histology of the lesion to confirm complete histologic characteristics. The authors have found that many elderly patients with lesions of the lower extremities do not do well in terms of cure or residual symptoms following radiation treatment. Young patients in whom there is risk of further radiation-induced malignancy are generally treated with surgery. The use of radiation as a primary treatment modality will often preclude its further use as an adjuvant modality in the same area, thus limiting the possibility of using radiation for the management of recurrence or new disease.

Radiation therapy has also been utilized as adjunctive treatment in patients in whom the margins are histologically but not clinically positive or for perineural involvement or where the danger of intralymphatic spread into adjacent skin is high. Patients who have extracapsular extension, referred to as *soft tissue disease,* of tumor are also candidates for postoperative radiation. Patients with more than two positive nodes will be considered for adjuvant radiation to the nodal basin.

CONSIDERATIONS FOR METASTATIC DISEASE

Treatment of metastatic disease often employs medical oncologic or radiotherapy. Some encouraging results have been obtained with immune modulators, such as vismodegib. Patients with disease remaining following radiation may be candidates for vismodegib, a hedgehog pathway inhibitor. This drug has shown some efficacy in the management of metastatic and inoperable BCC.

Although several chemotherapeutic agents have been described in case studies or small patient cohorts, only one randomized controlled trial (RCT) has been conducted, demonstrating a 34% overall response rate for a cisplatin-based regimen. EGFR inhibitors evaluated for use in cutaneous SCC by RCTs include cetuximab, panitumumab, and gefitinib; response rates ranged from 15% to 31%. Inhibitors of the immune checkpoint programmed death-1 (PD-1) have yielded promising outcomes in advanced cutaneous SCC. The PD-1 inhibitor cemiplimab recently received FDA approval for use in advanced cutaneous SCC. Despite these advances, the preferred regimen for systemic treatment of cutaneous SCC remains unclear, particularly in immunocompromised populations.

Long-Term Follow-up of Basal Cell and Squamous Cell Skin Cancers

All patients with BCC and SCC, especially those with high-risk lesions, should have a complete skin examination periodically with special attention to the area of origin, where recurrence, either locally or regionally, is likely. Although most recurrences of lesions develop within a 2-year period, rarely a tumor will recur after 5 to 10 years.

Nonaggressive skin cancer types will recur in about 50% of lesions with positive histologic margins. One-third to one-half of patients having a basal or squamous cell skin cancer will develop a second primary lesion within the next 5 to 10 years. Follow-up schedules should be tailored to the particular severity and extent of disease and to the risk of recurrence.

OTHER MALIGNANT CUTANEOUS ENTITIES

There are dozens of cutaneous malignancies that do not arise from keratinocytes, all of which are substantially less common than BCC and SCC. There is a handful worthy of a brief mention, but we encourage interested readers to pursue further reading in a cutaneous oncology text.

Merkle Cell Carcinoma

Merkle cell carcinoma is a rare neuroendocrine skin cancer with about 1600 cases diagnosed in the United States annually. It is characterized by rapid growth and very aggressive behavior. A firm, intradermal, red nodule rapidly progresses to ulceration. Recently, some lesions have been traced to a polyomavirus infection, and the disease is more frequent in patients receiving immunosuppression. The disease progresses rapidly by intravascular and lymphatic spread. Therefore, initial positron emission tomography (PET) imaging should evaluate the possibility of regional and distant spread. Prognosis is often predicted by positive regional lymph nodes, which occur in 25% to 30% of N0 patients (no clinical evidence of nodal disease). The disease often tends to be undertreated by limited surgical resections; thus, local failure is common (up to one-third of patients). Local control may be improved by larger resection margins that often generate the need for skin grafting. The current NCCN guidelines recommend excision with a 1- to 2-cm margin down to fascia or periosteum (level III evidence). The creation of surgical wide margins must be balanced with the potential morbidity of this surgery. For instance, would it be appropriate to resect upper and lower eyelids for a Merkel cell carcinoma of the lateral cheek? The rate of local recurrence, even in the face of wide local excision, ranges from 25% to 40%. Sentinel node biopsies are routinely recommended.

Periodic follow-up with local, regional, and systemic monitoring is recommended. Although most recurrences occur in the first 2 to 3 years, survival is best predicted by the presence of nodal and distant disease. The behavior of Merkle cell cancer is usually more aggressive than significant invasive melanomas, and in fact, the mortality exceeds that of melanoma. The histologic diagnosis is confirmed by performing immunohistochemical staining (IHC). Because of the frequency of local failure in treatment when surgical margins are compromised, some have recommended postoperative radiation therapy for the primary tumor, draining lymphatics, and regional lymph node basins. The added value of this treatment when surgical margins are generous, negative sentinel lymph node biopsy is obtained, and PET scans are negative has not been established. Adjuvant chemotherapy for regional disease has also been recommended (positive regional node disease) in addition to surgery, but its value is unproven. The diagnosis of Merkle cell cancer portends a high risk

of local, regional, and distant recurrence. The 5-year disease-specific survival ranges from 60% to 87% for local disease, 39% to 62% for nodal disease, and 20% for distant metastatic disease. The median time to recurrence is 7 to 9 months, with 80% to 90% of recurrences occurring within the first 2 years. The draining nodal basin is the most common site for recurrence. Because of the high recurrence rates, patients should be evaluated every 3 to 4 months for the first 2 years following treatment.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a rare intermediate-grade soft tissue sarcoma that usually features indolent irregular, trabecular, and infiltrative growth with projections a far distance from the primary tumor. The final diagnosis is often delayed because of the innocuous appearance of the initial tumor. This will often lead to inadequate resection and recurrence. Approximately 85% to 90% of DFSPs are low grade; the remainder contain a high-grade sarcomatous component (which is usually a fibrosarcoma, designated DFSP-FS) and are considered to be intermediate-grade sarcomas.

The age range of affected individuals is usually between 20 and 50 years of age. Most lesions are located on the trunk or proximal extremities, with the head and neck area affected less commonly. Some patients provide a causal history of trauma; however, the relationship has not been proven. The lesion is slowly growing as a rule (and for practical purposes does not metastasize); however, it has a strong tendency for local fascial extension along tissue planes in small, thin fingers, that defy clinical and pathologic perception. Standard surgical excisions without Mohs pathology have yielded up to a 60% recurrence rate, generating the recommendation that 3- to 4-cm clinical margins or better Mohs surgery be utilized.

The DFSP presents clinically as a painless, firm, red to brown or purple plaque. It can demonstrate soft areas or protrusions. This indolent presentation is often enough to prevent early diagnosis because of its benign nature. The diagnosis can prove difficult, and differentiating it from other fibrotic skin processes can require special stains. Negative biopsies in one area should not be reassuring but should prompt more biopsies and/or complete excision of a suspicious lesion. Immunostaining with CD-34 factor, XIIIA metallothionines, tenascin, and stromelysin-3 are helpful in making the diagnosis. The lesion is frequently misdiagnosed both clinically and pathologically and underestimated surgically.

Treatment

Treatment for DFSP is surgical excision with wide margins, and up to 3 to 4 cm have been recommended. Currently, Mohs micrographic surgery is the surgical method of choice, which has reduced recurrence rates to about 2%. Regional lymph node biopsies are *not* indicated because the incidence of metastatic spread is so low, probably 1%. Although adjuvant radiation has been recommended following standard surgical treatment, the value of supplemental radiation in patients who have widely negative surgical margins has not been established.

Cutaneous T-Cell Lymphoma

Lymphomas may present as cutaneous lesions and include mycosis fungoides and Sezary syndrome, which are cancers originating from T4-helper cells. These are rarer tumors that appear as a reddish patch, plaque, or lump. They are sometimes oozing or have a "psoriatic" appearance. Itching is a prominent clinical symptom. Because of its benign appearance, diagnosis is commonly delayed because it overlaps in appearance with many other cutaneous dermatologic conditions. Some patients progress to frank systemic lymphoma over time, and 5-year survival rates of the skin lesion itself vary from 50% to 100% and often relate to the development of another internal serious blood neoplasm.

Therapy varies from medication such as Rituxan to excision, chemotherapy agents, or topical radiation, such as skin electron-beam therapy. In some cases, surgery provides control of local symptoms and apparent cure for limited lesions.

Angiosarcoma

This rare and aggressive vascular tumor of the skin generally occurs as a rapidly enlarging nodule or plaque, sometimes simulating a bruise. In-transit metastasis occurs quickly, and initial presentation with satellite nodules is not uncommon. There is a predilection for occurrence in the head and neck area and in the elderly. In one series, the mean age was 70 years and seemed to favor male patients. Aggressive treatment is indicated with 3- to 5-cm margins, frequently requiring flap or skin graft reconstruction. Sentinel lymph node biopsy is recommended. Local and systemic recurrence is the routine because of the tendency for in-transit metastasis, and the prognosis is quite limited, with 20% survival. These statistics and the proven aggressive behavior of this tumor have generated the recommendation that radiotherapy and chemotherapy accompany the planned surgery. Despite these additions, the prognosis remains largely unaffected by additions to the surgical treatment proposed.

Adnexal Tumors of the Skin

Adnexal tumors occur from skin appendages such as eccrine, apocrine, and sebaceous glands as well as hair follicles. Some occur from fibrous or neural tissues. Sebaceous carcinomas usually present as a slightly reddened nodule whose diagnosis is dependent on biopsy. The prognosis varies with the aggressiveness of the lesion, and wide excision with 2-cm margins to the fascia are recommended. Although some practitioners perform sentinel lymph node evaluations in more aggressive lesions, the value of these interventions remains to be proven.

NMSCs vary in severity from the relatively common and benign varieties to very aggressive and frequently lethal lesions. Treatment favors surgical resection, predicated on accurate diagnosis and classification, with the aggressiveness of treatment based on good pathologic definition of the lesion type and proper margins.

Acknowledgment

The authors wish to express their appreciation for the contributions of the panels who created the NCCN guidelines, which form an excellent and carefully considered basis for the recommendations for diagnosis and treatment of these lesions that are summarized in this chapter. The authors recommend these guidelines in the strongest terms for those wishing further information and clarification as they serve as a yearly, up-to-date summary of current recommendations for diagnosis, evaluation, and treatment.

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Management of Cutaneous Melanoma

Nicholas Calotta, MD, Paul N. Manson, MD, and Anthony Tufaro, MD, DDS

Melanoma is a malignant neoplasm that arises from melanocytes, most often as a cutaneous lesion, but primary tumors also arise in other tissues where neural elements penetrate. Although melanoma accounts for approximately 5% of all cutaneous malignancies, it is the deadliest form of skin cancer, responsible for greater than 90% of deaths. It is the third most common malignancy responsible for death, and its rate of increase is much higher than for other common cancers except breast cancer. Melanoma is the ninth most common malignancy.

Ninety percent of cases present with local or regional disease, for which the primary treatment is surgical and potentially curative. Current surgical approaches have reduced disease extent and morbidity compared with historical techniques but have equivalent or superior effectiveness.

Melanoma is a rare disease, with an incidence of 22.1 per 100,000. Melanoma misdiagnosis accounts for more pathology and dermatology malpractice claims than any other cancer except breast cancer.

Prognostic factors relate to thickness, location, ulceration, and the presence of lymphatic and nodal disease. It may spread unpredictably to any organ. Melanoma also has a proclivity for arising in middle-aged adults compared with other cutaneous malignancies, which tend to appear in later life.

Given the substantial risk for morbidity and mortality, a thorough understanding of diagnosis, initial management, and subsequent follow-up care is important for surgeons who encounter melanoma in practice. Although there is an increasing trend toward nonsurgical treatment of melanoma in this era of advancing immunotherapy and targeted molecular therapy, we believe that identification by inspection and surgical tumor extirpation remains the backbone of comprehensive initial melanoma care. Thankfully, for the great majority of affected individuals, this is all that is necessary.

EPIDEMIOLOGY AND RISK FACTORS

There has been an alarming increase in the incidence of melanoma since the 1950s, especially in young Caucasian women. At that time, the incidence was approximately 1 per 100,000 in the adult population in the United States. Compare this to recent estimates reporting the incidence to be closer to 40 per 100,000 for the same population. This makes melanoma one of the fastest-growing neoplasms. Experts argue whether this is the result of heredity, environment (sun), or overdiagnosis.

Risk Factors

Substantial time and resources have been invested in identifying risk factors for the development of melanoma. From a patient-level perspective, relevant risk factors are lightly pigmented skin, red hair color, and an inability to tan/tendency to sunburn easily (Fitzpatrick types I and II; Fig. 1). Environmental factors include cumulative dose of ultraviolet (UV) radiation (either from chronic sun exposure or intense intermittent sun exposure), use of UV tanning beds, and immunosuppression. Important precursor lesions are dysplastic nevi. Finally, recent research has highlighted the important role that genetics play; numerous single-gene mutations have been implicated along with the classically associated DNA repair conditions such as xeroderma pigmentosum. Oncogenesis is thought to be based on gain-of-function mutations in oncogenes and loss-of-function mutations in suppressor genes. Two-thirds of the risk generation is felt to come from UV light exposure (natural or man made), and reduction of UV exposure, particularly sunburns, results in decreased frequency. The sun-drenched head and neck contains 9% of the body surface but accounts for 30% of melanoma cases. Whereas keratinocytes subjected to UV damage undergo programmed cell death, melanoma cells survive this insult and may change their characteristics toward malignant behavior.

Precursor Lesions

Important precursor lesions exist in melanoma in 30% of cases, some of which impart different risks for the subsequent development of malignancy. Currently the bulk of melanoma is felt to arise de novo. Acquired

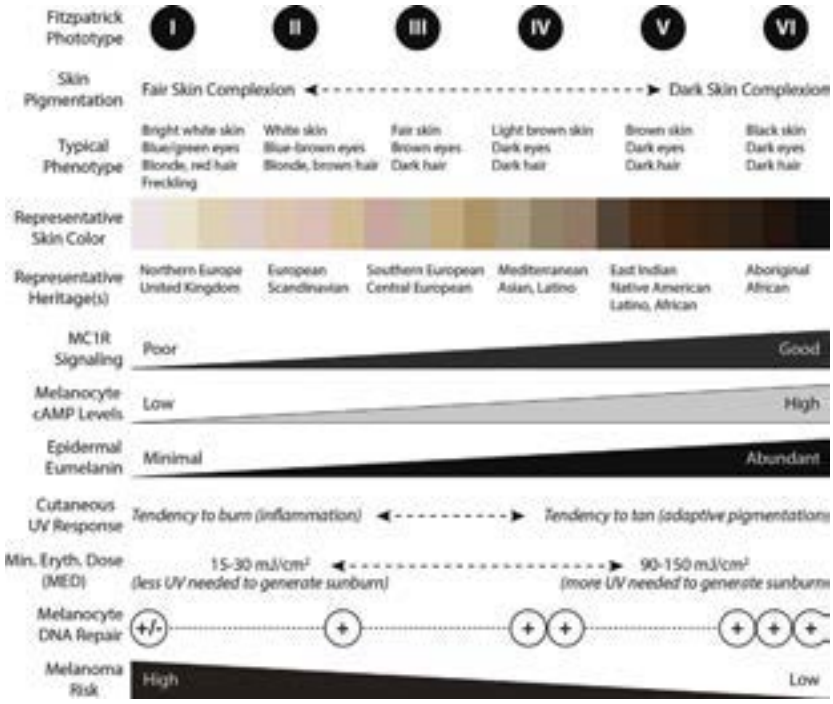


FIG. 1 Fitzpatrick skin types.

melanocytic nevi are considered the most closely related pathologic entities to melanoma; development of >100 acquired melanocytic nevi imparts a tenfold increase in risk for developing melanoma. Atypical melanocytic nevi (AMN) have both sporadic and dominant forms, as the development of >5 atypical melanocytic nevi carries a fivefold increase in risk for melanoma (Fig. 2). Finally, solar lentigines, when found in groups, are responsible for a fourfold increase in melanoma risk. Other risk groups include FAMMM (familial atypical multiple mole syndrome), AMS (atypical mole syndrome), DNS (dysplastic nevus syndrome), congenital nevi, and cellular blue nevi; all increase the frequency of malignancy. Elder in 1985 extended the theory of *nevus-melanoma transition,* postulating dysplastic nevi as a precursor to sporadic melanoma. Dysplastic nevi exist in 2% to 8% of the population.

MELANOMA, CLINICALLY AND PATHOLOGICALLY, DOES NOT HAVE SOLID DIAGNOSTIC CRITERIA

The plain fact, accounting for the challenge and difficulty of the diagnosis both clinically and pathologically, is that there are no ubiquitously agreed-upon criteria by which to make the diagnosis. Seventy percent of melanomas detected are now less than 1 mm, and many of these smaller lesions are in a diagnostic gray zone. Pathologists are increasingly evaluating lesions in a diagnostic "overlap" zone in which penalties exist for underdiagnosis but not overdiagnosis. Recently, in order to prove that a part of the increased frequency of melanoma is generated by overdiagnosis, a group of pathologists were asked to re-read their own slides from 20 years ago, and there was a significant increase (60%) in diagnoses of melanoma versus benign/dysplastic nevi. The conclusion is that a portion of the increased frequency of melanoma is physician generated by threat of litigation for "underdiagnosis." This fact would also account for some of the increased survival.

There are two forms of melanin produced by melanocytes: the black/brown pigment eumelanin, and the red/yellow pigment pheomelanin. The ratio of these compounds produces skin color, rather than the absolute number of melanocytes. Eumelanin is a better UV shield, whereas pheomelanin is less protective and has a higher DNA damage in response to sunlight.

MELANOMA CLASSIFICATION

Melanoma is an umbrella term that encompasses a collection of heterogenous neoplastic lesions arising from melanocytes. Understanding the major differences among these entities is paramount to providing appropriate surgical care. The heterogeneity of forms makes clinical and histologic diagnosis difficult. Melanomas of the skin start from the basal layer of pigment cells. They first grow horizontally or radially within the epidermis. In this stage, they are at first *melanoma in situ* (see Fig. 2) and are not invasive. This stage may be long or short. They then may change their surface antigens and cytogenetic profiles to develop a vertical growth phase. Steps in the process may be rapid or slow. As melanoma invades the mid-dermis, it reaches the area where blood vessels and lymphatics are present, and metastasis is then possible, either into the adjacent skin (in transit metastasis) or regionally and distally through lymph or blood.

Superficial Spreading Melanoma

This is the most common subtype of melanoma, accounting for approximately 75% of all cases (Fig. 3). Although the risk of any individual nevus progressing to melanoma is very low, nevi that progress to malignant transformation manifest as superficial spreading lesions most often. They have first a radial and then a vertical growth phase; 30% begin in a preexisting nevus, but the majority arise de novo.



FIG. 2 Dysplastic nevi (possible premelanomas). **(A)** Deeply pigmented dysplastic nevus. **(B)** Severe dysplastic nevus with some changes similar to melanoma; it looked like melanoma clinically, but it was a dysplastic nevus pathologically. **(C)** Melanoma in situ; early malignant melanoma is easily confused with benign lesions.

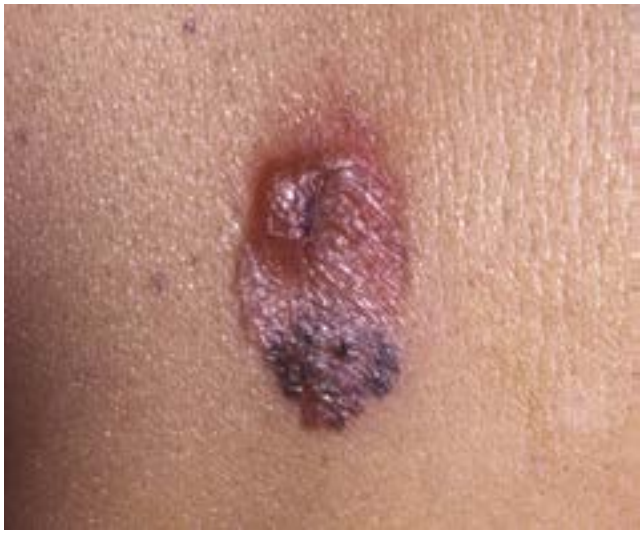


FIG. 3 Superficial spreading melanoma. Combinations of red, blue, and brown pigment are seen. A nodule is developing from one area, indicating that a vertical growth phase is arising contemporaneously with the horizontal or radial growth phase.

The majority of superficial spreading melanomas are observed on the trunk and extremities. Classically, these lesions develop with the widely known *ABCDE* characteristics: asymmetric shape, irregular borders, uneven/multiple colors, diameter in excess of 6 mm (though 50% of diagnosed lesions are now smaller than that threshold), and unpredictable evolution in time. Because smaller lesions are frequent, this criterion should now be modified. A very common history provided by the patient will be a period of slowly progressive expansion in a radial direction followed by comparatively rapid vertical growth, usually causing a papule or nodule. These changes relate to growth limited to the epidermis followed by invasion more deeply into the dermis. Partial regression with corresponding loss of pigment, interval pale and atrophic areas, are also common.

Nodular Melanoma

The second most common subtype of melanoma is the nodular melanoma, identified in 15% to 30% of all melanoma cases (Fig. 4). The physical manifestation of nodular melanomas can be variable, making clinical diagnosis challenging. The *ABCDE* criteria are less applicable because nodular tumors may be symmetric or asymmetric; pink, red, blue, black, and nonpigmented lesions are all well described; the tumor often appears as an isolated nodule or papule without an ensuing increase in size, and the timeline for growth is variable. Much of this clinical variability arises from the pathologic behavior of the tumor, namely that it lacks a superficial-radial phase and instead tends to grow almost exclusively in a vertical fashion. Much like an iceberg, the majority of the neoplasm often exists beneath the visible surface of the skin. A high index of suspicion is required to pursue further workup and accurately identify this tumor. Nodular melanoma is often diagnosed at a later stage than other subtypes of melanoma.

Lentigo Maligna Melanoma

Lentigo maligna melanoma is the third most common form of melanoma (10%–15%) and the subtype most strongly linked to chronic UV irradiation (Fig. 5). As a result, these lesions are almost exclusively identified in older adults in areas of chronic sun exposure, such as the distal extremities and the head and neck region. The clinical examination classically features a variably pigmented patch in the setting of notable photodamage. Radial growth is often slowly progressive, leading to highly irregular borders and substantial pigment variations. Lentigo maligna melanomas are notorious for exerting a



FIG. 4 Nodular melanoma. This is a dark, heavily pigmented lesion with rapid growth. Two examples are shown: lip **(A)** and back **(B).**

field effect in which surrounding dermis has suffered the cumulative mutagenic effects of chronic UV irradiation. This allows the primary tumor to infest its vulnerable surroundings with foci of malignant cells, termed *skip lesions.* Incisional biopsy specimens may fail to identify malignant cells surrounding the clinically obvious melanoma, placing patients at higher risk for recurrence, reoperation, or advanced disease. Negative margins at the time of definitive surgical excision may also be difficult to interpret as a result of the skip lesions/regression frequent in lentigo maligna melanoma.

Acral Lentiginous Melanoma

Acral lentiginous melanoma is an uncommon manifestation of melanoma, accounting for less than 5% of cases (Fig. 6). However, these lesions tend to make up a higher proportion of all melanoma cases in dark-skinned populations. Arising in the skin of the palms and soles or intimately within the nail structure, a high degree of suspicion is required for accurate and timely diagnosis. The usual presentation is similar to other melanoma subtypes; usual features include an asymmetric, brown to black macule with variable coloring and irregular borders. With regard to lesions of the nail bed itself, melanoma can be very difficult to distinguish from posttraumatic changes or benign nevi (Fig. 7). A guideline to help identify candidates for biopsy includes subungual lesions in fair-skinned patients, darkly pigmented lesions, irregularly pigmented lesions, those wider than 3 mm, or lesions that extend beyond the nail plate either into the hyponychium, paronychium, or eponychium (Hutchinson sign).

Amelanotic Melanoma

The majority of melanomas are pigmented in some manner, facilitating their detection. However, melanoma without any evidence of

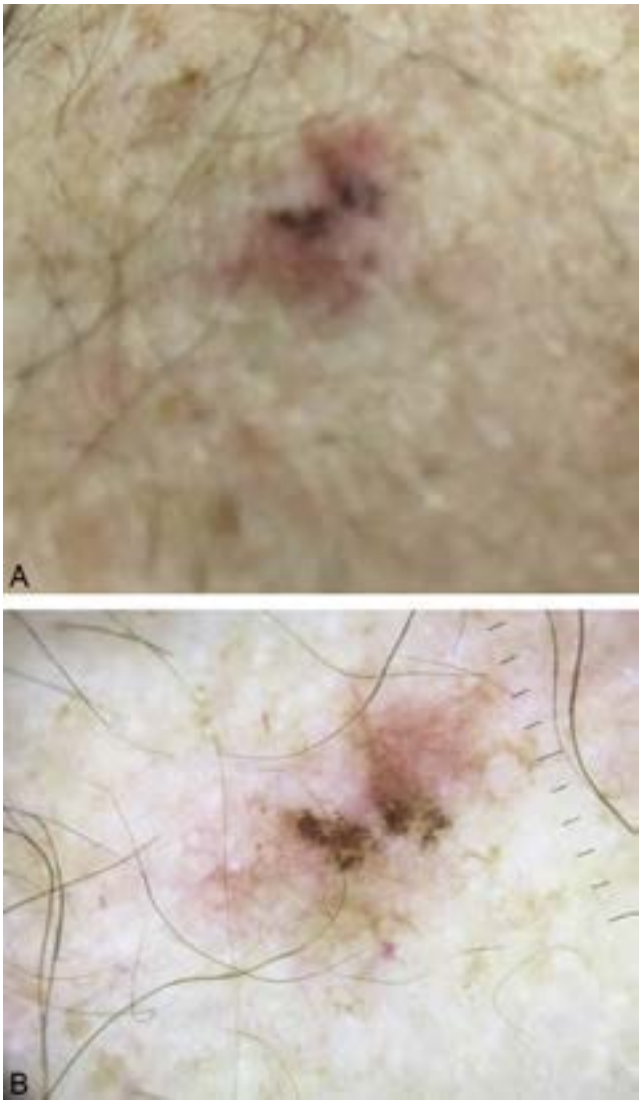


FIG. 5 Lentigo maligna melanoma. **(A)** Variegated colors of red, brown, and black with considerable pigment variation and multiple areas of regression are shown. **(B)** The same lesion under magnification clearly demonstrates areas of central and peripheral irregular regression.



FIG. 6 Acral melanoma. Two variations are shown: nodular **(A)** and flat **(B).**

pigmentation is also possible (Fig. 8). These lesions appear similar to a squamous cell carcinoma or a wart, and they may be red or occasionally pale. There should thus be a low threshold to biopsy unidentified lesions. Repeat observation of lesions in this category will reduce diagnostic errors, and clinicians should not hesitate to perform a full-thickness skin biopsy recognizing the atypical appearance of 10% of the subset of all melanomas. Odd lesion colors or the lack of pigment have no impact on prognosis.

Desmoplastic Melanoma

Desmoplastic melanoma is a particularly notable variant as this lesion poses substantial risk for destructively aggressive local growth and recurrence as a result of inadequate resection (Fig. 9). Because it has many of the appearances of a keratosis, the lesion is easily missed. The most frequent clinical manifestation of desmoplastic melanoma is a flesh colored plaque in sun-bathed skin, though red, pink, brown, or black lesions are possible. Exact identification of desmoplastic type is exclusively a histologic diagnosis. Identification and classification require full-thickness tissue sampling as the superficial layers of the lesion are classically nondiagnostic or vaguely resemble



FIG. 7 Nail bed melanoma. This lesion seems to extend beyond the nail bed into the perionychium.

fibrosis, cutaneous lesions, or even scars. Some feel that, because of the depth of the lesion, traditional depth-based staging may overestimate the seriousness of the tumor; this melanoma variant seems less likely to metastasize to nodes or beyond, and it is usually discovered at a later stage. **(Warning: Fully 10% of melanomas are not easily identifiable by their presenting color or clinical appearance characteristics. Adequate biopsy remains the single confirmation of pathologic type. Remember that pathologic identification may also be challenging.)**

Clear Cell Sarcoma

Clear cell sarcoma is a very rare tumor that recently has been identified as a molecular relative of melanoma. Most clear cell sarcomas arise from tendon sheaths and fascial aponeuroses, especially in the lower extremities; the trunk is the second most common site for tumor growth. Clinically, the lesion is almost always noted to be a tender flesh- or gray-colored mass that ranges in size from one to several centimeters. A hallmark is intimacy with underlying tendon or aponeurotic structures. Metastasis is common, and prognosis is poor.

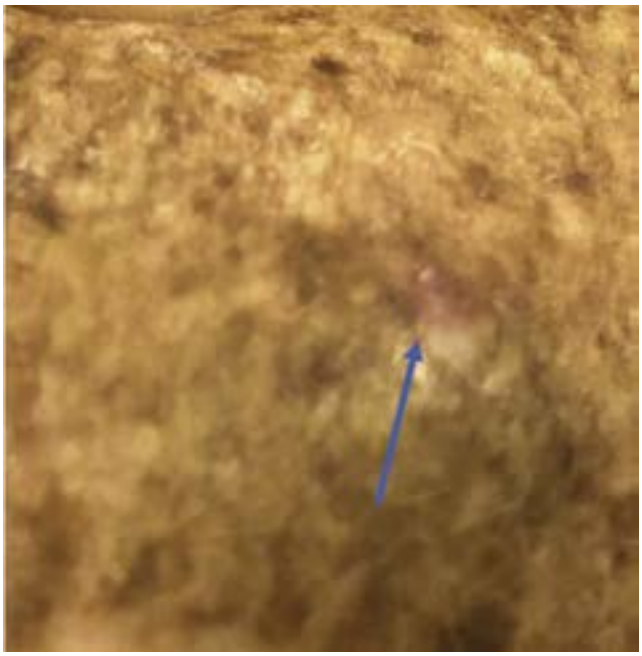


FIG. 8 Amelanotic melanoma. The appearance of these lesions may easily be confused with a benign lesion. The *arrow* indicates the subtle lesion.



FIG. 9 Desmoplastic melanoma. This lesion was interpreted by the screening dermatologist as a severe keratosis.

Mucosal Melanoma

The family of mucosal melanomas comprises a diverse group of tumors characterized by their anatomic locations and their unique genetic signatures. These tumors develop in the mucosa of the mouth, nasopharynx, larynx, and anogenital regions along the junction of epithelial morphologies. Clinical examination usually discloses a pigmented, sessile, or slightly raised mass, though as many as 40% may be amelanotic. As with several other variants, a low threshold to perform biopsies characterizes a prudent approach.

STAGING AND PROGNOSIS

The staging of melanoma is based on the American Joint Committee on Cancer (AJCC) staging system, which was most recently updated to the eighth edition and considers tumor size, node status, and metastases. We have provided the citation for the most updated AJCC system and encourage readers to review this. Specifically, T status is driven by tumor size and the presence or absence of ulceration. The N status characterizes both clinically apparent and clinically occult nodal metastases and non-nodal local spread. Finally, M status is determined by the anatomic site of distant spread and the serum lactate dehydrogenase level. Melanoma staging is vital for providing accurate prognosis.

Prognosis determination proceeds directly from staging. Four tumor features have been specifically repeatedly associated most closely with prognostic outcomes:

1. Primary tumor thickness
2. Presence of ulceration in the primary lesion
3. Mitotic rate of tumor cells
4. Presence of microscopic metastasis on analysis of resected lymph nodes

Survival varies from >95% at 10 years for promptly treated stage 1 tumors to <20% for metastatic stage 4 disease. These figures may be changing, however, in the era of advanced immunotherapies and targeted molecular therapies.

INITIAL WORKUP

Lesion History and Characteristics

A detailed history and physical examination are both very important in the initial encounter for a patient presenting with suspected melanoma. Specific historical elements that should be collected include risk factors for melanoma (see earlier) and family history of cutaneous malignancies. Questions pertaining to the lesion should include time course (including possible precursor lesions present at birth or in development thereafter), circumstances surrounding lesion development (e.g., in a preexisting nevus, following trauma), associated dermatologic symptoms such as itching or burning, and the presence of constitutional symptoms, ulceration, or bleeding.

Total Body Skin Examination

A total body skin examination is a must, especially if there are numerous melanocytic nevi or clinically atypical appearing nevi. It is very frequent that additional melanomas or melanoma precursor lesions will be discovered. Some dermatology experts utilize dermoscopy (examination with a magnified light device) in screening for atypical nevi.

Examination of Regional Nodes

Particular attention should be paid to the examination of local/regional lymph nodes. Clinically palpable nodes must be further evaluated, as one-half of the clinically palpable nodes are positive, and one-half are negative for melanoma involvement, emphasizing the importance of ultrasound or sentinel lymph node biopsy (SLNB).

Laboratory Examinations

Routine laboratory and imaging studies were formerly a cornerstone of preoperative workup in cases of suspected melanoma. Recent meta-analyses have determined that the diagnostic utility of these measures is minimal. Up-to-date recommendations from several national societies, both in the United States and elsewhere, do not include these evaluations for asymptomatic patients. For patients with concerning pathology or signs or symptoms of metastatic disease on presentation, targeted workup (e.g., head imaging for a patient with headaches and suspected central nervous metastasis) should be pursued and may be performed in coordination with a medical oncologist or other specialist.

BIOPSY

Excisional biopsy is the cornerstone of diagnosis in cases of suspected melanoma. The recommended technique is excisional biopsy with 1- to 2-mm margins, followed by straight-line closure with minimal undermining. If needed, closure with allograft skin or negative-pressure therapy devices are lesser options while awaiting final pathology. All samples should be appropriately oriented and sent for pathologic review. Ideally, a pathologist with specific expertise in the review of melanocytic neoplasms is identified for consultation.

Excisional biopsy is considered ideal because it allows for an accurate assessment of tumor architecture, including Breslow depth, mitotic rate, invasive characteristics, and identification of the deepest areas for classification. This method further reduces the error of a sampling bias that may occur with melanoma arising in a previously benign nevus or in cases of Lentigo maligna melanoma. An extremely important principle of biopsy technique is orientation of the incision. The surgeon's mindset should be that all suspicious lesions are malignant until proven otherwise, implying that wider resection may eventually be needed. The subsequent resection, therefore, must necessarily remove the scar of the biopsy incision plus the appropriate margins, which is best accomplished when the biopsy excision has been properly planned with the possibility of later excision in mind. On extremities especially, careful planning of the initial biopsy incision is crucial for facilitating tissue salvage in a radical future operation. Therefore, virtually all extremity incisions should be oriented longitudinally and within the relaxed skin tension lines (RSTLs) in a proximal-to-distal fashion, and not transversely (medial to lateral), as depicted in Figure 10. Some favor making the long ellipse of the skin excision parallel to the direction proximally of presumed lymphatic drainage to have a chance of capturing more lymphatics in the long axis of the excision.

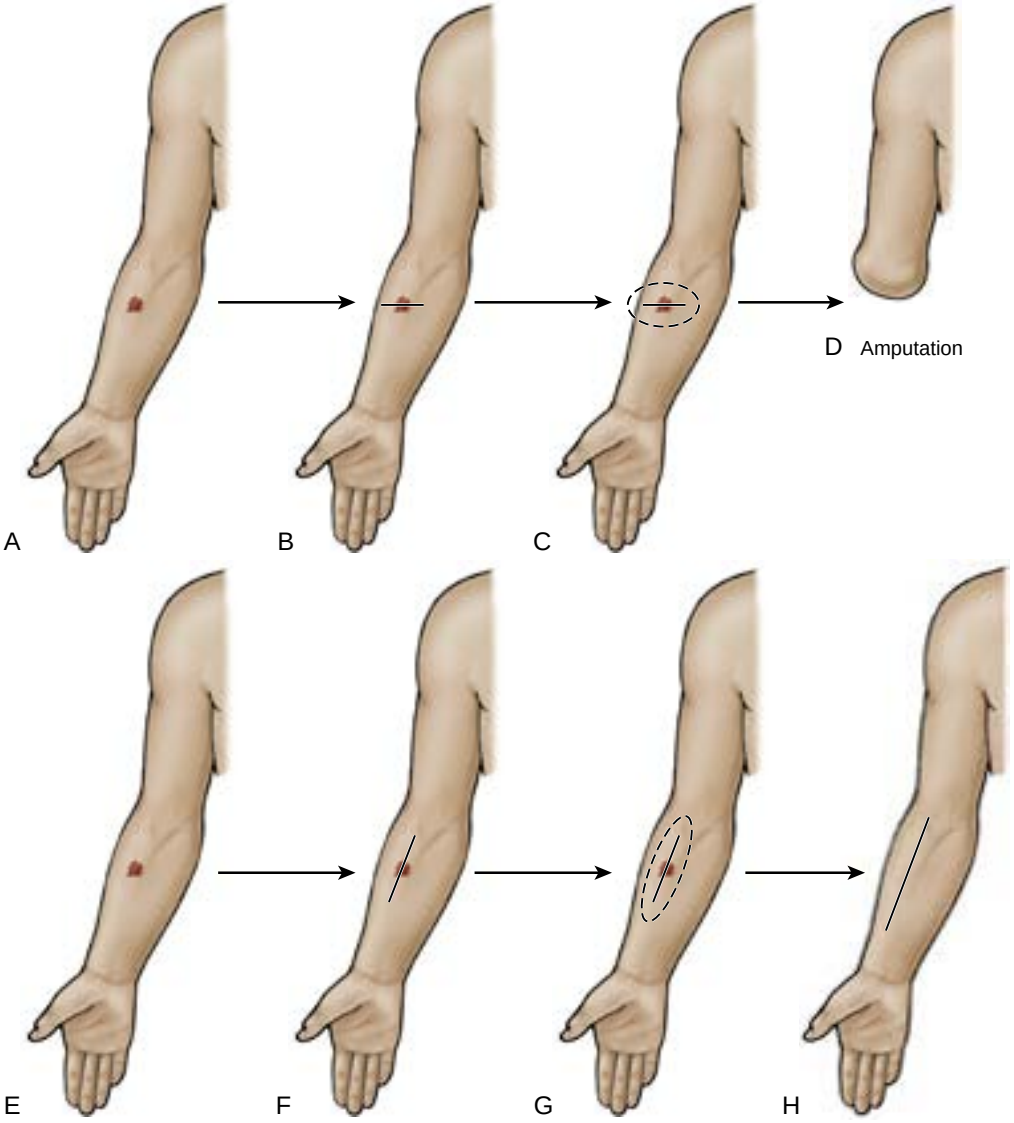


FIG. 10 **(A)** A suspected melanoma on the volar forearm. **(B)** A hypothetical transversely oriented incision for excisional biopsy, with a resulting straight-line scar in medial-lateral fashion. **(C)** The *dashed ellipse* represents standard excisional margins after pathologic review confirms melanoma. Note that standard margins fall outside the width of the extremity. **(D)** There are no margins that can be taken in such a fashion as to provide adequate oncologic treatment to preserve limb salvage. Thus, amputation is the only surgical option at this juncture. **(E)** The same suspected melanoma on the volar forearm. **(F)** A hypothetical longitudinally oriented incision for excisional biopsy, with a resulting straight-line scar of exact dimension as in **(B),** but instead in proximal-distal fashion. **(G)** The dashed ellipse again represents standard excisional margins after confirmed melanoma and is the exact dimension of the ellipse portrayed in **(C). (H)** Result of re-excision of confirmed melanoma with appropriate margin, though this situation clearly permits an anatomic solution consistent with maximum limb function and preservation.

If excisional biopsy is not a feasible option, full-thickness skin punch biopsy is the next best modality. Shave biopsy is discouraged because it does not permit conclusive review of tumor depth, which all too frequently cannot be accurately assessed once scar tissue from the shave biopsy is present. The biopsy process itself almost always obscures future attempts at depth determination. *Saucerization* is a partial-thickness skin sampling and is also discouraged.

Relevant Information Provided by Biopsy

Biopsy reports must include several crucial pieces of information: pathologic diagnosis (ultimately, the pathologist must confirm the suspected clinical diagnosis or provide an alternative diagnosis); tumor thickness (otherwise known as *Breslow depth*) must also be measured accurately to the nearest 0.1 mm; presence or absence of ulceration; the positive or negative status of both the deep and peripheral margins; and the mitotic rate of the lesion. Additional information includes any histologic subtyping presence or absence of vascular, lymph, or nerve invasion character of the inflammatory infiltrate and the presence or absence of microscopic satellite lesions. Immunohistochemical staining techniques also provide further characterization of tumors, but as yet are not of consequence to surgical planning. The Clarke level may also be mentioned, but please note that the Clarke level is clinically inconsequential in modern practice. Instead, the Breslow depth is used.

SURGICAL MANAGEMENT OF PRIMARY CUTANEOUS MELANOMA

Tumor Extirpation

Surgical excision is the principal treatment for cutaneous melanoma. There has been a trend away from radical excisions with very wide margins and extensive lymphadenectomy to conservative excisions with targeted lymphatic tissue removal. Results from important randomized, controlled trials have shed light on critical questions pertaining to surgical care, but many important components of surgical resection are still practiced based on traditional surgical experience.

The purpose of surgical excision is to provide complete excision of the lesion and its immediate surrounding area to provide durable, recurrence-free survival in the local area. Removal of tissue adequate to ensure elimination of the primary tumor, surrounding nests of malignant cells (microsatellites), and even closely situated second primary tumors is the major goal. Currently, there is a strong desire to avoid debilitating or disfiguring wide resections, large wounds that may necessitate advanced reconstructive techniques, or wounds of such size or location as to predispose to an unnecessarily high risk of surgical site infection, or cause disability. A number of high-quality, multicenter, randomized, controlled trials have evaluated the optimal margins for surgical excision and concluded that exceptionally wide margins offer no benefit in either survival or in local recurrence. Tumor thickness is the predominant factor that dictates the appropriate margin.

The recommended guidelines for surgical margins are shown in Table 1. It is crucial to point out that *margins* represent the distance from the scars of prior excisions and/or biopsies of the lesion or from the edges of any residual tissue that appears to be involved. In other words, if a punch biopsy is performed and there is residual pigmented tissue as well as a thin halo of erythematous tissue around the lesion that appears suspicious, the proper margins should be measured from the edge of the suspicious erythema, not just the pigmented lesion itself.

TABLE 1 American Joint Committee on Cancer Guidelines for Margins of Excision in Cases of Primary Cutaneous Melanoma

Tumor Thickness (mm)	Excision Margin (cm)
In situ	0.5–1.0
<1	1
1–2	2*
2–4	2
>4	2†

*For tumors in areas in which 2-cm margins would introduce substantial functional or aesthetic morbidity, 1-cm margins can be considered.
†Individual microscopic tumor characteristics, satellites, and tumor location should be considered, as "wider margins" have a degree of variability.

Optimal Deep Margins

Despite robust evidence supporting cutaneous margin dimensions when removing melanoma, there is relatively little published on the optimal deep margin. Thus, by tradition, the deep margin is typically through one extra tissue layer of clear uninvolved tissue (frequently to or less commonly including the muscle fascia or deep fascia). Although some surgeons resect fascia, many only resect this layer if the tumor appears to be closely invading the tissue layer above the fascia.

We do not recommend frozen/rapid section analysis of melanoma samples. Although skill can be obtained in the analysis of melanoma samples with stains made for nonpigmented basal cells or squamous cells, there is an error rate with rapid techniques both for margins and depth assessment of tumors. The techniques associated with frozen-section processing have been shown to introduce errors of up to 0.4 mm in the measurement of tumor depth. Surgeons should base their final judgment recommendations exclusively on final pathology measurements in fully stained specimens.

The role of Mohs micrographic surgery is unproven for invasive melanoma but seems valuable in challenging (repetitively positive) margin cases to provide temporary margin assessment. It is useful in those (less frequent) cases of melanoma in situ where the microscopic extent of the lesion exceeds the visible dimensions of the lesion. This assessment, using tissue stains developed for basal cell and squamous cell, is 75% accurate on the immediate Mohs stains for those who practice. Provisional analysis must be confirmed with standard pathologic processing before any reconstruction is accomplished. Less commonly, melanoma in situ is still present on permanent stains after clear temporary margins with Mohs surgery, but it has not been recognized. Society-level recommendations state that Mohs micrographic surgery can be considered for melanoma in situ or lentigo maligna melanoma for cases in which conventional margins may be disfiguring or disabling (e.g., the face) in order to limit extensive excisions. Definitive outcomes in these cases are not currently available.

The exact role of immunostains for margin assessment has not been confirmed. They may highlight extensive disease whose relevance for a particular patient may justify thought before extensive deforming resection is accomplished to clear an immunostain margin.

Our experience has shown that Mohs micrographic surgical excisions of melanoma in situ have a 25% rate of positive permanent margins on follow-up with regular hematoxylin and eosin (H&E) stains, so permanent sections should always be employed for confirmation of rapid margins by Mohs surgery or frozen sections. Reconstruction must be deferred awaiting permanent negative margins.

Management of Regional Lymph Nodes

Historically, patients with all but thin melanoma were treated with early, elective complete lymphadenectomy because experience demonstrated that cutaneous melanoma had a proclivity for nodal

and distant metastasis. The passage of time demonstrated that this approach introduced substantial morbidity without measurable reduction in regional or distant metastasis or improved survival for thin tumors. Two techniques have accurately predicted which patients are at risk for nodal and systemic disease: (1) specimen risk analysis outlined earlier with histologic examination and (2) analysis of the sentinel lymph node biopsy or ultrasound biopsy of the nodal basin. The evolution from routine widespread complete lymphadenectomy to targeted sentinel lymph node biopsy permit both approaches to have differing and sequential roles in the surgical management of regional lymphatic areas. Nodes that have a length-to-depth ratio of less than 2, a hypoechoic center, absent hilar vessels, or focal nodularity with increased vascularity are suspicious for tumor involvement.

Physical examination of regional nodes alone is unable to confirm 50% of those with clinically positive nodes, and similarly 20% of patients with clinically negative nodes have or will have microscopic involvement. Metastasis to regional nodes or into the bloodstream occurs when the melanoma reaches the mid-dermis, where blood vessels and lymphatics are present.

Most patients with regional lymph node metastasis on sentinel lymph node biopsy can select nodal observation, ultrasound observation, or completion nodal dissection, as approximately three-fourths of patients with positive sentinel nodes have one to two positive nodes.

MANAGEMENT OF PATIENTS WITHOUT CLINICALLY SUSPICIOUS OR CLINICALLY POSITIVE NODES

Staging of regional lymph nodes may be accomplished with SLNB or with ultrasound-guided sampling for regional lymphatic mapping-sampling, fine-needle biopsy, or excisional biopsy; one or several lymph nodes may be identified for lymphatic mapping.

The sentinel lymph node biopsy is much more commonly indicated than complete lymphadenectomy; the technique has a low false-negative rate, is very important for determining prognosis, and is a basis for surgical or adjuvant therapy or for clinical trials. When nonsentinel nodes in the basin are positive (11%), the prognosis for systemic spread is increased.

At a theoretical level, the sentinel node concept depends on proof that a given area of skin will reliably drain first into one single or perhaps several closely associated nodes within the larger lymph node basin. Sampling the sentinel nodes can thus provide an accurate pathologic examination of the relevant nodes in the basin, assuming that lymphatic fluid from the affected skin patch does indeed pass through the sentinel nodes before encountering the other nodes in the basin. Initially the accuracy of the technique was 75%, but with time and practice the accuracy now approaches 94%. Studies have shown variability in lymphatic drainage over time, and some sites drain to several node basins simultaneously. Some studies have demonstrated that the positive node may not be the node with the highest count, and node excision should define all nodes within 80% to 90% of the highest node sampled. The false-negative rate is 11%, and currently the procedure has a negative predictive value of 97%.

Survival is poorer in patients with thicker primary tumors, ulceration of the primary tumor, or involvement of nonsentinel nodes. SLNB is performed in thick melanomas more for purposes of regional disease control, adjuvant therapy, or investigational drug treatment.

Complications from sentinel lymph node biopsy are much less common than from complete lymphadenectomy; most recent high-quality studies show the rate of surgical site occurrences (e.g., seroma, wound infection, dehiscence) for sentinel lymph node biopsy to be 4% to 10% and for complete lymphadenectomy to be 25% to 40%. Complete lymphadenectomy also carries a substantially higher risk of extremity lymphedema, whereas lymphedema is rare after removal of one or two nodes (less than 1%) and probably reflects prior deficient lymphatics on a congenital or infectious basis. Extremity complications include lymphedema (sentinel node vs. completion lymphadenectomy) (0.7% vs. 12%), wound infection (1% vs. 7%), hematoma and seroma (2% vs. 6%), and sensory nerve injury (0.2% vs. 1.8%). Shoulder dysfunction occurs after axillary dissection, and arm delayed wound healing (16%). Lymphedema (32% overall in complete node removals) is more frequent with inguinal dissections, which have 8% and 51% complication rates for SNLB versus complete inguinal dissections.

The indications for sentinel lymph node biopsy have grown in recent years. Their rationale is to determine prognosis, to select patients who may benefit from lymphadenectomy or additional adjuvant therapy, or to select patients who may benefit from clinical trials. Current recommendations are to perform sentinel lymph node biopsy in all patients with clinically uninvolved nodes and melanoma ≥1 mm in thickness or those with melanoma <0.8 to 1 mm in thickness but with high-risk features (e.g., ulceration, >2 mitoses/mm^2, histologic evidence of lymphovascular invasion). The status of the sentinel node has been shown to have a profound effect on prognosis. The findings on sentinel lymph node biopsy may significantly change a patient's stage for a given T status. Patients with a positive sentinel lymph node biopsy are equally likely to have metastases elsewhere in the nodal basin or at distant sites. Moreover, the role of completion lymphadenectomy after positive sentinel lymph node biopsy has been called into more question considering the prevalence of systemic disease when multiple positive lymph nodes are found.

To perform the sentinel lymph node biopsy, a radioactive tracer, technetium-99 sulfur colloid is injected preoperatively into the dermis at the location of the suspicious skin lesion or directly into the scar from the prior excisional biopsy. It is of vital importance to ensure that the injection is done into the dermis because the subcutaneous tissue has a much less predictable lymphatic drainage pattern than the dermis. Radioactivity is then sensed with a scintillation counter as early as 15 minutes after injection of the radiotracer solution and for as many as 6 hours afterward. Simultaneously, a blue dye (isosulfan blue) may also be injected intradermally into the skin lesion in surgery. The dye will also transit via the lymphatics and help visually mark the involved lymphatic vessels and nodes with blue staining. Scintigraphy counts further direct the surgeon to the appropriate lymph nodes in the basin. An appropriately placed skin incision is made, and the combination of blue dye marking and radioactivity counts obtained via intraoperative probe identify the relevant sentinel node or nodes for excision. We inject the lesion with the radiotracer and dye and then perform the sentinel lymph node biopsy *before* the wide local excision of the lesion or biopsy scar. Some feel that more radical biopsy excisions of the original lesion may change the location of the draining node to a different and inappropriate node for consideration. Node harvest should continue until the count falls below 10% to 20% of that in the highest sentinel node.

In intermediate-thickness melanomas (1.2–3.5 mm), sentinel lymph node biopsy followed by regional lymph node dissection had a potential survival advantage (MSLT I) of up to 23% over those having delayed lymph node dissections when late lymphatic metastases (85% immediate survival vs 62% in delayed node dissection survival). With thicker melanomas, the survival statistics were 71% survival with early node dissections versus 64% observation. Thus, this study indicates there is the possibility of decreased nodal recurrence, decreased distant metastasis, and death with early complete node dissection.

More recent studies (MSLT II) have not shown a significant survival difference at 3 years, but they do show better local control of the appearance of new tumor deposits. This included a 69% decrease in local recurrence, 5% better survival at 3 years, and better disease control (92% vs. 77%). Long-term studies are awaited to highlight and further confirm survival differences.

In thick melanomas (>3.5 mm), these figures in MSLT 1 are 64% survival with immediate node dissection versus 48% in delayed-node dissection survival, with 17% of patients in the delayed group having

lymph nodes appear with an average presentation time of 19 months. Thick melanoma sentinel node biopsies had an average 9% relapse rate over time following the original lymph node sampling, where the initial positive rate was 33% and with follow-up reached 42% for delayed presentation of nodes in the sentinel basin.

NONSURGICAL MANAGEMENT OF LOW-VOLUME INVOLVEMENT IN SENTINEL LYMPH NODES

Low-volume involvement of a lymph node is infrequently accompanied by additional lymph node involvement in the node basin. The number, size, and character of lymph node tumor deposits yields a further classification of sentinel node involvement which predicts safe observation alone for minimal disease. Seventy percent of positive sentinel lymph nodes have single node involvement, and many have peripheral (less threatening location) as compared with central deposits, which indicate early lesions. Thus, many are observing these patients with serial ultrasound examinations of the remainder of the lymph node basin, doing delayed lymph node biopsies or delayed node dissection when indicated for late appearing and nonsentinel nodes. When the largest area in the involved lymph node is less than 0.1 mm, there is a 9% chance of further involvement; when the area is 0.1 to 1.0 mm, there is a 16% chance, and when it is greater than 1.0 mm, there is a 25% chance. One large study showed a sentinel lymph node biopsy group had a 4% late recurrence in the original lymph node basin. After thorough review of the original samples, 80% of those with late positive nodes could be identified in retrospect in the original slides. Immunostains increase detection accuracy of positive nodes as they are able to detect 1 in 100,000 cells versus 1 in 10,000 cells with H&E. Complex staging systems are offered for types and character of lymph node involvement, and observation and immunotherapy are now offered more widely versus completion lymph node dissection. In several studies, long-term disease-free 10-year survival occurred in a retrospective subset of 20% to 40% of intermediate-thickness melanoma patients after regional lymph node dissection.

MANAGEMENT OF PATIENTS WITH CLINICALLY SUSPICIOUS OR POSITIVE NODES

For patients with clinically suspicious nodes on physical examination, biopsy is still indicated. Only 50% of these are positive. Most often, ultrasound-guided fine-needle or core biopsy is appropriate, convenient, and 90% accurate. Once the pathologic diagnosis of nodal metastasis is made, complete lymph node dissection (preferred) versus frequent observation are considered to accurately characterize the patient's N status and manage regional disease. In summary, sentinel lymph node biopsy is not routinely performed for lesions less than 1 mm thick in the absence of aggressive histologic characteristics, but it is considered "therapeutic" for lesions 1 to 4 mm thick and "prognostic" for lesions greater than 4 mm thick. Early positive sentinel lymph node evaluations in intermediate-thickness melanoma occur with a 16% to 20% frequency, with 4% demonstrating late positivity after SLNB. In patients who did not undergo SLNB, late follow-up demonstrates appearance of positive nodes in 17% in intermediate-thickness melanoma, usually at around 20 months. In those who had SLNB and regional lymph node dissection, there was often a small but distinct survival advantage of 10% to 20% in both local control and survival; however, recent short-term studies have indicated that early survival statistics are identical. Lymph node metastases were found in 33% of patients with thick melanomas (>3.5 mm), and a further 9% had an additional late appearance of node metastases over time.

In 2% to 5% of patients, no clear sentinel node can be found; if no sentinel node can be identified, planned completion lymphadenectomy demonstrates 1% to 2% positive nonsentinel nodes. Curiously, late node dissections when interval follow-up demonstrates late appearance of further positive nodes have fewer complications (5% vs. 25% as compared with early lymphadenectomy).

Deep lymph node dissections (e.g., pelvis) may occasionally be individually considered based on the original pathology, despite their increased difficulty and morbidity.

MANAGEMENT OF RECURRENT MELANOMA

The management of recurrent melanoma becomes much more complicated than the relatively straightforward approach to the patient with primary cutaneous melanoma. Recurrence can be at the location of the initial lesion, along the dominant lymphatic pathway (termed *in-transit metastasis*), or in the draining lymph node basin. Accurate identification of the nature of recurrence is important for prognosis. Treatment options have become quite diverse in the past decade, with surgical resection now accompanied by systemic immunotherapy. Radiotherapy, various forms of isolated limb perfusion, intralesional injections, and topical medications are considered infrequently in some situations. These choices are generally managed by institutional tumor boards.

Tumor extirpation for recurrences still has the goal of achieving clear margins (foundational approach) as more than 20% of patients with locoregional recurrence survive and may even achieve a cure after such an operation. Unfortunately, unlike in the case of primary melanoma, there are little data available to guide appropriate margins for repeat excision or the consequences of residual microscopic disease foci within resection margins. The need for reconstructive operations after oncologic resection is also more common in cases of recurrent melanoma, which adds further complexity to surgical planning. Thus, patients with recurrent melanoma are usually managed under the care of a multidisciplinary team in the context of an institutional tumor board.

IMMUNOTHERAPY AND TARGETED THERAPY

There are 100,000 cases of melanoma per year in the United States with 9000 deaths. Distant metastases have a short-term survival rate of 26%, with metastasis the leading cause of melanoma death. In the past 10 years, melanoma has gone from one of the least responsive tumors to therapy (dacarbazine 20% response and little survival benefit, and interleukin 2 (IL-2), very toxic with few responses but occasional treatment victories) to one of the most responsive, with the lethality of advanced disease decreasing in the past 10 years. Immunotherapy has gone from a 10% response rate with a small survival benefit to a 56% response rate to multiple checkpoint drug therapy and 20% of patients requiring no further treatment in limited 10-year follow-up. Hence this turns the patient's problem in to a chronic disease, thanks to the long-term memory of the immune system. Although toxic effects increase with drug combinations, dose delays, glucocorticoids, and antitumor necrosis factor antibodies have decreased symptoms.

Melanoma is an immunologic malignancy with increased incidence in immunocompromised patients, evidence of lymphocyte infiltration, and recognition of melanoma antigens by tumor-infiltrating T lymphocytes. Melanoma tumors have high immunogenicity, and current immunotherapy is focused on counterregulatory mechanisms of the immune response. Immunotherapy also has immune-related adverse events. Melanoma cells are first in a stage of "equilibration" in metastasis, with a variable period of dormancy followed by escape to active metastatic cells with immunogenetic or non-immunogenic mutated or nonmutated melanoma cells. Anti–programmed cell death 1 (PD1) inhibitors have recently been employed for metastatic disease and have shown promise (nivolumab or pembrolizumab) as has targeted therapy versus BRAF V600 with dabrafenib or trametinib.

Since 2010, significant advances in the treatment of metastatic melanoma have occurred, and now also in adjuvant settings with high recurrence risk. These advances have led to immunotherapy with anti–PD-1 (pembrolizumab and nivolumab) and anti–CTLA-4 (ipilimumab) antibodies. These therapies have yielded up to 52% treatment improvement with significant survival in follow-up for 3 to 5 years.

Forty percent of melanomas harbor the *V600BRAF* mutation, leading to activation of the MAPK signaling pathway. Dual inhibition of this pathway with BRAF and MEK inhibitors has a rapid response rate with good effectiveness, but the survival benefit is short-lived because of the rapid development of resistance. Follow-up in these cases with traditional immunotherapy with PD-1 or targeted therapy has accomplished significant long-term results. A plateau effect in overall survival occurs, with most responders remaining in remission after treatment in limited 5-year follow-up in which response varies from 25% for single-drug trials to 52% for multiple drug trials, and 34% to 39% for targeted therapy. Other treatment regimens, such as the oncolytic viruses, may also have benefit in metastatic disease. These encouraging results are providing hope to the multitude of patients who face the grim diagnosis of metastatic melanoma.

Suggested Readings

Curti B, Faries M. Recent advances in the treatment of melanoma. *N Engl J Med*. 2021;384(23):2229–2240.

Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. *Cancer Biol Ther*. 2019;20(11):1366–1379.

Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472–492 *(We particularly encourage review of this document as the most up-to-date staging system for cutaneous melanoma.)*.

Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med*. 2014;370(7):599–609.

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Management of Soft Tissue Sarcomas

Adam S. Levin, MD, and Carol D. Morris, MD, MS

INTRODUCTION

Soft tissue sarcomas (STSs) represent a rare group of malignancies of mesenchymal origin. In the United States, there are approximately 13,000 new STS diagnoses per year, resulting in over 5000 deaths. Given the wide variety of mesenchymal tissues, including fat, muscle, connective tissues, and blood vessels, among others, these can be further subclassified into more than 50 recognized histologic subtypes, largely based on the tissue to which it most closely resembles.

The majority of soft tissue sarcomas present in adults and become more prevalent with increasing age. The incidence has slowly increased in the United States in recent decades, with an overall incidence of about 2 per 100,000, increasing to about 8 per 100,000 in patients over the age of 80 years (Figs. 1 and 2). However, although they are less commonly seen in the pediatric/adolescent population, soft tissue sarcomas are the third most common solid malignancy found in this age group, accounting for approximately 15% of all pediatric cancers.

There is a slight male predominance, though some histologic subtypes exhibit a small female predilection. Although nearly one-half of all sarcomas present in the extremities, they may arise in any anatomic region with connective tissue. The abdomen, pelvis, and retroperitoneum are common locations as well. Ultimately, these malignancies represent a broad family of diagnoses, with highly variable demographics, anatomic localizations, clinical presentations, imaging appearance, histopathologic findings, treatment considerations, and prognoses.

This chapter aims to outline general, anatomic-specific, and histopathology-specific considerations in the treatment of soft tissue sarcomas. The exception would be gastrointestinal stromal tumors (GISTs). The majority of soft tissue sarcomas require a multidisciplinary approach including surgery, radiation, and chemotherapy, alone or in combination. Treatment paradigms in the context of disease-specific considerations will be discussed in detail.

ETIOLOGY

The majority of soft tissue sarcomas arise without a clear inciting cause. Often, patients will relate a history of prior trauma to the site, though such events more likely reflect the initial identification of the mass rather than a true causative factor. There are, however, environmental exposures and predisposing conditions that appear to have close associations.

Radiation

Radiation exposure, either therapeutic or environmental, is perhaps the most recognized etiologic factor for soft tissue sarcoma development. This is most commonly associated with undifferentiated pleomorphic sarcomas, though several other histopathologic subtypes have been identified as well. Radiation may account for up to 5% of all soft tissue sarcoma diagnoses, despite being evident in less than 1% of exposed adults. Incidence appears to be higher in children, though this may be related to the underlying diagnoses being treated. Although some have suggested a higher risk of sarcomagenesis in patients exposed to orthovoltage radiation, more modern megavoltage radiation therapy has a clear association as well.

By definition, radiation-associated sarcomas must be histologically distinct from the original diagnosis and arise within the radiated field no sooner than 3 years postradiation. Sarcomas may develop at any point following 3 years, with an average latency of about 11 years. Radiation-associated sarcomas tend to follow an aggressive clinical course, and their management may be further limited by prior therapies.

Other Causative Factors

Angiosarcomas are closely associated with chronic lymphedema, or Stewart-Treves syndrome. Chemical exposures, such as Thorotrast, vinyl chloride, and arsenic, have been linked with hepatic angiosarcoma. Additional exposures to agents such as herbicides and defoliants have been associated as well. Exposure to chlorinated dioxins,

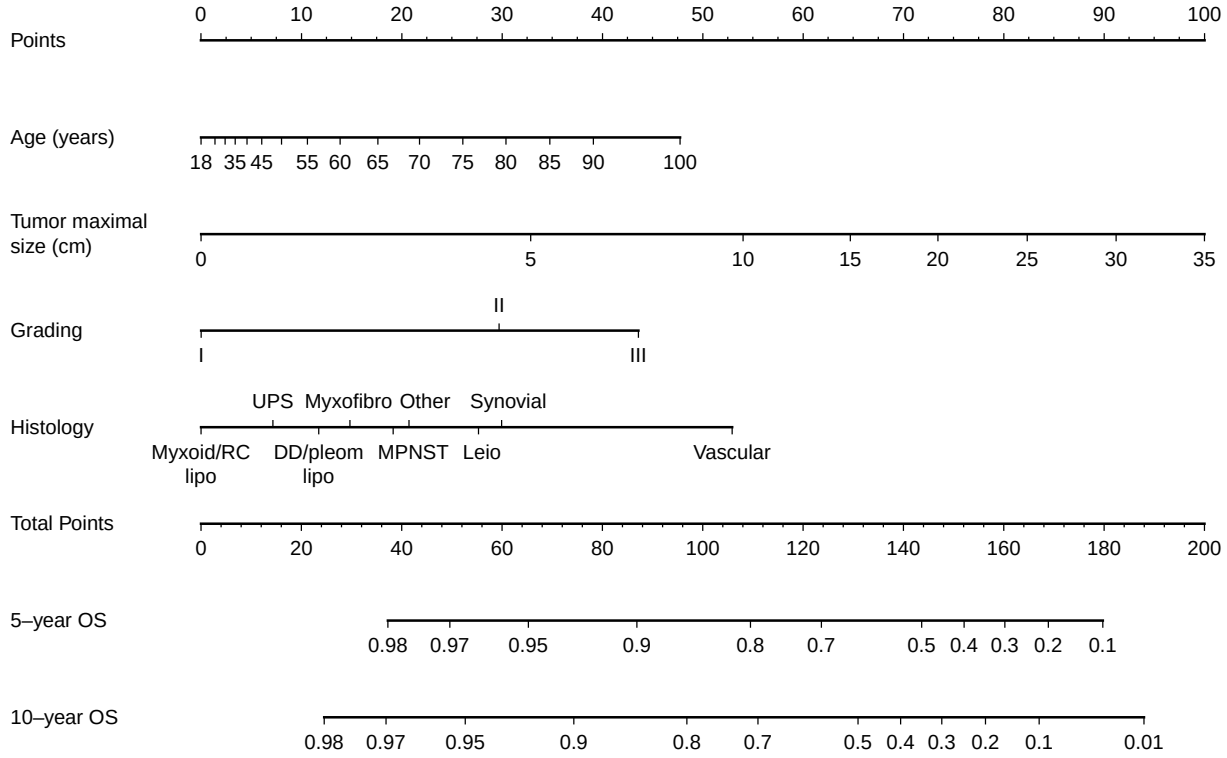


FIG. 1 Overall survival nomogram for extremity soft tissue sarcoma. *DD,* Dedifferentiated; *Leio*, leiomyosarcoma; *MPNST*, malignant peripheral nerve sheath tumors; *Myxofibro*, myxofibrosarcoma; *OS*, overall survival; *Pleo*, pleomorphic; *RC lipo*, round cell liposarcoma; *UPS*, undifferentiated pleomorphic sarcoma. *(From Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localized soft-tissue sarcomas of the extremities: a retrospective analysis.* Lancet Oncol. *2016;17:671–680.)*

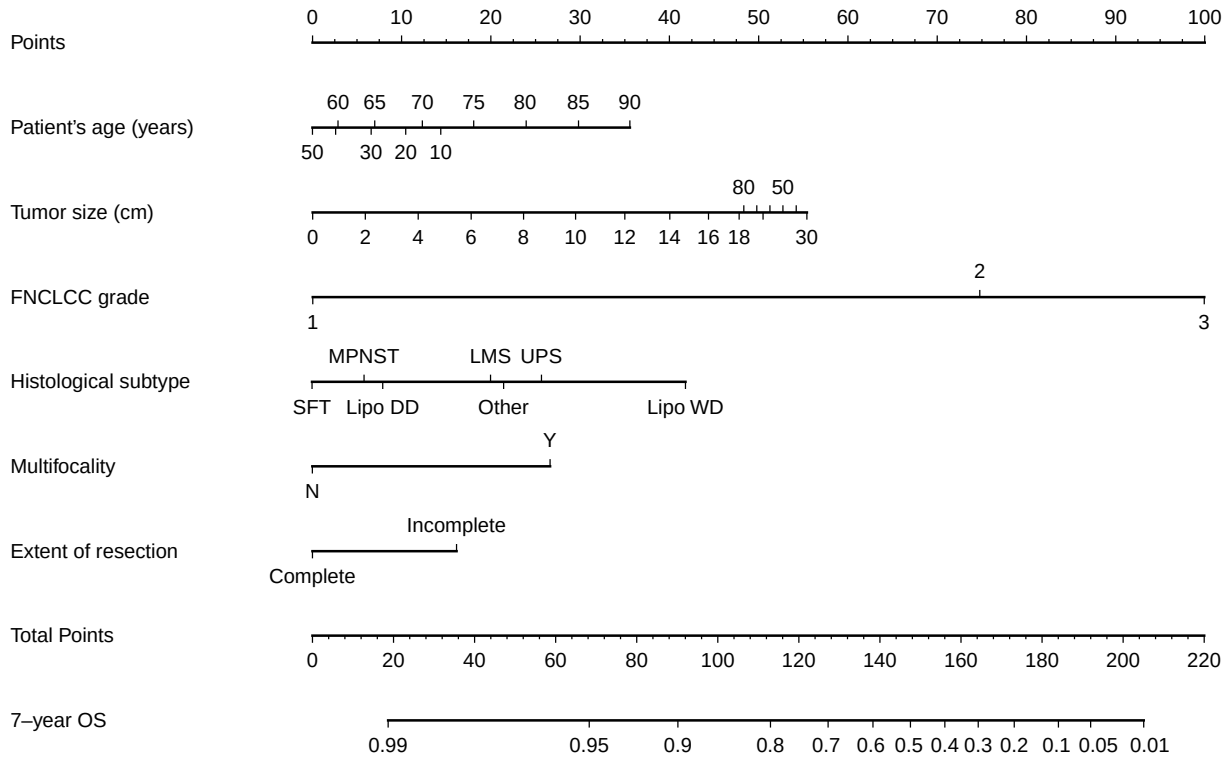


FIG. 2 Overall survival nomogram for retroperitoneal soft tissue sarcoma. *Lipo DD,* dedifferentiated liposarcoma; *FNCLCC*, National Federation of French Cancer Centres; *LMS*, leiomyosarcoma; *MPNST*, malignant peripheral nerve sheath tumors; *OS*, overall survival; *SFT*, solitary fibrous tumor; *UPS*, undifferentiated pleomorphic sarcoma; *Lipo WD*, well-differentiated liposarcoma. *(From Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets.* J Clin Oncol. *2013;31[13]:1649–1655.)*

such as that in Agent Orange, has also been implicated without clearly established causation.

Predisposing Genetic Conditions

Some heritable and sporadic genetic mutations and cellular alterations demonstrate a clear association with soft tissue sarcomas. Li Fraumeni syndrome, related to *p53* mutations, is implicated in numerous malignancies including bone and soft tissue sarcomas. Neurofibromatosis type 1, with mutations in *NF1,* carries an approximately 15% lifetime risk of developing a malignant peripheral nerve sheath tumor. Overall, nearly half of all malignant peripheral nerve sheath tumors are in patients with *NF1* mutations. Similarly, desmoid tumors are closely associated with Gardner's syndrome. As discussed later, some histopathologic subtypes of soft tissue sarcoma exhibit characteristic chromosomal rearrangements within the involved tumor cells, including the Ewing family of tumors, synovial sarcoma, clear cell sarcoma, among others.

DIAGNOSTIC EVALUATION

Although the diagnosis may be glaringly evident in some patients, the differentiation between benign and malignant soft tissue neoplasms can often be challenging. With careful attention to history, clinical examination, and imaging findings, the diagnosis of soft tissue sarcoma can often be reasonably suspected (Figs. 3–13).

Pain

The majority of soft tissue tumors, benign or malignant, are not painful. A painful soft tissue mass is typically an indication of nerve involvement or compression, bone invasion, or vascular etiology. Most commonly, a soft tissue mass localized to the nerve will be a schwannoma or neurofibroma. In patients with NF1, increasing pain within a neurofibroma may prompt evaluation for transformation into a malignant peripheral nerve sheath tumor (MPNST). As previously noted, nearly half of MPNSTs develop in patients without



FIG. 3 Biopsy of a soft tissue sarcoma.



FIG. 4 **(A)** Sagittal MRI of a superficial unclassified pleomorphic sarcoma. **(B)** Planned wide skin incision around the visible mass to achieve adequate skin margin.

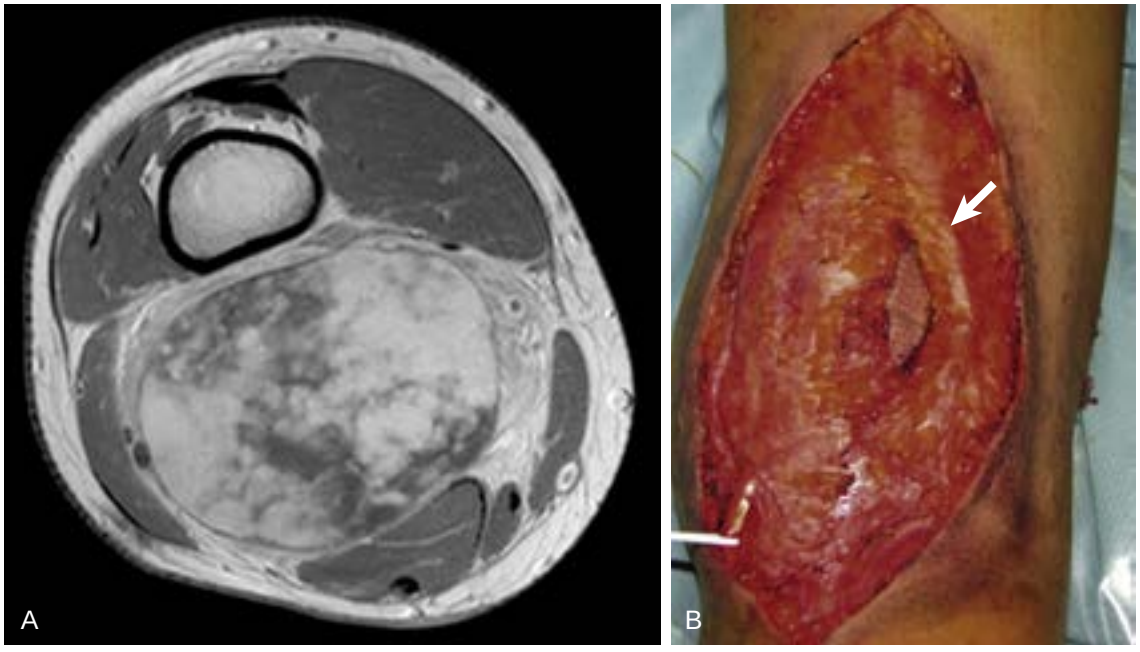


FIG. 5 **(A)** Axial MRI of malignant solitary fibrous tumor of the thigh demonstrating deep location. **(B)** Because of its deep location, only a minimal skin paddle around the biopsy tract is needed at resection.

neurofibromatosis. Less commonly, other soft tissue sarcoma subtypes may present as an intraneural neoplasm, with synovial sarcoma being the most common.

In the absence of a primary neural neoplasm, soft tissue masses may compress directly on nerves or blood vessels, resulting in pain as well. These may be insidious in onset, though often are associated with a positive Tinel sign. Alternatively, some soft tissue masses may erode into the underlying bone, leading to either discomfort from periosteal inflammation or potentially even a pathologic fracture from external compression. Although not common, sarcomas may elicit a robust surrounding inflammatory response that may be associated with pain.

Size

The size of the mass may be misleading regarding its local aggressiveness. Some benign conditions, such as desmoid-type fibromatosis or benign lipomatous neoplasms, may grow to be quite large. Similarly, high-grade sarcomas may initially present as small masses. Although an index of suspicion may be appropriate under many circumstances,

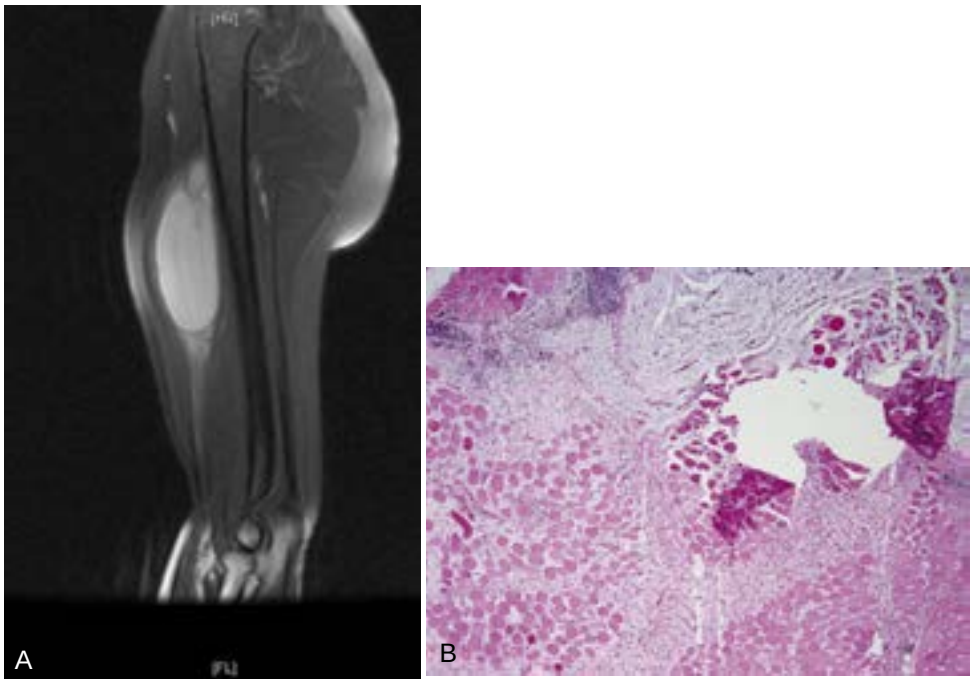


FIG. 6 Myxofibrosarcoma commonly presents on the superficial aspect of the fascia, typically with a wide peritumoral reactive zone extending along fascial planes **(A).** Histopathologically, this may demonstrate microscopic extension between muscle fibers **(B).**

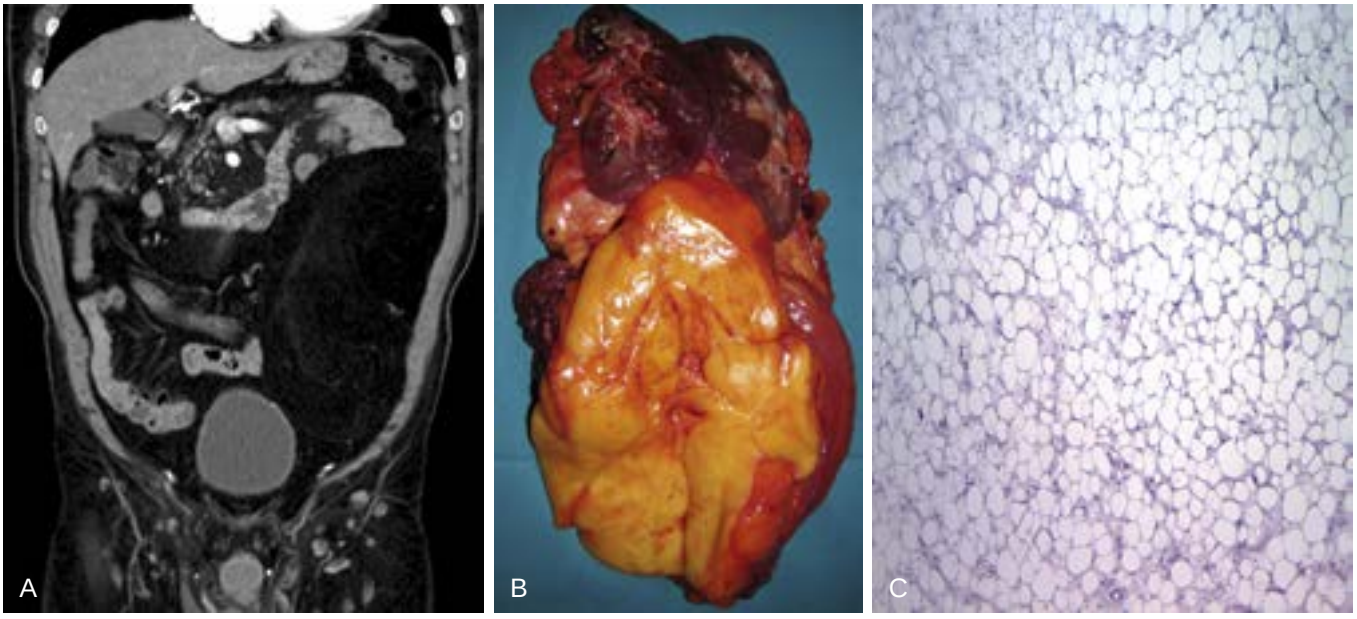


FIG. 7 **(A)** Coronal CT view of a left-sided retroperitoneal well-differentiated liposarcoma. Surgical specimen, together with macroscopic **(B)** and microscopic **(C)** appearance.

lesions greater than 5 cm should prompt evaluation and consideration that it may represent a soft tissue sarcoma.

Depth

In the extremities, more than two-thirds of soft tissue sarcomas are deep to the investing fascia of muscle. Although not pathognomonic, a mass greater than 5 cm that is deep to the fascia draws increased suspicion that this may represent a malignancy. Dermatofibrosarcoma protuberans and myxofibrosarcoma, however, are two exceptions as soft tissue sarcomas that most commonly present superficial to the deep fascia. Perhaps as a result of their superficial location, dermatofibrosarcoma protuberans and myxofibrosarcoma lend themselves to misdiagnosis or mistreatment, with providers presuming that they are benign conditions such as ganglion cysts or lipomas. Since superficial cysts and lipomas tend to be soft and commonly transilluminate on clinical examination, the lack of such findings should prompt advanced imaging to further characterize.

Mobility

At least in the extremity, most benign soft tissue masses are largely mobile on clinical palpation, whereas malignant tumors are typically fixed to the surrounding soft tissues. A firm mass that is relatively immobile should raise the suspicion for malignancy.

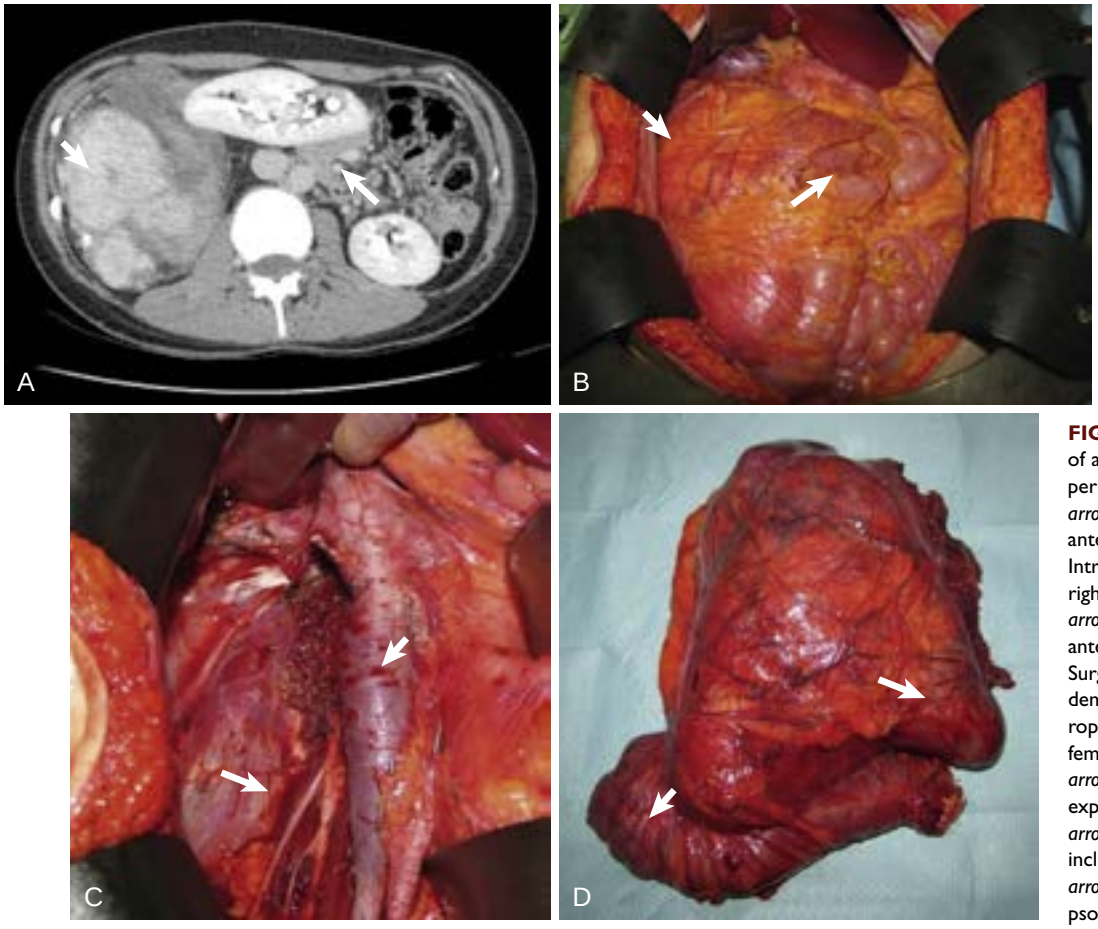


FIG. 8 **(A)** Axial CT image of a conventional right retroperitoneal liposarcoma *(left arrow)* displacing the right kidney anteromedially *(right arrow)*. **(B)** Intraoperative image of the same right retroperitoneal sarcoma *(left arrow)* with the kidney displaced anteromedially *(right arrow)*. **(C)** Surgical field after tumor removal demonstrating a clean right retroperitoneal space with visible femoral nerve roots *(bottom arrow)* after psoas resection and exposed inferior vena cava *(top arrow)*. **(D)** Surgical specimen including right colon *(bottom arrow)* and right kidney *(top arrow)*; psoas not shown but present.

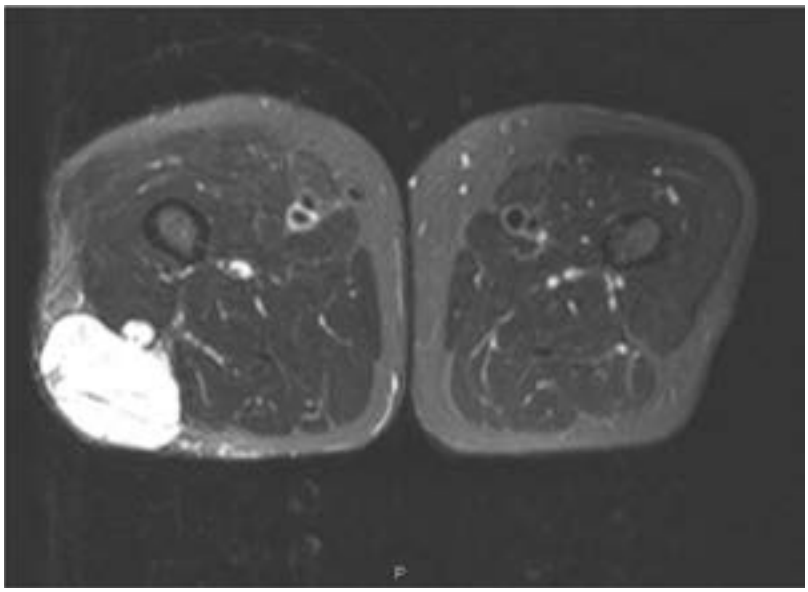


FIG. 9 Dermatofibrosarcoma protuberans (DFSP) is associated with a t(17;22) translocation. Because of its typical superficial location, it is often initially mistaken for a benign process and commonly identified after an unplanned surgical excision.

Growth

In light of their malignant nature, most soft tissue sarcomas will demonstrate progressive growth over time. Although this is overwhelmingly true, low-grade soft tissue sarcomas may sometimes grow at a very slow rate. In addition, some high-grade sarcomas, including synovial sarcoma and clear cell sarcoma as prime examples, may be notoriously slow growing over a prolonged period before rapid growth. These entities, in particular, may present a diagnostic challenge as there indolent growth pattern may lull the patient and provider into a false sense of security regarding its nature.

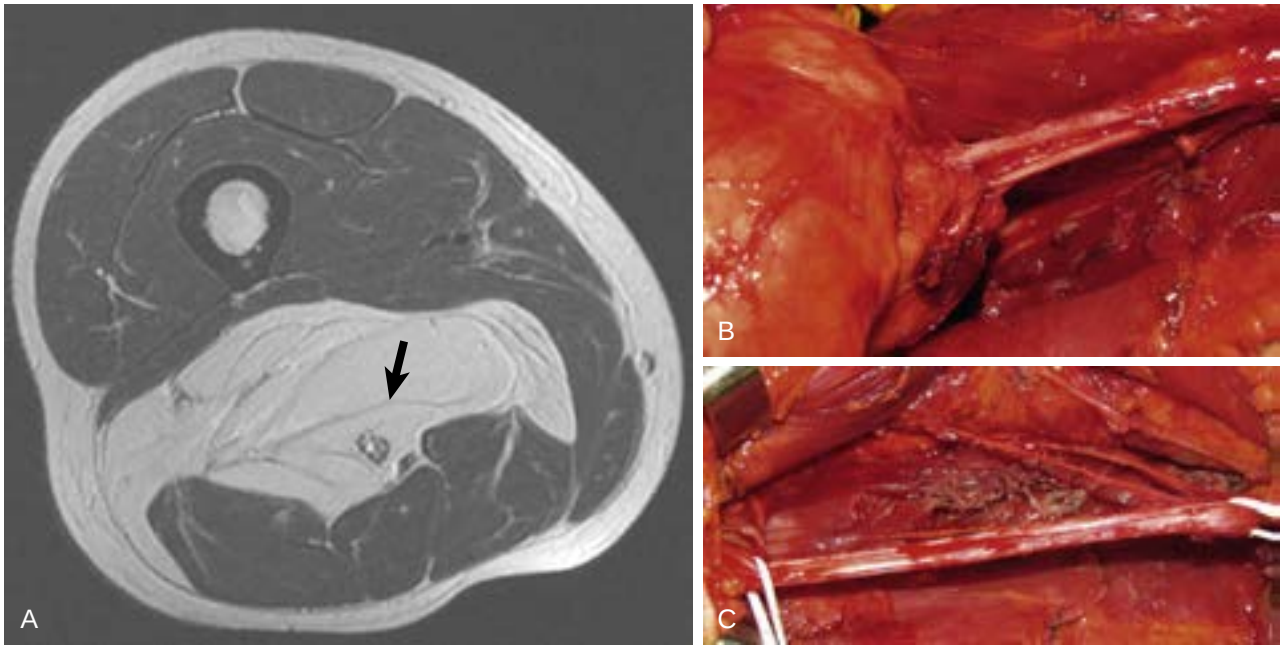


FIG. 10 **(A)** Axial MRI of the thigh shows a well-differentiated liposarcoma encasing the sciatic nerve *(arrow)*. **(B)** Tumor peeled off the sciatic nerve. **(C)** Surgical field after resection of the tumor, with skeletonized nerve.

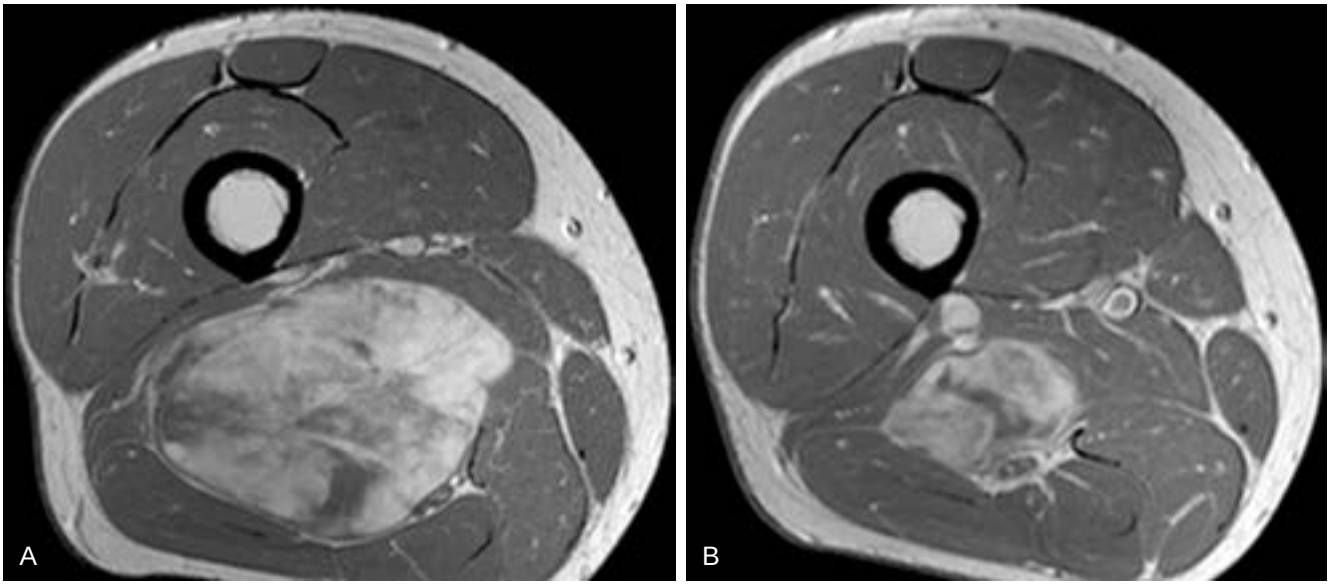


FIG. 11 High-grade myxoid liposarcoma of the right thigh. Contrast-enhanced T1-weighted axial MRI at baseline **(A)** and after administration of concurrent chemotherapy **(B)** with three courses of anthracycline + ifosfamide along with radiotherapy (for a total dose of 50 Gy).

Imaging Characteristics

As relatively inexpensive and widely available imaging tests, radiographs may be the initial imaging study to suggest a neoplasm, though most soft tissue masses are not easily identified on radiographs. In some cases, a soft tissue shadow may be evident. Dystrophic calcifications may be seen in extraskeletal osteosarcoma and about 30% of synovial sarcomas. Radiographs can also be helpful in patients with mechanical pain and suspected bone involvement. However, for the majority of patients, plain radiographs provide little value in the diagnosis and management of soft tissue sarcomas.

Contrast-enhanced CT is highly effective in the evaluation of abdominal or retroperitoneal sarcomas. In the extremities, however, MRI is overwhelmingly the most useful imaging modality for workup of a soft tissue mass. This is commonly performed with both T1 and fat-saturated T2 sequences, and both with and without gadolinium enhancement. The overall MR appearance may be highly variable, though it often will demonstrate isointensity to muscle on T1-weighted images and high signal on T2-weighted or fluid-sensitive sequences. A heterogeneously enhancing soft tissue mass, particularly deep to the fascia, is highly suspicious for representing a

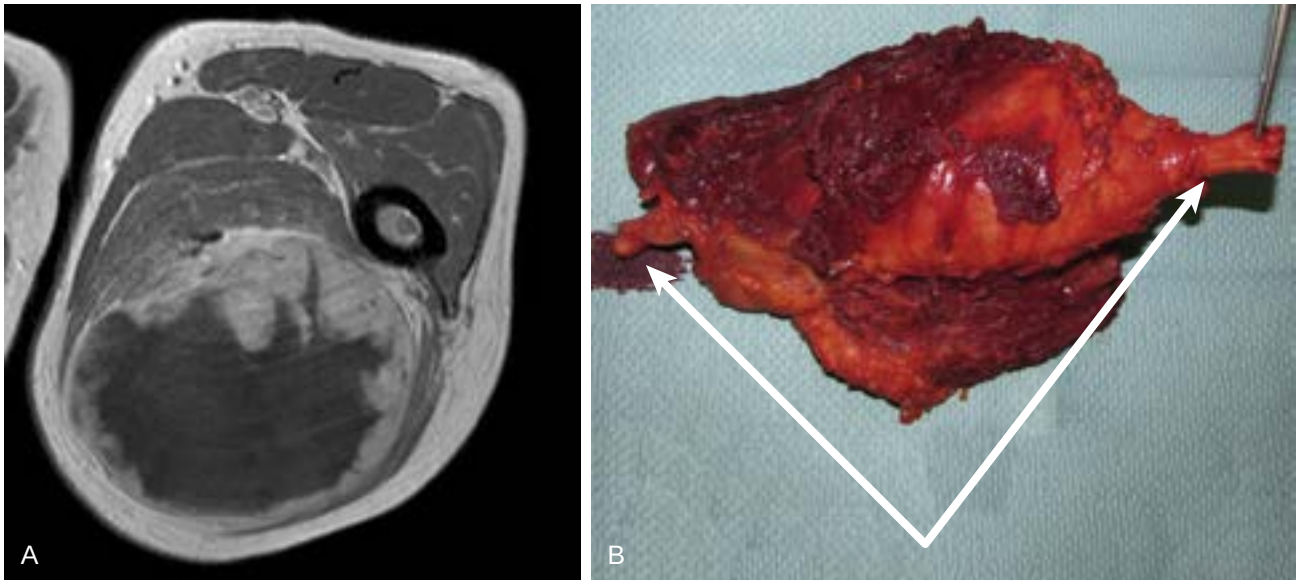


FIG. 12 Preoperative MRI **(A)** and surgical specimen **(B)** demonstrating malignant peripheral nerve sheath tumor arising from the sciatic nerve (*arrows* indicate nerve stumps).

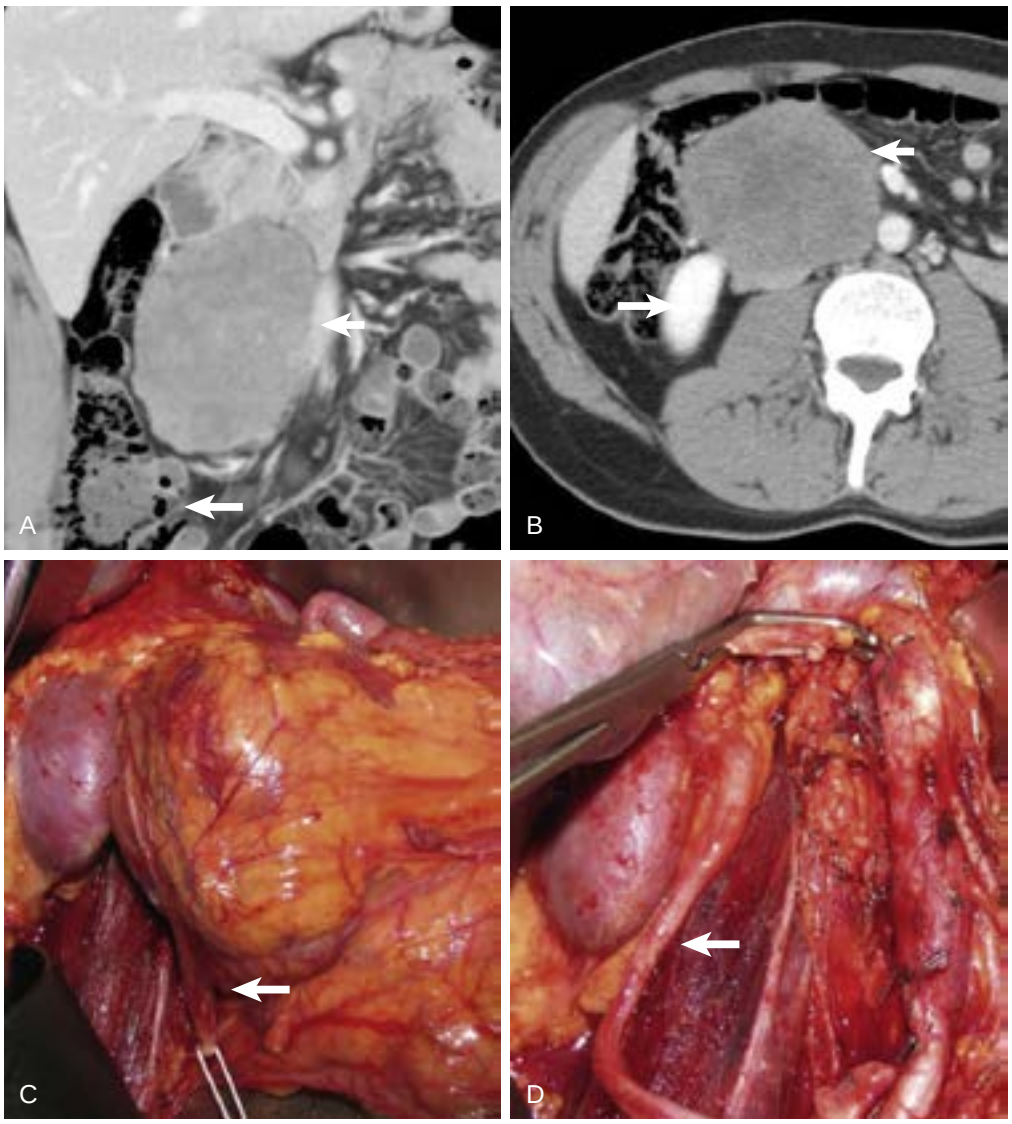


FIG. 13 **(A, B)** Coronal/axial CT images of a leiomyosarcoma of the inferior vena cava *(top arrow)* displacing the right kidney and the right colon *(bottom arrow)*. Intraoperative images showing displacement (**C,** *arrow*) and preservation of the right ureter and kidney **(D,** *arrow*).

soft tissue sarcoma. Cross-sectional imaging of the primary tumor is key to finding the extensive tumor involvement, including the depth of invasion and its anatomic relationship with neurovascular or other important structures.

Other imaging modalities, including ultrasound, PET/CT, and bone scan, are typically of little value in the initial evaluation of a soft tissue mass. In some histopathologic subtypes, particularly those with high rates of nodal metastasis, a PET/CT may be indicated as part of systemic staging.

Biopsy

In the vast majority of soft tissue masses suspicious for STS, a biopsy should be performed before definitive management including surgical excision. As a result of advances in pathologic interpretation of small amounts of tissue, core needle biopsy is usually sufficient for diagnostic purposes. Reviewing the images with the interventional radiologist will aid in maximizing the yield of diagnostic tissue. For extremity tumors, biopsies should be performed along a limb salvage incision minimizing cross-compartment contamination. Although abdominal and retroperitoneal tumors may present unique considerations, biopsy is still recommended before surgical manipulation. In certain instances, neoadjuvant treatment may be indicated. Open biopsies are typically reserved for when needle biopsy fails to provide a diagnosis. Finally, a small number of tumors may be indicated for primary wide excision in which an undiagnosed mass is taken out with intended negative margins. The indications for primary wide excision are narrow and require considerable expertise to navigate.

Regardless of whether performing an incisional biopsy or core needle biopsy, the anticipated extensive or limb salvage incision should be mapped out. In the extremities, the extensile approach for soft tissue masses will typically be longitudinal, rather than transverse or in line with skin creases. Ideally, the biopsy tract should be along or immediately adjacent to the anticipated extensile incision. This allows for the biopsy tract to be excised with the mass at the time of definitive surgical excision. Some controversy exists as to whether a needle biopsy tract requires excision as the risk of local recurrence along the needle tract is relatively low for most histopathologic subtypes, especially if radiation is incorporated in the local treatment plan.

At the time of biopsy, a direct approach should be used, preferably limiting potential contamination to a limited amount of noncritical structures. Whether performed as an incisional or needle biopsy, avoidance of critical neurovascular structures will limit contamination when planning for further local control management. A primary advantage of core needle biopsy over open incisional biopsy is the ability to target a specific area within the mass. This is particularly helpful in masses with suspected heterogenous grade (e.g., dedifferentiated liposarcoma) or necrotic regions.

For incisional biopsies of extremity tumors, an ideal approach would avoid dissection of neurovascular structures altogether. Strict oncologic surgical principles, with limited surgical incision lengths, avoidance of multiple muscle compartments, and separation of instruments contaminated by tumor, can greatly limit potential complications including further contamination of the surrounding soft tissues. Care should be taken for meticulous hemostasis to avoid a postoperative hematoma, which could iatrogenically spread tumor cells. At the time of biopsy, initial evaluation with frozen section may be helpful to ensure diagnostic quality tissue. Although the differentiation between neoplastic and infectious conditions can often be highly suspected on preoperative workup, these are not mutually exclusive. As such, a culture of every biopsy and a biopsy of every culture is often recommended.

Staging

The American Joint Committee on Cancer (AJCC) has a prognostic staging system specific for soft tissue sarcomas. This is based on the tumor histologic grade, tumor size, and the presence of nodal or visceral metastatic disease. Although the depth of the tumor relative to the fascia was once considered prognostically relevant, the most recent iteration of the AJCC staging manual (eighth edition) reflects the current literature, suggesting that tumor depth is not a significant factor in patient survival.

Histologic grading of soft tissue sarcomas is based on tumor differentiation, mitotic count, and spontaneous tumor necrosis. For other entities, such as myxoid/round cell liposarcoma, tumor grading may be based on the percent of round cells. Otherwise, tumors are most commonly graded on the three-tiered scale of the French Federation of Cancer Centers Sarcoma Group (FNCLCC): low grade (grade 1), intermediate grade (grade 2), or high grade (grade 3). Commonly, intermediate-grade tumors are treated similar to high-grade sarcomas.

Although the AJCC system is the most useful for prognostication in soft tissue sarcoma, the Musculoskeletal Tumor Society (MSTS) has developed a surgical staging system to help conceptualize extremity surgical excision. Similar to the AJCC, this system is based on tumor grade and the presence or absence of metastases, but instead of using size as a factor, the MSTS system further characterizes by whether the tumor is contained within a single anatomic compartment.

In light of the numerous histopathologic variant as well as other prognostic factors that are not included in the AJCC or MSTS staging systems (e.g., age, anatomic location, histologic subtype), these systems have intrinsic limitations. Precision medicine tools such as nomograms are prognostic calculators based on multiple patient and tumor variables. Several STS nomograms have been developed to aid clinicians in stratifying patients into more graded and hopefully meaningful risk tiers. Further, as our understanding of molecular/genetic and other cytologic factors continues to expand and novel targeted therapies are developed, our ability to prognosticate for specific tumor continues to improve.

As noted, the AJCC staging system considers nodal and visceral metastases. As part of routine staging for extremity soft tissue sarcomas, chest imaging is routinely included for routine staging and long-term surveillance. Patients with abdominal, pelvic, and retroperitoneal sarcomas would also typically include CT imaging of the abdomen and pelvis.

Nodal metastases are infrequent and have been reported to occur in 2.6% to 5.3% of extremity soft tissue sarcomas. There is some suggestion that this rate may be higher among patients with visceral and retroperitoneal tumors. Some histologic subtypes, however, exhibit higher rates of lymph node involvement, namely the CARE diagnoses: *c*lear cell sarcoma, *a*ngiosarcoma, *r*habdomyosarcoma, *e*pithelioid sarcoma, and *E*wing's sarcoma. Nodal metastasis rates across these particular diagnoses range from 12% to 55% in some series. Although synovial sarcoma has often been included in this group, more recent evidence suggests that synovial sarcoma does not portend an increased risk of nodal metastasis. In patients who present with these conditions, particularly the small round blue cell tumors (rhabdomyosarcoma and Ewing's sarcoma), consideration may be given for PET/CT as part of staging. Otherwise, PET/CT is rarely indicated as part of the diagnostic restaging workup for soft tissue sarcoma. Although controversy exists regarding the role of sentinel lymph node biopsy, the current literature is not conclusive as to a clear benefit, even in those histologic subtypes recognized to have higher rates of nodal involvement.

TREATMENT

Soft tissue sarcomas are best treated by a multidisciplinary team. The primary teams include surgery, radiation oncology, and medical oncology. Unique clinical scenarios may draw on the expertise of other subspecialties such as interventional radiology or palliative care.

Surgical Management

The cornerstone of treatment of nearly all soft tissue sarcomas is surgical excision. A landmark randomized control trial in the early 1980s by Rosenberg et al. evaluated oncologic outcomes following amputation versus limb-sparing surgery in 43 adult patients with high-grade soft tissue sarcoma of the extremity. Although there was suggestion of increased rate of local recurrence with limb salvage, there was no difference in disease-free survival or overall survival, laying the foundation for limb-sparing oncologic resections. Today, at experienced centers, more than 95% of extremity soft tissue sarcomas are managed with limb-sparing surgery.

Enneking and colleagues described a conceptual framework regarding surgical margins. Intralesional procedures involve incising into the tumor. In sarcoma surgery, this is essentially limited to incisional biopsies. Marginal excisions describe an en bloc mass excision that either abuts the tumor pseudocapsule or dissects through the peritumoral inflammatory zone. Wide surgical margins, the treatment of choice for STS, describes an en bloc excision with a rim of normal tissue entirely surrounding the tumor. In the Enneking description, radical excisions are limited to those that excised the entire involved compartment. Although, at the time of that description, radical resections were utilized for sarcomas without an effective adjuvant, excision of the entire compartment is rarely utilized in modern sarcoma management.

It is well recognized that the peritumoral inflammation, known as the "reactive zone," may contain microscopic deposits of malignant cells. This is perhaps best recognized in myxofibrosarcomas, which typically have a broad extension of peritumoral inflammation along fascial planes. Researchers have demonstrated neoplastic cells within the reactive zone of soft tissue sarcomas up to 4 cm from the grossly identified mass. As such, excision of the peritumoral inflammation together with the soft tissue sarcoma, with wide surgical margins through normal tissue planes, remains the ideal surgical management. Preoperative radiation therapy may help in decreasing cell viability within the reactive zone, though it may challenge the ability to distinguish between radiation-associated inflammation and the peritumoral reactive zone.

Several investigators have attempted to define margin adequacy both quantitively and qualitatively. For example, the Japanese Orthopedic Association advocated that biologically robust barriers such as fascia, periosteum, joint capsule, or epineurium can adequately substitute for centimeters of adipose tissue. Despite the clinical utility of these types of efforts, significant ambiguity remains on the concept of margins.

Reflecting the concept of wide surgical margins, the AJCC classification indicates R0 excisions as having no microscopic tumor cells exist at the excision margin. This is typically the goal for sarcoma excisions. More recently, consideration has been given to a goal of R0 +1 mm as being a target. With effective local adjuvant treatment, planned margins of less than 1 mm on critical structures like nerves and vessels did not demonstrate an increase in local recurrence at 10 years, though unplanned positive margins have markedly increased rates of local recurrence. For extremity tumors abutting a long bone, the periosteum may act as an excellent margin. In the absence of osseous erosion or invasion, data out of the MD Anderson Cancer Center suggest that resection of bone may not be necessary.

Ultimately, while considering the extent of surgical margins around a soft tissue sarcoma, one must weigh potential functional considerations against the risk of local recurrence. Low-grade sarcomas and those with a low risk of local recurrence following preoperative radiation may be appropriate for careful dissection, aiming to preserve critical neurovascular elements when feasible. However, for sarcomas that either originate from (e.g., leiomyosarcoma, MPNST) or encase critical vascular or neural structures, strong consideration should be given to excision of those elements with the soft tissue mass, with subsequent vascular bypass or nerve/tendon transfers. If the anticipated function of the limb after adequate oncologic resection is not superior to that of an amputation, limb-sparing surgery would no longer be favored.

Despite extensive data regarding the role of operative margins as it relates to local recurrence, there is no clear data to suggest that this translates to disease-specific or overall survival. Nonetheless, careful attention to margin status is integral to standard sarcoma care. Intraoperative frozen-section margin analysis, particularly of any abnormal-appearing tissue, may guide intraoperative decision making. For patients who have previously undergone either an unplanned excision or had positive margins on prior excision, a wide re-excision of the surgical bed may be appropriate. This may result in large soft tissue defects, and these patients may have an increased need for advanced soft tissue reconstructions. In circumstances with highly infiltrative tumors as well as those with prior unplanned excisions, consideration is given to a staged approach, awaiting final histopathologic margin assessment before soft tissue reconstruction.

Considerations Specific to Retroperitoneal Sarcomas

Approximately 15% of all soft tissue sarcomas present in the retroperitoneum. The nature of the retroperitoneum may lead to delayed recognition of soft tissue sarcomas until they reach a large size, at which point nonspecific symptoms such as early satiety, constipation, or abdominal discomfort may exist. In larger masses, a sarcoma may become palpable, though many remain asymptomatic and are identified incidentally on imaging.

The majority of retroperitoneal soft tissue sarcomas may be identified on CT of the abdomen and pelvis. The most common sarcomas in this location include liposarcomas and leiomyosarcomas, each of which have some characteristic imaging features on CT to assist in formulating a differential diagnosis. However, with the exception of well-differentiated/dedifferentiated liposarcoma, imaging alone is rarely diagnostic.

In this regard, a detailed history and careful clinical examination together with CT of the abdomen and pelvis can help point to a diagnosis. Typically, a staging CT of the chest is indicated. Although biomarkers for soft tissue sarcoma are not of current clinical utility, laboratory testing for a lactate dehydrogenase (LDH), alpha-fetoprotein, human chorionic gonadotropin (hCG), and CA-125 may help in screening for alternative diagnoses. PET/CT is rarely indicated.

Although MRI is the mainstay for evaluation of extremity soft tissue masses, its utility over CT in the retroperitoneum is less well defined. Ultimately, although imaging may be highly suggestive, nearly all retroperitoneal masses are appropriate for biopsy to ensure a correct diagnosis before treatment. This is most commonly performed with core needle biopsy under image guidance. Although biopsy tract recurrences are rare, transrectal and transvaginal approaches should be avoided.

Unlike extremity soft tissue sarcomas, for which local recurrence has not been clearly associated with disease-specific or overall survival, locoregional recurrence in retroperitoneal sarcomas is more closely associated with mortality. Local control can often be difficult, and even low-grade tumors such as well-differentiated liposarcomas can lead to mortality related to local recurrence. As such, the initial surgical management is of utmost importance to ensure the best chance at cure.

Given the location, retroperitoneal sarcomas may encase or displace vital organs or major vessels. A clear understanding of involved structures as well as those abutting the tumor is critical in determining an optimal operating room plan. The anatomic boundaries of the retroperitoneum typically involve the gastrointestinal structures such as the colon, pancreas, stomach, or liver anteriorly. The posterior extent is typically bordered by the kidney and/or iliopsoas, though it often includes the diaphragm. Medially, these tumors may frequently abut the aorta and/or vena cava, and the decision about whether to resect otherwise uninvolved viscera is often related to the safe dissection of the feeding vessels.

Because of challenges of visualization adjacent to vessels and viscera, vascular or organ excision may be necessary, even in the absence of direct tumor involvement. Variability exists in recommendations regarding the extent of excision appropriate in the retroperitoneum, though aggressive adjacent visceral resection has not demonstrated clear improvement in local control beyond that obtained with gross total resection. However, although more than 90% of planned primary excisions for retroperitoneal sarcomas will demonstrate grossly negative margins, up to 20% prove to have R1 resection margins on final pathology. In this regard, there is still considerable disagreement regarding the benefits of removing adjacent uninvolved anatomic structures when a planned R1 marginal excision is necessary on other structures such as the aorta.

Although there may be a role for a more extensive surgical excision involving viscera, particularly a primary presentation, careful consideration of the risk of local or distant recurrence based on anatomy and tumor biology must be weighed. In patients with planned ipsilateral nephrectomy, a renal scan may routinely be performed to ensure adequate function of the contralateral kidney. There is no clear role for a macroscopically positive excision in sarcoma surgery, even in the case of locally recurrent disease. Therefore, tumor "debulking" surgery or morcellation is usually worse than nonoperative management.

Radiation Therapy

Radiation therapy has been shown to decrease the risk of local recurrence for high-grade extremity soft tissue sarcomas in a randomized controlled trial. In high-grade extremity sarcomas measuring greater than 5 cm, especially those with anticipated close margins, infiltrative borders, deep anatomic locations, and radiosensitive histopathology, strong consideration should be given for radiation therapy. The benefit of radiation therapy is less clear in the retroperitoneum, however. Colocalization of the tumor around radiosensitive anatomic structures may limit its utility in some patients. A recent randomized controlled trial comparing preoperative radiation and surgery for retroperitoneal sarcomas to those receiving surgery alone demonstrated no improvement in recurrence-free survival and increased adverse events in those receiving preoperative radiation. As a result, although this may be considered on an individualized basis, preoperative radiation is not routinely utilized for retroperitoneal sarcomas.

For extremity soft tissue sarcomas, although radiation therapy may reduce the rate of local recurrence from about 25% to less than 10%, there is no clear impact on distant recurrence or overall survival. An improvement in local recurrence has been demonstrated in some studies for low-grade extremity soft tissue sarcomas as well, though one must carefully weigh the risks of radiation against the risks of local recurrence. For small (<5 cm), superficial, and noninfiltrative extremity sarcomas that can be adequately excised with wide margins, the benefit of radiation therapy remains less clear.

The timing of radiation has been investigated in various study designs. Radiation can be given preoperatively, intraoperatively, or postoperatively. Preoperative and postoperative radiation demonstrate equal efficacy for decreasing local recurrence. Typical doses range from 50 Gy preoperative to 66 Gy postoperative. Further, although preoperative radiation includes the tumor and the surrounding reactive zone, postoperative radiation involves a larger field to include the operative bed. The resulting smaller field and smaller dose when given preoperatively can decrease the long-term side effects of stiffness, contractures, edema, and myofibrosis when compared with postoperative radiation, resulting in greater impairment of physical function scores in the long term. Late toxicity, particularly fibrosis and stiffness, appears to correlate with the size of the radiation field.

The primary risk of preoperative radiation is an increased risk of wound complications. The best data suggest a doubling of postoperative wound complications, from 17% with postoperative radiation to 35% with preoperative radiation. With advances in surgical techniques and increased attention to wound management following radiation, this may be decreased in more recent analyses. Following radiation, patients typically require some time for skin inflammation to decrease before operative intervention. However, by approximately 6 weeks, the skin becomes more fibrotic and less elastic. An optimal window between 3 and 6 weeks following radiation was demonstrated to have the lowest risk of postoperative wound complications.

At the completion of radiation therapy, differentiating the perioperative inflammation of the reactive zone from the inflammation from radiation may be challenging. When feasible, excision of the entire area of peritumoral inflammation, even in the setting of preoperative radiation, is preferred. For patients treated with preoperative radiation, a postoperative boost of radiation does not appear to improve local recurrence rates, including patients with positive surgical resection margins. As such, paramount importance of surgical resection margin status remains.

Chemotherapy

Even in the setting of adequate local control, up to 50% of patients with high-grade extremity soft tissue sarcomas may develop evidence of distant metastases. The most recent (eighth) edition of the AJCC staging system for soft tissue sarcomas recognizes the prognostic significance of tumor size, further stratifying large tumors as >5 cm, >10 cm, and >15 cm. For patients at the highest risk of metastases (large, high-grade tumors), cytotoxic chemotherapy is often offered. The most commonly utilized active agents are doxorubicin and ifosfamide.

The true benefit of chemotherapy for management of STS remains unclear. Randomized trails have failed to demonstrate a clear benefit for chemotherapy. Institution-specific and histologic specific trials have demonstrated more variable results. Myxoid liposarcoma, synovial sarcoma, epithelioid sarcoma, leiomyosarcoma, and malignant peripheral nerve sheath tumors, in particular, are histopathologic subtypes for which systemic therapy may often be indicated in the neoadjuvant setting. Although there are conflicting results from individual trials, meta-analyses suggest an absolute risk reduction for overall survival of 11% with systemic chemotherapy for high-grade soft tissue sarcomas. Results may be somewhat higher in extremity primary locations. However, the risks and benefits must be weighed on an individual basis.

The timing and sequence of radiation, surgery, and chemotherapy is not standardized. Both sequential and interdigitated approaches have been reported with similar survival outcomes. Given the complexity of decision making and care coordination, these patients are usually best served by multidisciplinary tumor boards.

HISTOLOGY-SPECIFIC CONSIDERATIONS

Well-Differentiated Liposarcoma/Atypical Lipomatous Tumors

Atypical lipomatous tumors (ALTs) and well-differentiated liposarcomas (WDLSs) are histopathologically identical tumors. They each carry the *MDM* amplification and have similar imaging features. Although these entities do not demonstrate metastatic potential, they do have a high rate of local recurrence. Those identified in the extremities are classified as ALTs, whereas those in the retroperitoneum are classified as WDLSs. This nomenclature is somewhat reflective of the risk of the tumor itself. In the extremity, with a manageable risk of local recurrence and without metastatic potential, excision can be marginal, recognizing the potential for late local recurrence.

However, in the retroperitoneum, these are given a sarcoma diagnosis because of the risk of local recurrence around vital organs and increased associated mortality. In light of these anatomic

considerations, wide resection margins may be more challenging but also carry increased prognostic significance. Further, ALTs/WDLSs carry a risk of transformation to dedifferentiated liposarcoma.

Myxoid Liposarcoma

Unlike most other subtypes of soft tissue sarcoma, the histologic grade of myxoid liposarcoma is determined not by its pleomorphism or histopathologic aggressiveness, but rather by the percentage of round cells within the neoplasm. Tumors with a greater than 5% round cell component are considered high grade. In addition to the differences in histologic grading, myxoid liposarcomas demonstrate an atypical pattern of metastatic spread. Although the risk of pulmonary metastases remains, myxoid liposarcomas have a high predilection for extrapulmonary spread, namely to areas of high lipomatous content (e.g., bone marrow, retroperitoneal fat). MRI has shown to be most sensitive for identifying metastatic sites, with studies suggesting routine MRI of the spine as part of staging for this entity. Consideration may be given as well for whole-body MRI versus PET/CT to identify alternative sites of metastatic spread. High-grade myxoid liposarcomas appear to be particularly responsive to radiation therapy as well as systemic therapy, suggesting a potential role for neoadjuvant treatment.

Leiomyosarcoma

Leiomyosarcomas differentiate down a smooth muscle pathway such as seen in the uterus or vasculature. As such, these are commonly identified in the retroperitoneum. Differentiating a uterine leiomyosarcoma from the more common uterine leiomyoma may be challenging on preoperative imaging in some cases, suggesting a role for biopsy when the diagnosis is uncertain.

Extremity locations typically originate from venous structures and may demonstrate intramural or intravascular extension, with or without deep venous thrombosis. With wide surgical margins, local recurrence rates may be less than 5%, so preoperative radiation may be used more judiciously. However, distant recurrence rates remain high (up to 30%), indicating a potentially increased role for systemic therapy. Female patients with extremity leiomyosarcoma should undergo pelvic imaging to rule out a uterine primary site.

Synovial Sarcoma

Synovial sarcoma is the most common soft tissue sarcoma of the foot. On imaging, synovial sarcoma may demonstrate dystrophic calcifications in up to one-third of patients, which may help in the diagnosis. These may show a very slow initial growth kinetic, which may be confused for an indolent or benign process over several years, potentially delaying the diagnosis. This high-grade, translocation-associated sarcoma (t(X;18) SYT-SSX) may be seen in a younger age population than most other soft tissue sarcomas, including children and adolescents. In addition, synovial sarcomas have shown to be relatively chemosensitive to doxorubicin-ifosfamide–based therapy, and they may be considered for neoadjuvant therapy.

Epithelioid Sarcoma

Epithelioid sarcomas are the most common soft tissue sarcoma in the hand. Similar to synovial sarcoma, these may have a younger age demographic than most other soft tissue sarcomas. Histologic markers for cytokeratins and epithelial membrane antigen (EMA) may be confused for carcinomas. Epithelioid sarcomas commonly present as small, superficial soft tissue masses, which may ulcerate through the skin. Local satellite nodules may be seen in the surrounding soft tissues. In addition, a high rate of nodal metastasis (20%) suggests a potential role for PET/CT. The role for routine sentinel lymph node biopsy remains unclear for this diagnosis.

Malignant Peripheral Nerve Sheath Tumors

Up to 50% of malignant peripheral nerve sheath tumors (MPNSTs) may be seen in the setting of neurofibromatosis type 1 (NF-1). These typically high-grade malignancies originate either from peripheral nerves or from neurofibromas. These have a high rate of local or distant recurrence. Differentiation of the MPNST from surrounding neurofibroma may be challenging at the time of surgery in many cases, though functional MRI techniques and FDG-PET have been demonstrated to be discriminating in this regard.

Myxofibrosarcoma

Whereas most extremity soft tissue sarcomas present deep to the investing fascia, myxofibrosarcomas most commonly present on the superficial aspect of the fascia. These masses tend to infiltrate along fascial planes, often manifesting by a large area of peritumoral edema. This peritumoral "reactive zone" has been shown to harbor malignant cells along the entire area of enhancement, which can be quite sizable in some instances. Perhaps myxofibrosarcoma is associated with high rates of local recurrence because of this infiltrative nature.

Particular attention to margin status, excising the entire area of peritumoral inflammation with wide margins, is key for adequate local control. Fortunately, this entity tends to be relatively radiosensitive, and consideration may be given for preoperative radiation. The large area of superficial resection may often necessitate advanced soft tissue closure or flaps. Some advocate for a staged approach, with local wound care until final histopathologic margins can be confirmed, before performing soft tissue coverage procedures.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) represents another soft tissue sarcoma subtype that typically presents in the superficial soft tissues. Similar to myxofibrosarcomas, they tend to be quite infiltrative. Because of their superficial location and often indolent initial growth pattern, DFSPs often present to the sarcoma surgeon following an unplanned initial excision. In light of their infiltrative nature, local recurrence rates may be high. As such, microscopic margin status is of paramount importance. Similar to myxofibrosarcomas, a staged reconstructive approach may be considered.

These tumors are often low grade and are therefore not typically indicated for radiation therapy or chemotherapy. However, up to 10% may demonstrate fibrosarcomatous dedifferentiation, suggesting a more aggressive biologic behavior.

SUMMARY

Soft tissue sarcomas represent a wide variety of malignancies of mesenchymal origin, involving nearly all anatomic sites. Reflecting the range of underlying histopathologic entities, a carefully considered clinical approach is necessary. In extremity locations, limb-sparing surgical excision is typically achieved. A multidisciplinary approach among the surgical team, medical oncology team, and radiation oncology team is critical. In addition to wide surgical excision, most high-grade sarcomas may be treated with radiation therapy to improve local control. Careful consideration of the potential role of systemic chemotherapy and/or immunotherapy may be given on an individualized basis. Ultimately, a thorough understanding of this family of diseases and the unique attributes of each individual entity affords the best clinical results.

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Management of Solitary Neck Mass

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GENERAL PRINCIPLES

The neck is composed of a complex anatomic infrastructure that includes a rich lymphovascular supply and an intricate compartmentalization of various structures and tissues. Neck masses thus result from multiple etiologies, and the most crucial aspect of management of a solitary neck mass is obtaining a diagnosis. This requires consideration of the holistic view of the patient in conjunction with thorough knowledge of the anatomy of the neck. Proper workup includes a thorough history, focused physical examination, and an appropriate choice of ancillary studies to narrow the differential diagnosis (Fig. 1). Patient characteristics such as age and gender provide clues directing investigation of the diagnosis; however, the increasing incidence of human papilloma virus (HPV)-related head and neck cancer in younger patients warrants a critical evaluation of every neck mass to rule out malignancy. The purpose of this chapter is to provide a comprehensive overview of the workup and management of neck masses in the context of the complex anatomy of the neck for optimal treatment.

ANATOMIC CONSIDERATIONS

Understanding of the compartments and drainage pathways of the neck provide clues regarding the cause of the mass, and it is also important to consider when planning procedural intervention. Classically, the neck is divided into an anterior and posterior triangle by the sternocleidomastoid (SCM) muscle (Fig. 2A). These triangles can be further subdivided into occipital and supraclavicular triangles posteriorly, and submandibular, carotid, and muscular triangles anteriorly. Clinically, the Memorial Sloan-Kettering system, which denotes levels of the neck according to both radiographic and surgical anatomic boundaries, is used (Fig. 2B). If a neck mass is suspicious for a metastatic focus of malignancy, knowledge of the nodal basins of the neck and their associated primary sites helps guide both physical examination as well as subsequent testing.

A thorough knowledge of neck anatomy is vital for making a clinical diagnosis and avoiding procedural complications. In particular, the topography of the neck can be useful for assigning a location to a mass during physical examination, as well as for estimating the distance from vital structures. Palpable landmarks in the midline of the neck include the *hyoid bone* superiorly, followed by the *thyroid cartilage notch*, the *cricoid cartilage*, and the *sternal notch* moving inferiorly. These normal landmarks may be difficult to appreciate in a patient with excess subcutaneous tissue, and conversely may be mistaken as pathologic, by both patients and physicians, in a patient with minimal subcutaneous tissue. A prominent carotid bulb is also occasionally mistaken for a mass; its pulsatile nature provides reassurance of normal anatomy. Other structures that may be mistaken for pathology include the superior horns of the thyroid cartilage, the greater cornu of the hyoid bone, the transverse processes of C1, and a prominent submandibular gland.

One should be familiar with the proximity of a neck mass to the number of critical structures found within the different neck compartments. Most of these structures lie deep to the platysma muscle, which serves as a good landmark during dissection. The external jugular vein and the great auricular nerve, which provides sensation to the external ear, lie more superficially and are found within the same layer as the platysma deep to the superficial cervical fascia. Caution should be taken when attempting to excise masses found in level I, as the marginal mandibular branch of the facial nerve can be found superficial to the fascia of the submandibular gland. Injury to the marginal mandibular branch can result in weakness of the depressors of the lower lip, resulting in an asymmetric smile and, in severe cases, can lead to oral incompetence. Other nerves that lie deeper but are at risk of damage in this area include the lingual nerve, which provides sensation and taste to the anterior two-thirds of the tongue, and the hypoglossal nerve, which provides motor innervation to the intrinsic muscles of the tongue. The accessory nerve, which provides innervation to the trapezius and SCM muscles, is at risk when dissecting within level II and level V. Dissection within level IV can lead to a chyle leak due to injury of the thoracic duct. The midline overlying the trachea is generally safe for dissection; however, just lateral to midline within the tracheoesophageal groove lies the recurrent laryngeal nerve, which provides innervation to all the muscles of the

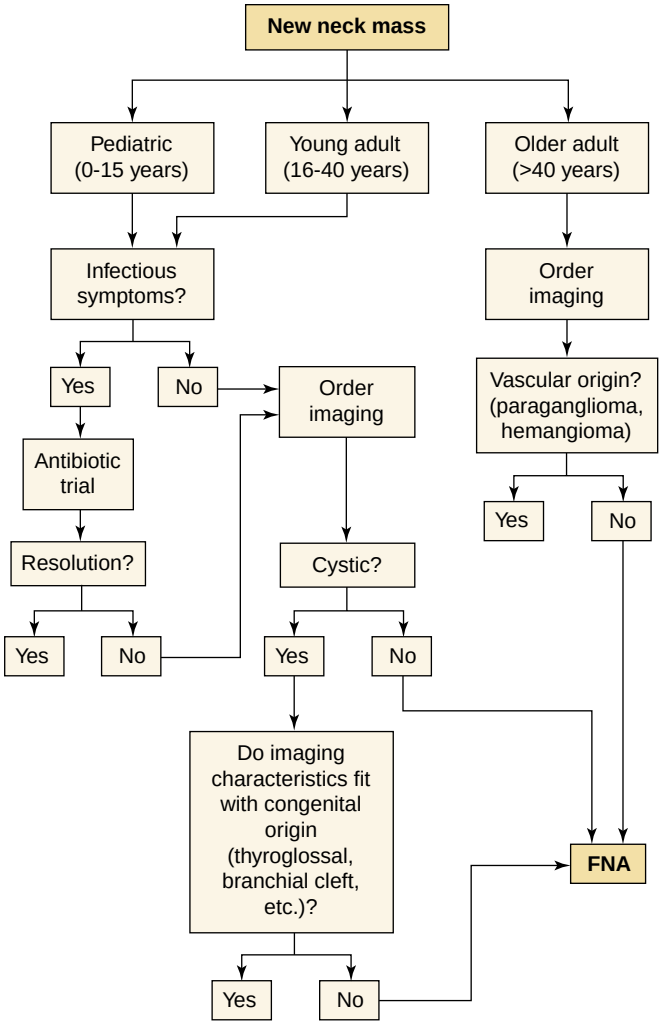


FIG. 1 Diagnostic algorithm for a new neck mass. The distinction made based on age of 40 years should be taken as a general guideline to be adjusted based on clinical evaluation and not as an absolute rule. *FNA*, Fine-needle aspiration. *(Modified from Flint PW, Haughey BH, Lund VJ, et al. editors:* Cummings Otolaryngology: Head & Neck Surgery. *5th ed. Philadelphia: Elsevier; 2010.)*

larynx except for the cricothyroid muscle. Damage to the recurrent laryngeal nerve can lead to vocal cord paresis, and bilateral injury can result in airway compromise due to an inability to adequately abduct the vocal cords.

DIFFERENTIAL DIAGNOSIS

Solitary neck masses can arise due to various causes: *neoplastic* (both benign and malignant), *congenital*, *infectious*, *traumatic*, and manifestations of *systemic* disease (Fig. 3). Age of the patient is a useful factor in guiding the differential diagnosis. In children, the most common cause of a solitary neck mass is cervical lymphadenitis. Congenital neck masses, such as branchial cleft cysts and thyroglossal duct cysts, are the second most common type. Most neck masses in children are benign, yet malignant tumors such as lymphoma, rhabdomyosarcoma, and neuroblastoma may manifest themselves as a solitary neck mass. In contrast, a neck mass in an adult, regardless of age and history of smoking and alcohol consumption, should be considered a malignancy until proven otherwise. This is especially true given the rising incidence of HPV-related head and neck cancer in recent decades.

DIAGNOSTIC EVALUATION

History

A thorough history should be obtained. Timing and evolution of the mass is important in determining the etiology. It is useful to delineate how and whether the patient first noticed the mass, as occasionally the mass itself will be preceded by other symptoms such as pain. Alternatively, the patient may not have noticed an asymptomatic mass and rather was referred due to an incidental finding on physical examination or imaging. Pain attributed to the mass itself is often not revealing on its own; however, throat pain and referred otalgia may be suggestive of a primary process in the oropharynx, hypopharynx, or larynx. Changes in size, appearance, and overlying skin changes including erythema, bleeding, and drainage are important to determine, as well as a recent history of trauma. Associated symptoms that may include epistaxis, nasal obstruction, hearing loss, dysphagia, dysphonia, dyspnea, and hemoptysis should always be evaluated. When present, they prompt a higher suspicion for malignancy. Systemic symptoms including fever, night sweats, weight loss, and symptoms of hyper- or hypothyroidism are also important to obtain. The evaluating physician should inquire about a personal or family history of head and neck cancer, as well as a history of radiation to the head and neck. Other medical comorbidities that may place patients at risk of contracting atypical infections include a history of immunodeficiency, diabetes mellitus, or autoimmune disease. Immunosuppression can also increase the risk for malignancy. Social factors such as a history of tobacco, alcohol, and marijuana consumption along with a sexual history should be obtained as further risk factors for malignancy. A history of sexually transmitted infections or multiple sex partners may increase the risk of developing an HPV-related oropharyngeal malignancy. Travel and occupational history can be important in some cases, where exposure to asbestos, saw dust, and other inhaled chemicals may increase the risk of malignancy or atypical infection. History of surgery to the head and neck area is important when considering operative intervention as prior surgery can change the surgical anatomy and place important anatomic structures at increased risk during dissection, secondary to fibrosis and the obfuscation of dissection planes. Anticoagulants and antiplatelet medications should be asked about because these may need to be stopped before and after surgery. A history of adverse reactions to general anesthesia or a history of difficult intubation is also important to consider when taking a patient to the operating suite. Prior interventions, including treatment with antibiotics, biopsies, and surgery should be elicited during any evaluation. A mass persistent through antibiotic treatment may represent an underlying anatomic abnormality or malignancy.

A rapidly growing tender mass in a pediatric patient most often represents cervical lymphadenitis. A mass that has been present for a while and periodically grows and shrinks or repeatedly becomes infected may suggest a congenital mass such as a branchial cleft or thyroglossal duct cyst. A history of trauma may suggest a hematoma or seroma. A slowly growing nontender mass may represent an atypical infection in a pediatric patient or a metastatic lymph node in an adult. This, accompanied with a progressive history of hoarseness, may suggest the presence of a laryngeal malignancy. Unilateral nasal obstruction may indicate a sinonasal malignancy. Unilateral hearing loss may represent an obstructive mass of the ear canal, a middle ear effusion secondary to a nasopharyngeal mass blocking the eustachian tube, or a tumor compressing the auditory nerve. A history of fevers, night sweats, and weight loss may be suggestive of lymphoma.

Physical Examination

A good physical examination includes the general appearance of the patient. A patient appearing cachectic or ill increases the suspicion for malignancy. Increased work of breathing as well as hoarseness can point toward a laryngeal primary process that may manifest as a metastatic neck mass. Evaluation of the mass itself should include an estimate of the size, shape, mobility, fluctuance, depth, and location. A

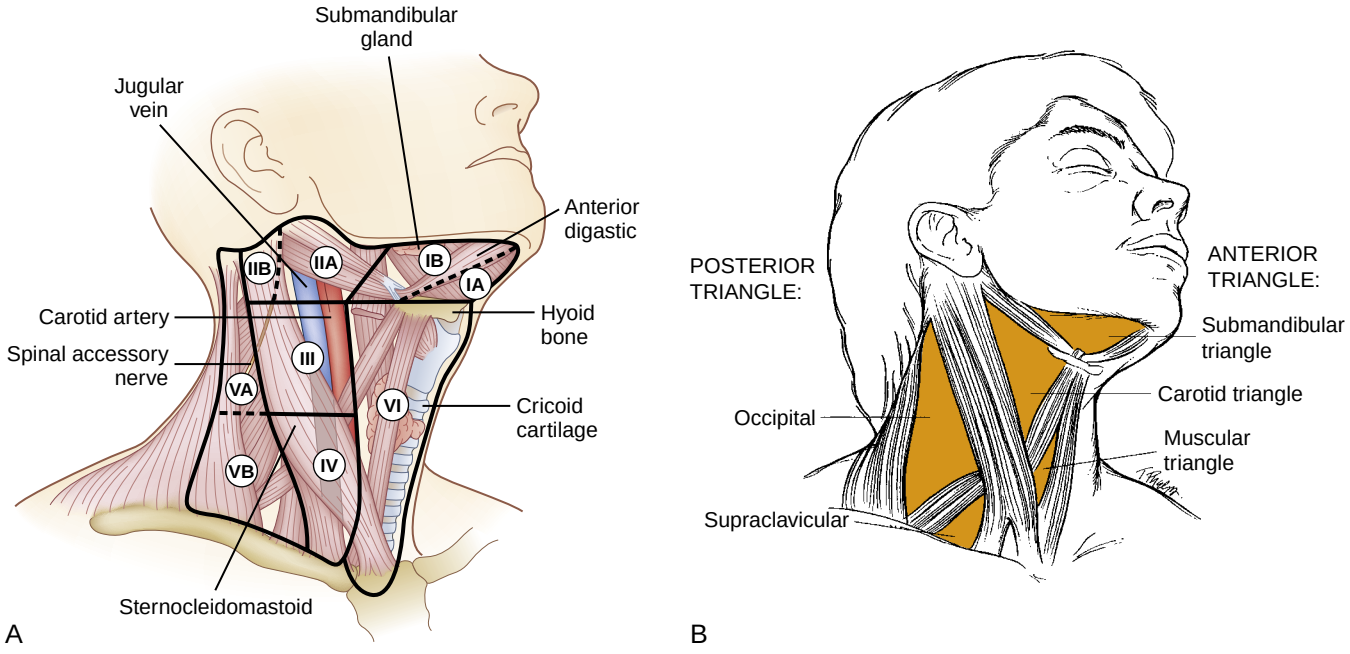


FIG. 2 Compartments of the neck. **(A)** Numbered lymph node levels of the neck. Boundaries are given in Table 1. Criteria exist to define these levels radiographically and surgically. **(B)** Anterior and posterior triangles of the neck, divided by the sternocleidomastoid muscle. The anterior triangle is further subdivided into the carotid, submandibular, submental, and muscular triangles; the posterior belly of the omohyoid divides the posterior triangle into occipital and supraclavicular triangles. (**A** *from Smith PW, Salomone LJ, Hanks JB. Thyroid. In:* Sabiston Textbook of Surgery, *ed 19. Philadelphia: Elsevier; 2012;* **B** *modified from Lingemon RE. Surgical anatomy. In: Cummings CW, et al, eds.* Otolaryngology—Head & Neck Surgery, *3rd ed. St. Louis: Mosby; 1998.)*

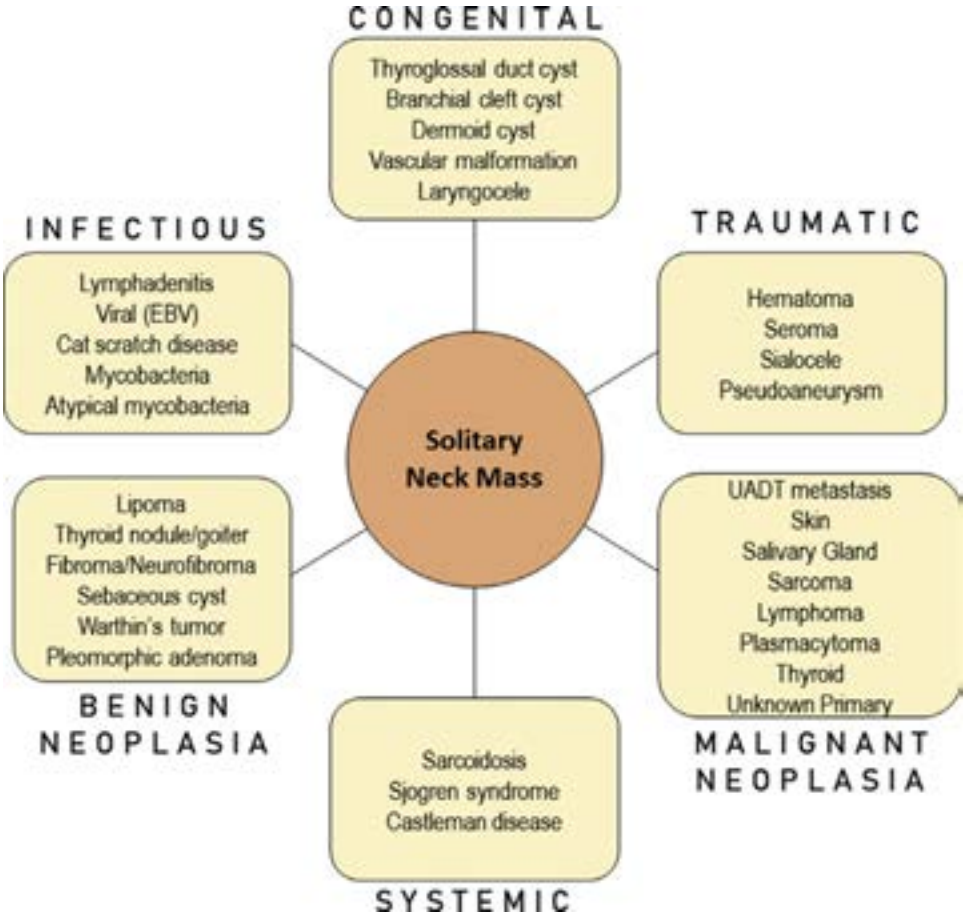


FIG. 3 Differential diagnosis of the solitary neck mass. *EBV*, Epstein-Barr virus. *UADT*, upper aerodigestive tract.

TABLE 1 Cervical Lymph Node Groups and Associated Primary Sites of Metastasis

Level	Lymph Node Group	Boundaries				Primary Sites of Metastasis
		Superior	Inferior	Anteromedial	Posterolateral	
IA, IB (subdivided by anterior belly of digastric)	Submental, submandibular, prevascular, and retrovascular facial nodes	Mandible	Hyoid	Midline	Stylohyoid	Skin, lip, oral cavity, submandibular gland, parotid gland, paranasal sinuses
IIA, IIB (subdivided by spinal accessory nerve)	Upper jugular nodes	Skull base	Inferior border of hyoid/ carotid bifurcation	Stylohyoid	Posterior border of SCM	Parotid, oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, thyroid
III	Middle jugular nodes	Inferior border of hyoid/ carotid bifurcation	Inferior border of cricoid/ omohyoid muscle	Sternohyoid	Posterior border of SCM	Oral cavity, oropharynx, hypopharynx, larynx, thyroid, cervical esophagus
IV	Lower jugular nodes	Inferior border of cricoid/ omohyoid	Clavicle	Sternohyoid	Posterior border of SCM	Oropharynx, hypopharynx, larynx, thyroid, cervical esophagus, Virchow's node (lung or abdominal malignancy)
VA, VB (subdivided by plane of inferior border of cricoid)	Posterior triangle nodes	Junction of SCM and trapezius	Clavicle	Posterior border of SCM	Anterior border of trapezius	Nasopharynx, skin including scalp, thyroid, infraclavicular primary
VI	Prelaryngeal, pretracheal, and paratracheal nodes (central compartment)	Hyoid bone	Sternum	Midline	Carotid sheath	Thyroid, larynx, hypopharynx, cervical esophagus
VII	Variably defined	Substernal extension of level VI to level of the innominate artery				-

superficial mass is more likely to be benign, such as a lipoma or epidermal inclusion cyst. The location of the mass should be described in relation to other anatomic structures (i.e., at the level of the hyoid bone or just inferior to the cricoid) as well as by cervical level. This provides a standard nomenclature to convey findings to other providers and is useful for identifying the source of the primary disease process.

A complete head and neck examination should be performed during the initial evaluation. This includes a thorough examination of the skin, including the scalp, which can reveal discrete lesions or more global evidence of sun damage. An otoscopic examination of the ears evaluates for lesions of the external auditory canal. A unilateral effusion in an adult should prompt endoscopic evaluation of the eustachian tube opening to rule out a primary nasopharyngeal malignancy. Anterior rhinoscopy should be performed to evaluate for lesions of the nasal vestibule, and in the absence of rhinologic complaints, is often sufficient for evaluation of the neck mass.

Examination of the oral cavity should include bimanual palpation as well as evaluation of all subsites of the oral cavity including the oral tongue, floor of mouth, the gingiva, and the teeth. Periodontal disease is important to note as this can lead to cervical lymphadenopathy. Dentures, if present, should be removed to examine the underlying mucosa. Clear saliva should be able to be expressed from the Stenson's (parotid) and Wharton's (submandibular) duct openings via gentle massage of the glands. If sialadenitis is suspected, purulence or turbid saliva may be expressed; obstructive stones may also be palpated. Mandibular and palatal tori are benign bony outgrowths that are commonly seen on examination and are unrelated to the presence of a neck mass.

The oropharynx is examined next. The soft palate is evaluated for lesions and symmetric elevation. Examination of the palatine tonsils may reveal asymmetry, which may warrant consideration of biopsy in a patient whose presentation is concerning for malignancy. A laryngeal mirror may be used; however, it is now standard to perform flexible fiberoptic nasopharyngoscopy to examine the mucosal surfaces of the base of tongue, the vallecula, the epiglottis, arytenoid cartilages, piriform sinuses, and the glottis. The vocal folds should be assessed for masses, lesions, and symmetric motion. Examination of the neck should include palpation of all nodal basins. Examination of the thyroid should include bimanual palpation, as well as observation of movement of any potential thyroid masses with swallowing. Palpation of the sternal notch may reveal substernal extension. A thorough cranial nerve examination should be performed on every patient, and knowledge of the anatomic trajectory of different cranial nerves can help locate a primary lesion when there is a deficit. Facial nerve weakness may suggest a parotid neoplasm, whereas asymmetric soft palate elevation or tongue protrusion may be caused by a skull base lesion.

Other examination findings that are specific to particular disease processes include movement of a midline mass with protrusion of the tongue, which may suggest the presence of a thyroglossal duct cyst. Branchial cleft cysts, in contrast, lie lateral to midline and may be associated with a fistula. First branchial cleft cysts are found inferior to the auricle and may communicate with the external auditory canal or be associated with the facial nerve. Second branchial cleft cysts are the most common branchial cleft cyst. They are found on the anterior border of the SCM and may communicate with the tonsillar fossae. Third branchial cleft cysts are also found on the anterior border of the SCM but lie lower in the neck and may communicate with the piriform sinus.

Office-Based Endoscopy

Office-based endoscopy is an important tool in the evaluation of the solitary neck mass. When the history or physical examination suggests the possibility of mucosal malignancy, the use of flexible laryngopharyngoscopy allows the physician to evaluate all mucosal surfaces of the upper aerodigestive tract. Risk factors such as alcohol, tobacco use, and repetitive trauma/inflammation can lead to genetic and molecular changes throughout the aerodigestive tract in a process termed *field cancerization*, increasing the risk of malignant transformation and presence of multiple synchronous primary tumors. Mucosal changes or concerning lesions seen on endoscopy may warrant an in-office or intraoperative biopsy depending on the location. Flexible laryngopharyngoscopy provides better visualization than the laryngeal mirror examination and can be used to evaluate the nasal passages, nasopharynx, eustachian tube openings, base of tongue, vallecula, piriform sinuses, postcricoid region, epiglottis, arytenoids, and false and true vocal folds; in some patients, even the subglottic region may be visualized.

Laboratory Testing

Laboratory testing in most cases is of limited utility in the evaluation of the solitary neck mass. In cases where infection is suspected, a complete blood count can be obtained to evaluate for leukocytosis. Additionally, an erythrocyte sedimentation rate or a C-reactive protein level can be useful for tracking degree of inflammation over time. In cases of a thyroid nodule, a thyroid-stimulating hormone level can be helpful for determining if the nodule is metabolically active. Other more specific laboratory tests may be ordered on a case-by-case basis.

Imaging

In many cases, imaging is essential in the evaluation of the neck mass. In cases where the history and physical examination suggests an acute process, such as a reactive lymphadenitis, it may be appropriate to treat empirically and follow up the response before obtaining imaging. However, in most other cases, imaging is warranted and can provide valuable information regarding the location and possible etiology of the mass.

While historically radiographs were often utilized, advancement in imaging technology has made radiographs of the head and neck of limited utility. Computed tomography (CT) of the neck is now often the imaging study of choice in the evaluation of the neck mass (Fig. 4). A contrast enhanced scan is warranted in almost all cases if the patient does not have a contraindication, such as renal dysfunction or an iodinated contrast allergy. CT of the neck is useful not only for evaluation of the mass and its relationship to surrounding structures, but it also may reveal the location of a primary malignancy if the neck mass is suspected to be metastatic to a lymph node. A rim-enhancing lesion can suggest an infectious process/abscess, whereas more uniform uptake of contrast may suggest a vascular malformation. Cystic-appearing lesions on CT, especially in an adult, should be biopsied to rule out malignancy. In an adult with a smoking history where malignancy is suspected, a CT of the chest may also be obtained concurrently to screen for lung cancer or metastatic disease. In cases where a CT scan is contraindicated, magnetic resonance imaging (MRI) may also be used. MRI provides better resolution of soft tissue structures and, in some cases, can be more useful than a CT scan, especially if a primary salivary mass or nerve invasion is suspected. MRI may also be more desirable if the suspected mass is related to a glomus tumor, carotid body tumor, or schwannoma. Angiography may be indicated if a primary vascular lesion is suspected, or if preoperative embolization may be required.

The positron emission tomography (PET/CT) scan has become a useful adjunct in recent years; however, it is often not indicated as a first-line imaging study for the evaluation of a neck mass. It can be useful to evaluate for distant metastasis or identification of the location of unknown primary malignancies manifesting as a metastatic lymph node. It should be noted that some tissues within the head and neck are inherently more metabolically active than others, which can lead to a false positive result. Specifically, the palatine and lingual tonsils, as well as some salivary tissue, can have increased avidity on PET/CT as a normal variation.

A bedside alternative to these imaging modalities is the point-of-care ultrasound (POCUS), which is gaining more popularity in the clinic setting. Ultrasound has the advantage of ease of use in clinic, and it can be combined with a fine-needle aspiration (FNA) or core needle biopsy to expeditiously obtain tissue for pathology during the initial patient encounter. Ultrasound assesses the consistency of the mass (solid versus cystic), size, vascularity with Doppler, and concerning features for malignancy such as microcalcifications in thyroid cancer. Nevertheless, the sonographic images obtained are often operator-dependent, and formal training is needed to perform and interpret them appropriately.

Pathology

Ultimately, definitive diagnosis is contingent on obtaining tissue for pathologic analysis. Indications for biopsy may include failure of empiric treatment or suspicion for malignancy. Depending on the location of the mass, patient tolerance, and comfort level of the physician, a biopsy may be obtained in clinic or the operating suite. Although easily palpable masses may be biopsied based on feel alone, the use of ultrasound in clinic has facilitated and expedited the process of obtaining tissue for pathologic evaluation. Ultrasound may be combined with either FNA or core needle biopsy (Fig. 5).

FNA is a minimally invasive method that has become a standard of care for diagnosis of most neck masses, as it has the lowest procedural risk compared with other biopsy methods. FNA samples may be sent for cytology or culture and can therefore be useful for diagnosis of both neoplastic and infectious processes. If an abscess, seroma, or hematoma is suspected, needle aspiration of the mass can be both diagnostic and therapeutic. Should surgery be needed at a later date, FNA does not alter the surgical anatomy, result in significant fibrosis, or spread the tumor through the needle tract. Although FNA is most commonly used for biopsies in the head and neck, tissue architecture cannot be evaluated from FNA alone, which in certain situations may lead to inconclusive results. A core biopsy may be indicated for evaluation of some malignancies, such as follicular thyroid cancer, lymphoma, and sarcomas where more tissue may be required. It is important to note that for the evaluation of lymphoma, specimens are sent in saline to the pathology lab, as flow cytometry used for characterization of lymphoma cannot be performed on formalin-fixed specimens.

FNA can be performed in the clinic under manual or preferably under ultrasound guidance. Local anesthetic is generally recommended since multiple passes are often required. A 20-gauge needle on a 10-mL syringe with short IV tubing is sufficient to perform the procedure by aspiration. An alternative method is to use a 25-gauge needle on a 10-mL syringe using capillary technique. If using manual guidance, the mass should be fixated using the thumb and forefinger

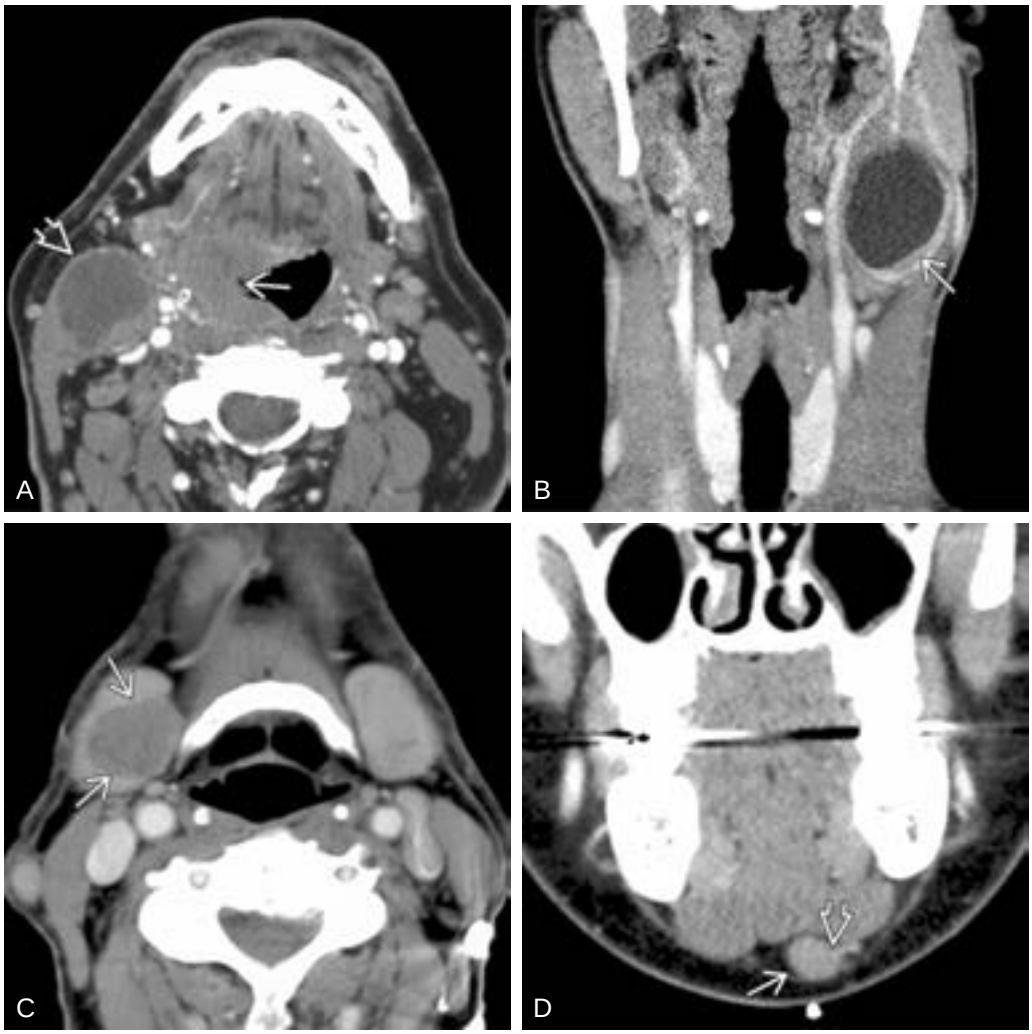


FIG. 4 Imaging characteristics of different neck masses on computed tomography. **(A)** Cystic metastatic lymph node with central necrosis in level IIA *(left arrow)*, with primary tumor found in the right oropharynx *(right arrow)*.**(B)** Coronal CT demonstrating a second branchial cleft cyst, anterior to the SCM and lateral to the carotid sheath. **(C)** Hypodense, well-defined mass enlarging the right submandibular gland, found to be a pleomorphic adenoma on histology. **(D)** Benign-appearing ovoid level IA node representing reactive adenopathy in a teenager. (**A,** *Nodal squamous cell carcinoma;* **B,** *2nd Branchial cleft cyst;* **C,** *Submandibular gland benign mixed tumor;* **D,** *Reactive lymph nodes. From Gurgel RK & Harnsberger R.* Imaging in Otolaryngology, *Elsevier; 2018.)*

to stabilize it for entry with the needle. If using ultrasound guidance, centering the mass on the probe while following the needle's trajectory in the long or short axis improves visualization and success of the biopsy. Constant negative pressure should be applied during entry toward the mass, and multiple passes should be made through the mass while aspirating. If a lesion is cystic, the wall should be targeted to increase the diagnostic yield. The obtained sample should then be placed in a conical tube with cytology preservative or onto a slide and fixed with either formalin or ethanol and sent for cytopathologic examination.

Excisional biopsy should generally be performed as a last resort when other methods for obtaining tissue have failed. Excisional biopsy, depending on the location in the neck, poses increased risk to nearby anatomic structures, can lead to unfavorable scarring, and places the patient at risk related to general anesthesia when performed in the operating room.

Nasopharyngeal carcinoma is often associated with Epstein-Barr virus (EBV); therefore, any nasopharyngeal mass or a metastatic node in the setting of a nasopharyngeal mass should be tested for EBV. In the head and neck, HPV-related tumors most commonly grow from the lymphoepithelial crypts within the oropharynx, with the tonsil being the most common site followed by the base of tongue. HPV testing is most commonly performed via p16 immunohistochemistry staining, which is highly sensitive for HPV-related malignancy. However, it should be noted that p16 is not specific to oropharyngeal tumors and may also be related to a cutaneous primary. HPV in situ hybridization (ISH) is a far more specific laboratory test that can confirm the presence of HPV within the tumor cells and therefore has had increasing utility in the evaluation of a metastatic lymph node.

MANAGEMENT

Definitive management of the solitary neck mass may include observation, empiric treatment with antibiotics, or operative management. In the pediatric patient, management is often geared toward preventing recurrence of a benign or infectious process, while in the adult patient, management often involves ruling out malignancy.

Thyroglossal duct cysts are found in the midline and can be located anywhere along the thyroglossal tract remnant, from the base of the tongue to the thyroid. They are often noticed after they become infected; however, they may also be asymptomatic. They are often diagnosed at a young age but may not present until later in life. Treatment is classically by excision via the Sistrunk procedure, which involves removing the cyst along with its tract and the central portion of the hyoid bone. This method has been shown to decrease the rate of recurrence. Branchial cleft cysts may present in a variety of locations in the lateral compartments of the neck. Similar to thyroglossal duct cysts, they may become repeatedly infected, and this is often when they are diagnosed. Treatment is by surgical excision, as simple incision and drainage of an infected cyst will almost certainly result in recurrence. In cases where the cyst is associated with a fistulous tract, the tract should be obliterated or excised to prevent recurrence. Care should be taken to evaluate a suspected branchial

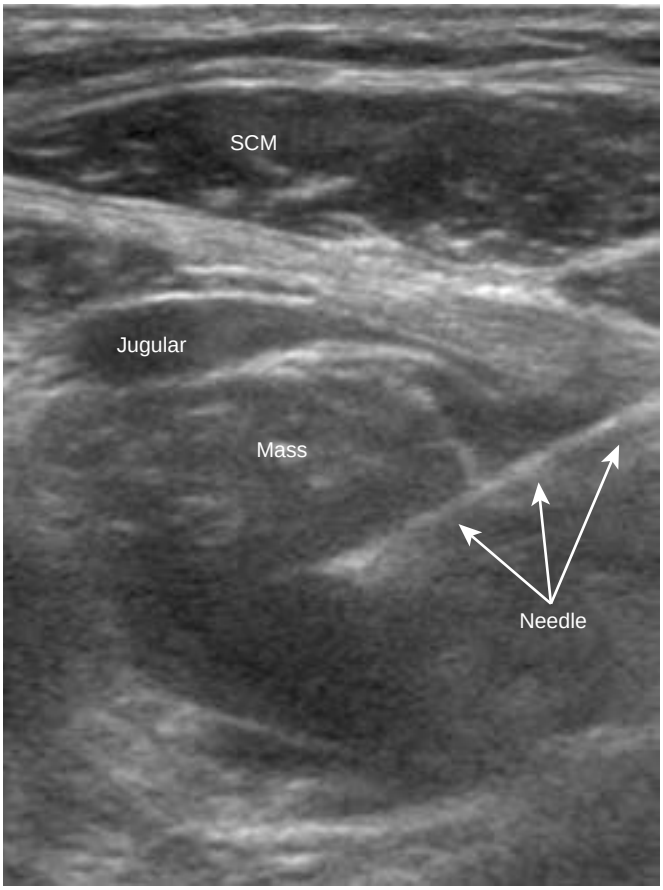


FIG. 5 Ultrasound-guided fine-needle aspiration biopsy of a neck mass lying posterior to the jugular vein. This biopsy was performed with a 22-gauge needle and confirmed metastatic papillary thyroid cancer. *SCM*, Sternocleidomastoid muscle.

cleft cyst for a metastatic cystic node in an adult as HPV-related cancers often manifest with an isolated neck mass.

Cervical lymphadenitis or a neck abscess can be treated with empiric antibiotics depending on the size, location, and associated symptoms. The immune status of the patient and other comorbidities may also play a role in the aggressiveness of treatment. Lesions not responding to antibiotics may require obtaining a culture and then directing antibiotic coverage appropriately. Atypical infections may require consultation with an infectious disease specialist to determine the appropriate antibiotic and duration of treatment. A deep neck abscess, depending on the size and location, may sometimes require more urgent operative intervention. Infection in the submandibular space may progress to Ludwig's angina, where floor of mouth swelling can cause prolapse of the tongue and rapid upper airway obstruction. A particularly large abscess in the parapharyngeal or retropharyngeal space can similarly narrow the airway. The retropharyngeal space communicates with the mediastinum, and infections in this area can lead to a life-threatening mediastinitis. Incision and drainage of a neck abscess alone is appropriate if there is no concern for an underlying congenital lesion or other anatomic abnormality. Should a neck abscess be related to IV drug use, one should take caution so as not to encounter any retained needles to avoid needlestick injury. Drainage of neck abscesses that are odontogenic in origin should always include removal of the involved tooth, either during the same procedure or shortly after abscess drainage.

Benign lesions may often be observed if they are asymptomatic, not rapidly growing, or not causing a cosmetic concern for the patient. Otherwise, the treatment of choice is most often surgical excision. Lipomas have a negligible risk for malignant transformation and may often be observed for years without significant change. They are often very superficial, mobile masses, and their removal generally poses a low risk of complications. Pleomorphic adenomas, however, are benign salivary gland tumors that have about a 1% risk of malignant transformation, termed *carcinoma ex pleomorphic adenoma*, and surgical excision is highly recommended. They are most commonly found in the superficial lobe of the parotid gland, followed by the submandibular gland. Care should be taken not to penetrate the tumor capsule during excision, as this can cause seeding of tumor throughout the surgical bed, resulting in increased risk for recurrence, along with the risk of a recurrent *carcinoma ex pleomorphic adenoma*. Thyroid nodules are best evaluated initially by ultrasound. The Thyroid Imaging Reporting and Data System (TIRADS) score can be used to evaluate for risk of malignancy and determine whether an FNA is warranted. Routine ultrasonographic surveillance may be warranted instead. If FNA is positive for malignancy, treatment with partial or total thyroidectomy with or without neck dissection may be indicated.

If a neck mass is found to be malignant, it most often represents metastasis from a primary tumor elsewhere in the head or neck. Effort should be made to find the primary tumor, and this search should be guided by the history, physical examination, and imaging when appropriate. Once a primary tumor is identified, it should be staged to determine the appropriate course of treatment. For squamous cell carcinoma (SCC) of the head and neck, a staging CT of the chest at minimum should be obtained. Treatment of the primary site may consist of single or multimodality therapy, including surgery, radiation, or chemotherapy. If surgery is pursued, depending on the location of the tumor and size of the expected defect, reconstruction for tissue coverage may be required. Treatment of the neck may include radiotherapy or modified radical neck dissection. The levels to be included are dictated by the primary tumor site and clinical involvement. Tumors that cross the midline often require bilateral neck dissection, and tumors in the base of tongue and hypopharynx have a much higher rate of bilateral nodal metastasis secondary to the rich lymphatic network in these anatomic sites. A multidisciplinary team should be involved in the management of head and neck cancer, and referrals should be made as appropriate to speech and language pathology, nutrition, medical oncology, and radiation oncology.

Almost 90% of patients with a metastatic SCC to the neck will have a primary tumor identified on physical examination, flexible laryngoscopy, or imaging. However, a number of patients will have no identifiable primary at initial evaluation. These patients should be taken to the operating room for examination under anesthesia and a comprehensive evaluation of the aerodigestive tract, including the nasopharynx, oropharynx, hypopharynx, and larynx. If a primary tumor still cannot be identified, ipsilateral or bilateral tonsillectomy may be performed and can reveal a primary tumor in approximately 40% of cases. Lingual tonsillectomy can also be considered. If the metastatic node is low in the neck, in levels IV or V, suspicion for an infraclavicular primary should also be raised and evaluation should include esophagoscopy, bronchoscopy, and imaging of the chest, abdomen, and pelvis.

Suggested Readings

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Surgical Infections of The Hand

Visakha Suresh, MD, and Jaimie T. Shores, MD

BACKGROUND

Hand infections can be secondary to a wide variety of pathogens, and proper management is important to prevent long-term sequelae that can compromise functionality. Complications from these infections can result in severe disabilities, ranging from joint stiffness and contracture to amputation. Although most infections do not necessitate immediate surgical intervention, it is imperative to understand the unique pathophysiology and relevant anatomy that differentiates serious infections requiring emergent treatment from less urgent diagnoses.

GENERAL PRINCIPLES

Initial management depends on a thorough patient history that elucidates the following: mechanism of injury (laceration, bite wound, puncture by and/or retained foreign body, etc.), the duration of symptoms, inciting or alleviating factors (increased pain with ranging of a specific joint, etc.), patient occupation, and any contributing medical comorbidities. Significant medical diagnoses such as diabetes, immunocompromised state, or recent intravenous drug usage may be indicative of infections by atypical or otherwise nonvirulent pathogens. Certain mechanisms of injury or risk factors are associated with specific pathogens: *Pasteurella multocida* with dog/cat bites, *Eikenella* with human bites, *Herpes simplex virus* in dentists and dental hygienists, and *Vibrio vulnificus* in fishermen or wounds exposed to salt or brackish water.

EXAMINATION

Initial visual inspection of the bilateral hands must be performed after removal of any dressings/bandages, jewelry, or clothing. Note the skin color, size, shape, and position of the hand and fingers at rest. Examine the skin of the hand and fingers for any lacerations, wounds, or punctures. Assess the motion of the hand and fingers at each joint (carpometacarpal, metacarpal, proximal and distal interphalangeal [DIP]); any limitations or aberrations between the affected and unaffected limb may provide clues regarding the underlying functional integrity of the joint or other soft tissue components. Examination of the hand using a handheld Doppler may also be performed if there is concern for vascular compromise due to a possible concomitant injury. Sensory examination should be performed before infiltration of local anesthetic.

TESTS AND IMAGING

Laboratory testing should include a complete blood count and electrolyte panel. Erythrocyte sedimentation rate and C-reactive protein may be helpful in cases of suspected osteomyelitis or septic arthritis. Cultures and gram stain may be useful in abscesses or deep space infections to help tailor antibiotic regimens; however, these studies are less useful in patients with chronic wounds. Consider sending cultures for atypical bacteria, mycobacteria, fungi, and viruses in high-risk patients (active chemotherapy, chronic immunosuppression, active or latent HIV infection). Standard three-view x-rays of the affected hand (posterior-anterior, lateral, and oblique) should be performed (with all jewelry and dressings removed) to rule out subcutaneous air, retained foreign body, or fractures. Arthrocentesis should be performed if septic arthritis is high on the differential Computed tomography is indicated in patients with multiple fractures or if there is concern for vascular injury or deep space infection. Magnetic resonance imaging is the gold standard for evaluation of osteomyelitis.

TREATMENT

Initial treatment for most hand infections includes antibiotics, immobilization, and elevation. Elevation is especially important in patients with significant edema and pain, and can be achieved with either pillows placed under the affected extremity or by using a soft, padded, vertical arm sling. If the patient is hemodynamically stable, antibiotics may be delayed until cultures have been obtained. Bedside procedures may be performed to remove accessible foreign bodies, lance superficial abscesses, or clean grossly contaminated wounds. These procedures may be performed after infiltration of local anesthetic with or without epinephrine.

If there is no clinical improvement after the first 48 hours, it is highly unlikely that a prolonged course of antibiotic will suffice. In the setting of infection, local vessels are often inflamed and thrombosed, compromising circulation and reducing the efficacy of intravenous antibiotics. The hand also has numerous compartments and closed spaces in which walled-off abscesses can form; these are not amenable to IV antibiotics alone.

Patients with delayed presentations (>48 hours), rapidly progressive symptoms, or deep abscess formation as seen on imaging studies are candidates for operative intervention. Due to the unique anatomy and functional requirements of the hand, placement of surgical incisions is of utmost importance; poorly placed incisions may lead to inadequate visualization of anatomic compartments or, in the long term, scarring and contracture formation that compromises range of motion.

Thorough irrigation and debridement of any obviously nonviable tissue must be performed. Afterward, the wound may require closed or open postoperative drainage. If a tourniquet is used, the arm should be elevated and direct pressure applied to the brachial artery for 1 minute before inflation. This minimizes the risk of systemic bacterial infection. Intraoperative cultures should be acquired and the hand splinted postoperatively for at least 3 days.

MINOR INFECTIONS

Cellulitis

Cellulitis is an infection of dermis and subcutaneous tissue and may be associated with lymphangitis. The most common infecting organisms are *Staphylococcus* and group A *Streptococcus*, with the former being more common (more than 80% of cases). Cellulitis may also be the cutaneous representation of a deeper infection or abscess. Patients may cite a recent history of abrasion, puncture wound, or concern for retained foreign body.

Symptoms

Patients often present with erythema, warmth, swelling, and local adenopathy. Localized swelling may result in moderate to severe discomfort on palpation of the affected digit or region of the hand or with active/passive ranging of the joint. A thorough history is necessary to establish the chronicity of the infection.

Treatment

Initial management involves hand immobilization, elevation, and antibiotics. The area of erythema and swelling should be demarcated with a surgical skin marker to establish the progression/regression of the infection after beginning treatment. If a foreign body or underlying abscess is present, this should be removed or drained.

The affected extremity should not be used for venipunctures so as to avoid more proximal seeding of the limb. Patients with more minor cases of cellulitis may be treated as an outpatient. However, patients with worsening cellulitis or purulence, minimal response to antibiotics, or high-risk medical comorbidities may require inpatient treatment with IV antibiotics. Given the high prevalence of *Staphylococcus* infections, penicillins or first-generation cephalosporins are often used as first-line therapy; patients with penicillin allergies may be prescribed clindamycin or a fluoroquinolone. Vancomycin should be considered if there are patient-specific risk factors for methicillin-resistant *Staphylococcus aureus*.

Paronychia

The fingernail is defined by four boundaries: the two lateral paronychia, the proximal eponychium, and the distal hyponychium. An infection along the lateral folds of the fingernail's paronychia is one of the most common infections of the hand. An infection along the eponychium is classified as an eponychia. These nailfold infections are often caused by bacteria that are inoculated into the soft tissue; common etiologies include nail biting or hang nails. Patients may also present with a recent history of manicures or penetrating trauma to the region. Common organisms include *Staphylococcus* and oral anaerobes.

Symptoms

Patients may initially present with erythema and swelling at the site of the original infection, which then may spread to involve the adjacent nailfold. Without treatment, the infection may progress to increased fluctuance, pain, and eventually spontaneous drainage. Severe infections may progress to ascending cellulitis of the affected digit and hand.

Treatment

In early paronychia with only erythema and swelling, patients may be treated with oral antibiotics, soaks in warm soapy water (three times a day, for 10–15 minutes), and gentle splint immobilization. Patients should be counseled to avoid fingernail biting.

In cases with palpable fluctuance, surgical drainage is necessary. Cultures should be collected at the time of the decompression. The finger should be anesthetized with a digital block. To control any bleeding, a finger tourniquet may be applied using a Penrose drain or a cut finger of a glove that is rolled down to the base of the affected finger. Once the patient endorses numbness, a large-bore needle (18G) or a Freer elevator may be inserted under the nailfold to separate the nailfold from the underlying nail bed (Fig. 1). If using a needle, the bevel side should be pointed down to avoid unintentionally cutting the nailfold. Once the abscess is identified, the needle or a small blade should be utilized to make an incision away from the nail bed to decompress the abscess while avoiding injury to the underlying nail bed. If a single incision does not adequately expose the involved tissues, another parallel incision may be made to allow the eponychial fold to be reflected above the nail plate.

If the abscess is found to be under the nail plate itself, a portion of the nail plate can be elevated off the nail bed using a Freer elevator and cut with a small sharp scissors or scalpel.

The wound should then be dressed with a 0.25-inch iodoform ribbon gauze, nonadherent dressing (such as Xeroform or Telfa), and then gently wrapped. These dressings should be changed two or three times a day, and the finger should be soaked in warm, soapy soaks for 10 to 15 minutes. Oral antibiotics (with activity against *Staphylococcus*) should be prescribed for 5 days, and the patient should follow up in clinic in 1 week.

Chronic paronychia is characterized by an indurated and rounded eponychium and can lead to thickening of the nail plate. These are often seen in patients with chronic exposure to irritants or frequent water immersion (such as dishwashers, swimmers, etc.). Treatment of this problem is by marsupialization of the eponychial fold.

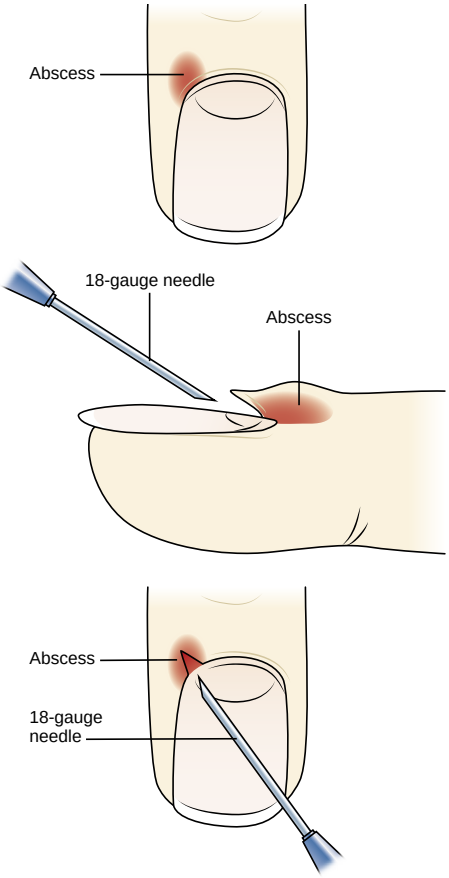


FIG. 1 Paronychia drainage. A large-bore intravenous needle (19- or 18-gauge) is inserted beneath the nailfold with the bevel side down and gently passed back and forth to lift the nailfold off the nail plate. This action allows for localization and puncturing of the abscess. The location of the abscess is noted. The needle is removed and turned 90 degrees. Using the sharp beveled edge as a knife, the nailfold is incised directly over the abscess to allow for drainage.

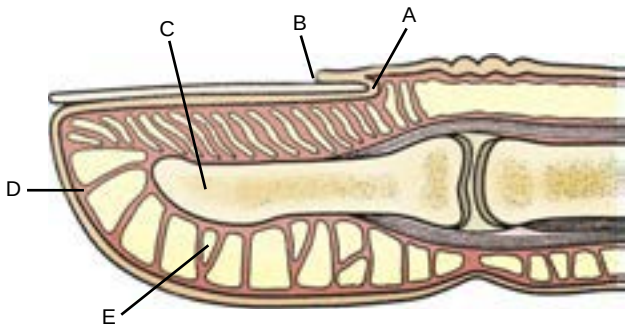


FIG. 2 Anatomy of the distal fingertip. Note the compartments formed by the vertical septae. *A,* Nail root; *B,* eponychium; *C,* distal phalanx; *D,* septum; *E,* finger pulp.

Felon

A felon is a subcutaneous abscess of the distal finger/thumb pulp. Note that not all abscesses of the distal fingertip are felons: superficial infections that only involve the skin are known as apical infections. Notably, a felon extends into the many compartments created by vertical fibers extending from the distal phalangeal periosteum into the epidermis (Fig. 2). Patients may describe a history of penetrating

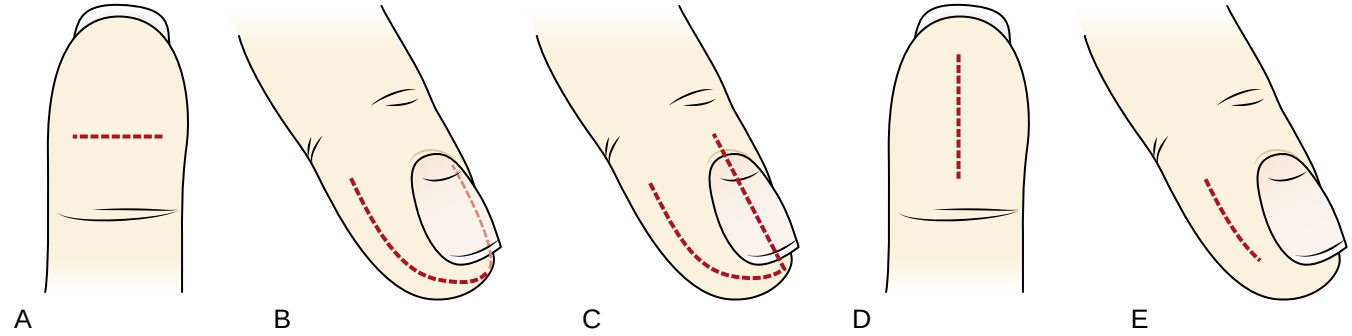


FIG. 3 Incisions used for draining felons. **(A)** Transverse palmar incision. **(B)** Fish-mouth incision; note the incision goes to the other side of the finger. **(C)** Hockey-stick, or J-incision. The two preferred incisions are **(D)** the longitudinal palmar incision and **(E)** unilateral longitudinal incision.

trauma or small cut. Diabetic patients who regularly use fingersticks for monitoring blood glucose levels are also at risk. Although *S. aureus* is the most common organisms, gram-negative rods and polymicrobial infections may be seen in immunocompromised or high-risk patients. Felons may progress to localized tissue necrosis, osteomyelitis of the distal phalanx, and septic arthritis of the DIP joint.

Symptoms

Patients often present with a rapid onset of pain, erythema, and significant swelling of the entire pulp of a fingertip. They may endorse a history of a localized injury or retained foreign body (such as a splinter). In severe cases with underlying cellulitis or septic arthritis, there may be some swelling that extends to the DIP crease.

Treatment

Oral antibiotics, warm soapy soaks, and elevation may be used in mild cases with minimal palpable fluctuance. However, fluctuance of the pulp or failure to improve with oral antibiotic treatment are indications for drainage. There are several locations for surgical incisions (Fig. 3). The midline of the fingertip in dorsal-volar axis contains several key anatomic structures that should be protected, namely the digital neurovascular bundle, flexor tendons, nail matrix, and the DIP joint space. After digital block and finger tourniquet application, a unilateral longitudinal incision is made (preferably on the side opposite the pinching surface of the finger but should be placed on the side where the patient reports maximal tenderness). A small mosquito clamp or Crile hemostat may be used to define the abscess cavity gently and bluntly without violating too much of the surrounding finger pulp. Afterward, the abscess cavity should be thoroughly drained and irrigated, and cultures should be obtained. The wound should be packed and changed two to three times a day with warm soapy soaks; patients should be prescribed a first-generation cephalosporin or clindamycin (if allergic to penicillin).

MAJOR INFECTIONS

Pyogenic Flexor Tenosynovitis

Pyogenic flexor tenosynovitis (FTS) is an infection within the flexor tendon sheath, between the visceral and parietal layers of the tenosynovium. This synovial sheath begins at the distal metacarpal neck, just proximal to the first annular pulley, and ends at the insertion of the flexor digitorum profundus on the distal phalanx. Of note, the flexor sheaths of the thumb and small fingers are continuous with the radial and ulnar bursae, respectively; thus, infections in these fingers can spread into these spaces if left untreated. Common causative organisms include *S. aureus* and group A *Streptococcus*. In immunocompromised patients or patients with a history of IV drug abuse, gram negatives and polymicrobial infections should be strongly considered.

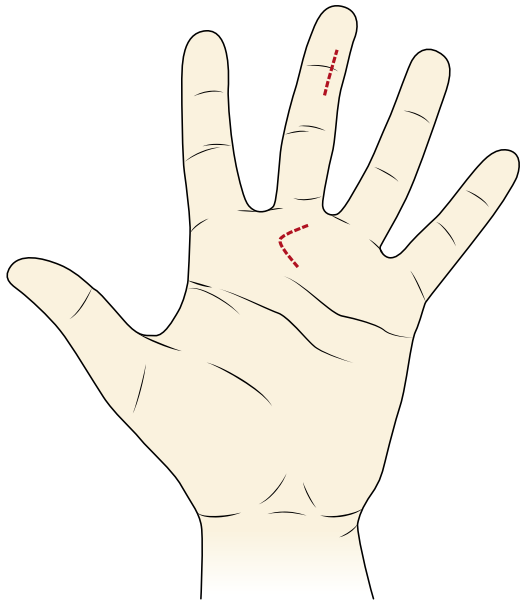


FIG. 4 Limited technique for draining pyogenic flexor tenosynovitis. The proximal incision is located over the A1 pulley. The second incision is made over the A5 pulley in the midaxial location.

Symptoms

Many patients will present with a history of penetrating injury. The most distinguishing features seen in a case of true flexor tenosynovitis include the four Kanavel signs: (1) marked, symmetrical swelling of the finger(s), resulting in a "sausage-like" shape; (2) fixed flexed posturing of the affected finger(s); (3) pain on passive extension of the involved finger(s); and (4) excruciating tenderness to palpation along the course of the flexor tendon sheath.

Treatment

Suspicions for flexor tenosynovitis necessitates immediate surgical intervention, along with initiation of broad-spectrum antibiotics.

Surgical drainage may be performed through a two-incision, limited exposure technique (Fig. 4). First, a proximal incision over the A1 pulley is made, which overlies the metacarpophalangeal joint of the affected finger. After dissecting down to the A1 pulley, the proximal half is incised, and a soft angiocatheter (16 or 18G) or pediatric feeding tube (5Fr) should gently be threaded into the underlying space. Cultures may be collected at this time. A second, midaxial incision should be made over the A5 pulley, overlying the distal phalanx, just distal to the DIP joint. The angiocatheter should then be sutured in place and the tendon sheath should be gently irrigated with 500 cc of normal saline. This second incision should serve as the

point of egress for the saline, and this should be noted during irrigation. If no fluid is seen, the angiocatheter should be repositioned. Afterward, the hand is loosely dressed, immobilized in a splint, and elevated. Irrigation may be continued for 48 hours. Afterward, the dressing may be removed and hand therapy may be initiated.

A more extensive and open debridement may be necessary in more severe cases, i.e., in immunocompromised patients or in the setting of frank purulence within the tendon sheath. A midaxial or volar zigzag (Bruner) incision (tracking between the joint creases) may be made at the cruciate pulleys with possible extension into the palm. The inflamed synovium should be visible and can be excised without damaging the delicate flexor pulley system and set for culture. The incisions are then closed loosely over an indwelling catheter for irrigation.

Infections of the Deep Spaces of the Hand

The hand is characterized by unique septae and investing fascia that anchors various soft tissues within well-delineated spaces. It is important to understand the borders and contents of these spaces to adequately treat them. There are six potential spaces (Fig. 5): five in the hand (the thenar, midpalmar, hypothenar, interdigital, and dorsal subaponeurotic spaces) and one in the volar (palmar) forearm (space of Parona). Common organisms are *S. aureus* and *Streptococcus* species. Common etiologies include penetrating trauma, retained foreign body, or contiguous spread from a subcutaneous abscess, flexor tenosynovitis, or from an adjacent deep space infection. Infections in any of these spaces necessitate surgical intervention with irrigation and packing.

Thenar Space

The borders of the thenar space are as follows: the interosseous muscles and the fascia of the adductor pollicis longus as the dorsal border; the tendon sheath of the index finger and the volar fascia as the volar border; the oblique fascial septum as the ulnar border; and the convergence of the adductor pollicis tendon and fascia at the thumb proximal phalanx as the radial border.

Symptoms

Patients will present with severe pain with both passive and active motion of the thumb; the thenar region will be extremely swollen. The thumb may be fixed in an abducted position due to swelling and/or a growing volume of purulence in this space.

Treatment

Surgical drainage is necessary for infections of the thenar space. Cultures should be obtained at the time of irrigation and drainage. A longitudinal volar incision is designed parallel to the thenar crease (Fig. 6). The palmar cutaneous branch and the recurrent branches of the median nerve are located in the subcutaneous and the deeper planes at the distal edge of the transverse carpal ligament, respectively, and must be protected when making the volar incision. Blunt dissection is performed carefully between the first and second metacarpal to decompress this space. The dorsal space between the adductor pollicis and the first dorsal interosseous muscle can also be accessed through this incision by extending it over the distal edge of the adductor.

A 1 to 2 cm longitudinal dorsal incision is designed over the most prominent dorsal aspect of the infection. However, the edge of the first webspace should not be included in the incision as this increases the risk of scar formation and possible webspace contracture. Dissection should be continued between the adductor pollicis and the first dorsal interosseous muscle, and the space thoroughly debrided. Note that a dorsal incision alone will not suffice for adequate irrigation of the thenar space.

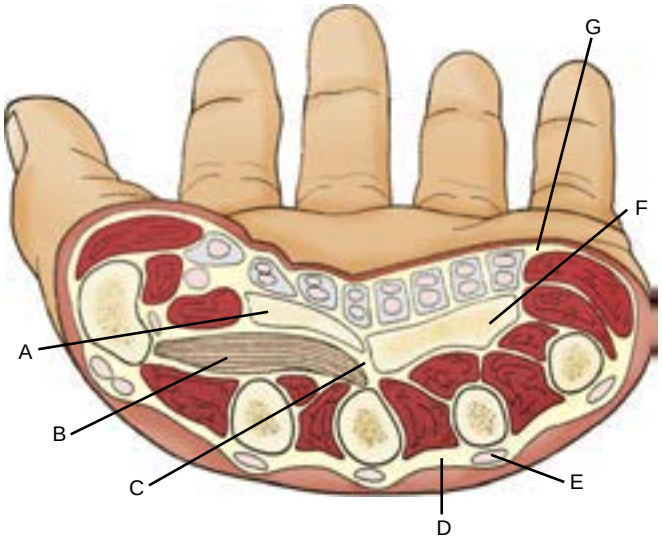


FIG. 5 Anatomy of the hand, cross-sectional view. The deep spaces are demonstrated: thenar space, midpalmar space, hypothenar space, and the dorsal subaponeurotic space. The interdigital webspace and the space of Parona are not shown. *A,* Thenar space; *B,* adductor pollicis muscle; *C,* midpalmar septum; *D,* dorsal subaponeurotic space; *E,* extensor tendon surrounded by dorsal aponeurosis; *F,* midpalmar space; *G,* palmar aponeurosis.

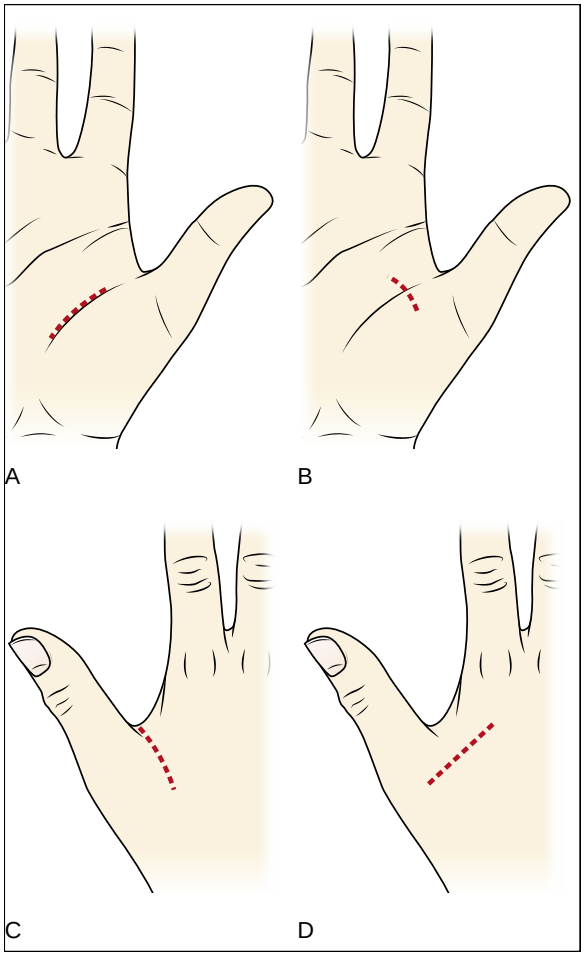


FIG. 6 Thenar space infection. **(A)** The palmar longitudinal incision is made parallel to or in the thenar crease. This is preferred over the palmar transverse incision **(B)**, dorsal incision, longitudinal incision **(C)**, and the transverse incision **(D)**.

Midpalmar Space

The midpalmar space lies between the hypothenar and thenar eminences. The borders are as follows: the fascia of the second and third volar interosseous muscles and periosteum of the third through fifth metacarpals as the dorsal border; the flexor sheaths of the long, ring, and small fingers and the palmar aponeurosis as the volar borders; the oblique septum as the radial border; and the hypothenar septum as the ulnar border.

Symptoms

Patients may present with paradoxical dorsal swelling of the hand due to the thick vertical fibrous septae of the palm that does not allow for much volar expansion. Fluctuance and erythema may be noted in the palm with loss of the typical concavity of the palm.

Treatment

Surgical drainage is the gold standard of treatment. A transverse, longitudinal, or combination incision may be used (Fig. 7). For example, the transverse incision can be designed either parallel or within the distal palmar flexion crease. The flexor tendons of the ring finger may be used as a guide for dissection, as deep dissection should be continued longitudinally on either side of the tendon to decompress the abscess. The oblique incision can be made proximal from the distal palmar flexion crease and extends along the long finger metacarpal, before stopping at the edge of the hypothenar muscles. Careful blunt dissection is performed until the midpalmar space is entered. Cultures should be collected and the abscess thoroughly irrigated and packed.

Hypothenar Space

Infections of this potential space between the fascia and muscle of the hypothenar eminence are rare. The borders are defined by the periosteum of the fifth metacarpal dorsally and the palmar fascia and fascia of the superficial hypothenar muscles volarly.

Symptoms

Patients present with erythema, swelling, and pain to palpation of the hypothenar space.

Treatment

A 3 cm volar incision should be made in line with the ulnar border of the ring finger, just proximal to the midpalmar crease toward the wrist flexion crease (Fig. 8). An ulnar incision may also be used instead, designed at the junction between the glabrous and dorsal skin of the hand. Most notably, blunt dissection in this area should proceed carefully to avoid injury to the ulnar artery and nerve contained within Guyon's canal.

Interdigital Webspace

The borders of this potential space are defined by the dorsal hand fascia and skin, the extensor mechanism, and metacarpophalangeal joint/capsule radially and ulnarly. These infections are often called "collar-button" abscesses. Patients may have a history of fissures within the skin of the webspace that put them at risk for infection.

Symptoms

Patients present with dorsal swelling due to the fibrous volar fascial attachments into the volar skin. Tenderness and fluctuance may be present as well. If the abscess is primarily volar, the fingers may be abducted.

Treatment

Surgical drainage and initiation of antibiotics are necessary for complete treatment of these abscesses. Incisions for surgical drainage must be carefully designed to prevent webspace contracture while also allowing for adequate exposure of the space (Fig. 9). A volar zigzag (Bruner) incision is placed between the metacarpal from the metacarpophalangeal joint to the base of the involved webspace.

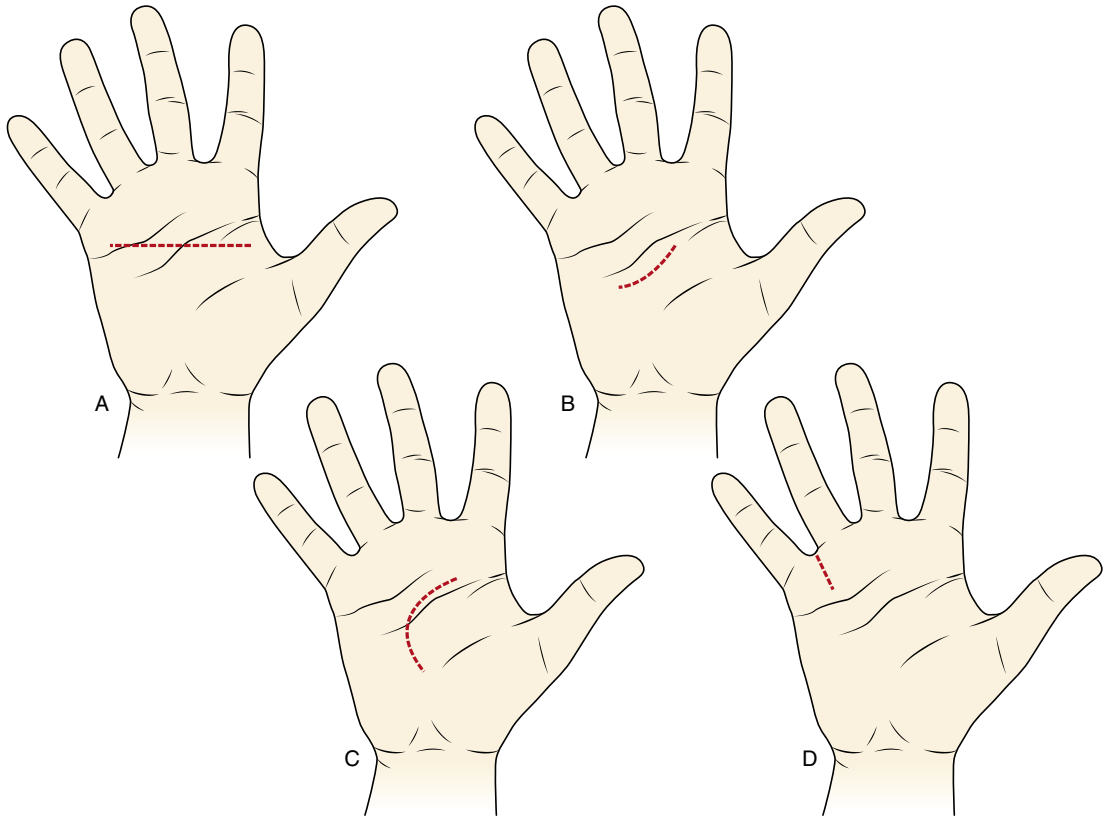


FIG. 7 Incisions used for draining midpalmar space infections. **(A)** Transverse incision. **(B)** Longitudinal or oblique incision. **(C)** Combined transverse and longitudinal incision. **(D)** Approach through the third lumbrical.

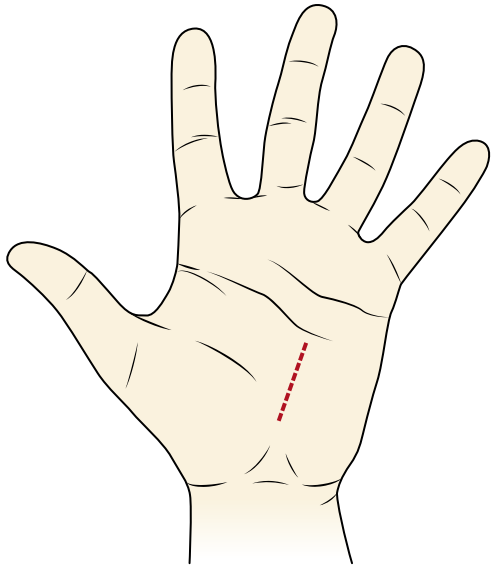


FIG. 8 Longitudinal incision for drainage of a hypothenar space is placed along the axis of the ring finger metacarpal in the proximal palm.

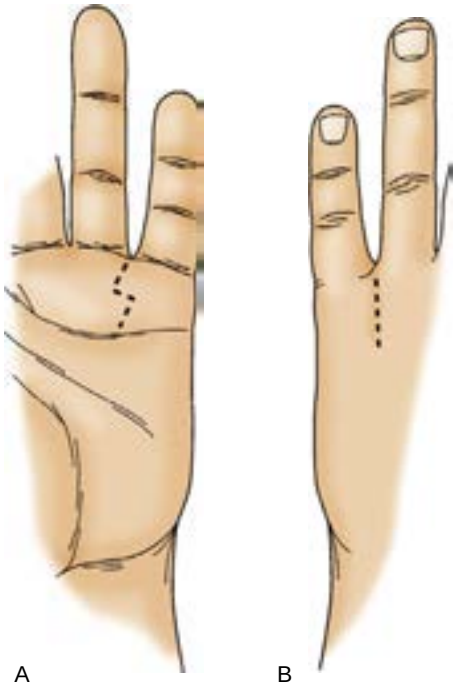


FIG. 9 Incisions for an interdigital webspace infection. Zigzag palmar incision **(A)** and dorsal longitudinal incision **(B)**.

Care must be taken to prevent injury to the neurovascular structures as they enter the affected fingers. A dorsal incision should also be made to thoroughly decompress and irrigate the space. Cultures should be collected, and the wound should be packed.

Dorsal Subaponeurotic Space

This is also another potential space on the dorsum of the hand deep to the extensor tendons and superficial to the interosseous muscle fascia and metacarpal periosteum.

Symptoms

The dorsal hand will be swollen, erythematous, and warm, similar to cellulitis. Fluctuance may also be present. Finger extension may be limited due to pain.

Treatment

In small abscesses, a single longitudinal incision over the most prominent aspect of the abscess may be used. In more diffuse infection, two dorsal longitudinal incisions over the second and fourth metacarpals can be made (Fig. 10). Incisions should be made in the fascia along the margin of the extensor tendon.

Space of Parona

Dorsal to the flexor digitorum profundus and volar to the pronator quadratus, the space of Parona is volarly located and continuous with the radial and ulnar bursae and the midpalmar space. Thus, infections in any of these other spaces may spread into the space of Parona. Untreated, advanced cases of flexor tenosynovitis may also result in infections in this area.

Symptoms

Patients present with erythema, tenderness, and potential fluctuance in the distal volar (palmar) forearm, with pain with active and passive flexion of the fingers.

Treatment

A longitudinal incision along the ulnar border of the palmaris longus should be designed, extending from the wrist flexion crease to the distal third of the forearm. The median nerve and tendons should be gently retracted radially to expose the space of Parona. Consider decompressing the midpalmar space as previously described, as infections from this area can spread into the space of Parona.

OTHER INFECTIONS

Animal and Human Bites

Bite injuries to the hand can result in significant morbidity if not treated in a timely manner; notably, the pathogens found in human bites are more virulent than that of animal bites. These "fight bite"

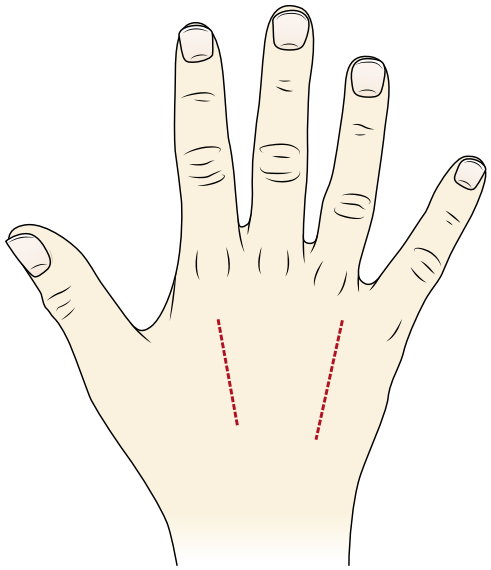


FIG. 10 Locations of the two dorsal incisions for draining a subaponeurotic space infection.

wounds are sometimes concomitant with other injuries, such as tendon lacerations and fractures. Human bites on any aspect of the hand or fingers have a high risk of infection and necessitate intraoperative exploration. If involving a joint, the wound should be extended to allow for complete arthrotomy, debridement of any devitalized tissue, and collection of multiple tissue cultures before thorough irrigation. Afterward, the hand should be splinted and elevated and intravenous antibiotics (typically a third-generation cephalosporin or gentamicin and a penicillinase-resistant penicillin) should be initiated.

Of the most common animal bites, dog bites are less likely to get infected but may be associated with significant soft tissue injury and/or fractures depending on the size of the animal; over half of all cat bites, on the other hand, get infected. It is imperative to take a thorough history including the rabies vaccination status of the animal. Cultures will show a mixed population of pathogens ranging from *S. aureus*, *Pasteurella multocida,* and *Streptococcus viridians* species. These wounds require thorough irrigation, local wound care, and IV ampicillin or oral Augmentin (for patients with penicillin allergies, antibiotic regimen may include fluoroquinolone and clindamycin).

Septic Arthritis

Infection of the interphalangeal and metacarpophalangeal joints of the fingers is rare. Incidence of septic arthritis of the wrist varies in the literature from 5% to 22% but is often associated with comorbid conditions such as immunosuppressed state, chronic renal disease, intravenous drug use, and diabetes. Although penetrating trauma is the most common cause, other mechanisms include hematogenous spread or contiguous spread from a local infection. Common pathogens include *S. aureus* and *Streptococcus*; *Eikenella* is a possibility if a human bite is present, whereas *Pasteurella multocida* should be considered in the setting of a cat or dog bite. Timely diagnosis is key to preventing destruction of articular cartilage that can then compromise the joint.

Symptoms

The patient may present with generalized symptoms such as low-grade fever, malaise, chills, and associated pain, erythema, and swelling in the involved joint. Active or passive motion of the joint will result in significant pain.

Treatment

Arthrocentesis is necessary to confirm the diagnosis. Samples should be sent for both cell counts, Gram stain, and microscopy to rule out other noninfective etiologies such as gout or pseudogout. Radiographs should be obtained; however, in acute infections, they will likely be normal. In chronic or severe cases, signs of osteomyelitis may be present. Septic arthritis is a surgical emergency; irrigation and drainage of the joint is the gold standard for treatment.

As with any surgical intervention on the hand, careful placement of incisions is key to prevent long-term complications. On the wrist, a longitudinal incision between the third and fourth dorsal compartments is preferred. For the metacarpophalangeal joints, a dorsal midline incision is made, and the extensor hood is then incised to exposed the joint. Damage to the sagittal bands, which originate from the volar plate and intermetacarpal ligament at the metacarpal neck and serve to stabilize the extensor tendon, must be avoided when exposing the joint. For the proximal interphalangeal joints, a midaxial incision from the DIP joint to the webspace should be designed. This will then avoid injury to the central slip; the accessory collateral ligaments and transverse retinacular ligaments are then incised to expose the joint. After cultures are obtained, the joint space should be copiously irrigated with normal saline (3–6 L), and any devitalized tissue should be debrided. Intravenous antibiotics are tailored according to surgical cultures and eventually transitioned to an oral regimen.

NECROTIZING INFECTIONS

Necrotizing fasciitis of the upper extremity is a true surgical emergency that necessitates immediate intervention to prevent further dissemination. Complications include amputations, septic shock, multisystem organ failure, and death. Patients may present with erythema, swelling, and significant pain; however, systemic symptoms such as hypotension, tachycardia, and altered mental status as well as soft tissue changes, such as skin sloughing/blistering or crepitus, differentiate this diagnosis from what is seen in more minor infections such as cellulitis. Subcutaneous air may be seen on plain films. Intravenous antibiotics and fluid resuscitation should be initiated immediately as the patient is transferred to the operating room for debridement. Infected tissues are superficial to the fascia, and grayish discharge ("dishwater drainage") may be seen intraoperatively. Multiple debridements may be needed before the infection is eradicated. Broad-spectrum antibiotics (such a multidrug regimen including vancomycin and piperacillin/tazobactam) should be continued until cultures are finalized.

SUMMARY

Hand infections need to be diagnosed accurately and in a timely manner to avoid long-term sequelae. A thorough understanding of anatomy and pathophysiology is necessary to treat these conditions effectively.

Suggested Readings

Kazmers NH, Fryhofer GW, Gittings D, et al. Acute Deep Infections of the Upper Extremity: The Utility of Obtaining Atypical Cultures in the Presence of Purulence. *J Hand Surg Am*. 2017;42(8):663.e1–663.e8.

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Nerve Injury and Repair

Christopher Frost, MD, and Gedge D. Rosson, MD

During the past 50 years, mainly due to the development of microsurgical techniques, surgeons have been routinely repairing severed peripheral nerves. This has paralleled the advances in microvascular reconstruction and digital replantation. Performance of nerve repair requires meticulous microsurgical technique and the use of both the science and art of peripheral nerve surgery. Furthermore, nerve repair is often an exercise in delayed gratification because many injuries can take months or even years to recover after repair.

BASIC ANATOMY

Nerve anatomy and physiology is fundamental to peripheral nerve surgery and guides the diagnosis of nerve injury. The basic subunit

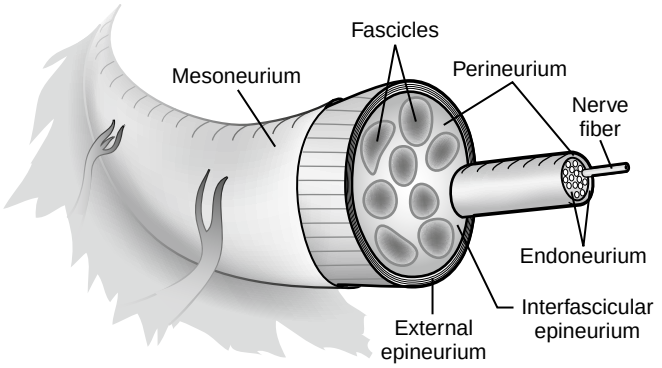


FIG. 1 Anatomy of a peripheral nerve.

of the peripheral nerve is the axon. These axons are surrounded by endoneurium and grouped into fascicles. Each fascicle is encapsulated by a perineurium, and groups of fascicles are in turn surrounded by an interfascicular epineurium. Each peripheral nerve is comprised of a group of fascicles surrounded by an external epineurium. Finally, the nerve sheath is contained within a mesoneurium, which both allows for nerve gliding during normal range of motion and contains the segmental blood supply to the nerve (Fig. 1).

FASCICULAR TOPOGRAPHY

When performing peripheral nerve surgery, it is important that proximal motor and sensory axons connect to their corresponding distal fascicles. More proximally there can be significant intermingling between sensory and motor axons with plexus formation in the nerve trunks proximally. As the nerves travel more distally, motor and sensory axons more clearly develop into distinct fascicles. This can have important clinical consequences after nerve repair. For example, repairing facial nerve injuries within the temporal bone often leads to improper connections between proximal and distal nerves. This can lead to a significant amount of disabling synkinesis and dyskinesis secondary to the lack of distinct fascicular architecture in the proximal facial nerve trunk. This is opposed to repairs distal within the face because these fascicles are organized into clear branches and errant innervation is less likely to occur.

PATHOPHYSIOLOGY

A clear understanding of the mechanism of injury, zone of injury, and degree of nerve injury is critical for successful management. Based on the mechanism of injury, lesions can be classified as open (laceration) or closed (overstretching, blunt, compressive trauma). Gunshot wounds behave like closed injuries typically because nerve injury is more likely due to blast effect rather than transection. Initial zone of injury can vary widely depending on the mechanism of injury. Sharp injury such as a scalpel blade produces a small zone of injury. More blunt mechanism such as a table saw, on the other hand, can produce a very wide zone of injury. The zone of injury can be difficult to determine on initial exploration if there is evidence of blunt trauma, crush, or nerve avulsion.

The degree of injury can be classified using several different systems (Table 1). The Seddon's classification divides injuries into neurapraxia, axonotmesis, and neurotmesis based on the anatomic nerve component that is damaged. The Sunderland classification I to V is based on the degree of injury and expected recovery. Mackinnon and Dellon added a VI degree to this system (combined nerve injury).

Focal or segmental demyelination with preservation of axon continuity is termed *neurapraxia* (Sunderland class I). In this case, functional recovery is expected to occur spontaneously as the myelin heals. This recovery occurs over a period of hours or days up to 6 weeks. No surgical intervention is required in this case. Radial nerve compression ("Saturday night palsy") with resulting wrist drop that spontaneously recovers is one common example.

Axonal injury with preservation of the endo and epineural sheath is known as axonotmesis (Sunderland class II–IV). In this case, the axon will die back to the nearest node of Ranvier. After initial stabilization, the axon will begin to form multiple "growth cones" and regrow at a rate of 1 mm/day or 1 inch/month through the distal endoneurial tubes. The axons distal to the injury site undergo Wallerian degeneration whereby myelin and cellular debris are phagocytosed and the axon replaced. Axonotmesis can result in a range from complete recovery to minimal or no recovery. Degree of recovery is dependent on the degree of damage to the surrounding structures (endoneurium, perineurium, and epineurium) and the resulting scar tissue. If the surrounding tissues remain intact, the axons will usually reach the distal endoneurial tubes and spontaneous recovery will occur (Sunderland class II–III). On the other hand, if the sprouting axons are unable to reach the distal endoneurium, then a neuroma in continuity will develop, and no spontaneous recovery will occur (Sunderland class IV).

Finally, complete transection of all neural structures is termed *neurotmesis* (Sunderland class V). Spontaneous recovery in this case is not expected. Surgical intervention is required in all cases of neurotmesis and in cases of axonotmesis where regenerating axons are unable to regenerate successfully through the distal endoneurium.

Importantly, the distal axon in all cases of nerve injury will have viable axons that can transmit electrical signals for between 72 and 96 hours after injury. After this time period, the distal axons will

TABLE 1 Classification and Expected Recovery of Nerve Injuries

Classifications		Nerve Component Injured					Expected Recovery		
Seddon	Sunderland Degree (Modified)	Myelin	Axon	Endoneurium	Perineurium	Epineurium	Extent	Rate	Surgery Indicated
Neurapraxia	First	X					Complete	Fast	No
Axonotmesis	Second	X	X				Good	Slow	Not usually
	Third	X	X	X			Variable	Slow	Variable
	Fourth	X	X	X	X		None	None	Yes
Neurotmesis	Fifth	X	X	X	X	X	None	None	Yes
	Sixth	Combination of injury					Variable	Variable	Variable

X, Injury.

irreversibly degrade and undergo Wallerian degeneration. In cases where it is critical to stimulate distal motor branches during repair such as in facial nerve injury, patients should be brought to the operating room within 72 hours of initial injury. Nerve repair between inappropriate proximal and distal motor fascicles can lead to synkinesis and dyskinesis.

After muscles lose innervation, they begin to degenerate from both disuse atrophy and denervation atrophy. Motor endplates within the muscle will irreversibly degenerate after 12 months and will be gone by 18 to 24 months. After this point, the muscle cannot be reinnervated, creating a relative deadline for recovery of motor function at 1 year after injury. On the other hand, sensory end organs do not undergo degeneration and reports have been made of successful sensory reinnervation many years after initial injury (Table 2).

TIMING

Optimal surgical timing is essential for successful nerve repair. Closed injuries should be approached differently from open injuries. Early recognition and treatment of nerves unlikely to recover spontaneously is key, and "time is muscle" remains a fundamental concept. Surgical timing can be summarized by the *3+1 rule* (Table 3), with early repair occurring within 3 days, subacute repair at 3 weeks, delayed repair at 3 to 6 months, and late repair after 1 year.

Early repair, occurring within 3 days after the injury or at presentation if evaluated after 3 days, is indicated in cases of suspected transection with sharp injuries. In this case, any neural deficits are likely to represent nerve transection (neurotmesis or Sunderland class V–VI) and will require surgical intervention. It is also indicated in situations with vascular (e.g., hematoma, pseudoaneurysm) or bony injuries causing acute nerve compression, especially if they occur in the vicinity of a closed compartment. If a neurologic examination worsens acutely under close observation, the nerve damage potentially can be reversed or reduced by immediate surgical intervention.

Subacute repair, occurring around 3 weeks after injury, is advocated by some for blunt or ragged transections (e.g., by propeller blades or chainsaw), but others still treat these injuries acutely. These injuries clearly represent neurotmesis and surgical intervention is

TABLE 2 Treatment Options and Indications for Repair of Nerve Injuries

Options	Indications
Observation	Recovering nerve injury Partial nerve injury
Neurolysis	Neuroma-in-continuity with positive NAP
Direct repair	Laceration Short gap after resection of a neuroma-in-continuity with negative NAP
Nerve graft	Laceration with retracted stumps (delayed repair) Larger gap after resection of a neuroma-in-continuity with negative NAP Direct repair without tension not possible
Nerve conduits (autogenous or synthetic)	Short gaps (<3 cm) of small diameter, usually sensory nerves (e.g., digital nerves)
Nerve transfer	Avulsions (brachial plexus avulsion) Specific cases of nerve injury for which nerve transfer may lead to a more rapid and reliable recovery (i.e., because of proximity to end organ) than proximal nerve grafting Innervation of free functioning muscle transfers
Direct neurotization	Under investigation for direct muscle reinnervation after severe trauma
Nerve reimplantation	Under investigation
Tendon or muscle transfers	Delayed (>1 year) for improvement of function
Bony or joint procedures	Delayed (>1 year) for improvement of function
Amputation	Rarely indicated; sometimes desired by patients

NAP, Nerve action potential.

TABLE 3 3+1 Rule for Timing of Nerve Repair

Timing	Time	Injury Type	Injury Classification
Early	3 days	Sharp laceration or transection Acute nerve compression resulting from vascular (e.g., hematoma, pseudoaneurysm) or bony injuries Acute neurologic worsening under close observation	Neurotmesis
Subacute	3 weeks	Blunt transection Ragged transection	Neurotmesis
Delayed	3 months	Lesions-in-continuity (nonpenetrating injuries such as stretch injuries, contusive injuries, gunshot wounds)	Axonotmesis
Late	>1 year	Salvage procedures	Neurotmesis or axonotmesis

required. Blunt injury can cause a large and unpredictable zone of injury, however. Delaying repair for a few weeks allows Wallerian degeneration to begin occurring, better defining the zone of injury. At the time of repair, the nerve endings can be resected back to healthy tissue. This would be difficult to evaluate if the injured nerves were explored immediately after the injury.

In contrast, advocates for earlier surgery feel that surgery is easier and more practical at an earlier time, especially if done at the same time that surgical intervention is performed by another team, such as a general, vascular, or orthopedic surgical team. Furthermore, the additional technical challenges of dealing with scarring can be avoided. For example, if a patient with a fracture and associated nerve palsy is being examined by an orthopedist, it would be reasonable to explore the nerve at the same time. If the nerve is found to be in continuity but nonfunctional, observation for several months is indicated. Note that because Wallerian degeneration does not occur until 72 to 96 hours after injury, intraoperative electrophysiologic testing would not be reliable or helpful in predicting recovery or acutely determining the grade of injury. If the nerve is found to be ruptured, some would repair it at the same time. Others would perform the surgery at a second stage, when the zone of injury can be better defined; nerve ends are tacked down under tension so they do not retract, using radiopaque clips or suture so that they can be identified easily. At a later time, a subacute nerve repair can be done.

Delayed repair, occurring approximately 3 months but up to 6 months after injury, is indicated for lesions-in-continuity, such as the majority of stretch injuries, contusive injuries, and gunshot wounds. In these cases, it is difficult to predict with certainty which path the nerve injury will follow from those described previously and whether the injury will recover spontaneously or require surgical repair. Nonoperative treatment can be continued in patients with early signs of spontaneous recovery or in partial lesions. Note that 90% of nerves that recover do so within 4 months. Surgery is indicated when there has been no evidence of clinical or electrical recovery after this period of observation. In these cases, the delay also will allow lesions-in-continuity to be evaluated during surgery with nerve action potential (NAP) testing to distinguish between recovering lesions (Sunderland class II–III) and nonrecovering (Sunderland class IV) lesions that require repair.

Late surgery, occurring more than 1 year after injury, may be considered a salvage procedure in patients who are seen in a delayed fashion or in those who either have not recovered or have recovered incompletely after spontaneous recovery or previous nerve surgery. Nerve repair and reconstruction typically does not work well after this period, which can be considered as short as 9 months by some surgeons because of permanent changes at the muscular level. The one exception might be distal nerve transfers (those performed close to the end organ), which can be performed in select cases even up to 18 months after injury. However, reconstructive options addressing muscles, tendons, bones, and joints may be useful.

TREATMENT FOR NERVE INJURY

The management and surgical treatment of nerve injury involves the application of general principles that are relevant to all nerve surgeries and of specific nerve repair techniques particular to each situation.

GENERAL PRINCIPLES

Preoperative Assessment

The optimal approach to nerve injury assessment includes a detailed history of the mechanism of injury and the onset of the deficit; a physical examination (neurologic, vascular, and musculoskeletal examination); and electrodiagnostic studies, such as electromyelography and nerve conduction studies. These three pillars (history, physical examination, and electrodiagnostic studies) help the clinician to determine the extent and severity of the nerve injury. Additionally, imaging studies (radiography, ultrasonography, computed tomography, magnetic resonance imaging and neurography, or myelography) can further enlighten the clinical scenario and the operative planning. Specifically, high-resolution (3 Tesla) magnetic resonance neurography (MRN) has been increasingly used to better define the anatomy of injured nerves. MRN provides a substantial benefit for the evaluation of large proximal nerve elements such as the brachial plexus, the lumbosacral plexus, the sciatic nerve in the pelvis, and other nerves that follow deep or complex courses, where electrodiagnostic studies are difficult to use. The clinician must also remember to use sensory and motor function grading scales, which will facilitate follow-up and assessment of the results of interventions (including observation).

Key Operative Principles

At surgery, the steps taken to expose the injured nerve before the nerve repair itself are important. Knowledge of the anatomy is crucial, especially when scarring from the injury is expected and likely will distort the anatomy. Adequate exposure should be planned, including the possibility of harvesting nerve grafts. Dissection usually is done between two muscle groups parallel to the long axis of the nerve. Ideally, a normal segment of the nerve is identified first, both proximally and distally, before dissection is carried toward the injured segment. If the injured segment is near a compression site, such as the median nerve near the carpal tunnel, then the site of compression should be released at this time. For practical purposes, there are two possibilities: the identification of a neuroma-in-continuity or nerve stumps.

If there is a neuroma-in-continuity, intraoperative NAP recordings can be performed to assess the degree of injury (recovery or no recovery) (Fig. 2). These are helpful because gross inspection or palpation of a neuroma-in-continuity does not predict histology, recovery, or outcomes. Furthermore, NAP can determine recovery across a short segment of nerve (i.e., proximal and distal to an injury) before recovery can be seen by physical examination or conventional electromyogram. When a NAP is present across a lesion, the lesion should not be resected because the outcome generally will be better with neurolysis alone. If a NAP is absent across a lesion,

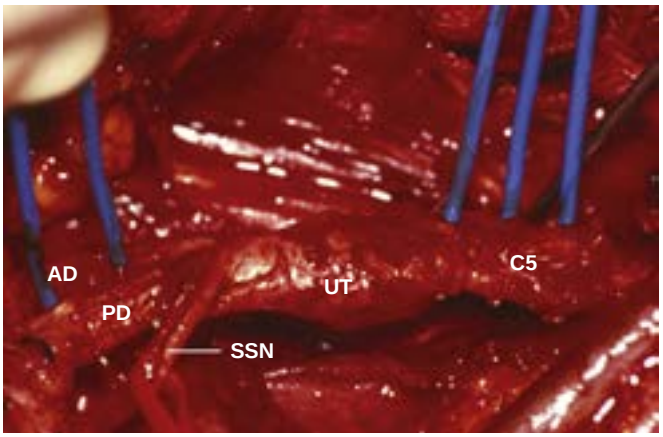


FIG. 2 Intraoperative photograph showing a nerve action potential (NAP) being recorded. The NAP is tested across a neuroma-in-continuity of the upper trunk *(UT)* of the brachial plexus. The C5 spinal nerve, the UT, the anterior *(AD)* and posterior *(PD)* divisions of the UT, and the suprascapular nerve *(SSN)* are seen. The C6 spinal nerve contributing to the UT is not seen in this view. The stimulating electrode (three prongs) is seen proximal to the neuroma-in-continuity; the recording electrode (two prongs) is seen distal to it.

the outcomes are generally poor if the lesion is left intact; therefore, surgical repair is indicated.

If two nerve ends suggestive of a rupture or transection are identified or if a nerve end suspicious for an avulsion is found, a nerve repair or reconstruction is indicated. The use of NAP recordings still can be helpful in these situations and can allow identification of the proximal location at which nerve grafting can be performed. Some use NAP in brachial plexus avulsion injuries to define preganglionic responses. Others use other techniques, including somatosensory-evoked potential and motor-evoked potential, to assess whether the proximal nerve stump is intact and can be used for reinnervation.

For the nerve repair, microsurgical techniques, which involve the use of micro instruments and of a microscope or magnifying loupes, should be used. The nerve ends on both sides should be prepared by removing sharply the neuroma and scar tissue, until normal fascicular structures are obtained. The nerve stumps should be sliced proximally and distally (like slicing a loaf of bread) until a healthy fascicular pattern is visualized. This is called *les yeux d'escargot* (snail's eyes). This pattern of healthy fascicles protruding from the cut nerve endings is due to the pressure within the endoneurium. The fascicles that protrude past the cut nerve ending should be divided further until all of the fascicles lie flush with the epineurial sheath. This is critical so that the fascicles do not overlap once the epineurium is sutured. Optimal microsurgical technique will cause minimal surgical trauma and permit an end-to-end repair or interpositional grafting; it is further recommended that 8-0, 9-0, or 10-0 sutures be used, and using the fewest number of sutures to approximate the nerve accurately is preferred. The repair must be without tension to obtain good results. Fibrin glue may be used to reinforce the suture line, but other methods involve the use of fibrin glue alone or with a variety of nerve conduits (entubulation).

If repair of a motor nerve is planned (and it is within 72 hours of the original injury), it is critical to remember that a tourniquet applied longer than 30 minutes can cause ischemia of the distal nerve, and intraoperative nerve stimulation will no longer be possible. Thus, the initial dissection must be well planned, focused, and directed to ensure that there is enough time to dissect the injured distal nerve and apply stimulation for 30 minutes afterward.

TECHNIQUES FOR NERVE SURGERY

Neurolysis

Neurolysis, defined as releasing scar tissue surrounding the injured nerve, is indicated when a neuroma-in-continuity with intact NAP conduction is found. In general, external neurolysis, which is completed during the nerve exposition, is sufficient. In select instances, some advocate limited internal neurolysis or removal of the scar tissue between the various nerve fascicles.

Direct Repair

Direct nerve repair is the end-to-end suture of nerve stumps. It is indicated when a short nerve gap exists, either from a sharply transected nerve—such as a cut from glass, a knife, or a razor—or after removing a focal neuroma-in-continuity that did not conduct a NAP. Direct repair is the preferred method of nerve repair whenever possible, assuming that the damaged segment of the nerve has been resected and that the sutures are without tension. This method allows direct delivery of proximal axons to the distal stump via a single suture line. It also usually permits fascicular alignment, which increases matching between motor and sensory axons and their targets.

For primary nerve repair, an epineurial repair is usually the most predictable (Figs. 3, 4, and 5). The external epineurial vessels can be arranged to ensure that the fascicles are appropriately aligned. Additionally, to facilitate restoration of fascicular orientation, it is important to be familiar with the serial cross-sectional fascicular topography, fascicular stimulation, histochemical stains, and gross fascicular matching. Often, only two or three interrupted sutures are necessary to align and coapt the nerve endings. It is critical at this stage to ensure that there is no overlapping of the fascicles (Fig. 6). The fascicles should just be gently coapted within the epineurium. It is also important to make sure that the needle passes only through the epineurium and does not catch a portion of one of the fascicles because this can lead to a small intraneural neuroma, and the fascicle will not heal properly.



FIG. 3 Nerve segment trimmed until healthy fascicles are encountered in a stepwise manner. In this case a neuroma is resected from the proximal nerve end.

Occasionally, it is appropriate to perform fascicular or grouped fascicular repairs. In a large nerve where the fascicles are easily identifiable, it may be possible to suture the internal epineurium between the fascicles with a few small, interrupted nylon sutures and then perform the epineurial repair. Some researchers have reported that grouped fascicular repair results in more intraneural scarring, so most peripheral nerve surgeons continue to use the epineurial repair. When performing nerve repairs, it is important to understand the difference between the fascicular topography in the proximal nerve trunk and the fascicular topography in the distal nerve (Fig. 7). Most nerves have a significant intermingling of sensory and motor fibers with plexus formation proximally, whereas more distally they usually become groups of sensory or motor fibers. This partially explains why more distal nerve repairs have better long-term functional outcomes.

If a small nerve gap is present, several methods can be used to reduce the gap and achieve a direct repair. Commonly used methods include nerve mobilization; nerve transposition, as with the ulnar and radial nerves; and joint positioning, such as repair and immobilization of a joint in some degree of flexion with gradual postoperative extension beginning at about 3 weeks. In some cases, bone shortening, as with comminuted fracture, may offer an opportunity for decreasing a nerve gap.

Nerve Graft

Nerve graft repair is performed when nerve stumps on either side of a gap cannot be opposed for a direct end-to-end repair without tension. Often this technique is necessary for neuromas-in-continuity of moderate or longer lengths with unrecordable (negative) NAP or for transected nerves with retracted stumps, which occurs when the initial surgery is delayed.

The most frequent source of nerve graft is the sural nerve (Fig. 8). However, the medial or lateral antebrachial cutaneous nerves, superficial sensory radial nerve, superficial peroneal nerve, distal posterior interosseous nerve, great auricular nerve, and cervical plexus nerves

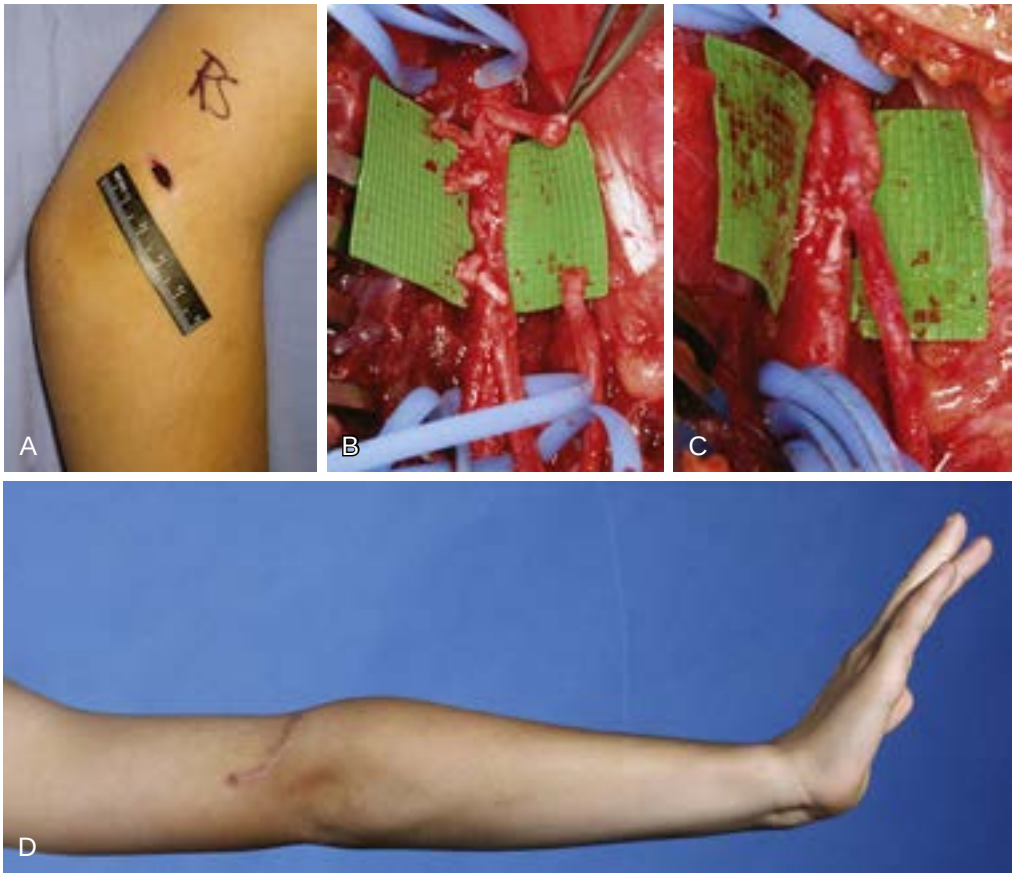


FIG. 4 Patient with a partial laceration of the radial nerve treated at presentation 1 week after injury. **(A)** The open knife-entry wound is seen in the right arm, slightly proximal to the elbow, near the interval between the brachioradialis and triceps. The knife blade had penetrated the arm to a depth of approximately 5 cm (2 inches). The patient had no thumb extension, partial weakness of the finger extensors and wrist extensors, and decreased sensation in the dorsum of the hand. **(B)** At exploration, the radial nerve was found to be partially lacerated at its bifurcation into the deep and superficial radial nerve. The complete laceration of the superficial (sensory) radial nerve is seen, as is the partial injury to multiple fascicles of the deep (motor) branch of the radial nerve. **(C)** Direct repair of the superficial sensory radial nerve and the fascicles of the deep branch of the radial nerve are shown; a 9-0 suture was used to perform this repair. **(D)** After 6 months, the patient had already regained good finger and wrist extension (Medical Research Council [MRC] grade 4). Thumb extension (the most distal motor target) improved to MRC grade 3, although the patient still had sensory abnormality in the dorsum of the hand.

are alternatives. The nerve graft should be sutured into place in a reversed fashion from its usual anatomic course (i.e., the more distal end of the nerve graft should be sutured to the proximal end of the nerve gap being repaired, and the proximal end of the nerve graft should be sutured to the distal end of the nerve gap). This ensures that axons will not be lost through small side branches in the nerve graft as the axons grow through the graft. When the diameter of the nerve at the site of repair is much larger than the diameter of the nerve graft, grouped fascicular repair may be used (Fig. 9). The disadvantage of nerve grafting is related to the minor sequelae associated with donor morbidity from the nerve harvest, such as expected permanent sensory loss and small chance of neuropathic pain.

The graft length is calculated by measuring the nerve gap and adding 10% to account for some desiccation of the graft and to avoid tension. One graft or several "cable" grafts are placed to maximize the surface area at the repair sites and to prevent mismatch. Interposed grafts may be sutured individually at both ends or may be glued together and then sutured as a single unit.

Vascularized nerve grafts have been advocated by some to improve the speed and quality of regeneration compared with standard, nonvascularized nerve grafts; however, this practice is controversial. Autogenous or synthetic conduits may be used for short gaps (<3 cm) of small diameter, usually sensory nerves (e.g., digital nerves). Using a nerve conduit requires an entubulation technique. The nerve conduit must be the correct diameter to accommodate the nerve and should be approximately 10 mm longer than the nerve gap. The entubulation technique involves placing the proximal nerve ending 5 mm within one end of the nerve tube and the distal nerve ending 5 mm within the distal end of the nerve tube, with horizontal mattress sutures tied on the outside of the nerve conduit.

Nerve Allografts

Decellularized grafts, which are devoid of all cellular material including Schwann cells, are increasingly used in nerve repair. These grafts are comprised of extracellular matrix, which provides a scaffold for axonal regeneration. Despite the lack of living Schwann cells, several smaller studies have reported good results with decellularized grafts. There are several additional randomized control trials with ongoing enrollment, and more data are required to fully evaluate their use and indication.

Nerve transplants have been reported, although specific indications are still evolving. The primary theoretical advantage of cadaveric donor nerve grafts is the presence of Schwann cells, which could aid in regeneration. However, their immunogenicity precludes their use in clinical practice. The use of nerve allografts almost always requires associated immunosuppressive therapies, without which graft rejection occurs.



FIG. 5 Patient with a spinal accessory nerve injury after a right retrosigmoid craniotomy for removal of a vestibular schwannoma. **(A)** Surgical incision used for the resection of the right vestibular schwannoma. After surgery, the patient developed prominent scapular winging, atrophy of the right trapezius muscle, and significant difficulty in abducting the right arm. Electromyography 3 months after surgery confirmed a right spinal accessory neuropathy affecting the motor branch to the trapezius (normal sternocleidomastoid) without evidence of reinnervation. **(B)** At exploration soon thereafter, the great auricular nerve (at the right of the nerve stump) and the greater occipital nerve (blue vasoloop) were identified. The proximal and distal stumps (clipped to a green background) of the spinal accessory nerve were found within the scar of the prior surgical exposure. **(C)** To achieve a direct repair, the two nerve stumps were mobilized proximally and distally. **(D)** A direct end-to-end repair was performed using an 8-0 suture. **(E)** The patient regained excellent function, scapular stability, and range of motion, shown here at 15 months after the repair.

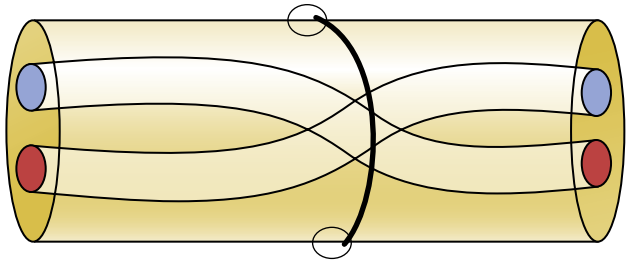


FIG. 7 Proximal nerve fascicles should be aligned to their corresponding distal fascicle. Mismatch between proximal and distal fascicles can lead to errant innervation of inappropriate distal targets and lead to synkinesis or dyskinesis.

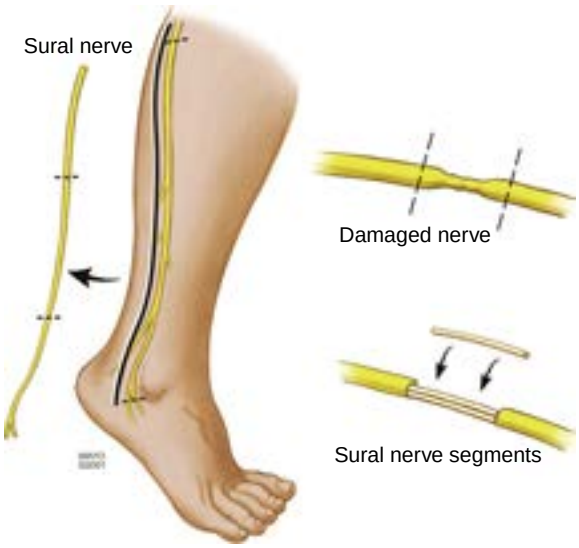


FIG. 8 The sural nerve is the most common source of nerve graft. A purely sensory nerve, it supplies sensation to a small area of the dorsolateral aspect of the foot. The sural nerve is up to 40 cm long in each leg; nerve grafts may be harvested bilaterally, and sural nerve segments are used to bridge the nerve gap.

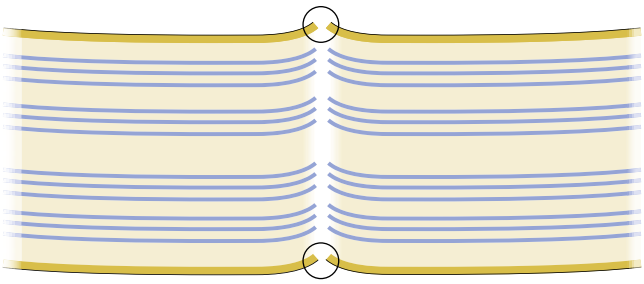


FIG. 6 Nerve ends should be trimmed to remove scarred tissue and reach healthy-appearing fascicles in a stepwise fashion. Nerve fascicles should be trimmed flush with the epineurium. Microsuture of the epineurium is performed with 8-0, 9-0, or 10-0 suture and should be done carefully to prevent bunching of the ends or inadvertent suturing through a fascicle. General topography can be aligned by examining blood vessels along the epineurium.

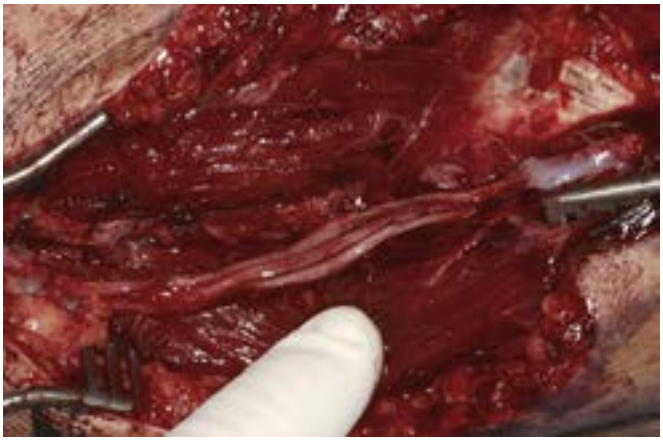


FIG. 9 Intraoperative image of three sural nerve segments bridging a radial nerve gap in the distal arm after a humeral fracture.

Nerve Transfers

Nerve transfer refers to the procedure of transecting an expendable working nerve, branch, or fascicle in the vicinity of an injured nerve to coapt it to the nonfunctioning nerve. The main advantages of nerve transfers are better proximity to the end organ (which in turn decreases the time to reinnervation) and the fact that distal nerves contain a larger number of relatively "pure" (motor or sensory) axons (i.e., because nerve transfers involve the distal components of the nerve, at this level the axons are either motor or sensory).

When nerve transfer is indicated, outcomes are improved because this can be performed more distally and closer to the muscles in question than other repair techniques. For example, an upper trunk brachial plexus injury would result in a loss of flexion of the elbow. If the lower trunk is intact, redundant fascicles of the ulnar nerve to the flexor carpi ulnaris muscle or from the median nerve going to superficial flexor muscles can be transferred to either the brachialis or the biceps motor nerve (Fig. 10). This will result in faster reinnervation of the muscles than if a repair of the upper trunk of the brachial plexus was performed because it would take many months for the axons to grow all the way down into the arm. Based on the expected time to reinnervation, the benefits of nerve transfers versus nerve grafts should be carefully evaluated for each clinical scenario. A variety of nerve transfer procedures have been described both for reconstruction of sensory and motor defects. Most surgeons advocate distal nerve transfers closer to the end organ as opposed to proximal nerve grafting farther from the end organ (Table 4).

Muscle and Tendon Transfer and Bone and Joint Procedures

These various procedures usually are performed in a delayed fashion, sometimes more than a year after the injury. Muscle or tendon transfer is the transfer of a muscle or tendon that is working and is expendable to achieve a new function. This technique, similar to nerve transfer, requires a functional expendable innervated muscle in the vicinity. Examples of reliable tendon transfers include opponensplasty, anticlaw procedure, thumb adductorplasty, flexor to extensor transfers, elbow flexorplasty, transfers for shoulder external rotation, antiwing (scapular) transfers, transfers for pronation, and extensor to flexor transfers. An alternative is the transfer of a free functioning muscle, such as the gracilis muscle from the lower extremity, which can be transferred at a late stage for elbow flexion or finger flexion. This requires the presence of an arterial and venous supply, as well as a functioning nerve to reinnervate the muscle. Bone and joint procedures, such as osteotomies and arthrodesis, also may improve function. Shoulder fusion may be an option for patients with brachial plexus palsy and refractory instability with pain.

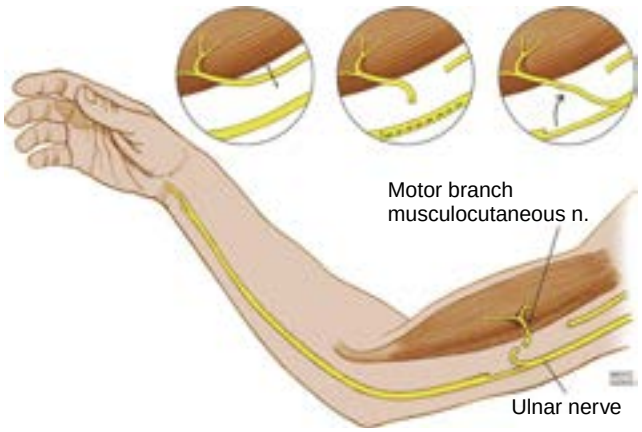


FIG. 10 Intraplexal nerve transfer technique (Oberlin procedure) used for the repair of injury to the brachial plexus or musculocutaneous nerve leading to loss of biceps motor function. To perform this transfer, the ulnar nerve function must be preserved. At the level of the middle or proximal third of the arm, a functioning ulnar nerve fascicle is used to reinnervate the biceps motor branch originating from the musculocutaneous nerve. In general, ulnar motor function is preserved (deficit in <1%), but the patient may experience transient sensory changes in the distribution of the ulnar nerve. A case series using this technique reports that 85% of patients recovered good elbow flexion after surgery.

EXPECTED OUTCOMES FROM REPAIR AND RECONSTRUCTION

Outcomes after nerve injury and repair are variable owing to a multitude of underlying factors. The best outcomes are achieved when spontaneous neural recovery occurs (i.e., when surgery is not indicated). Other factors influencing the recovery of nerve repair and reconstruction include the following:

Patient age: The younger the patient, the better the recovery because of inherent physiologic factors related to regeneration, limb length, and capacity for cortical reorganization and reeducation.

Level of injury: Distal injuries fare better because of the shorter distance to the end organ.

Type of nerve injured: Pure nerves fare better than mixed nerves because there is less chance of fascicular mismatch.

Specific nerve involved: Radial nerve recovers better than median nerve, which recovers better than ulnar nerve; nerves C5 and C6 and those of the upper trunk recover better than nerves C8 and T1 and those of the lower trunk; and tibial nerve recovers better than peroneal nerve.

Mechanism of injury: Lacerations have better outcomes than low-velocity gunshot injuries, which in turn have better outcomes than high-velocity gunshot injuries; transections have better outcomes than crush or avulsion injuries; and stretch injuries generally have better outcomes than ruptures, which fare better than avulsions. These variations in outcomes are related to the zone of injury and associated soft tissue and vascular damage.

Timing of repair and reconstruction: The earlier the better; outcomes are typically best before 6 months, but they depend on the size of the gap, the status of the end plate, and the status of the alpha motor neurons.

Type of repair or reconstruction: Patients in whom exploratory surgery is indicated, but in whom only neurolysis is performed because of a positive NAP, generally have favorable outcomes. Patients in whom direct end-to-end nerve repair can be performed generally have better outcomes than patients who undergo conventional interpositional nerve grafting. Improved techniques with nerve transfers, especially distal nerve transfers, have improved outcomes in peripheral nerve surgery in recent years. Direct nerve transfers have better outcomes than nerve transfers with interpositional grafts.

WHO SHOULD OPERATE

By extrapolation based on data related to other surgical techniques, it seems reasonable to expect improved outcomes in centers performing high-volume practice. Timely referral to centers specializing in evaluation and management of nerve injuries is important and should be considered.

TABLE 4 Common Motor Nerve Transfers of Upper Extremity

Motor Deficit	Recipient Nerve(s)	Donor Nerve(s)
Elbow flexion	Biceps, brachialis branches of MCN	Ulnar nerve fascicle to FCU Median nerve fascicle to FDS/PL/FCR
Elbow flexion	MCN	Medial pectoral nerve branches
Elbow flexion	MCN	Thoracodorsal nerve
Elbow flexion	MCN	Distal accessory nerve
Elbow flexion	MCN	Intercostal nerves
Shoulder abduction/external rotation	Suprascapular nerve	Accessory nerve (distal end-to-end or end-to-side with neurectomy and proximal crush injury)[a] Pectoral fascicle of C7, middle trunk
Shoulder abduction	Axillary nerve	Medial triceps branch
Shoulder abduction	Axillary nerve	Medial pectoral nerve
Shoulder abduction	Axillary nerve	Thoracodorsal nerve
Shoulder abduction	Axillary nerve	Intercostal nerves
Scapular winging/instability	Long thoracic nerve	Thoracodorsal nerve[b]
Scapular winging/instability	Long thoracic nerve	Pectoral fascicle of C7, middle trunk[b]
Scapular winging/instability	Long thoracic nerve	Intercostal nerves
Intrinsic hand	Deep motor branch/fascicle of ulnar nerve	Distal AIN
Pronation	Pronator teres branches of median nerve	ECRB branch of radial nerve FDS or FCR/palmaris longus branch of median nerve
Wrist, finger extension	ECRB, PIN branches of radial nerve	FDS, FCR/PL branches of median nerve[a]
Finger flexion	AIN branch of median nerve	Brachialis branch of MCN ECRB, supinator branches of radial nerve
Elbow extension	Triceps branch of radial nerve	FCU fascicle of ulnar nerve ECRL fascicle of radial nerve
Elbow extension	Triceps branch of radial nerve	Intercostal nerves

Donor nerves are listed in order of preference.
AIN, Anterior interosseous nerve; *ECRB*, extensor carpi radialis brevis; *ECRL*, extensor carpi radialis longus; *FCR*, flexor carpi radialis; *FCU*, flexor carpi ulnaris; *FDS*, flexor digitorum superficialis; *MCN*, musculocutaneous nerve; *PIN*, posterior interosseous nerve; *PL*, palmaris longus.
[a]With TP to ECRB transfer.
[b]When combined, these transfers give the most rapid recovery of long thoracic function as a double-level nerve transfer.
From Tung T, Mackinnon S. Nerve transfers: indications, techniques, and outcomes. *J Hand Surg*. 2010;35:332–341.

SUMMARY

The treatment and management of nerve injuries require thorough knowledge of anatomy, of the nerve injury process, and of the available repair and reconstructive options. They also require specific microsurgical skills in the context of a multidisciplinary team able to address the peripheral nerves and associated muscles, tendons, and joint problems, as well as concomitant injuries to the central nervous system (spinal cord and brain) and other systems.

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Necrotizing Skin and Soft Tissue Infections

Philip J. Wasicek, MD, and Arthur J. Nam, MD, MS

INTRODUCTION

Necrotizing skin and soft tissue infections (NSTIs), more colloquially referred to as "flesh-eating bacteria," represent a variety of rapidly progressive disease processes that requires prompt identification and aggressive surgical debridement and broad-spectrum antibiotic therapy. Although uncommon, with an incidence of 4 to 15.5 per 100,000 person-years, NSTIs are associated with high rates of morbidity and mortality due to aggressive bacterial infection of soft tissue, deep spaces, and/or muscle that result in tissue necrosis.

PATHOPHYSIOLOGY

NSTIs typically occur via microbial invasion of the subcutaneous tissues. Traumatic injury breaching skin or mucosal integrity, as well as surgery (including intestinal, urologic, and obstetric/gynecologic procedures) are risk factors for the development of NSTIs. Additional important risk factors include immunosuppression, age/frailty, peripheral vascular disease, obesity, and diabetes mellitus. Importantly, however, NSTIs can occur among otherwise healthy patients with no clear etiology of infection.

Once infection has been established, causative organisms may produce endotoxins and exotoxins resulting in obliterative endarteritis, thrombosis, and necrosis of blood vessels leading to further tissue necrosis. Consequently, compromised blood flow limits the effectiveness of intravenous antibiotic therapy. NSTIs frequently spread along fascial or subcutaneous planes where perfusion is less (compared with muscle). This allows for rapid progression of the infection despite potentially limited skin changes/manifestations. Furthermore, hematogenous spread of infection along with remote release of toxins and cytokines result in sepsis, multiorgan system failure, and death.

From a microbiologic standpoint, NSTIs are mainly distinguished by whether the infection is polymicrobial (type I) or monomicrobial (type II). Type I NSTIs are frequently seen in those with comorbidities and in the elderly. Gram-positive cocci, gram-negative rods, and anaerobes are the most frequent isolates including group A *Streptococcus*, *Staphylococcus aureus*, *Escherichia coli*, and clostridial species. Type II infections, in contrast to type I infections, are more indiscriminate and may affect any age group regardless of comorbidities. Type II NSTIs are frequently caused by group A *Streptococcus* or *Staphylococcus* aureus. A new and distinct type III NSTI has been proposed for *Vibrio* vulnificus and *Aeromonas* hydrophila, following exposure of seawater to wounds, but this has not reached widespread acceptance.

DIAGNOSIS

Early diagnosis and treatment of an NSTI is critical and a major factor determining outcome. NSTIs most commonly affect the extremities or perineum but can also originate from the trunk and head/neck. Additionally, noncontiguous multifocal NSTIs have been reported in the literature but are exceedingly rare.

A high index of suspicion must be maintained as NSTIs are uncommon and can present with a wide array of symptoms that are frequently nonspecific and may be confused with cellulitis. Pain out of proportion to examination (which may progress to tissues becoming insensate as the tissue dies), erythematous changes, blistering, fluctuance, and swelling/induration are frequently seen. A globally toxic-appearing patient (e.g., fever, tachycardia, diaphoresis), rapid progression of skin changes including necrotic skin and ecchymotic bullae, as well as crepitus are potential clues to distinguish NSTI.

As the disease course progresses, laboratory derangements are frequently seen. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score (Table 1) can help predict the likelihood of NSTI based on white blood cell count, creatinine, hemoglobin, sodium glucose, and C-reactive protein levels. Importantly, a low LRINEC score does not exclude or rule out NSTI.

Imaging including x-ray and computed tomography may assist in identifying crepitus as well as better defining the extent of disease, but it is not an essential part of establishing the diagnosis. In fact, obtaining imaging after concern for NSTI has been raised may lead to worse outcomes secondary to delaying treatment including operative intervention.

Once sufficient clinical suspicion has been established, emergent operative exploration is warranted to establish the diagnosis. This may be performed at the bedside using local anesthesia or in the operating room. Exploration must include the underlying subcutaneous tissues and fascial planes. NSTIs frequently demonstrate turbid/greyish (dishwater) foul-smelling fluid, subcutaneous tissue that bleeds minimally/not at all, as well as tissue that is easily bluntly dissected from the fascia. A negative exploration rate in cases for suspected NSTI has been reported as high has 21%; however, some cases with initial negative explorations subsequently progressed to NSTI.

TREATMENT

Once definitive diagnosis has been established, further surgical debridement must be performed (Figs. 1 to 3). Source control is imperative, frequently resulting in extensive resection of soft tissue. Debridement should be performed until healthy tissue is encountered at the wound margins. Large, extensive wounds and soft tissue defects will result that are frequently much greater than initially evident skin changes. Amputations may be indicated during the initial or subsequent operative trips secondary to extensive resection of entire muscle groups or resections rendering limbs nonfunctional. Temporary dressings should be placed with plans for short interval reassessment as additional debridement can frequently be indicated.

In conjunction with surgical debridement, broad-spectrum antibiotics should be initiated. Cultures in the operating room should be

TABLE 1 Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC)

Parameter	Range	Score
Hb (g/dL)	>13.5	0
	11–13.5	1
	<11	2
White cells (10^9/L)	<15k	0
	15–25k	1
	>25k	2
Sodium (mmol/L)	>135	2
Creatinine (mg/dL)	>1.6	2
Glucose (mg/dL)	>180	1
C-reactive protein (mg/dL)	>150	4

Risk category: low < 5 (<50% chance NSTI), intermediate 5–7 (50%–75% chance NSTI), high >7 (>75% chance NSTI)



FIG. 1 (A) Erythematous, edematous, bullae with skin sloughing, and necrotic tissue of the perineum, scrotum, penis, thigh, and abdominal wall. **(B)** Extensive debridement required to achieve source control. *(From Joury A, Mahendra A, Alshehri M, Downing A. Extensive necrotizing fasciitis from Fournier's gangrene.* Urol Case Rep. *2019;26:100943.)*



FIG. 2 (A) A man presenting with skin changes including ecchymotic bullae over his left upper extremity, chest, and flank. **(B)** Extensive soft tissue debridement required to achieve source control. **(C** and **D)** Postoperative follow-up after reconstruction with an omental flap and split thickness skin grafting. *(From Gürlek A, Firat C, Oztürk AE, Alaybeyoğlu N, Fariz A, Aslan S. Management of necrotizing fasciitis in diabetic patients.* J Diabetes Complications. *2007;21:265–71.)*

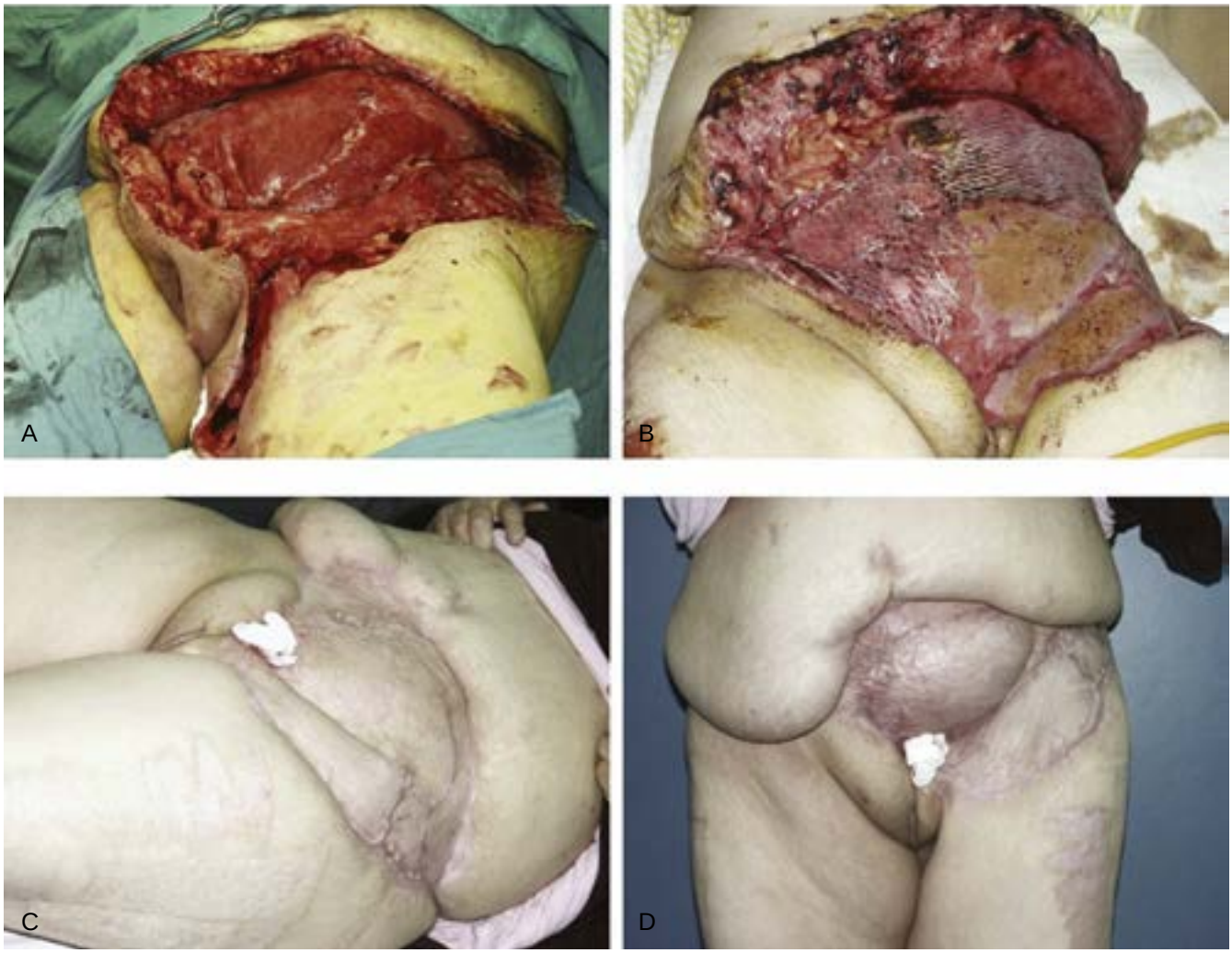


FIG. 3 **(A)** 50-year-old woman presented with NSTI and underwent extensive debridement of the abdominovulvoperineal area. **(B)** The wound was subsequently skin grafted. **(C** and **D)** Results 4 months postoperatively. *(From Gürlek A, Firat C, Oztürk AE, Alaybeyoğlu N, Fariz A, Aslan S. Management of necrotizing fasciitis in diabetic patients.* J Diabetes Complications. *2007;21:265–71.)*

obtained and antibiotic regimen tailored once speciation and susceptibilities are available. Initially, however, broad coverage including gram-positive cocci, gram-negative rods, and anaerobes are recommended. Common regimens include a carbapenem (imipenem, meropenem, or ertapenem) or piperacillin-tazobactam, in addition to an antibiotic with activity against methicillin-resistant *Staphylococcus aureus* (vancomycin or daptomycin). Clindamycin should also be added as it has been shown to decrease expression and production of virulence factors and exotoxins from group A *Streptococcus*.

Adjuvant therapy with intravenous immunoglobulin (IVIG) may be beneficial in those with *Streptococcal* NSTI with associated toxic shock syndrome. IVIG is thought to neutralize *Streptococcal* superantigens and enhance bacterial clearance.

The utility of hyperbaric oxygen in treatment (HBOT) of NSTI remains unclear secondary to a lack of high-quality evidence but may result in improved mortality and limb salvage. Importantly, the use of HBOT should be postponed until source control has been achieved and the patient stabilized.

Patients diagnosed with NSTI should continue their care postdebridement in the intensive care unit. These patients are often profoundly critically ill and require substantial ongoing resuscitation. Any clinical deterioration should prompt earlier return to the operating room to assess for inadequate source control.

Many patients require serial operative trips to acquire source control, and then additional subsequent operative trips to appropriately perform wound care followed by potential reconstruction. Vacuum-assisted closure dressings are frequently implemented to encourage wound healing and granulation, as well as having a practical advantage with regard to wound care type and frequency. Some wounds, in particular perineal wounds, are quite extensive, and wound care becomes problematic with regards to fecal contamination. Once the patient has stabilized, a diverting loop colostomy may be indicated. Perineal and scrotal involvement may necessitate transposition of the testes into pockets of the medial thighs. Surgical castration is rarely necessary. Further reconstruction with skin grafting, rotational flaps, or free tissue transfer may be warranted, and involvement/comanagement with plastic surgery is advised.

CONCLUSION

NSTIs represent a rapidly progressive and highly morbid disease process with a multitude of presentations. A high index of suspicion combined with early diagnosis and prompt aggressive treatment (primarily surgical source control, as well as intravenous antibiotics) are the cornerstones of successful outcomes.

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Management of Spontaneous and Secondary Pneumothorax

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PNEUMOTHORAX

Spontaneous pneumothorax is described as a pneumothorax that occurs in the absence of trauma or significant lung disease. Secondary pneumothorax occurs in the setting of significant underlying lung disease, which predisposes the patient to a pneumothorax. Air in the pleural space typically occurs because of a communication between the lung or the tracheobronchial tree, although it can also occur due to trauma, a significant esophageal rupture, or most rarely a gas-producing organism. As a result of a pneumothorax, there is a decrease in vital capacity of the lung and potentially a decrease in the PaO_2 depending upon the degree of pneumothorax. In young healthy people, this is typically very well-tolerated, but in patients with underlying cardiopulmonary disease, it can be quite physiologically significant. The time required to absorb all gases and the pneumothorax is thought to vary between 1% and 5% in 24 hours. The rate of resorption depends upon most importantly the gas present. Oxygen is absorbed about 60 times faster than nitrogen, whereas carbon dioxide is absorbed about 20 times faster than oxygen. This principal underlies the rationale for temporary administration of supplemental oxygen to patients with a pneumothorax to hasten resorption of the pneumothorax.

Primary Spontaneous Pneumothorax

Spontaneous pneumothorax is more common in men than in women. The classic characteristic profile is a young, tall, thin man in the second to fourth decade of life. The incidence is approximately 10 per 100,000 population in men and 3 per 100,000 and women. Cigarette smoking also increases the risk of a spontaneous pneumothorax approximately 10- to 20-fold, and the risk increases with the number of cigarettes smoked. The etiology of spontaneous pneumothorax is thought to be rupture of a subpleural bleb and are typically found at CT imaging or surgery in about 80% of patients (Fig. 1). The rate of recurrence after a primary spontaneous pneumothorax is about 25% and is usually within the first or second year after the first episode. The rate of recurrence does increase after each subsequent pneumothorax. Commonly quoted risks are 50% to 60% after the second pneumothorax and even higher after the third. Although the majority of patients have small blebs bilaterally, the risk of contralateral pneumothorax is typically quite low, around 10%.

Secondary Pneumothorax

Secondary pneumothorax occurs in patients with underlying lung disease, and this can cause more serious physiologic embarrassment of the patient. The incidence is fairly similar to primary spontaneous pneumothorax. Importantly, however, patients are typically 15 to 20 years older than patients with primary spontaneous pneumothorax largely due to a large number of patients with emphysema (Fig. 2). The risk of recurrence of a pneumothorax with underlying disease is higher than in spontaneous pneumothorax. A large number of potential lung diseases are associated with secondary spontaneous pneumothorax, but of course the most common is chronic obstructive pulmonary disease (Box 1). Although death is extremely rare with primary spontaneous pneumothorax, it is not uncommon for patients with secondary pneumothorax to die because of the underlying significant lung disease. Cystic fibrosis is probably the next most common cause of secondary pneumothorax, typically represents advanced disease, and is a marker of poor prognosis.

CLINICAL PRESENTATION

The most common symptom with a pneumothorax is localized sharp pleuritic chest pain, which is usually sudden in onset. This can be associated with dyspnea. Occasionally, a dry cough is present, and patients are rarely asymptomatic. Spontaneous pneumothorax typically occurs in the absence of any significant strenuous exercise or maneuvers that would increase airway pressures. Small to moderate pneumothoraces are typically not identified on physical examination by auscultation. Decreased breath sounds and percussion hyperresonance are occasionally present and can be confused with emphysema. Rarely, subcutaneous emphysema will be palpable in the neck or chest wall. Typically vital signs are normal, but tachycardia may be present in part due to anxiety; severe tachycardia and hypotension and tracheal deviation suggest a tension pneumothorax. If arterial blood gases are done, they may show mild hypoxemia and hypocarbia from hyperventilation.

IMAGING

Typically, a patient with a clinical presentation that suggests a pneumothorax has a chest x-ray performed that will demonstrate a pneumothorax and allow estimation of the severity (Fig. 3). If an initial inspiratory film is negative and the clinical suspicion is high, an expiratory film can be done. Of course, gas tends to collect at the apex with erect posture, whereas supine patients have gas collect anteriorly and the air may be harder to see if the amount is small.



FIG. 1 An apical bleb encountered at a video-assisted thoracoscopic exploration in a patient with a recurrent spontaneous pneumothorax.



FIG. 2 Axial CT scan of a patient with emphysema (*left arrow*) demonstrating a large bleb protruding from the right upper lobe and displacing the mediastinum *(right arrow)*.

Pleural lines need to be carefully sought for, and artifacts need to be excluded such as the edge of the scapula, a skin fold, or clothing. Although there are nomograms to estimate the size of a pneumothorax, most clinicians make a rough guess based on the amount of air in the apex and laterally. A tension pneumothorax is suggested by shift of the mediastinum away from the pneumothorax, depression of the diaphragm, and expansion of the rib spaces.

Lung ultrasound is increasingly being used in the emergency room department for rapid diagnosis of a pneumothorax. It is obviously user dependent. Although most commonly used in trauma patients, it is also useful in patients with spontaneous or secondary pneumothorax. In an experienced user's hands, lung ultrasound is more sensitive than a chest x-ray. Normal lung ultrasound findings including lung sliding with breathing and a granular pattern of aerated lung under the hyperechoic plural line in M mode (Video 1 and Fig. 4). A pneumothorax is detected by the absence of lung sliding and the loss of the granular pattern in the lung under the pleural line in M mode (Video 2 and Fig. 5).

BOX 1 Etiology of Secondary Pneumothorax

Obstructive Lung Disease

COPD and asthma
Infection tuberculosis
Coccidiomycosis
Pneumocystis jiroveci
Various bacterial pneumonias

Interstitial Lung Disease

Usual interstitial pneumonitis
Lymphangioleiomyomatosis
Sarcoidosis

Malignancy

Lung cancer
Lung metastases (especially sarcoma)

Connective Tissue Disease

Marfan syndrome
Ehlers-Danlos syndrome
Rheumatoid arthritis

Other Causes

Catamenial pneumothorax
Pulmonary alveolar proteinosis
Pulmonary embolism with infarction

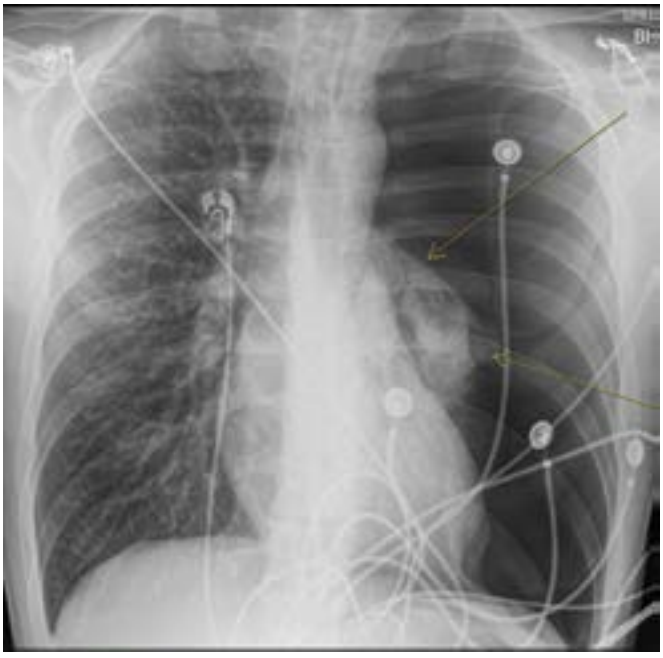


FIG. 3 Chest x-ray demonstrates a large left pneumothorax with complete collapse of the lung and evidence of mild tension with shift of the mediastinum and slight depression of the diaphragm in a patient with a spontaneous pneumothorax.

Computed Tomography

CT scans are now commonly performed in the emergency department when evaluating patients with pneumothoraces. Any underlying lung pathology will be quickly identified, and blebs typically at the apex of the upper lobes can be readily identified. It is not uncommon for a CT scan to identify a pneumothorax that was not seen on a plain chest x-ray, especially in the supine patient. CT scans are most

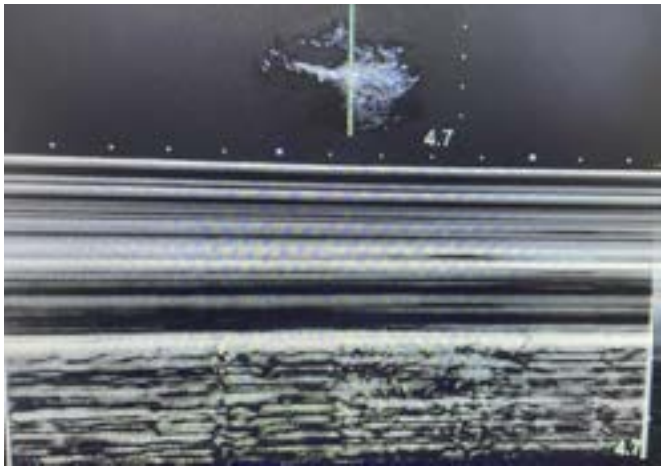


FIG. 4 Normal lung in M mode ultrasound. The small image at top illustrates the sample line along which the movement of tissues is recorded and displayed below. The chest wall demonstrates a series of horizontal lines. The white hyperechoic line is the pleura, and the aerated lung is somewhat granular below.

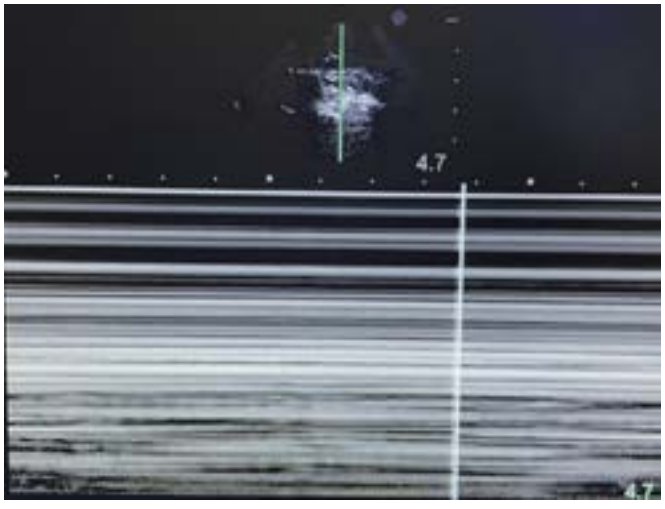


FIG. 5 Pneumothorax in M mode. The separation of the visceral and parietal pleura results in the loss of granular pattern of normal lung. A series of horizontal lines under the pleura are seen instead, also known as the "bar code" sign.

helpful in patients with secondary pneumothoraxes where there is a loculated pneumothorax from areas of pleural symphysis that make it extremely challenging to place non–image-guided catheters to drain the pneumothorax and reexpand the lung.

MANAGEMENT OF PNEUMOTHORAX

Although treatment of a pneumothorax is seemingly simple (i.e., placement of a drainage catheter), there are nuances to the management. Factors that weigh into treatment include the size of the pneumothorax, the timing of the presentation of the pneumothorax, the symptoms of the patient, whether it is a primary spontaneous or secondary pneumothorax, and the social aspects of the patient.

Observation

Although observation is rarely used in patients with secondary pneumothorax, occasionally healthy patients with spontaneous pneumothorax can be observed as an outpatient or with a brief stay in the emergency room observation area. Patients have to be reliable, have good social support, and be relatively close to an emergency room to be safely observed as an outpatient. The most important aspect of this management is that the patient has a history of a period of self-observation at home where the pain and dyspnea happened perhaps one to several days ago before presenting to the emergency department with a small, now relatively asymptomatic pneumothorax. They have already undergone a period of observation. And clinically it appears that the small leak from the lung has sealed since the pneumothorax has remained small. These patients, if reliable, can be sent home from the emergency department and be seen within the next day or two in the physician's office for a follow-up x-ray. Obviously if they develop a symptomatic pneumothorax, they are instructed to immediately return to the emergency room for treatment.

Aspiration

Aspiration is a controversial management strategy for a spontaneous pneumothorax. It is essentially never done with secondary pneumothorax. Aspiration does require a period of observation for at least several hours in the emergency department with repeat x-rays before discharge and thus does tie up resources in busy emergency rooms. It is most appropriate for patients who really want to avoid hospital admission with placement of a drainage catheter and again are reliable, well-supported patients. It is helpful if there has been at least some period of the patient tolerating the symptoms of pneumothorax before presentation to the emergency room, which presumably suggests that the air leak has sealed. A chest x-ray should confirm a sizable collection of air in the apex of the chest such that introduction of the intravenous catheter does not injure the anterior surface of the lung when inserted. Typically a 16-gauge or 18-gauge intravenous catheter is inserted after local anesthesia is used in the second interspace costal space anteriorly with a three-way stopcock and a large syringe. The metal inner needle cannula is removed as soon as air is aspirated to avoid injury to the underlying lung. Air is then aspirated through the plastic cannula until no further air can be aspirated. The patient is then observed for a period of several hours and a repeat x-ray done. If there is no recurrence, the patient is discharged again with a follow-up x-ray in 1 to 2 days and instructions to return immediately to the emergency room if symptoms recur. The patient should be seen in the office in a few days.

Tube Drainage

The classic treatment of the pneumothorax has been the surgical placement of the tube thoracostomy catheter. This is typically done as a bedside procedure with a thoracostomy tray for instrumentation. It can be a painful procedure, and often it is helpful to provide mild sedation with intravenous narcotics and/or benzodiazepines. The typical placement location recognizes that the chest wall muscle configuration allows placement through the least muscle possible below the axilla, between the anterior and posterior axillary lines, which mark the pectoralis muscle anteriorly and the latissimus muscle posteriorly. Typically, the tube is then placed through slips of the serratus muscle, which is thinner.

The area is widely prepped and draped in a sterile fashion. Typically 1% Xylocaine plain local anesthesia is used. Knowledge of the intercostal bundle and its relationship to the undersurface of the rib is important to avoid injury to the intercostal artery or vein. Accordingly, the pleural space is entered on top of the rib, which minimizes the chance of injury to these vessels that lie at the bottom of each rib. After a skin wheal is made, a small transverse incision is made that is at least as large as the catheter that is going to be placed. Additional local anesthesia is then given through this incision to the underlying soft tissue, the rib, and the interspace that is going to be used. The rib is then palpated with a finger to ensure that the surgeon is placing the

instrument just on top of the underlying rib. The rib is then palpated with a surgical clamp, typically a Kelly clamp, and once the top of the rib is found, controlled pressure on the clamp is used to enter the pleural space. The clamp is then spread to widen the passageway before the tube is placed. Thereafter, a clamp is used to squeeze and narrow the end of the chest tube; this is placed into the pleural space, and an attempt is made to thread the catheter apically. A technique of ballottement is often used to facilitate placement in the apex as the chest tube can hang up on the fissure of the lung, an osteophyte, or a rib. The surgeon should have a rough indication as to how far the tube should be inserted to reach the apex and should attempt to insert it to that distance. The tube is then connected to a pleural drainage device. The tube is then secured with heavy sutures to prevent dislodgment, and a dry sterile dressing is applied. Vaseline gauze is not used as that can promote infection. Typically, the tube is placed to suction if the pneumothorax was small, but with large pneumothorax it is often helpful to place it to waterseal for a period of time to allow slower lung expansion and avoid the phenomenon of reexpansion pulmonary edema, which is rarely seen. The reexpansion of a significantly shrunken lung often leads to paroxysms of coughing and pain, which the surgeon needs to talk the patient through. The coughing goes away once the lung is totally reexpanded. A chest x-ray is then performed to confirm the position of the chest tube and that the evacuation of the pneumothorax was appropriate. The patient is then monitored for air leakage, and subsequent chest x-rays are done as clinically appropriate. There are some chest tube insertion kits that come with a trocar insertion device. Care must be used when using a trocar technique to avoid inadvertent injury to the heart or lung. These are safe if there is a large pneumothorax and a significant air gap between the lung edge and ribs. If there is any pleural symphysis at the insertion point, lung injury will occur. Alternatively, there are some chest tube insertion kits that have a plastic insertion device that hooks onto the tip of the chest tube and can facilitate chest tube placement with much less possibility of damage to the lung.

In recent years, the numbers of tube thoracostomies have fallen off as the insertion of much smaller catheters that use the Seldinger technique have become very popular (Fig. 6). These catheters were first used many years ago by our interventional radiology colleagues and now have been widely used in emergency rooms, intensive care units, and at the bedside for less invasive chest drainage. The catheters themselves typically have a pigtail shape at the end once the insertion stylette is removed. These catheters are softer and smaller than typical chest tubes and cause less patient discomfort. As long as there is a significant pneumothorax, they are easy to insert. The disadvantage of these catheters is that they have very small diameter, are more easily kinked, and the small holes within the chest can become clogged with serum or blood. Furthermore, if there is a very large air leak, they may not be large enough to adequately evacuate the pleural space. However for most patients with a spontaneous pneumothorax, they are more than adequate.

The insertion technique mirrors that of open tube thoracostomy. A sterile field is created, local anesthesia is used, and the needle for the local anesthesia is aspirated for air once it enters the pleural space to confirm a pneumothorax is present, which is amenable to pigtail catheter placement. A guidewire is then passed through the needle, which has a soft flexible tip. A stiff dilator is then typically passed over the wire to slightly widen the insertion site, and then the dilator is carefully removed leaving the wire in place. Thereafter, the catheter is threaded onto the guidewire and advanced into the chest toward the apex. The catheter is then secured with a suture, a dry sterile dressing is applied, and the catheter is attached to a pleural drainage system. The catheter generally should be placed in a similar position as a tube thoracostomy. In men with relatively thin chest walls and an apical pneumothorax, they may be placed in the second intercostal space anteriorly in the midclavicular line. In general, we do not utilize this access point for a woman as it can cause unsightly scarring to the breast area.

The use of these small, less invasive pigtail catheters has led to an increased treatment of spontaneous pneumothorax in appropriate patients as an outpatient. The catheters can be hooked up to a Heimlich valve, a very small drainage collection receptacle that also has a one-way valve, or a small portable complete pleural drainage system that can be attached to a shoulder strap. The patients can then be discharged from the emergency room and seen in the office for follow-up in a couple of days at which time air leaks have usually sealed. An x-ray should have confirmed that the pneumothorax has resolved after pigtail placement, and obviously the patient must be carefully selected so they can safely manage such a device at home.



FIG. 6 Chest x-ray demonstrates a well-placed apical left pigtail chest tube catheter to reexpand the lung after a spontaneous pneumothorax.

Chemical Pleurodesis

The goal of the pleurodesis is to cause significant adhesions between the visceral and parietal pleura to obliterate the pleural space. This can seal an ongoing air leak or prevent future pneumothoraxes if the area of pleural symphysis is where a ruptured bleb occurs. Chemical pleurodesis is uncommonly performed for first-time spontaneous pneumothoraces. Chemical pleurodesis is typically performed for recurrent, difficult to control pneumothoraces, especially after a previous operative intervention. Bedside pleurodesis is much more commonly performed with secondary pneumothoraces to avoid operative intervention in patients at high risk for an operative procedure. Typically, a doxycycline solution (500 mg to 1 g) or a sterile talc slurry (4–5 g) is used for bedside pleurodesis. Talc is more effective than doxycycline at creating a pleural symphysis, but there are some concerns about using talc in young people with a spontaneous pneumothorax. Previous versions of talc were not guaranteed to be asbestos-free raising concern for late mesothelioma. However current versions of FDA-approved talc are asbestos-free. In addition, the symphysis caused by talc is usually quite strong, and if the patient was ever to need another thoracic operation, it makes that subsequent operation much more difficult because of the severe adhesions. Obviously, this is a relatively uncommon scenario. Pleurodesis with either these agents typically cause a fair degree of pleuritic chest pain, and the patient should be cautioned about this and pain medicine

made available for patient comfort. For pleurodesis to work, obviously there should be relatively complete apposition of the visceral and parietal pleura such that adhesions can form. If the patient has an ongoing air leak, the chest tube drainage system should not be clamped to allow pleurodesis to occur as this could lead to a tension pneumothorax. Typically, after sterilely prepping the drainage system tubing close to the chest tube insertion point, a needle is passed obliquely through the tubing such that it will seal quickly when the needle is removed. A large syringe is then used to inject the sclerosing solution, the needle is withdrawn, and then a clear plastic self-adherent dressing is placed over the insertion point to make sure that is sealed. If the patient has no air leak, the chest tube can be clamped to allow the solution to remain in the chest for 1 to 2 hours. If the patient has an ongoing air leak, the chest tube drainage tubing system can be hooked around an IV pole such that the solution remains in the chest once the injection is complete. There are rare cases of ARDS after talc is used related to both a very small particle size as well as doses over 5 g. For that reason, the typical adult dose is 4 to 5 g of talc. The chest drainage system is then placed on suction, typically for 1 to 2 days at a minimum, to ensure maximum pleural apposition to obtain the best possible pleurodesis.

Video-Assisted Thoracic Surgery

The advent of minimally invasive surgery for the chest, video-assisted thoracic surgery (VATS), has lowered the threshold for operative intervention for a pneumothorax. The indications for operative intervention are not particularly firm. The clearest indication for operative therapy is a recurrent pneumothorax, a patient with a first-time spontaneous pneumothorax with an ongoing air leak after 2 to 3 days, or the rare patient with a bilateral pneumothorax. Other indications include patients who present with a tension pneumothorax; patients with an identified large bleb; or patients with lifestyle issues such as pilots, scuba divers, or people who travel to areas without access to good medical care. Some patients elect to have operative intervention during the first hospital admission given the recurrence rate, which approaches about one-third, to reduce the chance of a recurrence.

VATS is typically performed under general anesthesia with three small incisions: one for the camera and the other ports for a stapler and forceps. It is, however, possible to do VATS under local anesthesia with sedation in thin, appropriately selected, compliant patients. In addition, uniportal VATS is certainly possible with a slightly larger main incision with this relatively simple surgical procedure. The lung is carefully explored, concentrating on the apex of the upper lobe and the tip of the superior segment of the lower lobe, which is where most blebs occur. Blebs are then typically stapled off with an endoscopic stapler. Most surgeons perform some sort of mechanical pleurodesis with a small gauze sponge, an electrocautery scratchpad, or with an energy device such as an argon beam coagulator. Alternatively, for high-risk patients, an apical pleurectomy is sometimes done, which is the most effective operative pleurodesis technique. However, this comes at the cost of longer operative times, increased risk of bleeding, and a slight risk of injury to adjacent structures such as the intercostal bundle or the stellate ganglion. A drainage catheter is placed after the procedure, and most patients can be discharged in 1 or 2 days. In patients with severe chronic obstructive pulmonary disease (COPD) who are being operated on, there can be significant leakage from the poor-quality lung at the staple line; these can be reinforced with commercially available buttressed staple loads or sealed with commercially available lung sealants. Talc pleurodesis is often used in patients with a secondary pneumothorax secondary to COPD to minimize the chance of recurrence.

Suggested Readings

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Management of Primary Chest Wall Tumors

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OVERVIEW

A chest wall mass may represent any one of a broad spectrum of entities including benign or malignant primary chest wall tumors; locally invasive tumors originating from the lungs, pleura, mediastinum, or breast; metastatic lesions; and non-neoplastic (infectious or inflammatory) lesions. Of these, primary chest wall tumors, whether benign or malignant, are the least common; they comprise only 5% of all thoracic neoplasms. This creates a diagnostic challenge for surgeons as more commonly seen metastatic lesions must be ruled out. Primary chest wall tumors are best classified according to their tissue of origin and are further subdivided as either benign or bearing malignant potential. In this chapter, we review the most common primary chest wall tumors and focus on surgical management options, including chest wall resection and reconstruction. A list of benign and malignant primary chest wall tumors is provided in Box 1.

DIAGNOSIS

The vast majority of patients with primary chest wall tumors present with a painless, enlarging mass. Other patients who are entirely asymptomatic may have a primary chest wall tumor detected with thoracic imaging studies performed for unrelated indications. Pain in a patient with a primary chest wall tumor likely represents bony erosion or involvement of adjacent nerves, and it is often a harbinger of malignant tumor behavior. Workup includes a history and physical examination, with attention directed to a history of other malignancies, radiation exposure (therapeutic or environmental), and overt signs of infection or inflammation on physical examination.

A plain film chest radiograph may reveal a soft tissue or bony abnormality. Contrast-enhanced thoracic CT can help delineate the extent of bony, soft tissue, pleural, lung, or mediastinal involvement and can also exclude nodal or pulmonary metastatic disease. Contrast-enhanced MRI can help delineate vascular or

BOX 1 Primary Chest Wall Tumors

Benign

Chondroma
Fibrous dysplasia
Osteochondroma
Lipoma
  Fibroma
  Neurilemmoma
Eosinophilic granuloma
Aneurysmal bone cyst
Osteoid osteoma
Osteoblastoma
Giant cell tumor

Malignant

Chondrosarcoma
Osteosarcoma
Liposarcoma
Malignant fibrous histiocytoma
Rhabdomyosarcoma
Angiosarcoma
Fibrosarcoma
Neurofibrosarcoma
Ewing sarcoma, primitive neuroectodermal tumor (PNET), small round blue cell tumor
Plasmacytoma

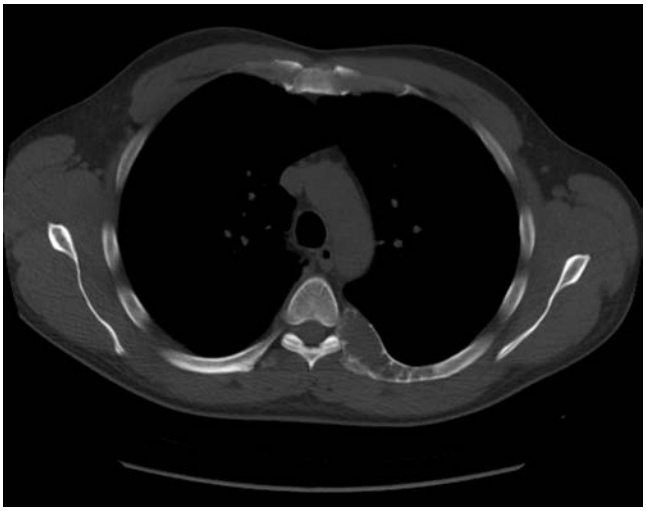


FIG. 1 Chest CT demonstrating fibrous dysplasia of the posterior left sixth rib.

nerve involvement. A freely mobile mass less than 2 cm in size can generally be excised with clear margins, with both diagnostic and therapeutic intent. In contrast, larger lesions or those that are fixed to the underlying bone or soft tissue should undergo core needle biopsy or open incisional biopsy before definitive resection. Care must be taken to plan these biopsies with a subsequent curative resection in mind, with incisions placed appropriately so as not to preclude subsequent complete resection as indicated. Tissue diagnosis before surgical resection can help exclude infectious or inflammatory lesions for which resection may not be indicated, and it may allow for neoadjuvant radiation or chemotherapy, when appropriate, if the lesion is malignant.

CHEST WALL NEOPLASMS

Benign Bony and Cartilaginous Tumors

Fibrous Dysplasia

The most common benign bony tumor of the chest wall, fibrous dysplasia represents a lesion in which normal marrow and cancellous bone is replaced with a fibrous stroma (Fig. 1). It typically presents as a painless mass of the rib, commonly located posteriorly or laterally on the chest wall. Radiographic findings are variable but often include a central ground-glass appearance with punctate calcifications and peripheral cortical thinning. These tumors most commonly present as a solitary lesion in otherwise healthy individuals 20 to 30 years of age. They can, however, be multiple and are associated with McCune-Albright syndrome, which includes cutaneous manifestations and endocrine abnormalities in the context of short stature and precocious puberty. Surgical therapy is only indicated if the diagnosis is in doubt or if the lesion is symptomatic. In such cases, limited partial rib resection is the definitive treatment.

Osteochondroma

A benign bony lesion that typically presents in the third decade of life, an osteochondroma classically involves the costochondral junction. This lesion can present either as a small, palpable, painless mass or can grow to a larger size when unnoticed within the chest cavity. Punctate central calcifications with a mineralized hyaline cartilage are characteristic radiologic findings of osteochondroma. Observation with serial imaging is appropriate when lesions are small and asymptomatic. Symptomatic or enlarging lesions can be resected with local excision. Although malignant degeneration is rare (less than 1% of patients), resection should be considered if cartilage thickness exceeds 2 cm; malignant transformation to chondrosarcoma or osteosarcoma has been reported.

Chondroma

Chondromas are benign cartilaginous tumors that originate from the medullary cavity. They are more commonly found anteriorly in the rib and have no gender predilection. They present either as a painless mass or an incidentally documented lesion on imaging. On chest radiograph, chondromas are characteristically osteolytic lesions with well-defined sclerotic margins. On CT or MRI, punctate calcifications and cortical scalloping may be seen. These benign lesions are often difficult to differentiate from low-grade chondrosarcomas (both radiographically and histologically) and therefore should be resected with wide local excision.

Malignant Bony and Cartilaginous Tumors

Chondrosarcomas

Chondrosarcomas are the most common primary malignant chest wall tumor (Fig. 2). They occur most frequently in the fourth to seventh decades of life and are slightly more common in men than in women. They are typically located anteriorly and involve either the costochondral junction or the sternum. On imaging, irregular margins and bony destruction are typical. Early-stage lesions can retain a thickened cortical cap, whereas more advanced tumors progress to complete cortical destruction and an associated soft tissue mass. Suspected benign chondromas in which the cortical cap thickens over time may be in the process of malignant degeneration into chondrosarcoma. All suspected chondrosarcomas should undergo wide local excision; they often require chest wall reconstruction. Poor prognostic factors include hypercellularity, cytologic atypia, high mitotic index, and larger tumor size. High-grade tumors have a 75% chance of distant spread at the time of diagnosis. Because these tumors respond poorly to chemotherapy or radiation, complete surgical excision is the primary treatment modality. Studies demonstrate

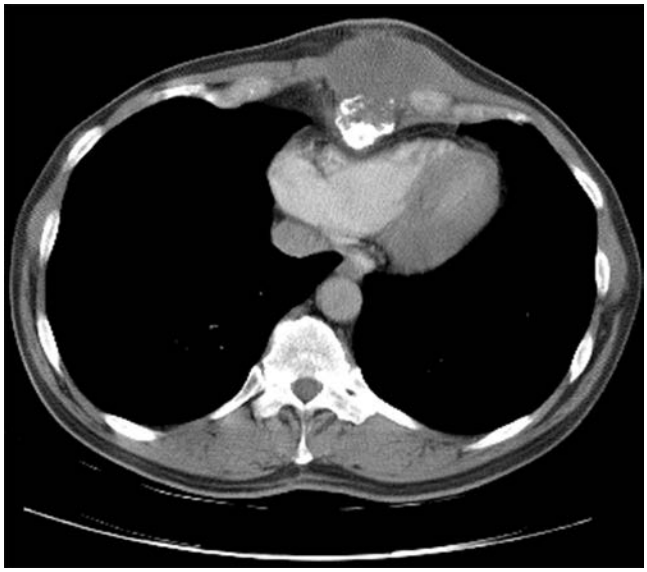


FIG. 2 Chest CT demonstrating a chondrosarcoma of the lower sternum and xyphoid.

that inadequate resection margins in chondrosarcoma are associated with significantly higher local recurrence and lower overall survival.

Osteosarcomas

Osteosarcomas of the chest wall have a bimodal presentation, with most cases occurring at puberty but with a secondary peak after 40 years of age. They present as a rapidly expanding mass and arise from the rib, scapula, or clavicle. Environmental factors (fluoride exposure, farmworkers) and genetic predisposition (young age at puberty, familial history, retinoblastoma, Li Fraumeni syndrome) increase the lifetime risk of development of osteosarcoma. Radiographic findings include bony destruction with an associated large, heterogeneous mass composed of necrotic tumor and hemorrhage and often punctate calcification. Because distant metastasis (typically to the lung) is common and good systemic options for therapy exist, complete staging with PET/CT imaging and biopsy for tissue confirmation is indicated for suspected osteosarcoma. Induction chemotherapy followed by surgical resection (wide local excision with reconstruction as needed) is the treatment of choice for localized disease. Overall 5-year survival rates have increased to 60% when the osteosarcoma is localized but remains below 30% in patients with distant metastases.

Ewing Sarcomas and Askin Tumors

Ewing sarcomas and primitive neuroectodermal tumors (PNETs), also known as Askin tumors, are malignant, small, round cell tumors with genetic translocation between chromosomes 11 and 12. They typically occur in children and young adults and are almost exclusively seen in Caucasians. Around 15% of Ewing sarcomas and up to 5% of PNETs arise in the chest wall and can involve a single rib, clavicle, or the scapula, in descending frequency. They often present as a painful enlarging chest mass with constitutional symptoms that include fever, weight loss, and generalized malaise. Associated pleural effusions are also common. Radiographic findings include a large, noncalcified mass with bony destruction. As with osteosarcomas, systemic disease at diagnosis is frequent and staging with PET/CT and consideration of neoadjuvant systemic therapy followed by complete surgical resection and chest wall reconstruction is warranted. Postoperative radiation should be reserved for a margin-positive resection. Bilateral whole-lung irradiation may be used in the adjuvant setting to increase event-free survival in patients with documented pulmonary metastases. Overall 5-year survival rates for Ewing sarcoma can approach 70%, whereas for PNETs, long-term survival remains about 30%.

Solitary Plasmacytomas

Plasmacytomas tend to occur in men in their 60s and 70s and present with pain, typically without a palpable mass. Imaging documents a punched-out osteolytic lesion of the bone. The role of surgery in these patients is generally limited to obtaining tissue for histologic diagnosis. After tissue diagnosis is confirmed, local therapy with radiation is indicated. Up to two-thirds of patients will develop systemic involvement with multiple myeloma, which carries a 5-year survival rate around 35%. However, solitary plasmacytomas that are successfully irradiated and do not progress to systemic multiple myeloma have an excellent long-term prognosis, with over 90% 5-year survival. Surgical resection as local therapy for isolated disease can be indicated for patients in whom radiation therapy is not an option.

Benign Soft Tissue Tumors

Lipomas

Chest wall lipomas are typically larger and deeper than those soft tissue lipomas found in other anatomic locations. They are rarely symptomatic. Imaging reveals a homogenous mass consistent with mature fatty tissue. Resection is only indicated for symptomatic or enlarging lesions or for suspicion of a low-grade liposarcoma.

Fibromas (Desmoid Tumors) and Fibromatosis

Desmoid tumors arise from fibroblasts deep within the chest wall musculature and often occur in patients in their teenage years to early 30s. They present as a slowly growing, sometimes painful mass, often in the context of prior trauma or prior thoracotomy; they are also sometimes seen in the context of systemic fibromatosis (Gardner syndrome). Complete surgical resection with wide margins (up to 4 cm if possible) with chest wall reconstruction is the optimal therapy. Local recurrence rates are quite high; adjuvant radiation therapy can be used both prophylactically and in the context of microscopically positive margins. Recurrence rates for margin-positive disease remain as high as 90%, even with radiation therapy.

Hemangiomas

Hemangiomas of the chest wall are benign proliferations of blood vessels that form in the context of muscle, rib, or subcutaneous tissues. They are most typically seen in children, and MRI or ultrasound can be used to confirm the diagnosis. Resection is only indicated if symptoms develop; bleeding, ulceration, and (rarely) heart failure from arteriovenous malformation and shunting (cavernous hemangiomas) can occur. In these cases, local excision is curative, with chest wall reconstruction reserved for larger lesions.

Benign Peripheral Nerve Sheath Tumors

Chest wall schwannomas are encapsulated tumors that develop from intercostal nerves or thoracic spinal nerve roots. They are typically asymptomatic and identified incidentally during thoracic imaging. CT and/or MRI are usually sufficient for diagnosis and, in asymptomatic cases, serial imaging and observation suffice. Needle biopsy can be confirmatory in cases of diagnostic uncertainty. Resection is reserved for symptomatic or enlarging lesions and may require contiguous chest wall or vertebral body resection and reconstruction.

Malignant Soft Tissue Tumors

Malignant Fibrous Histiocytomas

Malignant fibrous histiocytoma (MFH) has a bimodal distribution at diagnosis, with peaks at 20 to 30 years of age and 50 to 60 years of age, with the latter being more prevalent. These tumors rarely arise

from the chest wall; when they do, they are generally associated with prior radiation exposure. Imaging reveals a heterogeneous mass with irregular borders; bony involvement is rare. A well-planned needle biopsy for tissue diagnosis is indicated for MFH with induction chemotherapy followed by surgical resection and reconstruction being the therapy of choice. Postoperative radiation can be reserved for margin-positive disease. Even with complete resection and systemic therapy, metastatic disease is common, and 5-year survival remains less than 50%.

Synovial Sarcomas

These malignant tumors rarely present as a primary chest wall malignancy, and the thoracic surgeon is more typically involved with the management of oligometastatic lung involvement from systemic disease. Nevertheless, primary synovial cell sarcomas of the chest wall can occur, typically in early adulthood. Imaging generally reveals a mass with heterogeneous foci resulting from necrosis or hemorrhage within cystic components, with about one-half of the tumors showing calcification. Treatment includes complete surgical resection, with chemotherapy or radiotherapy being utilized in either the neoadjuvant or adjuvant setting. Five-year survival remains around 50%, irrespective of the timing of chemoradiotherapy.

Rhabdomyosarcomas

Rare in adults, rhabdomyosarcomas are the second most common malignant primary chest wall tumor in children. As the vast majority of cases present with distant metastases, complete staging should be undertaken to determine which patients are candidates for primary site resection. Staging in children can include CT scan of the thorax, abdominal ultrasound, and bone scan, although PET/CT scans are being used increasingly in the pediatric population. Tissue confirmation is important because, when resectable, these aggressive tumors are treated with induction chemoradiation followed by wide local excision with chest wall reconstruction. Sometimes adjuvant chemotherapy or radiation are also indicated. Survival remains poor with surgical resection alone; however, trimodal therapy has resulted in a significant improvement in 5-year survival, with rates as high as 75% in patients without documented metastatic disease at the time of diagnosis.

SURGICAL TREATMENT OF CHEST WALL TUMORS

Chest Wall Resection

Surgical resection remains the mainstay of therapy for primary chest wall tumors, whether benign or malignant. Benign lesions should be resected to microscopically negative margins. Many malignant chest wall lesions have high recurrence rates; therefore, aggressive wide local excision with chest wall reconstruction as indicated is recommended. The general guidelines for planning surgical resection of primary chest wall tumors are as follows. Primary malignant tumors of the chest wall should be resected with a 4-cm margin. This margin has been shown to afford better long-term survival. Tumors arising from adjacent structures (most commonly lung cancers) should be resected to include the involved rib as well as the rib above and below the area of invasion. Metastatic lesions can generally be resected to microscopically clear margins, but only in carefully selected patients in whom the solitary chest wall metastasis is thought to be the only site of systemic disease.

Adequate oncologic resection is critical in the management of chest wall tumors, so surgical resection should not be compromised because of concern for the resulting skeletal defect. However, this means that initial planning for resection must also include a plan for reconstruction of the resulting defect to restore function and optimize cosmesis. Surgical planning for resection should begin at the time of original tissue diagnosis, with care taken to place biopsy incisions in areas that can be subsequently incorporated into wide local excisions. Therefore, involvement of the surgeon in planning therapy for these patients and collaboration with plastic and reconstructive surgeons as needed should occur early in the treatment course.

Chest Wall Reconstruction

The thorax is a rigid structure that protects the underlying viscera, supports the upper extremities and shoulder girdle, and allows for ventilation. Anatomic defects in the bony framework of the chest may result in exposure of vital structures to the external environment or alteration of chest wall mechanics that lead to subsequent paradoxical chest wall motion and ventilatory impairment. Large defects may result in lung herniation, contraction of the resected hemithorax, or scapular entrapment. The goals of reconstruction are to mitigate these alterations of the chest wall and the potential complications, while maintaining optimal cosmesis. More specifically, the primary goals of chest wall reconstruction are to restore chest wall rigidity and integrity to protect intrathoracic organs and maintain proper pulmonary mechanics, while minimizing deformity of anatomic chest wall structure and overlying soft tissues. No formal guidelines exist for skeletal reconstruction after chest wall resection, thus rendering surgical judgment essential. A multidisciplinary approach involving thoracic and plastic surgery teams as appropriate is crucial in obtaining optimal functional and aesthetic outcomes.

General Principles of Chest Wall Reconstruction

When planning chest wall reconstruction, the surgeon must take into account defect location, size, local tissue condition, and patient comorbidities. See Table 1 for an overview of the following general principles for chest wall reconstruction after tumor resection. Anterior and lateral defects of two consecutive ribs with a resultant defect less than 5 cm in size are generally well tolerated with no functional consequence. Anterior resections of the first to third ribs may be especially well tolerated without reconstruction because of support provided by the overlying pectoralis muscles. When more than three adjacent ribs in the anterolateral location are resected or the resulting defect is 5 cm or greater, the possibility of paradoxical chest wall motion and its associated complications arises, suggesting that reconstruction is necessary. This is especially true for anterolateral defects and full-thickness defects. Posterior defects can often tolerate up to twice the size of anterior and lateral defects because of overlying scapular support and back musculature, and they may be left without skeletal reconstruction if the defect is less than 10 cm in diameter. If the posterior rib defect encompasses the fourth, fifth, or sixth ribs, special attention must be paid to the location of the scapular tip because it may become entrapped within the chest wall.

TABLE 1 General Principles for Chest Wall Reconstruction

Characteristics of Chest Wall Defect	Reconstructive Principle
1–2 consecutive ribs and/or defects <5 cm	No specific reconstruction is required Cover with autologous tissue alone
≥3 ribs and/or defects >5 cm	Require chest wall stabilization with semirigid and/or rigid material
Apicoposterior defect (up to 10 cm) entirely beneath scapula	May not require reconstruction (scapula may prevent lung herniation)
Posterior resection involving fourth, fifth, or sixth rib(s)	Consider notching inferior rib, removing tip of scapula, or covering defect with mesh to prevent painful/dysfunctional entrapment of scapula

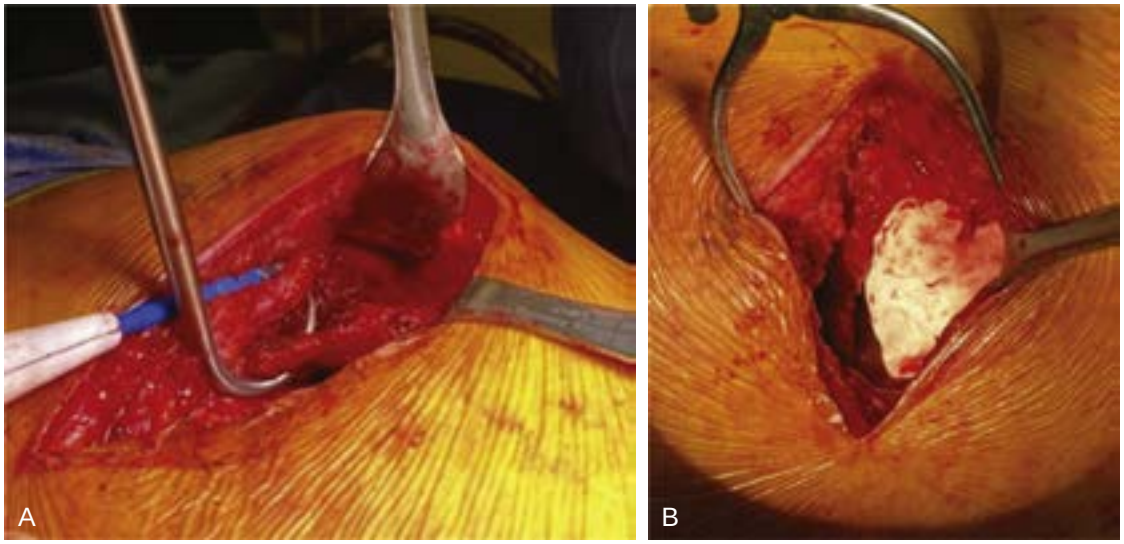


FIG. 3 A 64-year-old woman with a history of intermittent right scapular entrapment following prior chest wall resection. The surgical team used a bone hook to isolate the tip of the scapula and then resected the inferior component to prevent further impingement **(A).** Part of the fifth rib was also resected as this was identified as the rib causing entrapment on dynamic intraoperative manipulation of the shoulder. To prevent future impingement of the remaining scapula, the defect was covered by circumferentially securing polytetrafluoroethylene (PTFE) over the chest wall beneath the serratus anterior with interrupted 2-0 Prolene sutures **(B).**

In these cases, we recommend covering the defect with mesh (e.g., acellular dermal matrix [ADM], polytetrafluoroethylene [PTFE]) to prevent the scapular tip from entering the chest wall. Resection of the scapular tip and/or notching ribs adjacent to the scapular tip are also options to prevent entrapment (Fig. 3).

The author's practice is to reconstruct defects 4 cm or greater in size if pulmonary function is borderline, thus minimizing the chance of postoperative pulmonary insufficiency in these patients with marginal reserve. In patients who have dense underlying adhesions or pulmonary scarring from prior radiation or surgery, the authors may choose not to reconstruct defects larger than 5 cm as ventilation may not be affected. Tolerance for defect size also increases in the setting of infection as graft infection may develop. Finally, complete soft tissue coverage is imperative in all cases and varies greatly depending on defect size and location.

Options for Chest Wall Reconstruction

After the decision has been made to perform skeletal stabilization, a suitable graft option must be selected for both the bony defect and the overlying soft tissue coverage. The ideal materials for skeletal reconstruction provide strength and stability with acceptable cosmesis. Options for chest wall reconstruction include autogenous reconstruction (e.g., bone, fascia), bioprosthetic mesh (e.g., ADM), and synthetic materials (e.g., metals, plastics, synthetic mesh). The choice of which material to use depends on defect size, shape, and location; availability and cost of materials; patient comorbidities and pulmonary status; and surgeon preference.

Very large chest wall resections leading to severe skeletal destabilization requiring reconstruction with primarily rigid materials is quite uncommon. Synthetic rigid materials such as polymethylmethacrylate (PMMA) have largely fallen out of favor as they can cause significant pain and excessive chest wall rigidity, so they should be used judiciously in reconstruction. Semirigid materials such as ADM or PTFE are widely used for chest wall reconstruction as they provide initial stability until scar tissue envelops the materials over time, ultimately providing durable rigidity while allowing flexibility for chest wall movement. Semirigid materials can also be used in conjunction with rigid materials such as titanium struts to provide more stability in very large defects. PTFE is watertight and causes minimal foreign-body reaction, but it cannot be used in the setting of acute infection. One benefit of using ADM in chest wall reconstruction is its ability to withstand postoperative infections. Unlike infection involving synthetic mesh, ADM-adjacent infection can often be treated conservatively with antibiotics and ultimately salvaged. This is accomplished oftentimes with percutaneous drainage of the fluid collection, debridement of infected tissues, antibiotics, negative pressure wound therapy, and local wound care without ADM removal.

Again, complete soft tissue coverage is imperative regardless of defect size. Smaller defects may be closed primarily or covered by skin grafts or simple local advancement flaps (Table 2). Larger defects require coverage by more robust and richly vascularized autologous flaps such as pedicled myocutaneous flaps or free flaps to minimize the risk of graft exposure and infection. The latissimus dorsi flap is considered the workhorse in chest wall reconstruction as it has a robust blood supply and can cover the majority of the ipsilateral chest wall. Some patients with especially large defects may benefit from a combination of flaps, usually latissimus dorsi, pectoralis major, and/or omental flaps. Omental flaps lack musculocutaneous coverage but are an excellent option for eliminating dead space, and they can be used to cover intrathoracic structures or chest wall prostheses. Omental flaps are ideally passed into the thorax through a cruciate incision in the right hemidiaphragm, where the liver can help prevent herniation through the defect. Because the omentum is largely composed of fat, the size of the omental flap depends greatly on the patient's body habitus and may not be an option in malnourished or very thin individuals. Omental flaps can easily reach most areas of the thorax, but they require some sort of definitive soft tissue coverage. Patients who have undergone chest wall radiation may not be candidates for latissimus dorsi or pectoralis flaps if that tissue has been heavily irradiated because there is an increased risk of poor wound healing of both the donor site and flap as well as concern for decreased flap vascularity. Free flaps such as anterior lateral thigh (ATL), deep inferior epigastric perforator (DIEP), or tensor fascia lata (TFL) flaps are reserved for such patients in whom local flap options are not possible or have failed. While free flaps can provide excellent soft tissue coverage in these more complicated patients, one

TABLE 2 Flaps Used to Cover Thoracic Soft Tissue Defects After Chest Wall Resection

Type of Flap	Arterial Supply	Location of Defect
Latissimus dorsi	*Primary:* thoracodorsal *Secondary/turnover flap:* perforating vessels from posterior intercostal vessels/thoracolumbar perforators	Lateral, posterior, and anterior
Pectoralis major	*Primary:* thoracoacromial *Secondary/turnover flap:* internal mammary perforators	Anterior
Serratus anterior	Subscapular artery	Anterolateral Intrathoracic coverage
Rectus abdominis	Deep superior or inferior epigastric	Anterior (e.g., midline, lower sternum)
External oblique	Deep circumflex iliac, posterior intercostals	Anterior
Omentum	Gastroepiploic	Anterior and midline Intrathoracic coverage (no myocutaneous coverage)

must consider the need for a microvascular surgeon, more intensive postoperative surveillance, and donor site morbidity.

Surgical Technique for Chest Wall Reconstruction

The authors' preference is to use ADM or PTFE for chest wall reconstruction in conjunction with local rotational or pedicled myocutaneous flaps for soft tissue coverage of defects as needed. The authors' greatest clinical experience with ADM for chest wall reconstruction has been with AlloDerm (Lifecell Corporation, Bridgewater, NJ). Based on the estimated size of the defect during surgery before resection, we request that the AlloDerm be brought to the operating room for rehydration, which can take on average 30 to 60 minutes. We generally prefer the extra-thick, non–cross-linked graft to provide better skeletal support, although this observation is based on anecdotal evidence, and objective data do not currently exist. Graft selection is based on the defect, and multiple grafts may be sutured together for additional coverage.

After skeletal resection is complete, rib margins are blunted to avoid sharp injury to the graft or underlying viscera. Thorough inspection for hemostasis is performed, and the wound is irrigated with copious saline solution. ADM is then sized to the defect and prepared for inset. The authors generally do not prestretch the ADM more than 10% to 15% as the goal for graft placement is to maintain a taut and drumlike tension across the defect to prevent redundancy and leaking. During ADM sizing, it is essential to account for patient positioning. Most surgical approaches for chest wall resection are with the patient in the lateral decubitus position with maximal table flexion to increase interspace distance for chest entry. Thus, it is imperative to restore the operating table to a neutral position during determination of graft size to reduce the chance of inadequate tension. The AlloDerm matrix has two distinct surfaces, and the proper orientation of the allograft before insertion is important for optimal tissue integration. The authors use a heavy nonabsorbable suture with a cutting ½-circle 4-mm needle for graft implantation. This suture allows for ease of passage through the dense dermal graft and facilitates bone penetration when necessary. Single interrupted sutures for secondary support are placed in four quadrants and at any area where there is pleating or a tighter seal is desired. A combination of running or interrupted sutures is then placed circumferentially. Suture is passed through fascia when available or directly through the adjacent rib when fascia is not in proximity, and the superficial portion of the tissue flap is secured to the ADM to obliterate the dead space.

After implantation, the graft is thoroughly irrigated and tested for leakage by insufflating the underlying lung after submersion of the graft in saline solution. Once the ADM has been placed to provide the structural support, soft tissue coverage is generally achieved with a muscle flap to allow for cellular infiltration, vascularization, and tissue ingrowth. The authors then place a 28Fr chest tube in a posteroapical position through the interspace ideally two rib spaces below where the ADM is secured. The pleural tube is managed as for any standard lung resection. To help prevent seroma formation, at least two 19Fr closed-suction drains are placed to close the subcutaneous dead space below the tissue flap and ADM. The drains remain in place until the patient has been ambulating for 24 to 48 hours and once the drain output is less than 30 cc over 24 hours.

SUMMARY

Primary chest wall tumors are rare. When therapy is indicated, surgical resection remains the primary modality of treatment, alone or in combination with chemotherapy or radiation, in the neoadjuvant or adjuvant setting. Margin negative resection affords the best chance of cure. Careful planning and collaboration are critical to ensure outstanding oncologic outcomes with optimal functional and cosmetic results after reconstruction.

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Mediastinal Masses

Hamza Khan, MD, Wasay Nizam, MBBS, and Malcolm V. Brock, MD

APPROACH TO A PATIENT WITH A MEDIASTINAL MASS

Mediastinal masses include a variety of entities—both benign and malignant—and are relatively uncommon. These masses should be considered when evaluating for signs and symptoms such as dyspnea, dysphagia, or head and neck swelling caused by compression of the trachea, esophagus, or great vessels, respectively. They should also be considered in the evaluation of general systemic symptoms such as fever, fatigue, or immunosuppression that may result from associated paraneoplastic syndromes. Mediastinal masses are often diagnosed incidentally on imaging performed for unrelated reasons. Laboratory studies such as alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), or beta human chorionic gonadotrophin (B-HCG) play an important role in diagnosis. CT scans of the neck and chest provide valuable information regarding the location of the tumor, size, relationship to surrounding structures, and other characteristics important in narrowing the differential diagnosis. Core-needle biopsy is preferred where tissue histopathology is required for accurate diagnosis. In cases where the risk of tumor seeding is high, a surgical resection is often performed instead of biopsy. High volume centers are now minimally invasively resecting these masses using procedures such as video-assisted thoracoscopic surgery (VATS) or robot-assisted thoracoscopic surgery (RATS) over traditional open approaches.

ANTERIOR MEDIASTINAL MASSES

Of all mediastinal masses, 50% or more lie within the anterior mediastinum. The most common among these are commonly referred to as the "four T's" or "terrible T's"; namely thymic tumors, thyroid masses, "terrible" lymphoma, and teratoma (germ cell tumor). Approximately 60% of all anterior mediastinal masses are malignant, and most of these are symptomatic at presentation.

Thymic Tumors

Lesions of the thymus account for the majority of anterior mediastinal masses. These range from well-differentiated lesions such as thymoma to more menacing conditions such as invasive thymic carcinoma. Of these, thymomas are the most common entity with a similar incidence in both genders. The usual presenting complaints include the presence of a cough, chest pain, or shortness of breath that results from locoregional compressive effects. Additionally, patients may present with generalized systemic complaints due to associated paraneoplastic disorders. Up to 50% of the patients with thymoma can develop myasthenia gravis (MG), whereas 15% of the patients with MG have any underlying thymoma. Patients with MG and thymoma present with ptosis, fatigue, dysphagia, and less advanced thymic disease possibly because symptoms lead to earlier diagnosis. Other paraneoplastic disorders include myositis, acquired neuromyotonia, and Morvan's syndrome. In certain instances, hematologic disturbances may also be encountered. Red cell aplasia may be seen in 5% to 15% of the patients and immunodeficiency from white cell aplasia and hypogammaglobulinemia in less than 5% of the patients—both disorders more common in older females.

A CT scan with IV contrast is the imaging modality of choice for thymic lesions (Fig. 1). Tumors with well-circumscribed, smooth margins favor the presence of a thymoma. In the context of a typical clinical presentation, these radiographic findings may be sufficient to proceed with surgical resection, as preoperative biopsies carry the risk of tumor seeding and do not provide further diagnostic utility. In contrast, thymic carcinoma can be distinguished by the presence of an infiltrating mass, with central necrosis and irregular borders. In this setting, a biopsy may be considered to establish the malignant nature and to allow adequate staging and options for neoadjuvant treatment. Ideally, fine-needle aspiration (FNA) should be avoided since it lacks the architectural platform necessary to distinguish thymoma from lymphoma. In cases of diagnostic uncertainty, other imaging modalities like MRI can prove as useful adjuncts. For example, when differentiating thymoma from thymic hyperplasia, the latter will have a smooth and symmetric morphology with the presence of adipose tissue.

The eighth edition of the American Joint Committee on Cancer (AJCC) TNM Staging system now incorporates TNM staging for tumors of the thymus. This classification is dependent upon the invasion of the primary tumor and its dissemination. This new system, therefore, supersedes the Masaoka staging system that is still widely used and upon which many existing treatment guidelines are based. Prognosis for thymoma depends on the presence of invasion and the resectability of the mass. For patients where R0 (complete) resection is achievable, surgery is recommended. These patients with early-stage disease who undergo a complete resection can achieve a 5-year survival rate as high as 100%. Careful preoperative planning is needed for patients with MG that includes medical treatment with anticholinesterase or plasmapheresis preoperatively and avoids the use of neuromuscular blocking agents for anesthesia. For patients with tumor invasion into critical structures (great vessels, heart, or trachea) or metastatic disease, a combination of neoadjuvant chemotherapy or radiotherapy, radical resection, and postoperative chemoradiotherapy is indicated. Chemotherapy regimens are typically cisplatin-based; however, they are currently still poorly defined so treatments are individualized for patients or given as part of a clinical trial. Small-scale studies have shown response rates to neoadjuvant therapy in 70% to 100% of patients who have partially resectable tumors. For patients with thymic carcinomas who have a poor response to neoadjuvant chemotherapy, pembrolizumab, an immune checkpoint inhibitor, or sunitinib, a tyrosine kinase inhibitor, can be considered. In patients who develop recurrent disease, if localized, repeat surgical resection with adjuvant therapy for curative intent is advocated. Posttreatment surveillance is recommended with CT scanning performed annually for 10 years.

Thyroid and Parathyroid

Mediastinal goiters can either be an inferior extension of cervical thyroid tissue through the thoracic inlet or a proliferation of native ectopic thyroid tissue present within the mediastinum. For a goiter to be termed substernal, 50% or more of the mass should lie inferior to the thoracic inlet. For it to be called "aberrant," the thyroid tissue in the mediastinum must have no connection with its cervical counterpart and should not share its blood supply. Even though 15% of mediastinal masses can be thyroid lesions, only 2% or less of these goiters are substernally aberrant. Large masses can cause obstructive symptoms like dyspnea or dysphagia from compression of the esophagus or trachea. Often, these masses grow slowly over time, but hemorrhage into a nodule often precipitates an acute presentation such as compression of a vital structure such as the trachea. Other symptoms include chronic coughing, a choking sensation, sleep apnea, and nerve paralysis depending upon the location and size of the mass. Surgical resection is the gold standard treatment for such patients. Radioactive iodine ablation carries with it the risk of acute inflammation leading to worsening

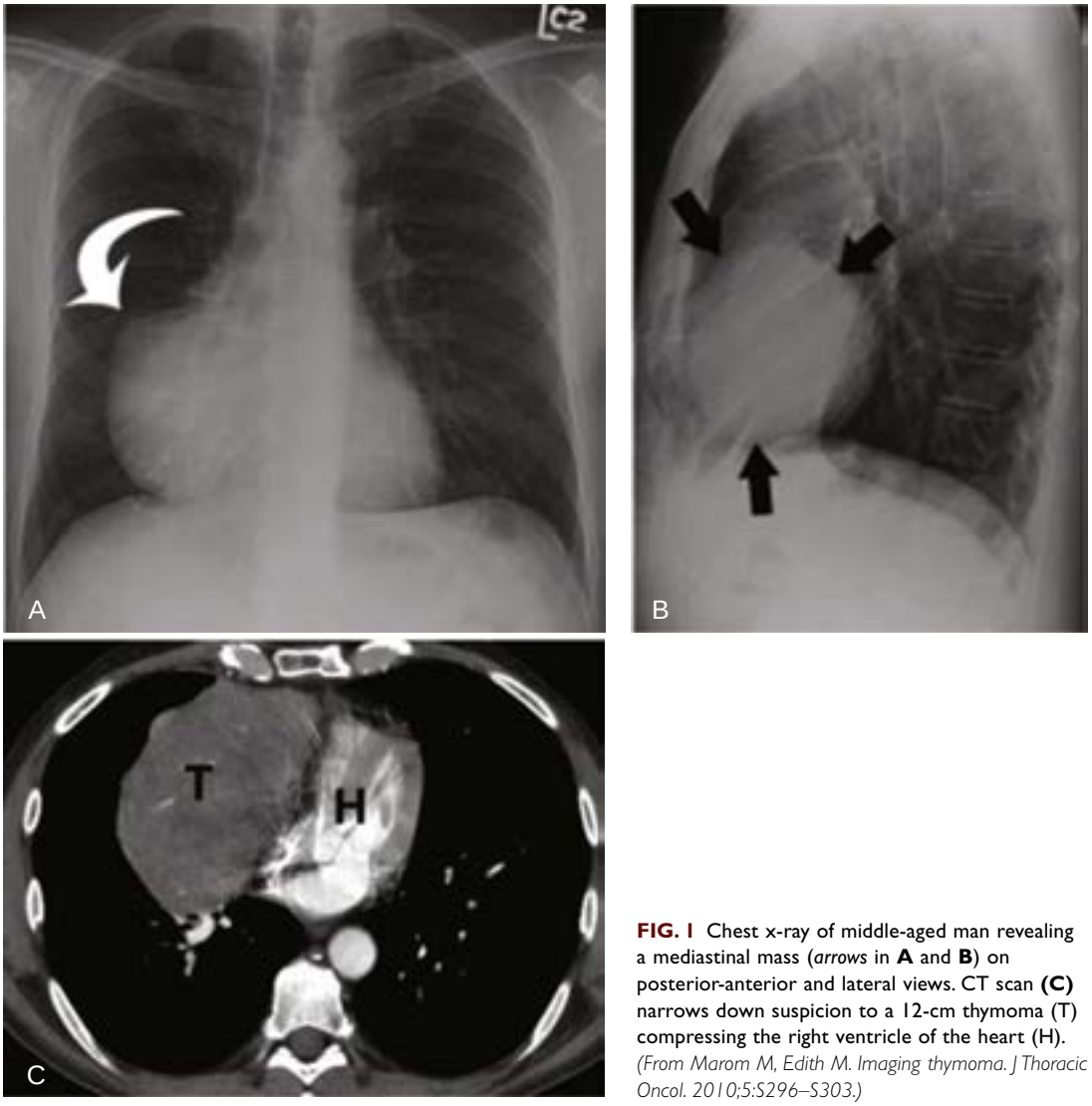


FIG. 1 Chest x-ray of middle-aged man revealing a mediastinal mass (*arrows* in **A** and **B**) on posterior-anterior and lateral views. CT scan **(C)** narrows down suspicion to a 12-cm thymoma (T) compressing the right ventricle of the heart (H). *(From Marom M, Edith M. Imaging thymoma. J Thoracic Oncol. 2010;5:S296–S303.)*

compression and is reserved for nonsurgical candidates only. Preoperative planning includes measuring a thyroid-stimulating hormone (TSH) level to ensure adequate medical management of hyperthyroidism. Laryngeal examination and imaging are also warranted to determine if any compromised function is solely from the mediastinal thyroid tissue. Surgical resection can be safely performed transcervically via a low collar neck incision in most cases (Fig. 2). Under certain circumstances where lesions are deeper or involve multiple mediastinal compartments, a partial or complete sternotomy is required for complete resection. Minimally invasive approaches including VATS are increasingly being employed at high volume centers. Postoperatively, patients who undergo total thyroidectomy require lifelong levothyroxine.

Parathyroid adenomas are rare causes of mediastinal masses but nonetheless important given their shared embryologic origin with the thymus. Up to 20% of patients with hyperparathyroidism can have mediastinal parathyroid adenomas. It is important to realize that a mediastinal parathyroid is a frequent cause of failure to localize the parathyroid during surgery. Typically, the inferior parathyroid glands descend along the thyrothymic tract, or a fifth parathyroid gland is found in the mediastinum. Patients present with symptoms of hypercalcemia—abdominal pain, kidney stones, polyuria, constipation, altered mentation, bone-related complications, or with an incidental finding on CT scan (stones, bones, groans, thrones, and psychic overtones). Accurate preoperative localization can be achieved with CT/Sestamibi fusion scan with up to 90% sensitivity (Figs. 3 and 4). Surgical resection via transcervical approach can be achieved in most cases; however, tumors present deep within the thorax require either a sternotomy or VATS.

Lymphoma

Lymphomas are broadly classified as Hodgkin's and non-Hodgkin's and comprise up to 25% of the masses in the anterior mediastinum. Primary mediastinal B-cell lymphoma (PMBL) and nodular sclerosing Hodgkin's lymphoma (HL) are the most common subtypes. Patients commonly present with B-type symptoms—fatigue, low-grade fevers, weight loss, and night sweats—or with compression effects on the surrounding structures (Fig. 5). CT/MR imaging

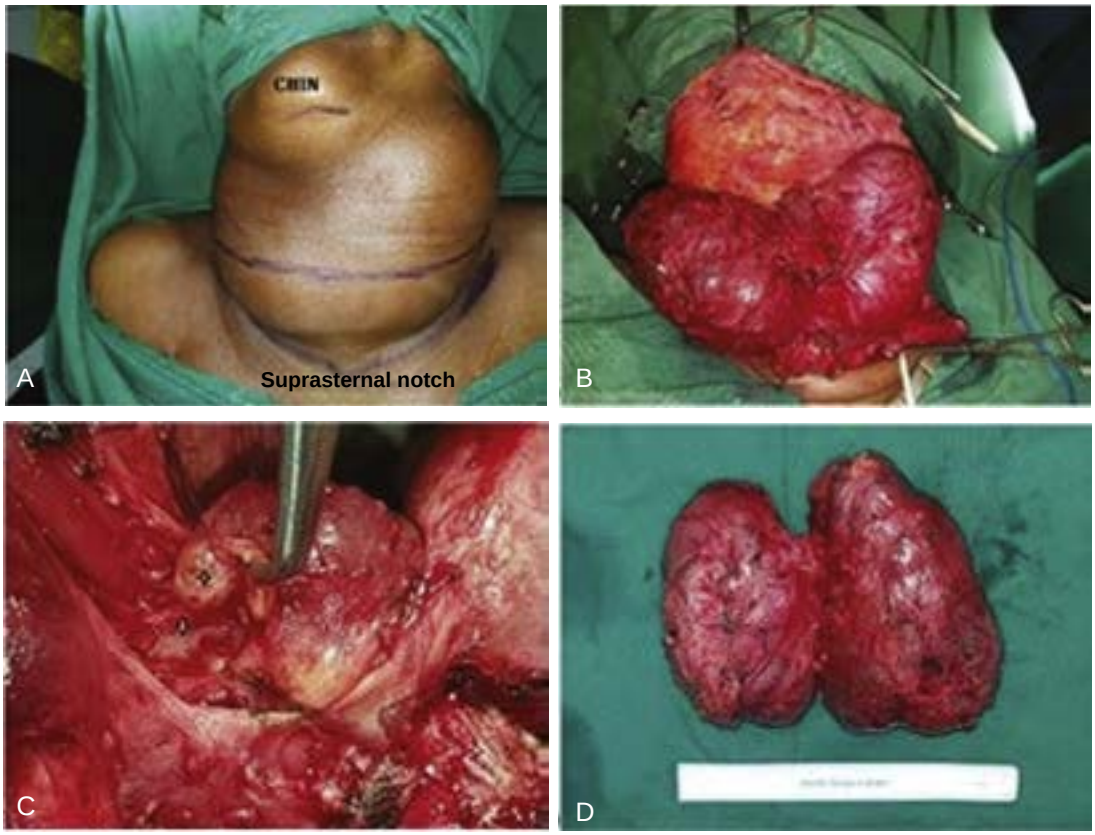


FIG. 2 **(A)** Large neck swelling measuring 10 cm in the longest dimension. **(B).** Horizontal neck incision extending bilaterally to the mastoid tips with exposure of the thyroid gland along with the mass. Enlarged pyramidal lobe of thyroid extending into the pre-cervical space **(C)** and gross specimen after removal **(D).** Pathologic diagnosis later confirmed toxic multinodular goiter. *(From Alaguvelsamy S, Sujeethra S, et al. Giant toxic multinodular goiter with dyspnea: A case report.* Int J Surg Case Rep. *2020;73:190–195.)*

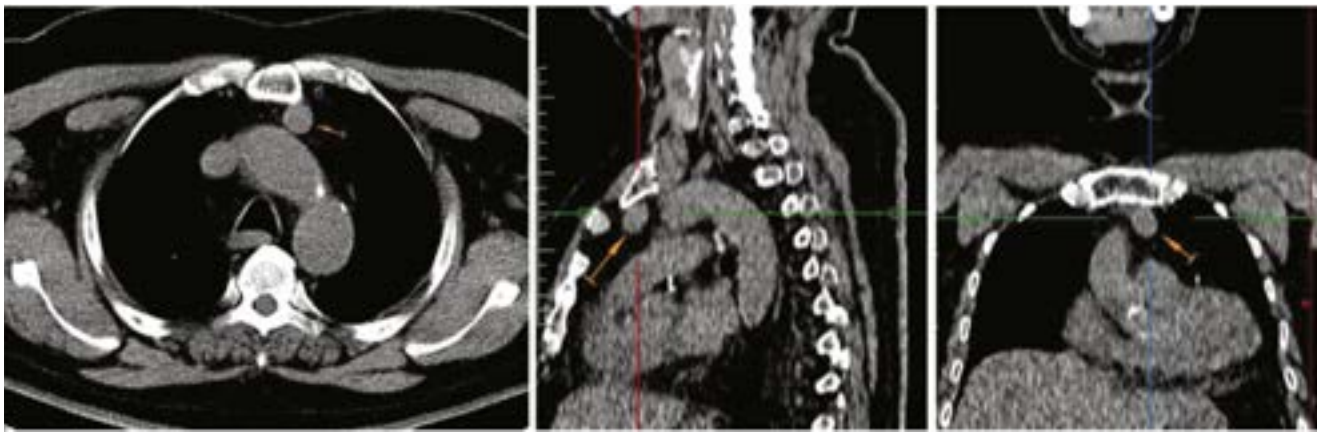


FIG. 3 CT scans show a well-defined circular mass (orange arrows) in the anterior mediastinum posterior to the manubrium of the sternum and anterior to the aortic arch that measures 1.7 × 1.7 × 2.8 cm. *(From Khalaf SH, Sarwani, AA, George SM, et al. Primary hyperparathyroidism caused by an ectopic parathyroid adenoma in an uncommon location: a case report.* J Taibah Univ Med Sci. *2021;16:782–787.)*

often reveals enlarged mediastinal lymph nodes along with vascular encasement and a pleural/pericardial effusion (Fig. 6). However, a formal diagnosis requires a core needle biopsy to evaluate the structural composition of the tissue in addition to flow cytometric analysis. Given the success of chemotherapy, the role of the surgeon in this instance is limited to the occasional need for a surgical biopsy for adequate tissue specimen. Management is primarily based on chemotherapy followed by consolidation radiotherapy. Such treatment regimens risk tumor lysis syndrome, and hence close monitoring of potassium, phosphate and uric acid is employed. Functional imaging

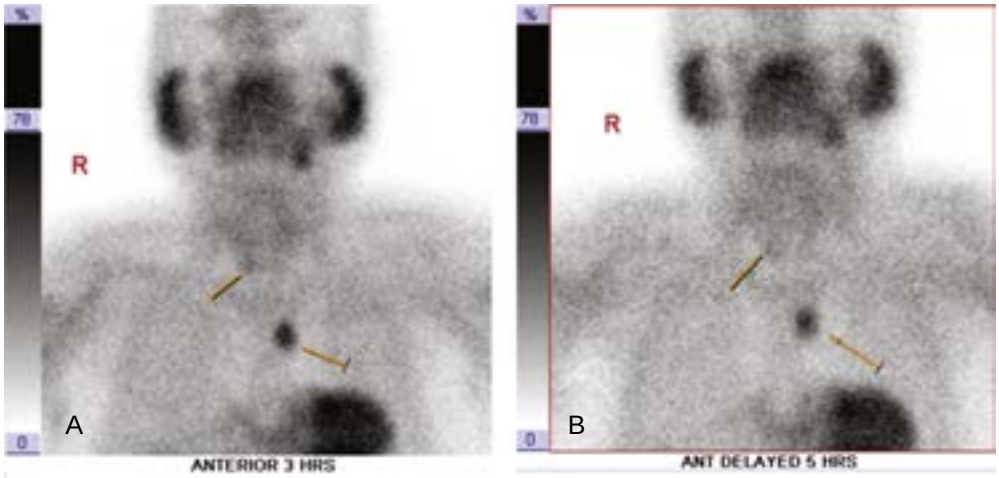


FIG. 4 Parathyroid sestamibi scan showing a MIBI-avid focus on 3 hr **(A)** and 5 hr **(B)** images (inferior left, *orange arrow*). Also seen is a faint focus corresponding to the location of the right lower pole of the thyroid (superior right, *orange arrow*). Pathology later confirmed a diagnosis of a parathyroid adenoma of the left paraaortic mediastinal mass. *(From Khalaf SH, Sarwani, AA, George SM, et al. Primary hyperparathyroidism caused by an ectopic parathyroid adenoma in an uncommon location: a case report.* J Taibah Univ Med Sci. *2021;16:782–787.)*

modalities such as PET-CT may be utilized for long-term disease monitoring and to assess for possible recurrence.

Germ Cell Tumors

Mediastinal germ cell tumors (GCTs) are believed to originate from embryonic germ cells as a result of failed migration or from primordial thymic cells. Among the three subtypes—teratoma, seminoma, and nonseminoma—teratomas are the most common. A careful physical examination of the testicles along with an ultrasonographic workup is important to exclude a potential metastatic lesion arising from a testicular source. Diagnostic workup includes imaging of the chest, serologic markers, and most importantly, a tissue biopsy.

Teratoma

Mature teratomas are benign tumors containing two or more of the embryonic layers: endoderm, mesoderm, or ectoderm. They are the most common GCT of the mediastinum comprising up to 60% of all masses with an equal prevalence in both genders. Teratomas mostly present incidentally, although they can also come to attention from symptoms of obstruction on surrounding structures. Imaging reveals a heterogenous calcified cystic mass containing fat, fluid, or bone (Fig. 7). Gross appearance is that of a tan-brown cystic structure (Fig. 8). These tumors are often resistant to chemotherapy and radiotherapy, and therefore surgical resection is the mainstay of treatment. The surgical approach (sternotomy vs. thoracotomy or VATS) depends on the location and size of the tumor. Postresection recurrence rates are low with an excellent prognosis.

Seminoma

Mediastinal seminoma is a slow-growing mass; however, metastasis may be present in up to 70% of the patients. The majority are symptomatic with chest pain being the most common symptom. These tumors account for one-third of all mediastinal GCTs and are mostly seen in males during the second to fourth decade of life. Diagnosis requires CT imaging, tissue biopsy, and a testicular examination to rule out the gonads as a potential primary source. On serology, AFP is found to be negative, and B-HCG is mildly elevated. Surgical management is limited to occasional biopsy when the diagnosis is uncertain. Chemotherapy based on cisplatin, etoposide, and bleomycin is the standard of care. Radiation therapy (RT) is used only in cases where contraindications to chemotherapy exist because of mediastinal toxicity concerns like constrictive pericarditis or valvular disease. Overall, seminomas have an excellent prognosis, with treatment offering 90% survival at 5 years. Often patients, regardless of systemic treatment, are found to have residual masses that are mostly necrotic tissue and can be followed if small in size.

Nonseminoma

Nonseminomatous GCTs, like their counterparts, occur in young to middle-aged males. However, unlike seminomas, these lesions are more aggressive and present with an invasive mass in addition to elevated levels of both AFP and B-HCG. Imaging reveals a heterogeneous mass in the anterior mediastinum. At some institutions, if the presentation is pathognomonic—young male with symptoms of obstruction/invasion, typical imaging, and elevated markers—chemotherapy may even be started without a definitive histologic evaluation. Systemic therapy typically consists of cisplatin-based chemotherapy. In patients with limited pulmonary reserve, bleomycin is avoided due to the risk of pulmonary toxicity. Posttreatment, surgical resection of any residual mass is recommended due to the high likelihood of malignancy. Often these masses invade surrounding structures like the pericardium, pulmonary parenchyma, or phrenic nerve, thereby necessitating an en-bloc resection to achieve complete disease control. Compared with teratomas and seminomas, the prognosis for mediastinal nonseminomatous GCTs is comparatively worse: a 40% to 45% survival rate in 5 years. Serial monitoring of serologic tumor markers is employed for long-term surveillance.

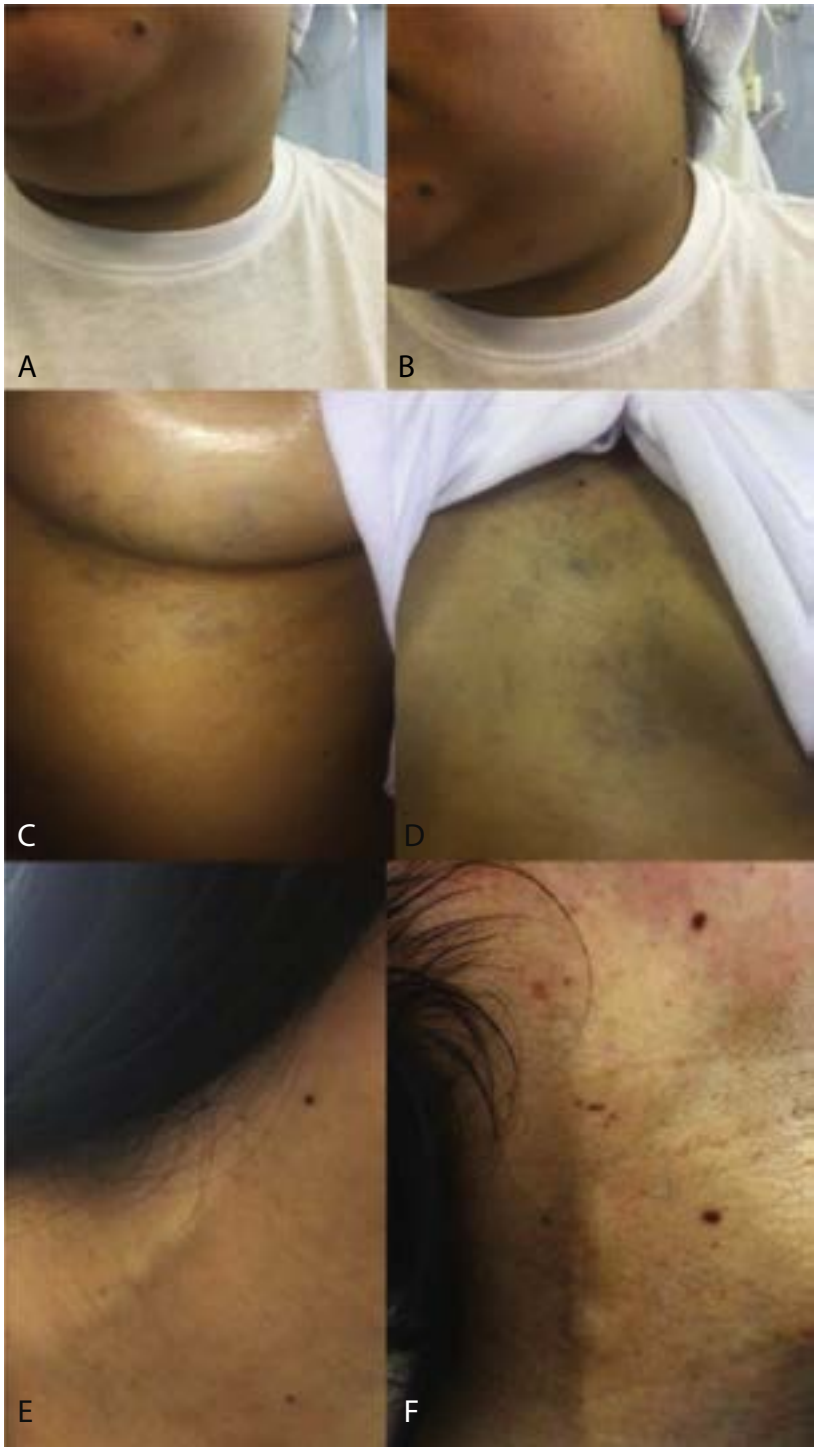


FIG. 5 **(A, B)** A 21-year-old woman with swelling of the face and neck. **(C, D)** Superficial veins in the chest/infra-mammary region are dilated and engorged. **(E, F)** Jugular venous distension noted in the neck.
(From Besteiro B, Teixeira C, Gullo I, et al. Superior vena cava syndrome caused by mediastinal lymphoma: a rare clinical case. Radiol Case Rep. *2021;16:929-933.)*

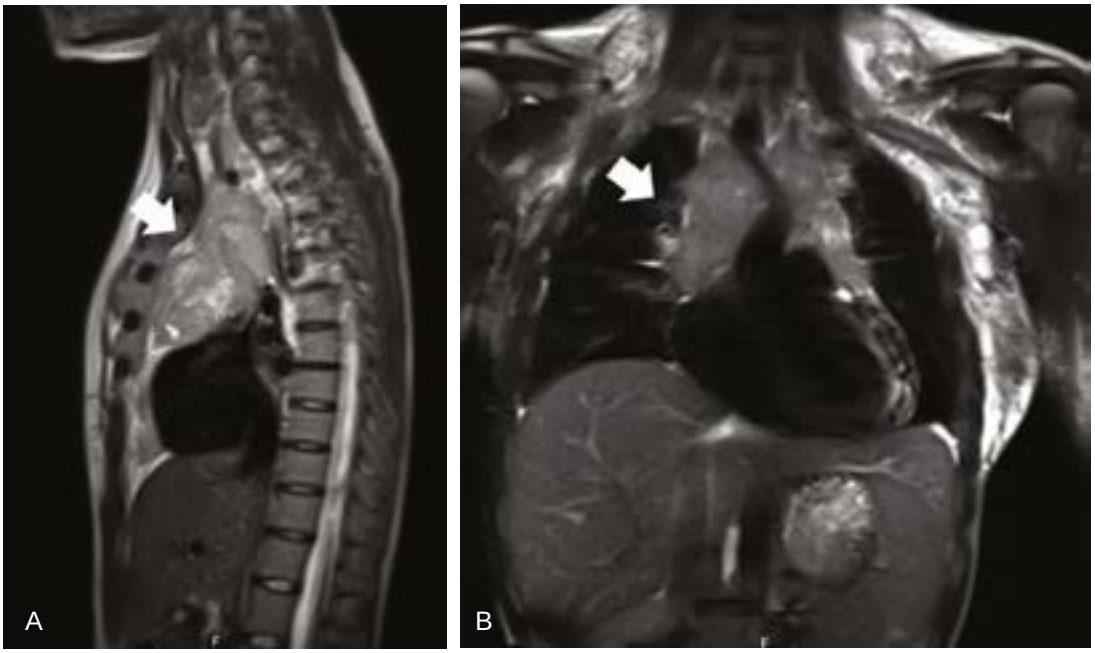


FIG. 6 Weighted MRI scans in coronal **(A)** and sagittal **(B)** views showing mediastinal mass encapsulating the SVC *(arrows)*. Histopathologic diagnosis revealed primary mediastinal large B cell lymphoma. *(From Besteiro B, Teixeira C, Gullo I, et al. Superior vena cava syndrome caused by mediastinal lymphoma: a rare clinical case.* Radiol Case Rep. *2021;16:929-933.)*

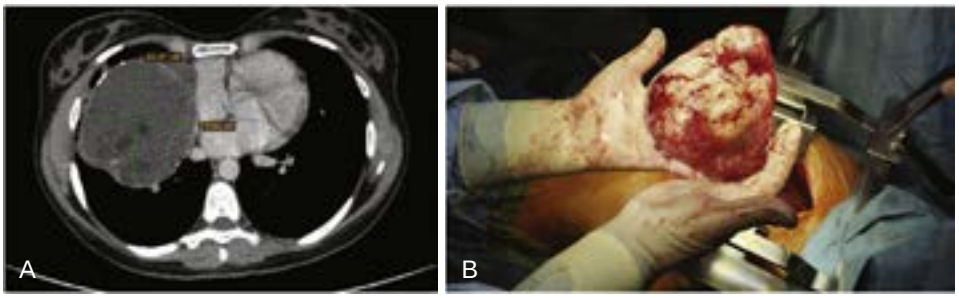


FIG. 7 **(A)** CT scan of large well-circumscribed mass with multiple cysts in the anterior mediastinum displacing the heart slightly to the left and measuring 12 × 11cm. **(B)** Gross specimen after resection via a median sternotomy. Histopathology confirmed a mature mediastinal teratoma. *(From Rachwalik M, Kosiorowska K, Bochenek M, et al. Mature mediastinal teratoma with somatic type malignancy including neuroblastoma and intestinal type of adenocarcinoma: A Case Report.* Int J Surg Case Rep. *2021;80:105680.)*

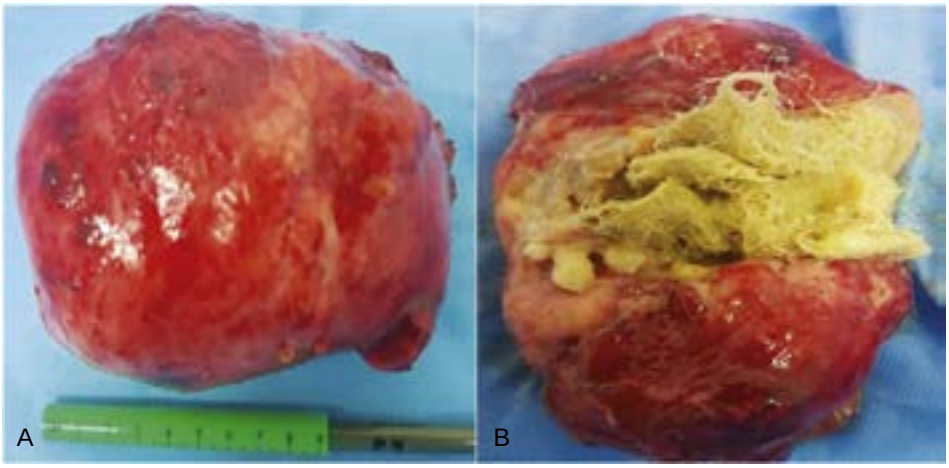


FIG. 8 A 41-year-old woman with shortness of breath was found to have right ventricular outflow obstruction from pulmonary artery compression by a large anterior mediastinal mass **(A)**. Gross dissection shows hair, teeth, and bone—characteristic features of a teratoma **(B)**. *(From Chaudhry IUH, Cheema A, Aqeel C, et al. A rare cause of right ventricle outflow tract obstruction: anterior mediastinal teratoma.* Ann Med Surg. *2021;62:258-260.)*

MIDDLE MEDIASTINAL MASSES

Castleman's Disease

This lymphoproliferative disorder, also known as Angiofollicular lymph node hyperplasia, primarily affects the young and has increased risk in immunocompromised patients. Though the precise etiology is unknown, an association with HHV-8 has been postulated. Castleman's disease (CD) can occur in any lymph node location but is most commonly found in the mediastinum and is asymptomatic on evaluation. CT scan shows lymphadenopathy with or without an associated mass and postcontrast enhancement. Diagnosis is confirmed on histopathology. For unicentric CD, complete surgical resection is the definitive treatment. For multicentric disease, a multimodal approach including radiation and immunotherapy is employed.

Mediastinal Cysts

Cystic masses in the middle mediastinum are typically bronchogenic cysts that, along with esophageal cysts, are known as *foregut duplication cysts* (Figs. 9 and 10). Less common middle mediastinal masses are pericardial and neuroenteric cysts. All can present secondary to symptoms of compression or obstruction. CT imaging reveals the cysts as smooth-walled soft tissue density that are nonenhancing. The CT also identifies the structure associated with the cystic lesions. Other imaging modalities, like MRI and EBUS, are employed when CT imaging is unequivocal. Management depends on the type of cyst and presentation; if symptomatic, surgical resection is indicated. Biopsy of the cyst is generally avoided to prevent the risk of secondary infection. Some types of cysts, like bronchogenic cysts, also have the potential for malignant degeneration, and excision is recommended in patients with low operative risk.

Mediastinal Lymphadenopathy

The most common mass arising in the middle mediastinum is an enlarged lymph node. Among the variable causes—malignant, infectious, or inflammatory—malignancy is the most prevalent. Advanced lung cancer may spread to the subcarinal or paratracheal lymph nodes. For patients presenting with a cough, polyarthralgia and

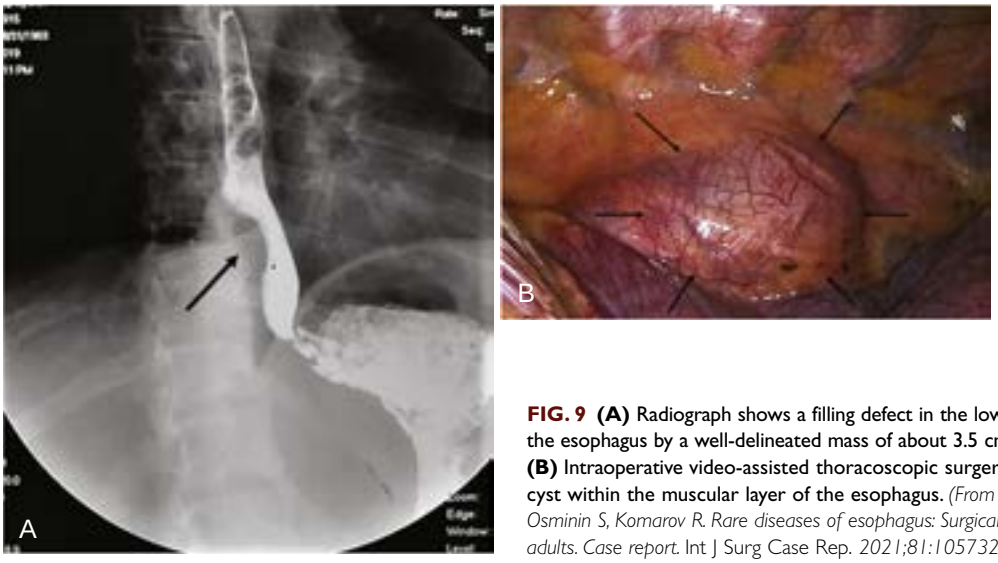


FIG. 9 **(A)** Radiograph shows a filling defect in the lower third of the esophagus by a well-delineated mass of about 3.5 cm in length. **(B)** Intraoperative video-assisted thoracoscopic surgery image of a 5-cm cyst within the muscular layer of the esophagus. *(From Parshin V, Vetshev S, Osminin S, Komarov R. Rare diseases of esophagus: Surgical treatment of cysts in adults. Case report.* Int J Surg Case Rep. *2021;81:105732.)*

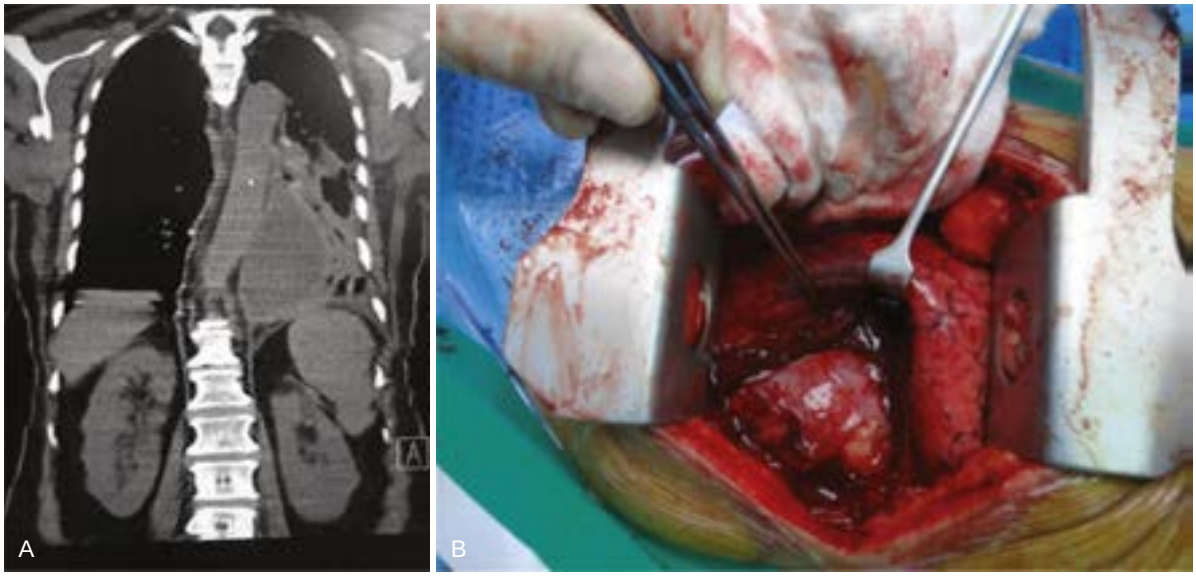


FIG. 10 **(A)** CT scan of a large cystic structure in the mediastinum. **(B)** Operative view for excision of the mass. Pathology later confirmed the initial suspicion of a bronchogenic cyst. *(From Eldib OS, Abdelmeged S. Surgical management of mediastinal cysts.* J Egyptian Soc Cardiothorac Surg. *2016;24:58–64.)*

hypercalcemia, along with mediastinal lymph node enlargement (sarcoidosis) become important in the differential diagnosis. Histoplasmosis, coccidiomycosis, and other infectious agents are also common causes for lymphadenopathy in the middle mediastinum depending on the specific location. While serology may aid in the diagnosis, pathologic evaluation remains the gold standard for diagnosis. EBUS, cervical mediastinoscopy, or CT-guided tissue biopsy are amongst the many options for obtaining the pathologic specimen.

POSTERIOR MEDIASTINAL MASSES

Schwannomas and Neurofibromas

Most posterior mediastinal tumors are neurogenic in nature and arise from either the peripheral nerves or sympathetic and parasympathetic ganglia. The most common posterior mediastinal tumor, Schwannoma, arises from the Schwann cells that form the nerve sheath. With equal predominance in both genders, these tumors are mostly asymptomatic but can present with compression effects and paralysis. CT scan reveals a well-circumscribed mass with focal calcifications. Surgical resection is curative. Similarly, neurofibromas are also nerve sheath tumors that present in the second or third decade of life. They are associated with neurofibromatosis type-1 especially when multiple tumors are present. Both of these tumors have malignant variants that are highly aggressive and often present with unremitting symptoms as well as distant metastasis.

Ganglion and Paraganglion Cell Tumors

Ganglion cell tumors arise from the sympathetic ganglion cells. Their benign subtype, ganglioneuroma, is due to their embryonic neural crest cell origin. They can occur anywhere along the sympathetic chain. Arising mostly before the second decade, these tumors are asymptomatic unless large enough to cause compressive symptoms which then requires surgical resection (Fig. 11). Their malignant counterparts, ganglioneuroblastoma and neuroblastoma, are highly aggressive and more commonly encountered in the pediatric population. Biochemical workup can show elevated levels of catecholamine metabolites, VMA, and HMA. WDHA (watery diarrhea, hypokalemia, and achlorhydria) as well as Cushing's syndrome have been described in such patients. Postoperative treatment involves adjuvant systemic or RT.

Paraganglion cell tumors give rise to mediastinal pheochromocytomas that can secrete catecholamines resulting in the classic symptoms of hypertension, headache, tremors, and diaphoresis. Only 10% of pheochromocytomas are extraadrenal. Diagnosis is confirmed with plasma and/or urinary metanephrines and catecholamines.

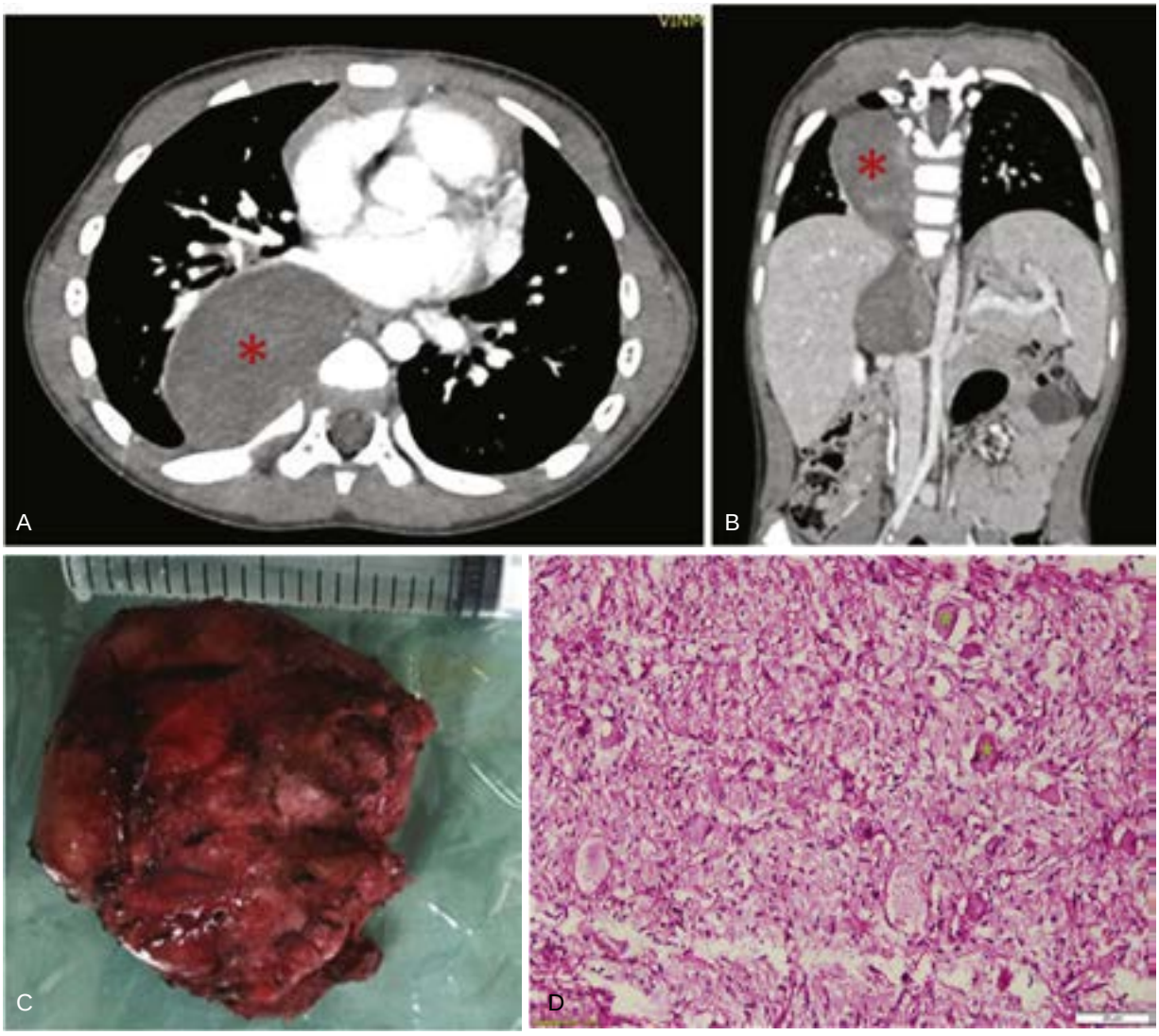


FIG. 11 **(A, B)** CT scans of 8 × 6 cm mass in the right posterior mediastinum *(asterisk)*. **(C)** Gross specimen after resection. **(D)** Microscopic image after hematoxylin-eosin stain showing mature ganglion cells *(green stars)* and Schwann cells characteristic of ganglioneuroma. *(From Son BBB, Nguyen TKH, Rodriguez-Galindo C. Ganglioneuroma of mediastinum and adrenal gland.* J Pediatr Surg Case Rep. *2020;61:101628.)*

MIBG scanning can aid in localizing the disease if a CT scan is nondiagnostic. Preoperative alpha- and beta-blockade are imperative before surgical resection to prevent intraoperative sympathetic crises.

SURGICAL APPROACHES

Biopsy vs. Surgery

Routine biopsies of mediastinal masses are avoided. This is primarily due to the risk of spreading disease as well as the cost and morbidity of an additional procedure. In cases where the lesion appears to be well encapsulated and imaging is classic for masses like teratoma, thymoma, or cysts, surgical resection is considered first-line. However, with our improved understanding of induction therapy and advanced biopsy techniques, many physicians are now opting for pathologic confirmation when lymphoma or thymic carcinoma is suspected so that appropriate neoadjuvant treatment can be offered first.

When selecting the operative approach, optimal exposure is key since the most important prognostic indicator is complete resection. It is not uncommon to resect adjacent serosal membranes, lung parenchyma, and even great vessels to achieve en bloc resection of the tumor mass. Preoperative planning for patients with mediastinal masses hence includes consultation with a pulmonologist in a multidisciplinary setting to optimize the patient's condition a priori and determine if their respiratory reserve allows pulmonary resection.

Anterior Mediastinotomy

Chamberlain procedure—anterior parasternal mediastinotomy—allows good exposure and the ability to obtain adequate biopsy specimens from the anterior mediastinum as well as the aortopulmonary window. The operation can be performed as an outpatient procedure and does not require single-lung ventilation. A small incision is made over the second costal cartilage on the side of interest followed by dissection of the pectoralis and resection of the chondral cartilage if needed (Fig. 12). The posterior perichondrium is then incised, and the tumor mass is accessed.

Median Sternotomy

A full median sternotomy provides the most ideal exposure to masses in the anterior mediastinum; most commonly, it is used for a thymoma. Combined with an anterior thoracotomy, access is enhanced to all critical structures including the anterior pericardium, great vessels, phrenic, and laryngeal nerves. An upper sternal split may be performed if access is only required in the superior compartment. However, this approach has not been proven to give better patient outcomes. The incision for the median sternotomy extends from below the jugular notch to the xiphisternal junction. Mobilization of the thymus begins caudally, dissecting the attached mediastinal fat, and continues cranially in the neck to the superior poles. Small vessels are clipped, and care is taken to stay clear of the phrenic nerves. In cases where invasion of the great vessels is encountered, access in the groin is obtained for possible cardiopulmonary bypass.

Transcervical Approach

This approach is used in a minority of the cases where resection of parathyroid adenomas, goiter, or thymic resection is needed. There has been a recent resurgence of interest in using the transcervical approach for resection of thymomas given early operative recovery and same-day return to home for the majority of patients. To expose the thymic gland, a 5-cm curvilinear incision is made above the jugular notch followed by creating subplatysmal flaps and separating strap muscles in the midline. The superior poles of the thymus are mobilized first using blunt dissection that is then carried down as far as possible. The use of a Cooper retractor to elevate the sternum opens up a sizeable space and allows appropriate visualization (Fig. 13). Patients must have good cervical spine extension for this procedure. Although this procedure avoids the morbidity of a sternotomy, conclusive evidence is not available yet of oncologic outcomes, and the judgment of the surgeon prevails.

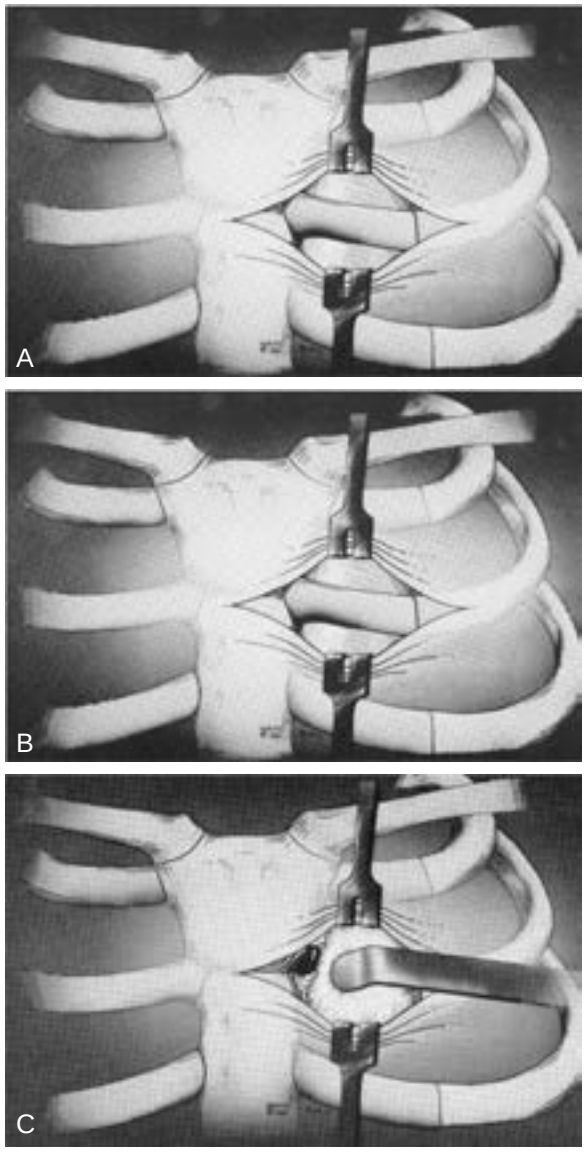


FIG. 12 Surgical technique of anterior mediastinotomy. Incision is made over the second costal cartilage on the left **(A)** after which the costal cartilage is resected, and pleura exposed **(B)** and underlying mass dissected for resection **(C)**. *(From Ravipati NB, Mclemore EC, Schlinkert RT, Argueta R. Anterior mediastinotomy for parathyroidectomy.* Am J Surg. *2008;195:799–802.)*

Thoracotomy

Thoracotomy readily provides access to the middle and posterior compartments of the mediastinum. Combined with unilateral or bilateral thoracosternotomy (clamshell incision), not even bulky anterior masses extending into the pleura are out of reach. A clamshell incision involves creating an incision in the fourth intercostal space from one midaxillary line to the other connected via a transverse sternotomy and provides excellent exposure.

Minimally Invasive Approaches

VATS and RATS are gaining popularity for selected mediastinal masses including benign tumors, thymomas, and cysts (Fig. 14). In experienced hands, they offer improved visualization, decreased postoperative pain, and earlier recovery than an open procedure. Caution is advised however when invasive malignancies are encountered as the risk of leaving microscopic disease behind or

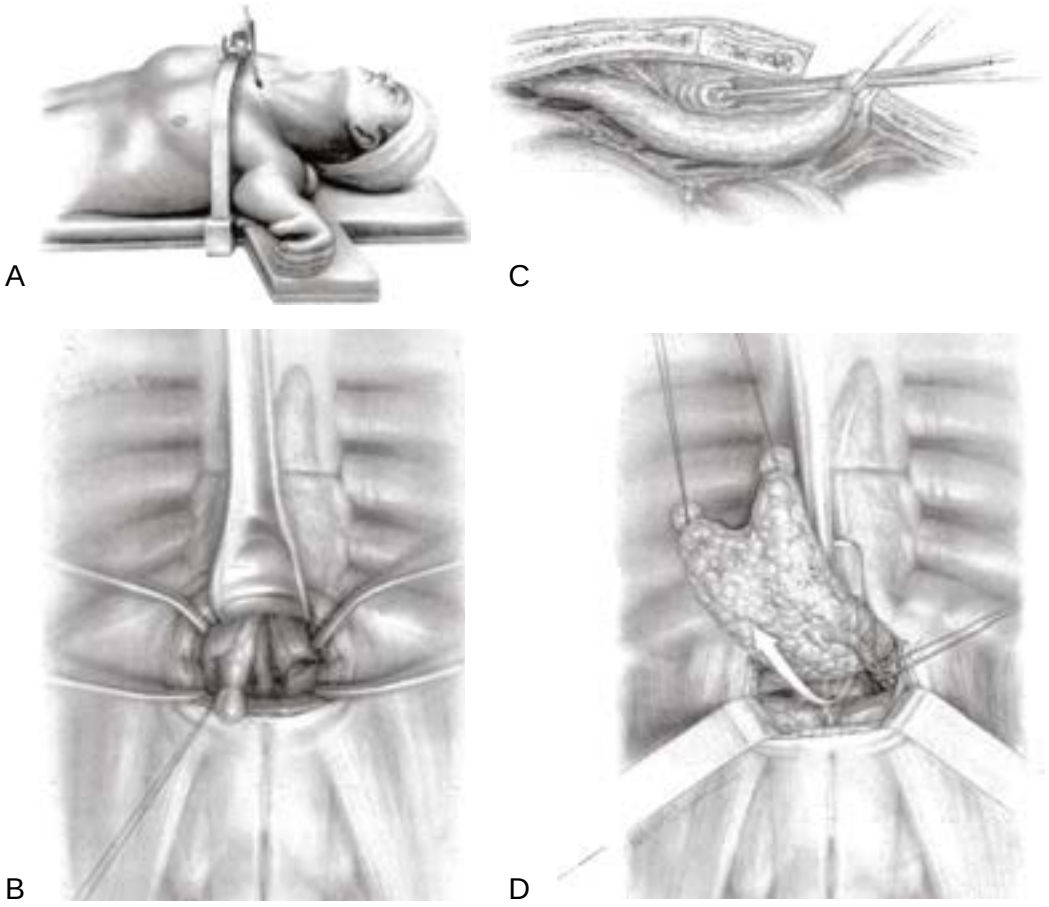


FIG. 13 **(A)** Patient is positioned supine on a surgical bed with an inflatable pillow under the shoulders for elevation and hyperextension of the neck. A transverse incision is made 2 cm above the sternal notch for a transcervical thymectomy. A sternal retractor is later used at the inferior edge for adequate visualization in the mediastinum. In some instances, the patient is nearly lifted off the bed. **(B)** Surgeon's view from the cranial end after early dissection. A silk tie on the thymus helps with retraction. **(C)** Blunt dissection using a sponge stick for creating a substernal plane. Silk ties help with gentle cephalad retraction. **(D)** Thymus after further dissection has been carried into the mediastinum. *(From Meyers BF. Transcervical thymectomy.* Op Tech Thorac Cardiovasc Surg. *2001;6:201–208.)*



FIG. 14 Single site video-assisted thoracoscopic surgery **(A).** Prior chest tube site that is enlarged for insertion of GelPoint Mini that can accommodate three trocars – two 5 mm and one 12 mm **(B)**. Wedge resection of right apical blebs using endoGIA stapler **(C).** *(From Won TM, Munoz A, Sacks MA, et al. Single site video assisted thoracoscopic wedge resection for spontaneous pneumothorax in a pediatric patient.* J Pediatr Surg Case Rep. *2020;61:101614.)*

port-site malignancy increases. Other circumstances advocating for thoracotomy include active infection in a cyst or tumor size larger than 6 cm. Accordingly, when obtaining informed consent for VATS from patients, it is prudent also to discuss thoracotomy as an option.

Suggested Readings

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Primary Tumors of the Thymus

Joshua E. Preiss, MD, and Douglas E. Wood, MD, FRCSEd

INTRODUCTION

Primary tumors of the thymus are rare, with approximately 1.5 cases per million worldwide. Although uncommon, they represent the most frequent tumors found in the anterior mediastinum in adults. *Primary thymic tumors* are often referred to as *thymic epithelial neoplasms*. Both terms describe the main types of malignancies that arise from the epithelial elements of the thymus, which include thymoma, thymic carcinoma, and neuroendocrine tumors of the thymus (NETTs). These thymic malignancies have distinct histopathologies and natural histories but are grouped by similar classification and staging systems. These diseases are in contrast to benign tumors of the anterior mediastinum or malignancies of nonthymic origin, including thymic cysts, thymic hyperplasia, retrosternal goiter, lymphoma, and germ cell tumors. There is a strong association of thymomas with myasthenia gravis and other autoimmune diseases. Long-term outcomes for thymomas are good, with 5-year survival rates approaching 95%. Thymic carcinomas have a higher propensity for local invasion and metastasis, with 5-year survival rates approximately 55%. The mainstay of treatment for primary tumors of the thymus is complete surgical resection, which relies on thorough preoperative diagnostic imaging and staging to determine resectability. Neoadjuvant systemic therapy followed by surgery can be considered for large or marginally resectable tumors, and chemotherapy with radiation can be utilized for potentially unresectable and residual/recurrent disease, respectively.

CLINICAL PRESENTATION

The majority of anterior mediastinal masses are discovered incidentally on imaging in patients who are otherwise asymptomatic. Patients who do present with symptoms can display effects from local tumor invasion or associated paraneoplastic disorders. Locally advanced tumors can cause mass effect with associated cough, dyspnea, chest pain, or superior vena cava syndrome. Invasion of intercostal, phrenic, or recurrent laryngeal nerves can also contribute to symptoms. Thymomas have a more indolent course compared with the rapid onset of symptoms seen in patients with other mediastinal masses, such as lymphoma or germ cell tumors. Compared with thymomas, thymic carcinomas have higher rates of local invasion and therefore symptoms at time of presentation. Additionally, thymic carcinomas can frequently present with associated pleural or pericardial effusions. Thymomas mainly occur in adults, while thymic carcinomas can occur over a wide range of ages. Thymic tumors affect males and females equally, and the majority are thought to be idiopathic.

Paraneoplastic syndromes are more commonly associated with thymomas, with the most common being myasthenia gravis. Up to 50% of patients with thymomas have myasthenia gravis, whereas approximately 20% of patients diagnosed with myasthenia gravis will have an associated thymoma. (Note that, for this reason, a chest CT is a necessary part of the evaluation during a new diagnosis of myasthenia. Conversely, imaging that demonstrates a probable thymoma requires eliciting possible symptoms of myasthenia.) Additional autoimmune disorders associated with thymomas include red cell aplasia and hypogammaglobulinemia. Thymic carcinomas are rarely associated with these autoimmune conditions. The most common NETTs are carcinoid tumors, which can be associated with Cushing's syndrome and multiple endocrine neoplasia type 1 (MEN1).

Laboratory testing is less critical in the diagnosis of thymic tumors compared with clinical signs and imaging. When myasthenia gravis is suspected, antiacetylcholine receptor antibody levels should be obtained. When narrowing the differential for anterior mediastinal masses, individualized testing may include complete blood count, LDH, alpha-fetoprotein, serum beta-HCG, and thyroid function studies.

IMAGING

Diagnosis of thymic tumors relies on thorough radiologic assessment of the mediastinum and chest. Computed tomography (CT) scan with intravenous (IV) contrast is recommended as the initial study to evaluate a mediastinal mass. Patients referred with noncontrast CT scans should obtain further imaging with IV contrast to assess enhancement of the mass and its relationship to vascular structures. Small thymic neoplasms are most often found in the normal anatomic thymic bed located in the cephalad portion of the substernal area, bounded by the innominate vein superiorly and the phrenic nerves laterally. Early stage thymomas are most often homogenous discrete masses, within the thymus with smooth, rounded borders (Figs. 1 and 2).

Both thymic carcinomas and invasive thymomas can have indistinct borders between contiguous mediastinal structures as well as internal heterogeneity representing necrosis, hemorrhage, or calcifications (Fig. 3). It is these presentations, where diagnosis and resectability are uncertain, where tissue diagnosis is important. Thymomas can be locally invasive but rarely metastasize to lymph nodes. In contrast, thymic carcinomas are aggressive tumors that frequently metastasize to regional lymph nodes. Although more common with thymic carcinomas, both can exhibit direct invasion of the lung, pericardium, innominate vein, great vessels, and phrenic nerves with associated hemidiaphragm elevation. Additional findings of more

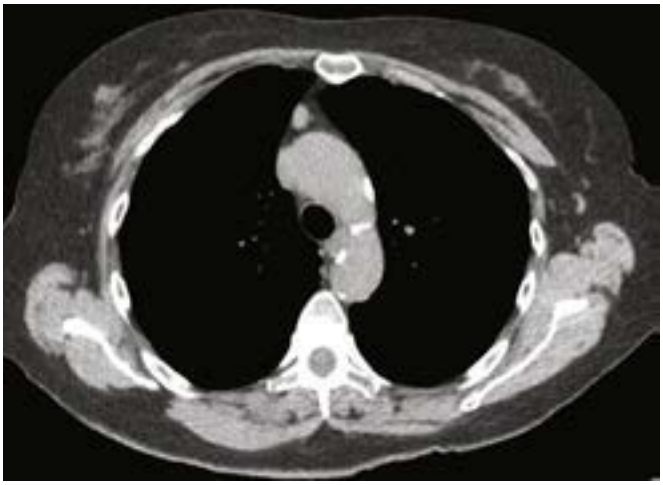


FIG. 1 A small, well-circumscribed stage I thymoma located just anterior to the aorta.



FIG. 2 A moderate size homogenous thymoma abutting the pericardium and right pleural space.

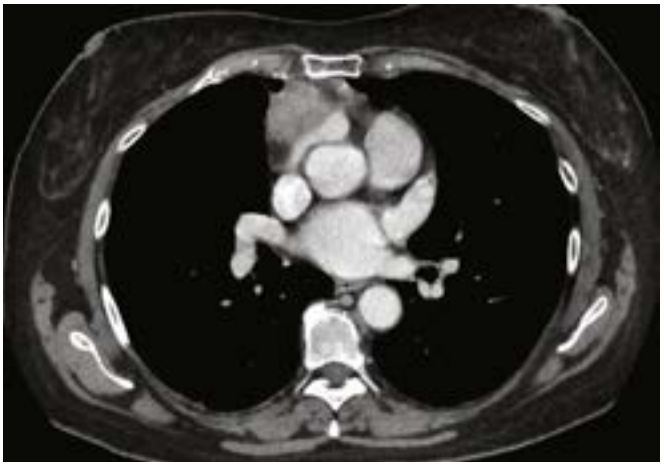


FIG. 3 A heterogenous, poorly defined anterior mediastinal mass representing a locally advanced thymic carcinoma with invasion into the pericardium.

aggressive disease include pleural implants or "drop metastases," pericardial effusions, and pleural effusions.

Magnetic resonance imaging (MRI) with thymic protocols are also frequently used in the evaluation of thymic tumors. MRI is recommended for patients with contraindications to obtaining contrast-enhanced CT, including renal dysfunction or contrast allergy. Thymic MRI can increase diagnostic specificity to distinguish thymic cysts from thymic neoplasms. Use of chemical shift sequence can aid in differentiating thymic hyperplasia from a thymic malignancy. Compared with CT, MRI can improve differentiation of tissue planes when there is concern for chest wall or vascular invasion. The role of positron emission tomography (PET) imaging is less clearly defined. PET can be utilized for determining whether extrathoracic metastases are present, especially for thymic carcinoma. PET is less useful for differentiation of thymic masses themselves, as avidity can be seen in normal thymic tissue as well as benign and malignant lesions.

TISSUE DIAGNOSIS

Anterior mediastinal masses have the classic differential of lymphoma, thymoma, teratoma, and substernal thyroid. Careful review of the radiologic characteristics and patient demographics, symptoms, and signs are usually diagnostic. Lymphomas rarely present as an isolated and discrete mediastinal mass; very large infiltrating tumors and those with associated lymphadenopathy elsewhere are those likely to be lymphoma (or unresectable thymic carcinoma) and warrant biopsy. Thyroid masses generally demonstrate continuity with the cervical thyroid and teratoma has a characteristic pattern of heterogeneous fat, calcifications, and soft tissue density. A well-circumscribed mass in the thymic bed without associated lymphadenopathy is highly likely to be a thymoma and usually does not need tissue confirmation before resection.

Pretreatment tissue diagnosis is not generally necessary, or advisable, for resectable masses in the anterior mediastinum that are likely to be thymoma. They do not change the indication for surgery and, depending on biopsy technique, may run the risk of tumor seeding in the mediastinum, biopsy tract, or pleural space. Bulky tumors and those that are infiltrating and appear unresectable do require tissue diagnosis to differentiate between lymphoma, thymic carcinoma, or an aggressive locally advanced thymoma. Usually a CT-guided core needle biopsy is feasible and has a high likelihood of being diagnostic. However, sometimes a surgical biopsy is needed. If a thymic neoplasm is in the differential, it is critically important to avoid a transpleural approach for surgical biopsy as this runs a very real potential of seeding the pleural space and converting a localized tumor to stage IV disease. Therefore, video-assisted thoracic surgery (VATS) or transpleural robotic approaches are contraindicated for biopsy in most cases. The most direct and safest approach for surgical biopsy is usually an anterior mediastinotomy or Chamberlain procedure.

HISTOLOGIC CLASSIFICATION

Historically, thymic epithelial tumors have been pathologically classified in three groups: thymomas without cellular atypia, atypical thymomas with cellular atypia or well-differentiated thymic carcinomas, and thymic carcinomas that are not well-differentiated and with aggressive features. NETTs were often a subgroup of thymic carcinoma, despite differing histology and behavior. It is also important to note that thymomas have different natural histories than thymic carcinomas and are not "advanced thymomas." The World Health Organization (WHO) proposed a histologic classification system in 1999 that was further refined in 2015. This system is the most widely used for pathologic differentiation between thymomas, thymic carcinomas, and NETTs. The WHO system provides the histologic diagnostic criteria for thymomas (Table 1) as well as the pathologic variants of thymic carcinoma (Table 2), with the most common being squamous cell carcinoma. The progression through the classification

TABLE 1 World Health Organization Histologic Classification of Thymomas

Thymoma Subtype	Obligatory Criteria
Type A	Occurrence of bland, spindle shaped epithelial cells, paucity or absence of T cells
Atypical type A variant	Criteria of type A thymoma; in addition: comedo-type tumor necrosis, increased mitotic count, nuclear crowding
Type AB	Occurrence of bland, spindle shaped epithelial cells, abundance of T cells focally or throughout tumor
Type B1	Thymus-like architecture and cytology: abundance of immature T cells, areas of medullary differentiation, paucity of polygonal or dendritic epithelial cells without clustering
Type B2	Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant T cells
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells, absent or rare intercellular bridges, paucity, or absence of intermingled T cells
Micronodular thymoma	Nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma
Metaplastic thymoma	Biphasic tumor composed of solid areas of epithelial cells in a background of bland-looking spindle cells; absence of T cells

Adapted from Marx A, Chan JK, Coindre JM, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol.* 2015;10:1383–1395.

system correlates with increasing invasiveness and worse prognosis, but there is often poor inter-reader reliability among pathologists in clinical practice and multiple cell types represented on final pathology. Prognosis is better determined by complete surgical resection and tumor stage.

STAGING

Multiple staging systems for thymic tumors have been proposed over the past decades. The most widely adopted is the Masaoka-Koga staging system (Table 3), which incorporates degree of tumor invasion and presence of metastases in staging both thymomas and thymic carcinomas. This system has been validated with mortality data from multiple studies, with 5-year survival rates for stage I disease up to 95% and rates for stage IVb disease less than 50%. More recently, the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) proposed a TNM classification for the staging of thymomas and thymic carcinomas, which was subsequently incorporated into the eighth edition of the American Joint Committee on Cancer (AJCC) staging manual.

TABLE 2 World Health Organization Thymic Carcinoma Subtypes (Type C)

Thymic Carcinoma
Squamous cell carcinoma
Basaloid carcinoma
Mucoepidermoid carcinoma
Lymphoepithelioma-like carcinoma
Clear cell carcinoma
Sarcomatoid carcinoma
Adenocarcinomas
- Papillary adenocarcinoma
- Thymic carcinoma with adenoid cystic carcinoma-like features
- Mucinous adenocarcinoma

NUT carcinoma
Undifferentiated carcinoma
Other rare thymic carcinomas
- Adenosquamous carcinoma
- Hepatoid carcinoma

Adapted from Marx A, Chan JK, Coindre JM, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. *J Thorac Oncol.* 2015;10:1383–1395.

PRINCIPLES OF SURGERY

The treatment of primary tumors of the thymus should be led by a thoracic surgery team with experience in caring for patients with thymic malignancies. The most effective treatment for thymic malignancies is complete surgical resection, which requires careful review of preoperative imaging by the thoracic surgeon to determine resectability. The main goal of surgery is a complete (R0) resection, as this has been shown to have a greater impact on prognosis than either preoperative stage or WHO histologic classification. Complete surgical resection necessitates total thymectomy, removal of all mediastinal fat, and en bloc resection of tumor with contiguous and noncontiguous disease. The standard borders of resection are bound by the phrenic nerves bilaterally, the sternum anteriorly, the

TABLE 3 Masaoka-Koga Staging System

Masaoka Stage	Diagnostic Criteria
I	Macroscopically encapsulated without microscopic capsular invasion
II	A: Microscopic transcapsular invasion B: Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs – pericardium, great vessels, lung A: Without invasion of great vessels B: With invasion of great vessels
IV	A: Pleural or pericardial dissemination B: Lymphogenous or hematogenous metastasis

Adapted from Detterbeck FC, Nicholson AG, Kondo K, et al. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. *J Thorac Oncol.* 2011;6:S1710–S1716.

pericardium posteriorly, the cervical thymic horns superiorly, and the diaphragm inferiorly. Removal of direct tumor invasion into adjacent tissues, including lung, pleura, pericardium, phrenic nerve, innominate vein, and other vascular structures, may be required to obtain R0 resection. Of course, preservation of the phrenic nerves is important for long-term pulmonary function. Sometimes it is possible to carefully skeletonize the phrenic nerve away from an adjacent mass, but occasionally it may be necessary to sacrifice one phrenic nerve that is invaded by tumor. Bilateral phrenic nerve resection is contraindicated due to its severe effect on respiratory function. In areas where there are close margins, surgical clips should be placed to guide potential adjuvant radiation therapy. Additionally, the specimen should be carefully marked and oriented after removal to assist the pathologist in determination of margins. The surgeon should avoid violation of the tumor capsule or overhandling the specimen to prevent dispersion of tumor cells and propagation of drop metastases. This should also include protection of the edges of the tumor extraction incision from exposure to tumor cells. The pleural surfaces should be examined for evidence of noncontiguous pleural-based disease, with resection of theses metastases if discovered. Mediastinal lymph nodes should be evaluated when resecting thymic carcinomas or NETTs, but this is not routinely necessary for thymomas as they rarely metastasize to lymph nodes. For patients with thymomas and associated myasthenia gravis, preoperative medical optimization is necessary to reduce the risk of postoperative myasthenic crisis or complication.

TRANS-STERNAL THYMECTOMY

Midline sternotomy is the gold standard surgical approach for resection of thymic malignancies. The incision provides adequate exposure to the lower neck and bilateral pleural spaces that can aid in performing an oncologically sound surgery in most cases. Additional transsternal approaches have been utilized depending on the degree of tumor invasion and planned extent of resection, including clamshell thoracotomy and combined sternotomy with anterolateral thoracotomy. Anesthesia placement of a double-lumen endotracheal tube allows single lung ventilation as needed to improve visualization of the pleural spaces. For a midline sternotomy, the patient is positioned supine, both arms tucked at sides, with a shoulder roll to improve exposure of the lower neck structures. Skin incision is made from sternal notch to xiphoid process, and dissection is carried down to the midline of the sternal periosteum. Sternotomy is performed with sternal saw. Standard sternal spreader provides adequate exposure of the anterior mediastinum. Internal mammary retractors can also be used for additional exposure to the pleural spaces. The pleura should be opened on both sides to expose the bilateral phrenic nerves and assess for pleural metastases. Dissection of the thymus and mediastinal fat is typically performed caudad to cephalad, beginning at the cardiophrenic angles near the diaphragm. All mediastinal fat should be removed to the level of the phrenic nerves bilaterally. Bipolar cautery can be used near the phrenic nerves to limit thermal spread and potential nerve injury. As the dissection continues cephalad, feeding vessels from the internal mammary vessels can be sequentially ligated and divided. Stapled wedge resections of involved lung tissue may be required for en bloc tumor removal. The thymus is reflected upward off of the pericardium, which can be resected with the specimen if there is noted tumor involvement. The cephalad portion of the dissection involves ligation of thymic branches from the innominate vein, gentle retraction of the specimen to deliver the superior poles of the thymus from the cervical space, and division of the thyrothymic ligament with associated feeding vessels. Ligation of the innominate vein can be considered in cases of gross tumor involvement. Direct invasion of the superior vena cava may require partial resection with repair or bypass grafting. Standard chest tube drains are placed in the pleural spaces and anterior mediastinum. The majority of patients are able to be extubated in the operating room and do not require intensive care unit monitoring. Drainage tubes are typically removed on postop days 1 or 2, and patients can be discharged in the following days with standard sternal precautions.

MINIMALLY INVASIVE RESECTION

Thoracic surgery as a whole has seen a broadening use of minimally invasive techniques, including video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS). These techniques have been adopted for the elective resection of benign thymus for management of myasthenia gravis. The role of minimally invasive surgery (MIS) for resection of thymic malignancies is more controversial. There are no prospective randomized control trials comparing minimally invasive resection to open resection of thymic tumors. Retrospective studies have highlighted potential for MIS thymectomy to reduce hospital stay, blood loss, and postoperative pain with reports of similar rates of R0 resection compared with open surgery. These studies are limited by lack of long-term follow-up data. Given the indolent nature of thymic malignancies, long-term data are needed to determine the oncologic completeness of minimally invasive approaches to thymic tumors. The routine use of MIS for thymic malignancies is not currently recommended. In the United States, approximately 25% of thymic tumors are resected using VATS or RATS. If MIS is used for a thymic tumor, it must follow all principles of thymic surgery as highlighted previously, including a complete dissection of the thymic bed for ultimate goal of R0 resection. In general, we believe that minimally invasive resection should be reserved for small (<3 cm), well-encapsulated tumors.

Minimally invasive thymic tumor resection can be performed from either side of the chest, and laterality is dictated by preoperative imaging. Often, the thymic tumor favors one side of the mediastinum, and surgical access can be obtained on the ipsilateral side of the tumor. For tumors that are midline, right chest access is frequently favored as there is less interference with the heart and better exposure of the superior vena cava and innominate vein. The patient should have a double lumen endotracheal tube placed for single lung ventilation on the contralateral side of surgical access. The patient is positioned with a large roll under the operative side to achieve a partial lateral decubitus position. Prepping of both sides of the chest can allow camera access to the nonoperative side of dissection to aid in visualization of the contralateral phrenic nerve if needed. Typically, three ports are placed that triangulate the anterior mediastinum, one camera port and two operative ports. Exact port locations are patient dependent but are placed approximately in the 3rd intercostal space in the midaxillary line, the 5th intercostal space in the anterior-axillary line, and the 7th intercostal space in the midclavicular line. Carbon dioxide insufflation can be used to increase visualization and maneuverability in the chest. The operation can be carried out in a similar fashion as the open technique, starting with dissection of mediastinal fat off of the diaphragm. The ipsilateral phrenic nerve should be identified early and carefully protected throughout the dissection. The thymus and adipose tissue should be skeletonized off of the superior vena cava with dissection proceeding cephalad to the junction of the brachiocephalic vein. An energy device can be used to ligate feeding vessels. The specimen is elevated en bloc off the pericardium. The thymic horns are delivered down from the neck and divided. The specimen should be placed in a retrieval bag to prevent dissemination of tumor cells. A chest drainage tube is typically left in the pleural space with subsequent removal postoperative day 1. Patients typically can be discharged the day after their surgery.

SYSTEMIC THERAPY

Neoadjuvant chemotherapy can be considered for locally advanced thymic malignancies when resectability is uncertain. Repeat imaging is recommended following completion of induction therapy. Patients with ipsilateral pleural metastasis or solitary metastasis can also be evaluated for induction therapy vs upfront surgery. Adjuvant

chemotherapy is often indicated for thymic carcinomas with microscopic residual tumor (R1 resection) or thymomas with macroscopic residual tumor (R2 resection) on final pathology. Definitive chemotherapy or chemoradiotherapy is indicated for patients with unresectable disease and chemotherapy alone for patients with evidence of extrathoracic metastases. Chemotherapy response rates are variable for thymic malignancies. Platinum-based chemotherapy regimens remain first-line systemic therapy for thymic tumors. There is an evolving role for targeted therapies in the treatment of thymic malignancies, though these drugs are often considered second-line therapy at this time.

RADIATION THERAPY

Thymic tumors are largely radiosensitive. All patients with positive microscopic or macroscopic margins after surgical resection should be evaluated for adjuvant radiation therapy. It is critical for surgeons to mark areas of close margins with clips at time of resection to help guide postoperative radiation planning if needed. Neoadjuvant radiation is rarely indicated for thymic tumors, as this limits potential postresection radiation options in patients that have focal positive margins who can otherwise benefit from more directed postoperative radiation treatment. Adjuvant radiation for completely resected thymic tumors is more controversial but can be considered for advanced stage tumors or thymic carcinomas with aggressive features. Frequently recurrences occur in the pleural space, so the benefit from postoperative mediastinal radiation after R0 resection in these patients is less clear. Locally advanced unresectable thymic tumors should be considered for definitive radiation in combination with chemotherapy.

SURVEILLANCE AND RECURRENCE

Locoregional recurrence rates after complete surgical resection of thymic epithelial tumors range from approximately 5% for stage I tumors up to approximately 50% for stage III tumors. Given the indolent nature of these tumors, it is important to maintain thorough postoperative surveillance. This can be especially critical for thymomas, as they often exhibit slower growth with potential for later recurrences. Patients are typically followed with postoperative surveillance CT chest with contrast every 6 months for 2 years, then annually for 5 years for thymic carcinomas, and annually for 10 years for thymomas. Fortunately, complete surgical resection of recurrences is often feasible, and prognosis for these patients approach similar survival rates as compared with R0 resections at time of index operation.

Suggested Readings

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Management of Tracheal Stenosis

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INTRODUCTION

Tracheal stenosis is the most common postintubation injury to the trachea and is usually the result of endotracheal tube cuff ischemic necrosis of the underlying trachea or tracheostomy stomal injury. Injury at the stomal level can lead to side-to-side contraction and an "A"-shaped stenosis sparing the membranous wall. Tracheostomy can have a combined stenosis with stomal and cuff injury. Other causes of benign tracheal stenosis are trauma, inflammatory, and idiopathic. Tracheal infections and several collagen vascular disorders may result in chronic inflammation with secondary tracheal stenosis. Prolonged oral intubation, high tracheostomy, or erosion of tracheostomy through the cricoid cartilage may result in subglottic stenosis. Idiopathic tracheal stenosis occurs most commonly in women and is characterized by a circumferential fibrotic stenosis in the subglottic larynx and upper trachea. Patients with tracheal stenosis have signs and symptoms of upper airway obstruction: dyspnea on exertion, cough, wheezing, stridor, and obstructive pneumonia. The presentation of tracheal stenosis is often confused with adult-onset asthma; therefore, steroid therapy is often initiated before the correct diagnosis is ascertained.

INDICATIONS FOR TRACHEAL RESECTION

In general, any patient who has airway stenosis as a result of tracheal injury should be considered for a tracheal resection and reconstruction. Absolute contraindications are few and include a nonconstructible airway (usually due to an excessive length of damaged airway), severe comorbidities, or a prolonged need for mechanical ventilation. Relative contraindications include a history of radiation to the trachea, which limits tracheal mobility and impairs microvascular blood supply, active trachea mucosal inflammation, and active steroid therapy. Steroids should be weaned before tracheal reconstruction because they play no role in the amelioration of postintubation stenosis and interfere with healing of the tracheal anastomosis. Purulent, copious secretions are a relative contraindication. If necessary, tracheal dilation can be performed until inflammation subsides and steroids are discontinued. Surgery should be delayed 2 to 4 weeks after discontinuation of steroids. Other diagnoses such as relapsing polychondritis, scleroderma, polyarteritis, sarcoid, and granulomatosis with polyangiitis should be excluded.

PREOPERATIVE ASSESSMENT

Before tracheal resection and reconstruction is undertaken, the definitive diagnosis of the underlying pathology of the airway must be established. A preoperative assessment should include a history and physical, radiologic imaging, and bronchoscopy. Soft tissue radiographs of the neck can demonstrate the location of a subglottic/upper tracheal lesion, its linear extent, extratracheal involvement, and the amount of normal trachea. However, high resolution

computed axial tomography with 3D reconstruction has become the preferred method of imaging and allows measurements of the length and configuration of tracheal stenosis as well as its relationship to surrounding structures and thickness of tracheal walls (Fig. 1).

Bronchoscopy is invaluable in determining the extent of airway disease and the quality of the mucosa. The initial evaluation is best performed in the operating room with a rigid bronchoscope carefully inserted through the vocal cords just proximal to the point of stenosis. The rigid bronchoscope can then be used to measure the length of a stenotic segment of trachea, as well as assess the mucosa for inflammatory changes and granulation tissue (Fig. 2). Crucial to the management of tracheal stenosis is the ability to control the airway. Control of the airway is best accomplished in the operating room with an assortment of rigid bronchoscopes. Attempting to pass a large rigid bronchoscope beyond a tight inflammatory stricture is usually difficult and can result in tracheal rupture or total airway obstruction from bleeding and edema. Graduated rigid bronchoscopes (pediatric to adult) are preferred to dilate postintubation strictures serially. Balloon dilators are used by some but not preferred by us. Racemic epinephrine and steroids are often administered for 24 to 48 hours to minimize postdilatation edema. Caution should be exercised using flexible bronchoscopy in the outpatient setting when tracheal stenosis is suspected.

A complete morphologic and functional assessment of the larynx including voice and swallowing function can also be obtained preoperatively. This provides a baseline assessment of functional impairment and can be useful for tracking and comparing important functional outcomes postoperatively. A complete assessment includes transnasal video laryngoscopy, a flexible endoscopic evaluation of swallowing (FEES), and voice assessment, which can be assessed via a perceptual voice sound scaling, voice range profile, or Goettingen hoarseness diagram. Patient-based questionnaires are also increasingly used to determine voice quality and swallowing function and may include the Voice Handicap Index (VHI) or Dysphagia Handicap Index (DHI).

ANESTHESIA AND AIRWAY MANAGEMENT

Anesthesia for tracheal resection is best administered as total intravenous anesthesia (TIVA). This process provides satisfactory anesthesia and muscle relaxation before intubation, decouples ventilation and the delivery of anesthesia, and avoids environmental contamination of volatile anesthetics during the case. It also blunts airway reflexes, and its effects wear off quickly at the completion of the operation. Remifentanil and propofol are delivered by infusion and are excellent agents commonly used with TIVA, which has supplanted deep inhalation anesthetic techniques except in the case of critical stenosis when spontaneous ventilation must be preserved. This technique requires patience and time to reach the desired level of anesthesia. A laryngeal mask is placed, and the airway can be evaluated with a flexible bronchoscope and a pulmonary balloon can be used to dilate the airway. TIVA allows for a smoother, much more controlled emergence from anesthesia.

The surgeon should be available with an array of rigid bronchoscopes during induction of anesthesia to control the airway. A stricture less than 6 mm in diameter is dilated under direct vision with rigid pediatric bronchoscopes. It is not necessary to dilate a stricture beyond this diameter to accommodate a 5- or 5.5-mm endotracheal tube to avoid tearing or perforating the airway. If the stricture is more than 6 mm, a small endotracheal tube (5.5 mm) may be placed through the lesion. If the tracheal stenosis is located in the subglottic area, the lesion usually

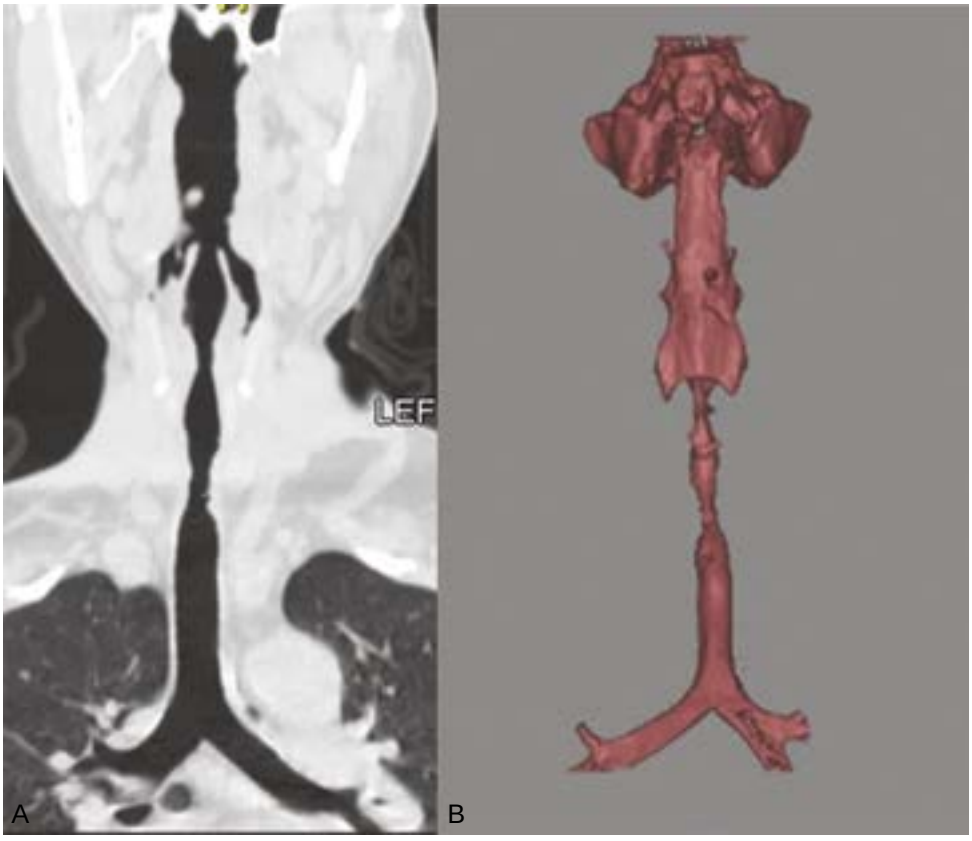


FIG. 1 Computed tomography **(A)** with 3D reconstruction **(B)** of a patient with tracheal stenosis.

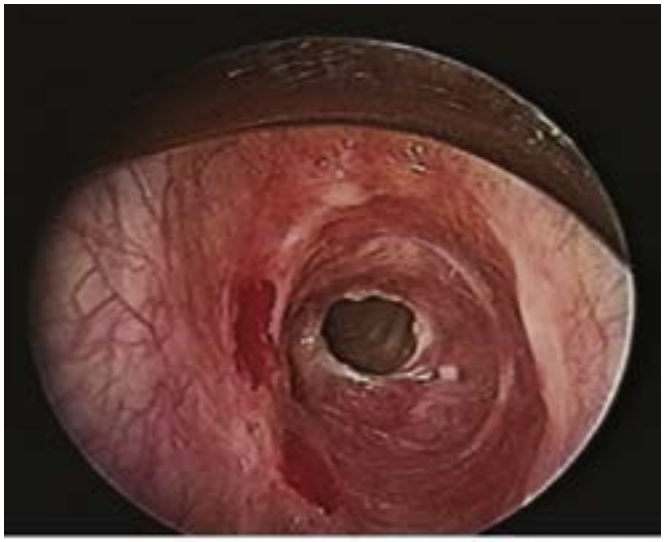


FIG. 2 Typical bronchoscopic appearance of an idiopathic subglottic tracheal stenosis.

requires dilation to allow passage of a small endotracheal tube. During resection of the trachea, the airway is divided, and the distal end of the trachea can be directly intubated with an armored, flexible endotracheal tube (Tovell tube). Sterile connecting tubes are passed off the surgical field to the anesthesiologist. The Tovell tube can be intermittently removed for brief periods of apnea to allow careful and precise placement of sutures. This technique allows ventilation during reconstruction of the trachea. Before completion of the tracheal anastomosis, the oral endotracheal tube is retrieved from the proximal trachea and passed distal to the suture line. Ideally, the patient should be extubated and breathe spontaneously at the conclusion of the operative procedure. This requires close coordination between surgeon and anesthesiologist. It is not desirable to have even a low-pressure cuff in close contact with the anastomosis for any period of time. If the patient does require intubation after surgery, a small, uncuffed endotracheal tube is preferred. The tube should be removed within 24 to 48 hours. If the airway is still a concern, a small tracheostomy should be placed two rings below the anastomosis. The innominate artery and tracheal anastomosis should be separated by a strap muscle flap carefully sutured to the trachea.

SURGICAL TECHNIQHE FOR TRACHEAL RESECTION

The patient is placed supine on the operating table with a roll or inflatable bag underneath the shoulders to extend the neck. A cervical or upper cervicomediastinal approach is used for benign strictures of the trachea at any level. The trachea is explored through a collar incision, which may encompass an existing tracheal stoma (Fig. 3A). Skin flaps are raised with platysma to the cricoid cartilage superiorly and the sternal notch inferiorly. The medial margins of the strap muscles are elevated, and the anterior surface of the trachea is bluntly exposed from the sternal notch to the carina. The thyroid isthmus is divided, dissected from the trachea, and retracted laterally with sutures. It is essential to keep the dissection absolutely close to the trachea to avoid injury to the recurrent laryngeal nerves, esophagus, and back wall of the innominate artery. If the innominate artery is adherent to the trachea and requires dissection, a strap muscle flap should be interposed between the artery and tracheal anastomosis at the completion of reconstruction. For lesions that are too far below the sternum to be accessible through a collar incision, the exposure can be increased by making a T incision in which the vertical arm extends downward to a point 1 cm below the sternal angle. The manubrium is divided to that point and separated with a pediatric chest spreader (Fig. 3B). No additional useful exposure is obtained by full median sternotomy because the carina lies at the level of the angle of Louis and the great vessels

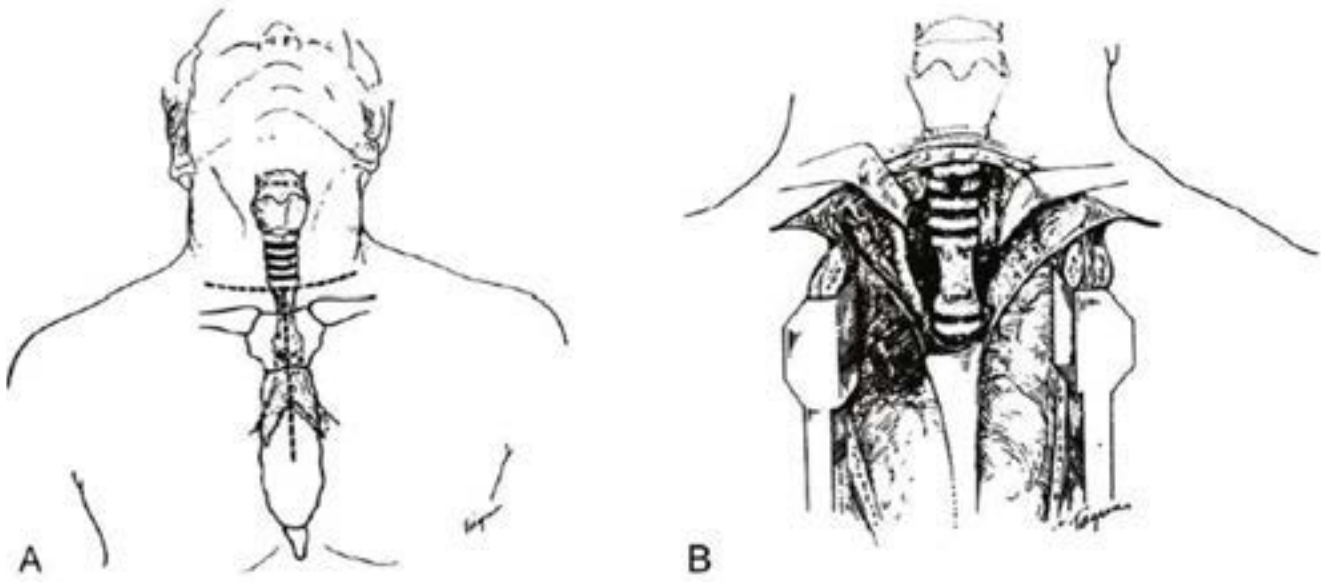


FIG. 3 Tracheal resection and reconstruction for postintubation stenosis. **(A)** A collar incision provides access for many upper tracheal lesions. For a wider access to the upper thoracic inlet and the mediastinum, a partial sternotomy is performed. Usually the incision is not carried more than 1 or 2 cm below the angle of Louis. This provides exposure even for the supracranial benign stenosis. **(B)** Partial sternotomy with retraction of innominate vein and artery without their exposure. The pretracheal plane is dissected only. Circumferential dissection is performed only just below the lesion. *(From Mathisen DJ. Curr Probl Surg. 1998;35:453.)*

obstruct access from an anterior approach. The upper sternal division provides access to the lower trachea. The innominate vein, which lies anterior and caudal to the dissection, is not divided. The innominate artery is dissected away from the trachea without exposing the wall of the artery. The anterior carina and the right and left tracheobronchial angles can be exposed as needed.

In cases of tracheal stenosis, the dissection is made meticulously along the lateral borders of the involved trachea and posteriorly approximately 1 cm below the lesion. If it is difficult to identify the level of the lesion, intraoperative bronchoscopy can help to localize the lesion. After carefully pulling the endotracheal tube back under bronchoscopic control, the position of the bronchoscope light is identified at the upper and then the lower end of the lesion while an assistant inserts a 25-gauge needle through the tracheal wall for precise localization. These levels are marked with fine sutures. Dissection close to the tracheal wall avoids injury to the recurrent laryngeal nerves, which lie in the tracheoesophageal groove on either side. This is particularly important if the stenosis lies just below the cricoid cartilage because the recurrent laryngeal nerves enter the larynx just medial to the inferior cornua of the thyroid cartilages. As the trachea is dissected circumferentially, great care must be taken to avoid perforation of the esophagus or the membranous wall of the trachea posteriorly. After the circumferential dissection of the trachea is completed, a tape is passed beneath the trachea for traction on the airway.

Before the division of the trachea, sterile anesthesia equipment is assembled on the field, and sterile corrugated tubing is passed off the table to the anesthetist. Lateral traction sutures of 2–0 Vicryl (Ethicon, Somerville, NJ) are placed on either side of the trachea in the midlateral position approximately 1 cm below the anticipated level of transection. These sutures pass vertically through the full thickness of the tracheal wall and around one ring. The trachea is opened anteriorly just distal to the lesion, staying close to the lesion if it is a benign stricture. Healthy cartilage should be present at the cut edge of the trachea. Transection of the trachea is generally above the ring, but it is acceptable to make the incision in the cartilage. When the airway is open, intermittent suctioning prevents seepage of blood into the distal airway. After transection, an assistant holds tension on the two lateral traction sutures and holds the flexible armored Tovell tube in the distal trachea. This maneuver draws the distal trachea and the ventilating tube away from the dissection. Circumferential dissection of the remaining proximal and distal trachea is limited to no more than 1 cm to protect the segmental blood supply, which enters laterally. Devascularization of healthy trachea that will be anastomosed invites possible necrosis and anastomotic dehiscence.

To test the ease with which the tracheal ends can be brought together, the anesthesiologist flexes the patient's neck, and the surgeons draw on the crossed proximal and distal traction sutures, bringing the tracheal ends together. The surgeon should be able to judge whether the tension is excessive. The length of trachea that may be safely removed should be determined before division of the trachea. The feasibility of resection is based on radiologic and bronchoscopic examinations made before the operation. The length of trachea that can be safely removed is influenced by the patient's age and body habitus, by the anatomy of the trachea, and by previous treatments. It is wise to open the trachea conservatively into slightly damaged trachea and resect conservatively, checking by approximation to be certain the airway will come together. After it has been demonstrated that the tracheal ends will come together without excessive tension, the neck is extended again. The first anastomotic suture (4–0 coated Vicryl) is placed in the posterior midline with the knots on the outside. These sutures pass vertically through the full thickness of the tracheal wall and around one ring (Fig. 4A). The sutures are carefully clipped to the drapes. The next suture is placed anterior to this and clipped to the drapes just caudad to the previous one. The sutures are placed serially until a point is reached at the midlateral tracheal traction suture (Fig. 4B). The same placement of

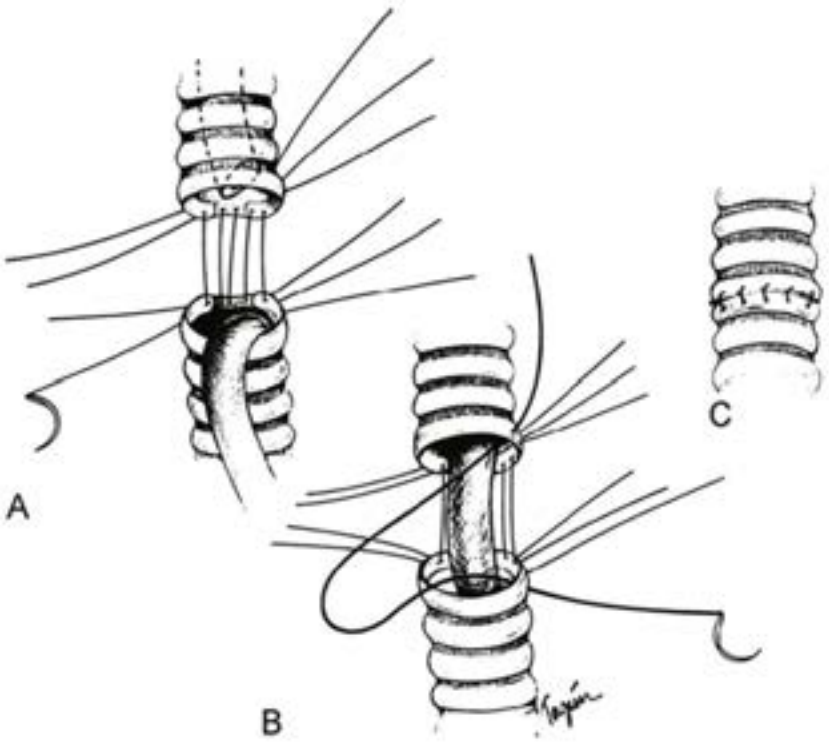


FIG. 4 Tracheal anastomosis. **(A)** Sutures are placed individually beginning in the midline posteriorly and ranging anteriorly on either side. **(B)** After the sutures are placed on either side up to the level of the midlateral traction sutures, the anterior sutures are then placed. Frequently, the endotracheal tube is not advanced from above until after all the sutures are placed. **(C)** The neck is placed in the flexed position, and the lateral traction sutures are tied on either side (not shown) to remove tension from the anastomotic sutures. After this, anastomotic sutures are tied from anterior to posterior on either side. The completed anastomosis is airtight. *(From Mathisen DJ.* Curr Probl Surg. *1998;35:453.)*

sutures is now carried out on the opposite side, from the posterior midline to the midlateral traction suture. Serial sutures are similarly placed anteriorly, proceeding from the lateral traction sutures to the midline. The sutures are placed through the cartilage approximately 4 mm from the cut edge of the trachea and 4 mm apart. When all the sutures are placed, the oral endotracheal tube is advanced from above until the tip is visible in the wound. The distal trachea is suctioned, and the endotracheal tube is advanced further, resuming ventilation through the original oral endotracheal tube. Care must be taken not to entangle the endotracheal tube in the anastomotic sutures. The patient's head is firmly supported on blankets in flexion. The crossed lateral traction sutures are pulled together on either side and tied with surgeon's knots opposing the tracheal ends.

The anterior anastomotic sutures are tied first without tension, and the ends are cut after each suture is tied. The assistant then rotates the trachea by carefully drawing medially on the traction sutures on the surgeon's side of the table. The surgeon ties the suture just behind the lateral traction suture and ties sutures in the direction of the posterior midline. This same technique is repeated on the opposite side (Fig. 4C). The cut traction sutures are left in place to guard against tension on the anastomotic sutures. The integrity of the anastomosis is checked by deflating the cuff and hearing a rush of air around the tube (confirms an adequate lumen), submerging the wound in saline solution, covering the mouth and nose, and insufflating to pressures between 20 and 30 cm H_2O. All anastomoses must be airtight, and a patient should not leave the operating room with an air leak. A leak must be repaired, even if it means taking the anastomosis down and redoing it again. The sternohyoid muscle or the thyroid isthmus is then used to cover all suture lines. This serves as a buttress, an adjunct to healing, and a barrier to superficial wound infections. If there is any concern regarding dissection of the innominate artery, a pedicled strap muscle should be interposed between the innominate artery and the trachea. Flat suction drains are placed in the pretracheal and substernal spaces, and the strap muscles are approximated in the midline. After the incision is closed, a heavy suture is placed through the submental skin crease beneath the chin and through the presternal skin. This suture is tied with the patient's neck in moderate flexion to prevent sudden hyperextension of the neck in the first week after the operation. Hyperflexion of the neck can result in ischemia to the spinal cord and quadriplegia and should be avoided.

If it is determined after neck flexion that excessive anastomotic tension exists, maneuvers should be performed to reduce tension. The most helpful maneuver for the upper and midtrachea is the Montgomery suprahyoid release. This can be performed by exposing the hyoid through a small horizontal incision just over the hyoid. The muscles inserting on the superior aspect of the hyoid between the lesser cornu are divided. The hyoid bone is divided just lateral to the lesser cornu on both sides. This release maneuver usually gives between 1 and 2 cm of additional mobility of the trachea.

After tracheal resection, patients are usually extubated in the operating room. If the airway is not satisfactory at this point, it is not likely to improve later unless the problem is caused by laryngeal edema. A small endotracheal tube with the cuff deflated can be left in place for 24 to 48 hours while the laryngeal edema resolves. The patient should be given 24 to 48 hours of steroids (Decadron, 4 mg intravenously every 6 hours), diuretics, fluid restriction, and have their head elevated in bed to reduce edema. We prefer to return to the operating room at the end of 48 hours and extubate the patient under anesthesia. If there is still a problem, a small tracheostomy tube is placed two rings below the anastomosis. A pedicled strap muscle flap should be employed to cover the anastomosis if not already performed. If doubt exists about the need for a protective tracheostomy, a "minitracheostomy" is useful to allow access of a more permanent tube. The minitracheostomy (5 mm lumen) allows suctioning and oxygen but is not a stable long-term solution. If the airway is determined to be stable, the minitracheostomy can be removed under bronchoscopic guidance at 7 days when the anastomosis is checked.

COMPLICATIONS OF TRACHEAL SURGERY

Complications after tracheal surgery are similar regardless of the problem for which resection and reconstruction is performed. Avoiding anastomotic tension and devascularization are the keys to minimizing complications. In general, resections greater than 4 cm should include additional maneuvers to avoid anastomotic tension. Standard techniques include dissection of the pretracheal plane, neck flexion, traction sutures, and suprahyoid laryngeal release in extreme cases.

One of the most common complications in the immediate postoperative period is edema, especially after subglottic resection. Edema generally manifests after 24 to 72 hours and is the most likely culprit for reduced airflow in the first few days after surgery if an adequate airway was demonstrated in the operating room. Separation and secretions are other explanations that must be considered. Edema is treated as previously described. Heliox can be used if shortness of breath is symptomatic.

If an air leak develops postoperatively, as manifested by subcutaneous emphysema, this could be a harbinger of separation and is a surgical emergency. The patient should be immediately returned to the operating room and the airway secured. In cases of separation, repair is unlikely and tracheostomy or a T-tube should be used to secure the airway. Local muscles can be used to buttress the tracheostomy or T-tube. If the airway is stable and the subcutaneous air is minimal, then CT imaging may be helpful in the initial assessment. Either way, the patient should undergo bronchoscopy to assess the competency of the airway. If a dehiscence is found, then surgical exploration and securing of the airway with a tracheostomy or T-tube is preferable. If the airway is secure and only a small leak from a suture or a small area of necrosis is identified, then attempted local repair buttressed by muscles utilizing suction to press the flaps securely in the damaged area is oftentimes successful. Alternatively, hyperbaric oxygen therapy (HBOT) has been used to enhance angiogenesis, improve wound healing, enhance reepithelialization, and avoid reoperation. Its use is predicated on a stable airway.

The most in-depth analysis of complications after tracheal surgery was reported by Wright and colleagues in patients with postintubation stenosis. The most common nonanastomotic complications are presented in Table 1. Of 392 patients treated between 1993 and 2017 in this series, only 3 (0.8%) died. The etiology of these deaths were pulmonary embolism, respiratory failure, and death after heart transplantation. Overall morbidity was 33%. There were no instances of postoperative tracheovascular fistula. Reintubation was required in 19 patients and usually represented an underlying anastomotic problem or inadequate airway due to structural issues or edema. Of the patients who required reintubation, 63% eventually had a good or satisfactory outcome, failure occurred in 26% (5 of 19), and death occurred in 10% (2 of 19). Voice changes occurred in 17 out of 392 patients. These changes reflected either vocal cord paresis (8 patients) or paralysis (9 patients).

Anastomotic complications are presented in Table 2. The most common complications were edema in 56 patients (14%) and granulation tissue formation in 70 (18%). Dehiscence or necrosis occurred in 16 patients (4%), with 10 patients having both. Wound infections occurred in 15 patients, all associated with necrosis or dehiscence. Risk factors for anastomotic complications include diabetes, resections greater than 4 cm, prior tracheostomy, age less than 17, and reoperations.

More recently, the use of HBOT has been studied as an intervention to enhance wound healing and avoid reoperation, tracheostomy, or T-tube placement in patients with anastomotic complications after tracheal resection and reconstruction. HBOT is the administration of 100% oxygen at pressures greater than 1 atm and is thought to promote wound healing by increasing angiogenesis and collagen synthesis. In a recent series published by Tapias and colleagues, patients with varying degrees of failed anastomotic healing, from cartilage necrosis to mild

TABLE 1 Most Common Postoperative Complications, Nonanastomotic

Complication	Total (% [n/N])	Good (n)	Satisfactory (n)	Failure (n)	Death (n)
Reintubation	4.8 (19/392)	3	9	5	2
Voice changes					
Vocal cord paralysis	2 (9/392)	2	5	2	—
Vocal cord paresis	2 (8/392)	4	2	2	—
Pneumonia	3 (13/392)	4	5	2	2
Cardiovascular	3 (13/392)	9	2	1	1
Neurologic	2.8 (11/392)	5	3	3	—
Tracheitis	2.5 (10/392)	6	1	3	—
Subcutaneous air	2.5 (10/392)	3	5	1	1
Renal failure	1.5 (6/392)	3	2	0	1

*Good outcome defined as the ability to perform usual activities and a patent airway at bronchoscopy; satisfactory outcome defined as no symptoms with normal activities but symptoms with exercise, vocal cord dysfunction, or evidence of narrowing by bronchoscopy; failure was determined by the need for postoperative tracheostomy or T-tube.

From Wright CD, et al. *Ann Thorac Surg.* 2019;108:1471–1477.

TABLE 2 Anastomotic Complications*

Complications	No.	Minor (n [%])	Major (n [%])
Anastomosis edema	56	52 (93)	4 (7)
Granulation	70	58 (83)	12 (17)
Necrosis	12	4 (33)	8 (66)
Dehiscence	14	3 (21)	11 (79)
Wound Infection	15	2 (13)	13 (87)

*Major required procedure intervention; minor treated conservatively.

From Wright CD, et al. *Ann Thorac Surg.* 2019;108:1471–1477.

separation identified by bronchoscopy, were treated with HBOT. A total of 23 patients underwent a median of 9.5 HBOT sessions that were administered in 90-minute intervals in a hyperbaric chamber pressurized to 2 atm with 100% oxygen over a median course of 8 days. In addition, patients were treated with broad-spectrum IV antibiotics, tobramycin nebulizers, and Heliox as clinically indicated. The airway anastomosis healed in 20 of 23 (87%) patients. Overall, a satisfactory long-term airway outcome was achieved in 19 (83%) patients. Four patients failed and required reoperation. Complications were minor and included inner ear discomfort and temporary blurry vision.

RESULTS

The results of tracheal resection and reconstruction have proven to be quite successful. In a series spanning from 1993 to 2017, a total of 392 patients underwent tracheal resection and reconstruction for postintubation stenosis, 45 of which were done for restenosis after an initial attempt at repair (Table 3). The amount of trachea resected ranged from 1 to 7.75 cm with a median length of 3 cm. Laryngeal release was performed in 3.8% of cases and 99% of the anastomoses were covered with a vascularized tissue buttress. Results were good (defined as an anatomically intact airway in a functionally normal patient) or satisfactory (defined as patients able to perform normal activities but with abnormalities such as stress with exercise, a paralyzed vocal cord, or

TABLE 3 Postintubation Tracheal Stenosis — MGH Experience 1993–2017

	% (n/N)
No. of resections [per year]	392 [16.3]
Mortality	0.8 (3/392)
Overall complications	33 (130/392)
Subglottic stenosis	23.2 (91/392)
Prior procedures	92 (361/392)
Preoperative tracheostomy	70 (275/392)
Release	3.8 (15/392)
Reoperations	11.5 (45/392)
Stent	11 (44/392)
Laser use	21 (82/392)
Length of resection, cm [range]	3 [1–7.75]
Mean age, years	46

From Wright CD, et al. *Ann Thorac Surg.* 2019;108:1471–1477.

bronchoscopic evidence of narrowing) in 365 (93%) patients. Patients who underwent a primary tracheal resection and reconstruction had a good/satisfactory outcome in 96% of cases compared with 84% of patients who underwent a laryngotracheal resection. There were 24 failures (6%) and 3 deaths (0.8%).

The effect of additional treatments on outcomes can be seen in Table 4. Patients who had a prior tracheostomy that was removed before surgery had a good or satisfactory outcome in 96% of cases compared with 85% of patients who had a tracheostomy present at the time of surgery. At the conclusion of surgery, 27 patients required a protective tracheostomy, of which a good or satisfactory outcome was achieved in 74%. In contrast, 24 patients left the operating room without a tracheostomy but later required an emergent tracheostomy early in their postoperative course. In these patients, a good or satisfactory outcome was only achieved in 38%, 54% failed, and 8% died. Prior T-tube and stents also led to worse outcomes, whereas prior dilations and laser treatments did not have a significant effect on outcomes. In patients who underwent a reoperation, 91% had a good or satisfactory outcome and 9% failed. Additional prognostic factors are presented in Table 5. Multivariable analysis

TABLE 4 Effect of Additional Treatment on Outcomes

Additional Treatment	No of Patients	Good/Satisfactory (% [n])	Failure (% [n])	Death (% [n])	*P*-value
No prior treatment[a]	31	97 (30)		3% (n = 1)	—
Tracheostomies					
Removed before surgery	152	96 (146)	4 (6)	—	0.150
Present at time of surgery	124	85 (105)	15 (18)	0.8 (n = 1)	0.017
Postoperative protecting	27	74 (20)	26 (7)	—	<0.001
After surgery	24	38 (9)	54 (13)	8 (2/24)	<0.001
T tubes	62	90 (55)	110 (76)	—	0.034
Stents	44	89 (39)	11 (5)	—	0.038
Dilations	201	96.5 (194)	3.5 (78)	0.5 (n = 1)	0.196
Laser	82	95 (78)	5 (4)	—	0.202
Reoperation	45	91 (41)	9 (4)	—	0.075

[a]Reference group

*Good outcome defined as the ability to perform usual activities and a patent airway at bronchoscopy; satisfactory outcome defined as no symptoms with normal activities but symptoms with exercise, vocal cord dysfunction, or evidence of narrowing by bronchoscopy; failure was determined by the need for postoperative tracheostomy or T-tube.

From Wright CD, et al. *Ann Thorac Surg.* 2019;108:1471–1477.

TABLE 5 Outcomes Based on Possible Prognostic Factors

Outcome	No of Patients	Good/Satisfactory (% [n])	Failure (% [n])	Univariate *P*-value	Multivariate *P*-value
Trachea to trachea anastomosis	301	96 (289)	4 (12)	—	
Laryngotracheal	91	84 (77)	16 (14)	<0.001	0.001
Reoperation	45	91 (41)	9 (4)	0.512	
Complications	130	80 (104)	18 (23)	<0.001	
Calcified airway	70	89 (62)	11 (8)	0.058	0.562
Steroids at surgery	34	91 (31)	9 (3)	0.458	
Length ≥5 cm	12	89 (11)	8.5 (1)	0.554	
Diabetes mellitus	97	93 (90)	7 (7)	0.708	
Tracheostomy at surgery	123	85 (105)	15 (18)	<0.001	0.001
Release	15	87 (13)	13 (2)	0.250	
Age, yr, mean ± SD		46 ± 18	47 ± 18	0.650	
Sex				0.820	
Male	196	94 (184/196)	6 (12/196)		
Female	196	93 (183/196)	7 (13/196)		

*Good outcome defined as the ability to perform usual activities and a patent airway at bronchoscopy; satisfactory outcome defined as no symptoms with normal activities but symptoms with exercise, vocal cord dysfunction, or evidence of narrowing by bronchoscopy; failure was determined by the need for postoperative tracheostomy or T-tube

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indicated that laryngotracheal resections and tracheostomy at the time of surgery led to the worst results. Age, sex, a history of diabetes mellitus, and the use of a hyoid release did not influence outcomes. Low-dose steroids were needed at the time of surgery in 34 patients despite attempts to wean them off. Good or satisfactory results were achieved in 91% ($P = 0.458$) of patients still receiving steroids at the time of surgery.

Long-term results after laryngotracheal resection and reconstruction have also proven to be successful. Nauta and colleagues reported a series of 43 patients who underwent laryngotracheal resection for benign subglottic stenosis. At a mean of 53 months of follow-up, 95% of patients had late surgical success. Functional questionnaires were also administered, and overall, patients reported a significant improvement in dyspnea during rest and exercise. Swallowing was unchanged before and after surgery, voice impairment was absent to moderate in 88%, and 85% of patients reported an improvement in quality of life.

Suggested Readings

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Management of Acquired Esophageal Respiratory Tract Fistula

James T. Nawalaniec, MD, and Christopher R. Morse, MD

OVERVIEW

A tracheoesophageal fistula (TEF) is a pathologic communication between the respiratory tract and esophagus. These fistulas develop in the setting of benign or malignant conditions. In adults, benign fistulas are most commonly acquired as a result of prolonged endotracheal intubation in mechanically ventilated patients and are typically managed with surgery. Malignant fistulas are challenging to manage, and a conservative approach directed at patient palliation remains the mainstay of therapy. This chapter reviews the cause, clinical manifestation, diagnostic approach, and surgical management of acquired TEF.

PATHOGENESIS

An acquired TEF is caused by tissue necrosis and breakdown of the respiratory tract and esophagus, which results in a pathologic communication between the two structures. They are most commonly located in the upper one-third of the esophagus, where the membranous wall of the trachea lies adjacent to the esophagus. Any TEF can be broadly classified as either benign or malignant. The latter is the most common cause of acquired TEF, and esophageal carcinoma, particularly squamous cell carcinoma, is responsible for the majority of cases. Other causes include direct invasion by bronchogenic or thyroid carcinoma or, more rarely, mediastinal lymphoma. In addition, radiation therapy, often necessitated by these malignancies, poses an increased risk for TEF. Benign TEF can be subclassified as iatrogenic, infectious, or traumatic based on the cause.

Iatrogenic

The most common cause of benign TEF is prolonged mechanical ventilation. The inflated cuff of an endotracheal tube presses against a hard esophageal tube, usually a nasogastric tube or temperature probe, which leads to pressure necrosis at the posterior membranous tracheal wall and anterior esophagus. Over time, there is full thickness necrosis, resulting in a pathologic connection between the trachea and esophagus. The risk of developing a TEF is increased in patients with impaired wound healing, such as the immunocompromised, those on corticosteroids, or those with poorly controlled diabetes. Because these connections develop insidiously, gross contamination of the mediastinum is not common. Other iatrogenic causes of TEF include injuries sustained during procedures, such as intubation, tracheostomy tube placement, and esophageal or airway surgery. For example, postsurgical anastomotic leak or devascularization of the trachea from close bilateral paratracheal dissection potentiates the risk for TEF, as does dilation of benign esophageal strictures or surgical anastomoses of the trachea or esophagus. Moreover, stenting of the trachea or esophagus can result in erosion or injury, especially if placement or extraction of the stent is difficult or traumatic.

Infectious

Infectious TEF is most seen with pathogens that cause granulomatous inflammation, including histoplasmosis and tuberculosis. These infections are both more common and more severe in patients with immunodeficiency syndromes, including human immunodeficiency virus.

Traumatic

A TEF can be acquired as a result of a traumatic process, such as foreign body impaction and erosion, ingestion of caustic agents, or penetrating or blunt trauma to the neck. Unlike most iatrogenic TEF, traumatic TEF develops acutely, which often leads to gross contamination of the mediastinum. It is important to recognize that, in cases of polytrauma, the diagnosis of TEF may be delayed during the treatment of other life-threatening injuries. As is discussed in this chapter, the surgical management of traumatic TEF may therefore follow an alternate algorithm.

CLINICAL FEATURES

Despite the broad spectrum of causes, the clinical features of acquired TEF in adults are similar and represent the sequelae of an abnormal connection between the upper respiratory and gastrointestinal tracts. Patients generally present with chronic cough, often exacerbated by oral intake with expectoration of food. Secondary to recurrent aspiration across the TEF, they often develop recurrent bronchopulmonary infections, which may manifest as hemoptysis, fevers, or frank and life-threatening pneumonia or mediastinitis; the latter is more likely in an acutely acquired TEF. Notably, TEF caused by malignancy often becomes apparent after chemotherapy or radiotherapy treatment of the primary tumor.

In the mechanically ventilated patient, signs suggestive of TEF include inadequate return of tidal volumes, often in the setting of gastric abdominal distension on physical examination or a large gastric bubble on abdominal imaging. Additional clues include increased secretions, aspiration of tube feeds from the airway on manual suction, difficulty maintaining seal with the cuff of the endotracheal tube, or persistent sepsis, pneumonia, or pulmonary infiltrates not attributable to other causes.

DIAGNOSIS

In patients with suspected TEF, diagnostic workup begins with chest radiography. This may reveal sequelae of a TEF, including aspiration pneumonitis or a dilated stomach and distal esophagus in patients on positive pressure ventilation. In patients with recurrent aspiration, swallow evaluation may be beneficial to rule out oropharyngeal dysphagia as a cause. Small fistulas (<1 cm) are difficult to diagnose and are best detected with barium swallow using dilute barium (Fig. 1). Large fistulas are best diagnosed with bronchoscopy and esophagoscopy. Bronchoscopy is essential to locate the fistula and to perform a mucosal survey. Rigid bronchoscopy allows for complete inspection of the airway, including careful measurements such as fistula size and distance between the fistula and the vocal cords proximally, as well as the carina distally. Bronchoscopy also provides the opportunity for biopsy if malignancy is suspected and cultures to guide antibiotic therapy, if necessary. Although esophagoscopy is less reliable in the diagnosis of TEF, it can be used in conjunction with bronchoscopy to instill air and methylene blue to define the anatomy, particularly for small fistulas. Further imaging with modalities such as computed tomography scanning is not necessary or helpful in benign disease, but it is useful in TEF secondary to a suspected or confirmed malignant process.

TREATMENT

Preop Care

The treatment of acquired TEF begins with preoperative planning and patient optimization. Preoperative chest radiography, barium swallow, bronchoscopy, and esophagoscopy must be reviewed to determine the anatomy of the fistula, which will guide surgical exposure. Patients with pulmonary sepsis as a result of chronic airway contamination from aspiration of enteric contents should be adequately treated with antibiotics and stabilized before surgery. In situations where mechanical ventilation can be weaned, it is paramount to delay surgery until ventilation can be definitively ceased to minimize postoperative manipulation and positive pressure within the reconstructed trachea. In patients who are intubated, it is important to advance the endotracheal tube below the level of the fistula and inflate the cuff to prevent further contamination. Nutrition should be optimized with enteral feeding via a jejunostomy tube with a venting gastrostomy tube. Nasogastric and orogastric tubes should be avoided to minimize further esophageal trauma. Lastly, preoperative coordination with an experienced team of anesthesiologists familiar with the challenges of induction and intraoperative ventilation during tracheal resections is paramount.

Some centers advocate for placement of esophageal or airway stents as a temporizing measure against ongoing complications of the TEF. Although stents may help reduce ongoing aspiration through the fistula, they do carry the risk of increasing the size of the defect, sometimes to an extent where operative repair becomes infeasible. For benign TEF, we prefer to avoid stents and instead use distal intubation with a cuffed tracheostomy tube below the airway defect. We also place a venting gastrostomy tube with a feeding jejunostomy tube. This strategy protects the distal airways from ongoing aspiration and should reduce gastric aspiration with the gastrostomy tube open to gravity. The jejunostomy tube is utilized for enteral feeding.

Operative Management

Benign TEF is managed primarily with surgery. For more proximal TEF, the patient is placed supine with the head extended as far as possible. Exposure is achieved via an anterior collar incision, encompassing



FIG. 1 Barium contrast esophagram showing fistulous communication between the esophagus and airway.

the tracheostomy stoma, if present (Fig. 2). Subplatysmal flaps are raised, the strap muscles are separated at the midline, and the thyroid isthmus is divided. Alternatively, a left cervical incision along the anterior border of the sternocleidomastoid can be used. Importantly, both approaches may be extended to include a sternotomy for exposure of the distal trachea and for proximal control of the great vessels.

For more distal TEF or bronchoesophageal fistulas, a right posterolateral thoracotomy through the fourth or fifth interspace provides adequate exposure. Conservative surgical management includes two stages: initial tracheal resection and reconstruction with esophageal diversion via cervical esophagostomy, followed by delayed primary esophageal reconstruction. This approach may be appropriate for patients with traumatic TEF, where the degree of local contamination, loss of viable tissue, or other traumatic injuries may preclude a single stage repair. When feasible, a single-stage repair is advisable because it avoids neck reoperation, as well as loss of esophageal length during the takedown of the cervical esophagostomy. Principles of single-stage surgical repair as originally described by Hermes Grillo include complete dissection and division of the fistula with tracheal transection to expose the esophagus, a two-layer esophageal closure, reanastomosis of the trachea, and buttressing of the repair with a pedicled tissue flap. There are several technical considerations in each of these steps.

First, during the exposure and dissection of the fistula, the trachea often requires segmental resection with distal tracheal intubation. This is especially true for TEF acquired from prolonged intubation given the circumferential damage sustained from the endotracheal tube cuff. Segmental resection of the trachea then provides excellent exposure to the esophagus (Fig. 3). During dissection of the esophagus, care must be taken to avoid damage to the recurrent laryngeal nerves that lie within the tracheoesophageal groove on either side. The nerves may be found cranial or caudal to the fistula, and identification can be challenging from local inflammation and scarring.

Second, once identified and divided, the esophagus is closed over a nasogastric tube to avoid narrowing the lumen. We advocate for a two-layer closure with interrupted nonabsorbable sutures: an inner layer to approximate and invert the esophageal mucosa, with an outer layer of approximated esophageal musculature to cover the inner repair (Fig. 4). It is important to debride the esophageal defect to healthy tissue to ensure the integrity of this primary repair.

Third, during tracheal repair, we recommend placing stay sutures (2-0 Vicryl) in the tracheal rings cranial and caudal to the transection, at the 3 o'clock and 9 o'clock positions in both rings. This reduces tension for the tracheal anastomosis, which is accomplished with interrupted absorbable sutures (4-0 Vicryl) placed circumferentially around the trachea, every 5 mm, with the knots tied outside of the lumen of the trachea. This minimizes the formation of postoperative granulomas at the suture line (Fig. 5). Once the sutures are in place, the neck is flexed to reduce tension, the stay sutures are tied first, followed by the finer sutures placed circumferentially, proceeding anteriorly to posteriorly.

Fourth, in cases of long-segment tracheal damage and resection where simple neck flexion does not allow for primary repair, the trachea may be repaired over a T-tube. Alternatively, experienced surgeons may perform a variety of release maneuvers, including a suprahyoid laryngeal release, right pulmonary hilar mobilization, or pericardial release.

Last, the use of a pedicled muscle flap to buttress both the esophageal repair and tracheal reconstruction is paramount to prevent recurrence of the TEF from the abutting suture lines. An infrahyoid muscle, typically the sternohyoid, is of adequate length and size to be secured to the repair with interrupted nonabsorbable sutures (Fig. 6). At the conclusion of the repair, a subcutaneous drain is placed before the incision is closed. The nasogastric tube is gently removed from the esophagus and a "guardian suture" is placed from the chin to the sternal angle to maintain neck flexion at approximately 30 degrees. The patient is extubated to prevent prolonged positive pressure ventilation within the reconstructed trachea. In situations where mechanical ventilation is necessary after surgery, a tracheostomy tube may be placed at least two tracheal rings below the level of the repair.

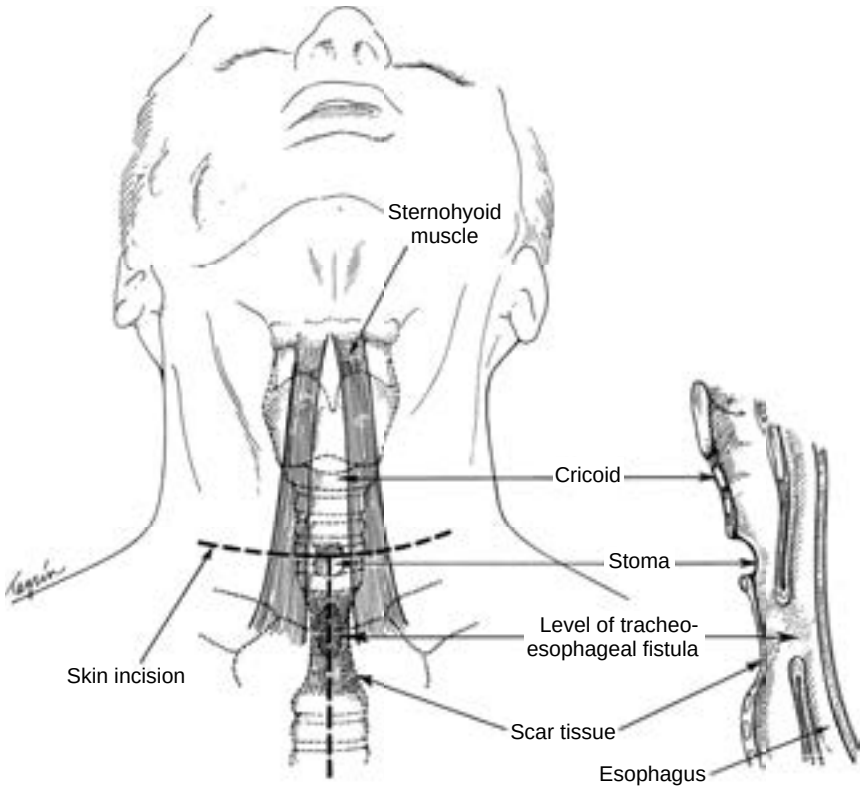


FIG. 2 Surgical exposure for repair of tracheoesophageal fistula. Both a transverse anterior collar incision incorporating a tracheotomy or left cervical incision provides necessary exposure. Additional exposure for distal fistulas can be exposed with division of the manubrium.

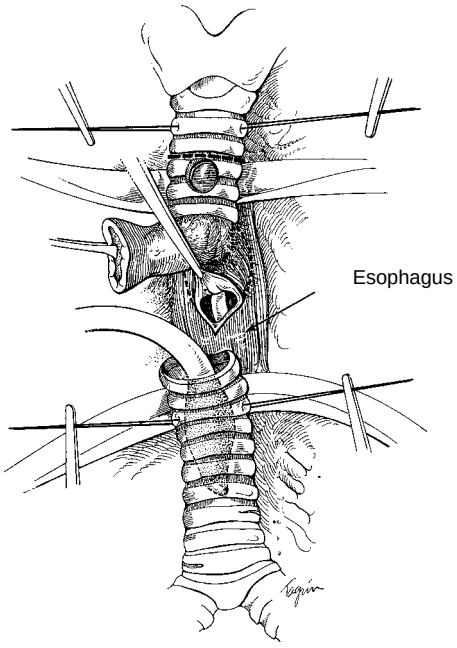


FIG. 3 Tracheal resection. Esophageal exposure after segmental tracheal resection in cases of acquired postintubation tracheoesophageal fistula.

Extensive TEF

For very large TEF, operative solutions may be limited or even infeasible. This usually occurs when the airway defect is so large (typically >5 cm) that it precludes segmental tracheal resection and primary anastomosis. For these complex defects, bioprosthetic grafts are emerging as a solution for operative repair. In this scenario, operative resection of the fistula and primary esophageal repair may still be pursued, with use of aortic homograft or acellular dermal matrix to cover the airway defect. A vascularized flap should still be used to buttress the repair. There have been several reports of successful bioprosthetic patching for large airway defects in TEF. Although primary repair of the airway is preferred when feasible, bioprosthetic grafts are emerging as a useful alternative to primary repair for giant TEF. Management of a large esophageal defect can involve primary repair as mentioned earlier or resection and reconstruction either at the time of the primary airway repair or at a later interval.

Postop Management

Postoperative care is focused on pain and nausea control to prevent cough or emesis. The patient is maintained nil per os; nutrition is provided via preoperative enteral access or parenteral nutrition. The patient returns to the operating room 7 days after surgery for bronchoscopic surveillance of the tracheal reconstruction, at which time the guardian suture is removed. A barium swallow is also performed to confirm the integrity of the esophageal repair before initiating a liquid diet.

Malignant TEF Management

While patients with malignant TEF have very poor prognosis, usually less than 10 weeks' survival in most series, aspiration pneumonia from the TEF can lead to more rapid demise. The management of malignant TEF is thus focused on palliation. Surgery, in many of these cases, is not within the initial oncologic principles of management. Furthermore, these patients are often significantly deconditioned and malnourished as a result of their disease burden, systemic chemotherapy, and local radiation. For these reasons, outcomes from radical and palliative surgery to address malignant TEF result in significant rates of morbidity and mortality.

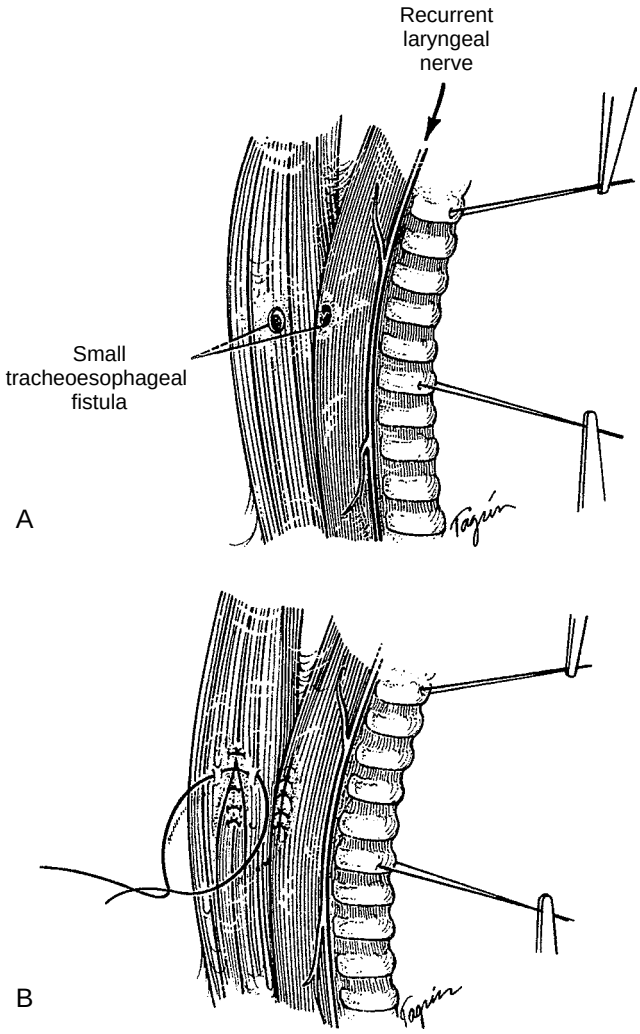


FIG. 4 Esophageal repair. **(A)** Lateral cervical approach to a small proximal tracheoesophageal fistula. **(B)** The esophageal defect is repaired in a two-layer fashion with interrupted sutures. The defect in the membranous wall of the trachea is repaired with a single layer of interrupted sutures.

In cases of incurable disease, airway and esophageal stenting has emerged as a viable option to achieve palliation. Either an individual or a combination of stents is placed across the fistula to prevent further spillage of enteric contents across it. This minimizes pulmonary contamination and alleviates the symptoms of chronic aspiration and pulmonary sepsis. The principals of preoperative planning in benign TEF also apply to patients with malignant disease. Preoperative imaging, including barium swallow, should be obtained to determine the anatomy and level of the fistula. Pulmonary sepsis should be treated with antibiotics, mechanical ventilation should be weaned as allowed, and nutrition should be optimized. Most malignant TEF may be sealed using a self-expanding covered or partially covered metal or plastic esophageal stents. These stents are typically placed under general anesthesia, using direct endoscopic guidance with the assistance of bedside fluoroscopy.

In some cases, tracheal stents may also be needed and should be placed under bronchoscopic vision before the esophageal stent. This technique decreases the incidence of tracheal narrowing from initial esophageal stenting. For fistulas located at or above the cricopharyngeus, the placement of a stent is not recommended because a

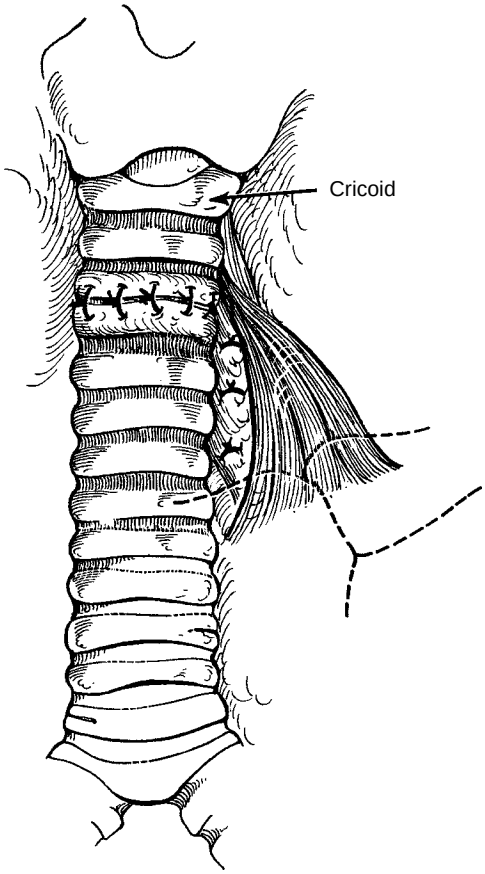


FIG. 5 Tracheal reconstruction. Placement of interrupted nonabsorbable sutures for tracheal reconstruction.

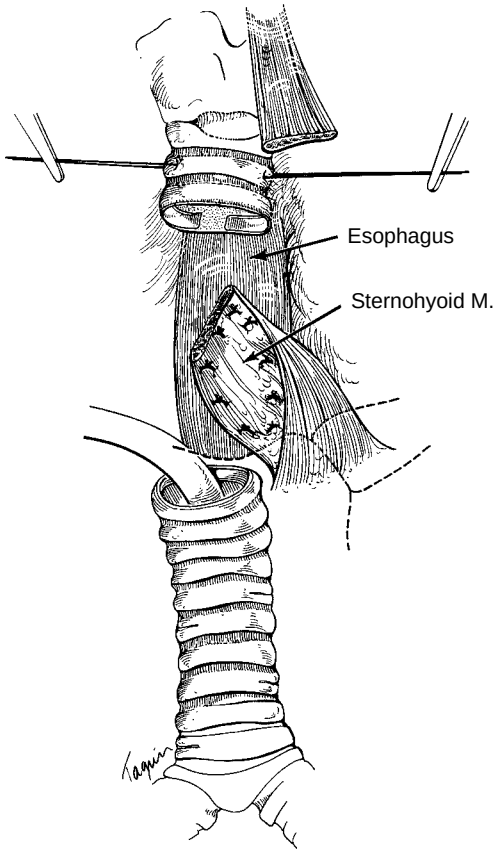


FIG. 6 Placement of pedicled infrahyoid strap muscle in between tracheal and esophageal suture lines to buttress repair and prevent fistula recurrence.

foreign body in the pharynx or larynx results in significant patient discomfort and the inability to swallow. In such cases, a definitive tracheostomy tube with inflatable cuff to protect the distal airways may be placed. Likewise, fistulas to the lobar or segmental bronchi are difficult to seal via bronchial stenting because there is a lack of healthy tissue proximally and distally. Typically treated with an esophageal stent alone, these peripheral fistulas may also be managed with the addition of a tracheobronchial stent.

Success rates of 80% to 100% have been reported with self-expanding stents to seal malignant TEF. Although well tolerated, patients should be counseled on the complications of esophageal and airway stenting, which can be minor to devastating. These include bleeding, migration, erosion, and further progression of the fistula, leak, and occlusion.

OUTCOMES

Surgical treatment of benign TEF results in successful fistula closure and is associated with minimal morbidity and mortality. In the largest recent series reporting the outcomes of a cervical approach to primarily postintubation TEF repair, successful fistula closure occurred in 95% of patients. Approximately 83% of patients resume oral feeding, and 72% are free from a tracheostomy or T-tube. Postoperative complications include fistula recurrence, pneumonia, wound infection, and postoperative tracheal stenosis. Death after TEF repair is rare. Patient survival in malignant TEF is poor regardless of supportive care, stent placement, or aggressive surgical treatment. Life expectancy is on the order of weeks to months. However, self-expanding stents have successfully palliated symptoms of dysphagia and chronic aspiration for patients with malignant TEF.

SUMMARY

Most benign acquired TEF are amenable to surgical repair. We emphasize the importance of a comprehensive preoperative evaluation to determine the anatomy of the fistula and optimize respiratory status and nutrition. A single-stage repair with division of the fistula, two-layer esophageal closure, tension-free tracheal resection and reconstruction, and buttressing of the repair with a pedicled interposition tissue flap has yielded excellent results. Malignant TEF are challenging to manage but are primarily treated nonoperatively with the use of self-expanding stents to maximize patient palliation.

SUGGESTED READINGS

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Repair of Pectus Excavatum

Jennine H. Weller, MD, PhD, and Isam W. Nasr, MD

INTRODUCTION

Pectus excavatum (PE), also known as *funnel chest*, is the most common pediatric chest wall deformity, occurring in approximately 1 in 400 to 1000 children. Patients with PE present with progressive posterior displacement of the sternum and costal cartilage (Fig. 1). Although the pathophysiology is incompletely understood, PE is likely due to abnormal costal cartilage development and has an association with connective tissue disorders including Marfan and Ehlers Danlos. No genetic markers have yet been identified for PE, but there is a familial association in 40% of patients, and PE is three times more common in male as compared to female patients.

Pectus excavatum can be detected in young children, but the deformity becomes more pronounced during the pubertal growth spurt. The typical patient is a tall, thin adolescent with poor posture, scoliosis, and an anterior chest wall deformity. Pectus excavatum is frequently asymmetric and is more common on the right hemithorax. There is a wide spectrum of disease severity, ranging from asymptomatic to severe cardiac compression and cardiopulmonary compromise. Most patients report no PE symptoms at rest but experience exercise intolerance with associated pain or shortness of breath. Pectus excavatum also impacts psychosocial development, and children with PE often report self-consciousness, body-image distress, and impaired quality of life.

EVALUATION OF PECTUS EXCAVATUM

When assessing a patient for PE, it is important to ascertain the severity of the deformity, assess cardiopulmonary function, and when indicated, perform preoperative planning including metal allergy testing as well as patient and family education.



FIG. 1 Pectus excavatum. *(From Janes S. Encyclopedia of Respiratory Medicine, 2nd edition. Elsevier, 2021.)*

Disease Severity

Most surgeons rely on the Haller index to assess severity based on a noncontrast chest CT scan. The Haller index divides the transverse chest diameter by the anteroposterior chest diameter measured at the deepest point of the deformity (Fig. 2). Generally, a Haller index of 3.25 or greater is an indication for operative repair. However, studies suggest the Haller index may underestimate PE severity. A correction index, which measures the percentage of sternal depression on cross-sectional imaging, may better estimate PE severity. A correction index 28% or higher is considered significant. Chest CT scans can also assess for signs of atelectasis, asymmetry, or sternal torsion that may provide evidence of impaired function and inform operative strategies. An MRI can be used to minimize chest radiation, although the ribs and sternum are not visualized as clearly as on CT. Alternatively, caliper measures correlate well with CT findings. Calipers measure the external distance between the posterior midline chest and three anterior points: the deepest point of the deformity and each of the bilateral pectus ridges. Regardless of the method used to assess PE severity, we also recommend obtaining photographic documentation of the deformity in the medical records.

Cardiopulmonary Evaluation

Surgeons should assess the cardiopulmonary function of patients with PE using pulmonary function tests (PFTs), electrocardiogram (ECG), and transthoracic echocardiogram (TTE). On PFTs, patients with severe PE typically have a mild or moderate restrictive pattern at rest, but O_2 pulse and VO_2 max significantly decrease during exercise due to restricted diastolic filling. A preoperative ECG and TTE may reveal mitral valve prolapse in up to 65% of patients with PE. Patients with more severe disease may also have right ventricular compression or decreased stroke volume, which are correctable with PE repair.

Indications for Surgery and Operative Timing

Spontaneous resolution of PE is rare, thus operative repair to recontour the chest wall is the primary correction for PE deformities. Operative repair of PE is relatively safe and improves physical symptoms and psychological distress. Patients should be offered an operation if they have severe deformities with a Haller index ≥3.25 or a correction index ≥28%. Other operative indications include symptomatic disease, such as abnormal PFT or TTE findings, reported exercise intolerance, or evidence of impaired quality of life or psychosocial distress caused by the deformity. So long as a patient can tolerate general anesthesia, there are no absolute contraindications to surgery. However, most insurance policies require documented evidence of significant PE symptoms or impaired cardiopulmonary function to recognize the procedure as noncosmetic and cover the repair.

Whenever possible, it is important to plan surgery during the adolescent growth spurt to minimize complications of recurrence or asphyxiating chondrodystrophy. The latter was historically seen in children who underwent open PE repairs around four years of age and developed arrested growth of the thoracic cavity, likely due to iatrogenic damage of costochondral growth plates. For this reason, open PE repairs are contraindicated before the pubertal growth spurt. Prepubescent patients with mild or moderate disease should be referred to an exercise and posture program to minimize disease progression and should be followed annually. If a prepubescent patient has a severe deformity or disease progression, they should then undergo formal PE evaluation, including chest CT, PFTs, and TTE.

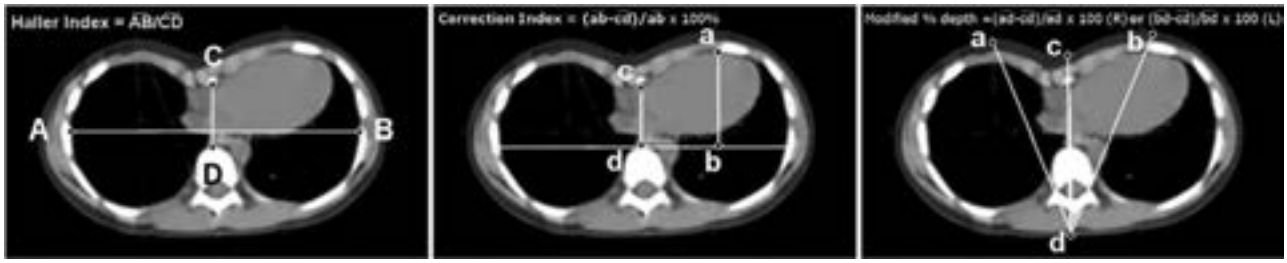


FIG. 2 Measurement of pectus excavatum severity using the Haller index *(left)*, correction index *(center)*, and modified percent depth *(right)*. The modified percent depth can be accurately measured with calipers. *(Snyder CW, Farach SM, Litz CN, et al. The modified percent depth: Another step toward quantifying severity of pectus excavatum without cross-sectional imaging.* J Pediatr Surg. *2017;52:1098–1101.)*

Other Preoperative Considerations

Approximately 1 in 10 patients with pectus excavatum have or will develop an allergy to metal alloys in the stainless-steel bars used for PE repairs. We recommend screening all patients for a personal or family history of metal allergies, and those with a positive history should get metal patch skin testing. For patients with documented metal allergies, the surgeon can order a customized titanium bar. Titanium bars are not routinely used because they are less malleable, harder to remove, and four times more expensive as they are shaped in the factory based on a patient's CT or MRI scan.

In the preoperative setting, it is also important to counsel patients on pectus exercises and expected postoperative recovery. Before surgery, the surgeon should encourage patients to do deep breathing exercises using an incentive spirometer or by breath-holding 10 to 15 seconds after inspiration, back and chest stretches, and aerobic exercise such as running, soccer, basketball, or swimming. These exercises help expand lung volume and should continue postoperatively to maximize the success of the repair. Recovery expectations should be discussed preoperatively as pain management is the major driver of postoperative hospital length of stay (LOS).

Finally, at our institution, we have initiated a preoperative pain management pathway. Three days before surgery, we recommend patients initiate 300 mg of gabapentin nightly as well as 8.5 g of MiraLAX twice daily. In the preoperative setting, patients are also given oral gabapentin, acetaminophen, tizanidine, and bisacodyl, as well as an intravenous ketamine infusion. We have found that this regimen helps minimize postoperative pain and hospital LOS for patients.

OPERATIVE REPAIR

There are two primary operative repairs for pectus excavatum, the open Ravitch procedure and the Nuss procedure or minimally invasive repair of PE (MIRPE). Most surgeons use the MIRPE as it reduces complications and improves cosmetic outcomes. Other techniques, such as the use of a vacuum bell device to lift the sternum, have shown some promise for smaller deformities in single center studies but are not widely adopted. Use of the Magnetic Mini-Mover, which uses magnetic attraction between an implanted sternal magnet and an external chest wall brace, was hindered by recurrence and device breakage in a pilot study.

Minimally Invasive Repair

First performed in 1987 by Nuss, the MIRPE places a substernal convex bar that, over a 2- to 4-year period, remodels the sternum and deformed cartilage (Fig. 3). The MIRPE has three key steps: substernal tunneling, placing the bar, and securing the bar to the surrounding ribs. The addition of thoracoscopy has modified the original Nuss operation to improve safe dissection of the substernal plane and allow for bar fixation with pericostal suturing and bar stabilizers.

We begin the MIRPE by positioning the patient supine with arms abducted and elbows slightly flexed. Before incision, the surgeon locates the horizontal position for the bar by marking the deepest point of the PE deformity or, if this is inferior to the sternum, marking the inferior edge of the sternum. We also recommend marking the pectus ridge at the horizontal level of the bar placement. When using a stainless-steel bar, the bar length is then measured so that it is 1 inch shorter (2.5 cm) than the distance between the midaxillary lines at the planned bar location. The surgeon should bend the bar to the desired chest wall shape, leaving a 2 to 4 cm flat section in the middle. This bar-shaping step is unnecessary if the patient requires a titanium bar due to a metal allergy as the bar is already preshaped. Most deformities only require one bar. However, we recommend considering placing a second bar if the deformity is complex or asymmetric, and if the patient is older than 30 years, has a connective tissue disorder, or has recurrence of their deformity.

After preparing the bar, a midaxillary incision is placed two intercostal spaces below the planned level of the bar placement. A 5-mm trocar is inserted and a 5-mm 30-degree thoracoscope is used to visualize the internal anatomy and confirm that it matches the external anatomy. We typically place the trocar on the right side with the plan to tunnel an introducer from right to left. Symmetric 4 cm incisions are then made laterally at the horizontal level of the planned bar placement. If the surgeon plans to perform cryoablation for pain management, this is now done through these lateral incisions. For the cryoablation procedure, the surgeon visualizes the intercostal nerves on the posterolateral chest wall. A cryoprobe is inserted into the thoracic cavity through the lateral incision, cooled to −60°C, and carefully applied bilaterally for 2 minutes to each posterolateral intercostal nerve between T3-T7, which is typically two levels above and two levels below the site of the incision.

After the cryoablation procedure is completed, the surgeon should raise skin flaps through the lateral incisions to the marked pectus ridge. Under direct visualization via skin retraction and thoracoscopy, a Lorenz introducer is gently pushed into the thoracic cavity through the intercostal space underlying the marked pectus ridge. Keeping the introducer tip always in view and facing away from the mediastinum, the surgeon should carefully dissect the pleura and pericardium off the sternum to create a substernal tunnel. We recommend always dissecting with a gentle, anterior to posterior motion before advancing the introducer to avoid mediastinal injury. This dissection can also be made safer with sternal elevation using a Rultract Skyhook Retractor through a subxiphoid incision.

Once the introducer reaches the contralateral pectus ridge, the surgeon gently pushes the introducer through the intercostal space into the contralateral subcutaneous tunnel. At this point, the introducer spans the chest wall, entering through one lateral chest wall incision and exiting the through the other. The surgeon and assistant should repeatedly lift on each side of the externalized introducer to elevate the sternum and begin the chest wall remodeling. This can help minimize postoperative pain or future bar displacement. An umbilical tape is attached to the introducer tip and threaded through the chest as the introducer is slowly removed. The umbilical tape is then attached to the bar. The bar should be positioned with the

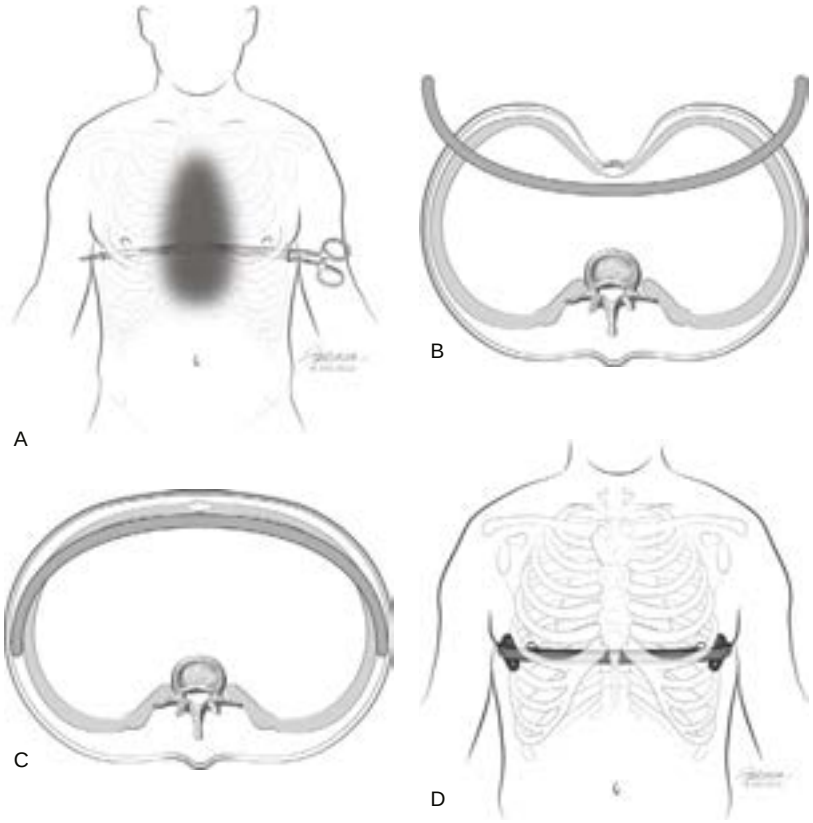


FIG. 3 Minimally invasive pectus excavatum repair. **(A)** Long clamp passing posterior to the sternum through bilateral intercostal incisions. **(B)** Initial orientation of bar after passage through chest. **(C)** Position of bar after flipping. **(D)** Bar stabilizers in position. *(Courtesy Johns Hopkins University illustrations, Jennifer E. Fairman, MA, MPS, CMI, FAMI.)*

convex side facing posteriorly and then pulled through the retrosternal tunnel by slowly pulling the umbilical tape through the chest cavity. If needed, anterior sternal retraction and direct thoracoscopic visualization aids bar placement across the mediastinum. Once the bar is in place, it is flipped 180 degrees using bar flippers so that the convex side faces anteriorly and elevates the sternum, correcting the PE deformity. The bar should be bent as needed so that it loosely fits against the lateral chest wall. This helps reduce pain and prevents the bar from eroding or adhering to the ribs.

The final step of the operation is to secure the bar to the chest wall bilaterally to prevent postoperative bar displacement. Typically, the surgeon applies a bar stabilizer on one side of the chest and uses pericostal sutures on the other side. We usually place the bar stabilizer under and perpendicular to the pectus bar on the left side. The bar is then secured to the stabilizer and underlying rib using nonabsorbable suture such as FiberWire or No. 3 surgical steel wire. The stabilizer is also secured to the chest wall fascia in multiple places using heavy absorbable suture such as 0 Vicryl. If two bars are required, the stabilizers should be placed on opposite sides. On the contralateral side to the bar stabilizer, the surgeon can use an EndoClose needle or Carter-Thomason port closure system under thoracoscopic visualization to place heavy absorbable suture, such as 0 or 1 polydioxanone (PDS), in a figure of eight around the underlying rib. It is important to place pericostal sutures in at least two locations and surrounding two or more separate ribs to prevent bar rotation. Once the bar is secured bilaterally, we ensure hemostasis in the pleural cavity, remove the thoracoscope, evacuate residual air, and close all incisions.

Open Repair

The open PE repair, as modified from the technique Ravitch described in 1949, involves excision of defective costal cartilage and placement of a metal strut for sternal support (Fig. 4). This procedure is a reasonable alternative to the MIRPE for older patients and is the preferred method to treat rare chondromanubrial deformities. The open procedure and MIRPE have comparable long-term outcomes, but a recent meta-analysis suggests that MIRPE results in shorter operations and less intraoperative blood loss.

The open procedure begins with a transverse inframammary incision. The surgeon should raise skin and pectoral muscle flaps to expose the costochondral junctions of ribs 3-8. After incising the anterior perichondrium, the surgeon carefully resects 1 to 2 cm of deformed cartilage, taking care to not devascularize the perichondrium. The xiphoid is mobilized and then pleural and pericardial attachments are dissected off the posterior sternum. The surgeon should make a wedge-shaped osteotomy at the sternal angle to correct the sternal depression. Formation of a retrosternal tunnel allows the surgeon to place a metal strut behind the sternum and to secure it to the bilateral periosteum with heavy nonabsorbable sutures. Alternatives to the metal strut include fixation of a retrosternal wire to an external brace or use of Marlex Mesh. Leaving retrosternal and subcutaneous drains, the pectoral flaps are reapproximated and the skin incision closed. Drains should remain in place for 2 to 3 days and the strut left in place for 1 year.

POSTOPERATIVE MANAGEMENT

Pain Management

Pain management is the primary postoperative concern for patients after a PE repair and drives postoperative hospital LOS. Most surgeons utilize multimodal pain management, combining IV analgesics, epidural catheters, intercostal nerve blocks, oral pain medications, and intercostal cryoablation. At our institution, we use a pain management pathway modeled after the ERAS pathway. This includes immediate initiation of patient-controlled anesthesia (PCA), ketamine infusion, Valium, and a bowel regimen postoperatively. We transition from the



FIG. 4 Open repair of pectus excavatum. **(A)** Following a transverse inframammary incision and bilateral elevation of the pectoralis major muscles, costal cartilages are freed circumferentially from the perichondrium and divided at the junctions with the sternum and with the ribs. **(B)** A cuneiform osteotomy allows the sternum to rise to a level position. **(C)** An Adkins strut in place maintains elevation. *(Courtesy Johns Hopkins University illustrations, Jennifer E. Fairman, MA, MPS, CMI, FAMI.)*

PCA to oral opioids, ibuprofen, acetaminophen, and gabapentin on postoperative day one, discontinue all IV analgesia by postoperative day two, and discharge on postoperative day two or three once medically cleared.

Cryoablation techniques are relatively new but are gaining popularity as they shorten hospital LOS and minimize opioid requirements. Intercostal nerve cryoablation is typically performed before Nuss bar placement and can utilize the same incision sites as the planned MIS repair. Cryoablation freezes the intercostal nerve axons and limits nerve signal conduction for months postoperatively. This provides effective analgesia and can reduce postoperative hospital LOS to as little as one day. Complications of cryoablation are rare, although long-term nerve damage has been reported.

Upon hospital discharge after a PE repair, patients should expect to continue oral opioids for 2 to 3 days as needed and acetaminophen, ibuprofen, and gabapentin for at least 1 week. It is also important to counsel patients about the small risk of experiencing chronic pain while the bar remains in place.

Physical Therapy Guidelines

Postoperative physical therapy is crucial to the success of a PE repair. For the first 8 weeks postoperatively, we recommend a 10-pound weight restriction. During this time, patients should avoid twisting, shoulder rotation, or movement that causes a pinching or pulling chest sensation. They can initiate other range of motion exercises including daily stretching, core-strengthening exercises, and aerobic activities by week three. We recommend jogging, swimming, or stationary biking. After 8 weeks, patients can slowly increase their weightlifting and aerobic exercise to preoperative levels. Except for full contact sports and sports that involve significant trunk rotation, such as baseball or golfing, we remove all other movement restrictions by postoperative week 12.

EARLY COMPLICATIONS

Postoperative complications for open or MIRPE repairs are relatively rare, occurring in 4% of patients. The most common complication is postoperative pneumothorax, while the most serious complication is mediastinal injury.

Approximately 4% of patients will develop a pneumothorax postoperatively. Small bilateral pneumothoraces are common and can be managed expectantly. A larger pneumothorax is usually a result of air introduced during the thoracoscopy rather than lung parenchymal injury and may require a thoracostomy tube if symptomatic. Therefore, it is important to ensure that all air is evacuated from the pleural cavity before closing incisions. We recommend obtaining a routine chest radiograph in the immediate postoperative period to assess for a pneumothorax.

Although extremely rare, technical errors during dissection of the substernal plane can result in life-threatening myocardial or lung parenchymal injuries. This is more common with the MIRPE repair as compared with the open repair. Surgeons should minimize the risk of this complication by directly visualizing the substernal dissection and keeping the tip of the introducer in view at all times during the dissection.

Other postoperative complications after a PE repair are relatively rare and include suture site infection (2%), pneumonia (1%), and pleural or pericardial effusions (1%–3.5%). Complication rates are not associated with the severity or asymmetry of a deformity but are reduced with surgeon operative experience.

LATE COMPLICATIONS

The most common late postoperative complication is bar displacement, which occurs in approximately 1.5% to 4% of patients. Bar displacement can range from mild lateral sliding of the bar to complete detachment from the lateral chest wall or flipping of the bar. Surgeons have reduced the incidence of bar displacement down from 15% by using lateral stabilizers and pericostal suturing. Minor displacement can be managed expectantly, but significant or symptomatic displacement, such as bar flip, should undergo urgent reoperation.

The use of allergy testing and titanium bar placement has reduced allergy complications, which occur in less than 1% of patients. In extremely rare circumstances the implanted bar triggers an allergic reaction and pericarditis. Most patients with metal allergies are medically managed and do not require bar excision. Another rare complication of a PE repair is overcorrection of the deformity. Overcorrection occurs in 1% to 3% of patients and is typically managed nonoperatively.

OUTCOMES

Outcomes of both open and MIRPE repairs are favorable with improvement in cosmesis, cardiopulmonary function, and quality of life. Symptomatic patients will frequently have immediate improvement in cardiac function and increased stroke volume. Pulmonary function will also improve more gradually and usually requires physical rehabilitation. It is extremely important for patients to participate in aerobic exercises, such as running or swimming, and deep breathing exercises to optimize lung expansion after their PE repair.

Reversal

We recommend removing the bar 2 to 3 years after placement. Removing the bar prematurely increases the risk of PE recurrence while delaying removal can increase the difficulty of the removal

procedure. The optimal timing of bar removal is individualized based on a patient's growth, activity level, and pulmonary function as assessed postoperatively at 6 months and then annually. For example, younger patients can tolerate the bar for 3 to 4 years while teenagers with rapid pubertal growth spurts may need only 2 years.

For bar removal, the patient undergoes general anesthesia, and the lateral incision sites from the bar placement procedure are reopened. The pericostal sutures and bar stabilizer are removed. The surgeon should then mobilize the lateral portions of the bar, pull them through the overlying skin incision, and straighten their ends. If there is osseous growth of the rib over the bar, a rongeur or hammer and chisel can help with bar mobilization. Slightly rotating the bar can also help free the bar but should be coordinated with the anesthesiology team as it can cause arrythmias. Once the bar is fully mobilized, the surgeon grasps it with a Kocher clamp and then slowly slides the bar out of the chest. Sternal elevation and thoracoscopy can aid difficult bar removal.

Vascular complications from bar removal are rare but serious. There have been case reports of life-threatening hemorrhage from laceration of the pulmonary vessels or erosion of the bar into the aorta, internal mammary artery, or sternum.

Recurrence

Recurrence of PE is defined as chest well depression after bar removal. Patients are at increased risk for recurrence if they have the bar removed prematurely, have a severe deformity, or are repaired as adults, when the chest wall is less compliant. Additionally, some young children who require operative repair will redevelop their PE during their pubertal growth spurt. Historical rates of recurrence were as high as 37%, but surgeons have lowered this rate to 1.4% with the use of stabilizers and pericostal sutures. Postoperative deep breathing exercises also improve chest wall mobility and reduce the risk of recurrence. Most patients with recurrence can be repaired with a repeat MIRPE, but surgeons should consider an open approach for patients with severe deformities or with abnormal sternocostal cartilage growth.

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Open Repair of Abdominal Aortic Aneurysms

Erin E. McIntosh, MD, and Richard P. Cambria, MD

Abdominal aortic aneurysm (AAA) affects 15% of men over age 65 and accounts for up to 15,000 deaths annually in the United States. Average yearly growth is about 3 mm, though more rapid growth tends to occur in patients with risk factors such as active smoking, uncontrolled hypertension, and significant chronic obstructive pulmonary disease (COPD). Data published from multiple trials have shown that AAA should be repaired at a diameter of 5.5 cm in men and 5 cm in women, as the annual risk of rupture increases dramatically when the aneurysm sac enlarges beyond these values, and, once rupture occurs, mortality is extremely high. Current preventive medicine practices focus on screening high-risk patients for AAA and modifying risk factors, so as to decrease aneurysm sac growth and minimize rupture risk.

It is said that the overall incidence of AAA is declining. This is, in turn, felt to be related to better risk factor control—specifically improved control of hypertension and decreasing use of tobacco. As expected, there has been a resultant overall decrease in AAA repair among the Medicare population. The total number of AAA repairs in the Medicare population declined by 26% over the course of a decade, from 31,582 in 2003 to 23,421 in 2013. More specifically, the number of open AAA repairs declined by 76% during this same time period, 20,533 in 2003 to 4916 in 2013. While the total number of endovascular aneurysm repairs (EVARs) increased concurrently throughout most of the period from 2003 to 2011, they also declined a total of 15% from 2011 to 2013. Despite this, rupture of an AAA is associated with a mortality rate up to 90% and ranks 15th among the leading causes of death in North America.

Progress has been made in the early detection of AAA, as screening programs among at-risk individuals are both supported and reimbursed by insurance payors. Recommendations for screening of AAA have focused on those patients with well-appreciated risk factors of smoking, male sex, family history of aortic aneurysm, hypertension, and COPD. The latter has been amply demonstrated as a significant risk factor for aneurysm expansion and rupture. While male sex has been a well-established risk factor for AAA, more recent data suggest that the prevalence of AAA in females, especially in the setting of active smoking and positive family history, is higher than previously expected. Moreover, when the disease occurs in females, it appears to be more lethal, characterized by more extensive aneurysms, with rupture occurring at smaller sizes.

AAAs are frequently discovered as an incidental finding on imaging studies directed at other pathologies. While sequential surveillance of AAA with ultrasound is convenient and cost effective, both the precise measurement of aneurysm diameter and treatment planning, when indicated, are best determined by contrast-enhanced fine cut computed tomography angiography (CTA). As to the mode of surgical repair, it is estimated that up to 80% of elective AAA repairs are performed with endovascular technology. However, it has been our observation that operative misadventures and/or failed repair with EVAR are strongly correlated with attempts to push stent graft repair in anatomic circumstances where a considerable risk of failure exists both in the short and long term. It is certainly true that all sorts of endovascular mayhem, sometimes referred to as *chimneys, snorkels,* and even *physician-modified grafts*, has been attempted to extend endovascular repair into anatomically inappropriate circumstances. Such patients, with the proviso that they are appropriate open surgical candidates, are best treated with open surgical repair. Given the efficacy of EVAR for appropriate infrarenal lesions, open surgical repair is the technique of choice for more complex AAAs. It is our belief that there will always be a role for open surgical repair with its demonstrated durability and safety in the appropriate hands. Obviously, younger patients may prefer definitive open surgical repair and defer the perceived nuisance and/or safety considerations in lifelong radiographic surveillance. Herein we outline the principles for safe and effective open repair of AAAs.

PREOPERATIVE EVALUATION AND PLANNING FOR OPEN REPAIR

Although it is certainly true that the operative insult of open repair is substantially greater than EVAR, clinical decision making must include an assessment of life expectancy, as well as the ability to recover from a major (or minor) operation. As an example, patients with chronic or end-stage renal disease have such poor overall survival that elective repair is seldom indicated. In our practice, the overwhelming majority of AAA patients whose anatomy is amenable to stent graft repair are treated with EVAR. When the best technical option for treating the aneurysm is open surgery, risk stratification for a major operation is certainly indicated. This includes assessment of cardiac, pulmonary, renal function reserve, and perhaps most importantly, the extant functional status of the patient. Although surgeons have always appreciated that a given patient's strength and functional status is likely the most important variable in predicting complete recovery, there now exists objective criteria and scoring parameters to quantify same. Various scoring systems have been used to evaluate a patient's functional status and/or frailty to inform the decision to operate. Certain data demonstrate that preoperative functional dependency is an independent risk factor for mortality after major open surgery, including open AAA repair and EVAR. Although frailty may be more difficult than functional status to assess, data suggests that frailty is also a predictor of mortality and complications after major vascular surgical interventions.

A pertinent history will usually suffice to quantify the patient's pulmonary reserve, but pulmonary function studies may be added or desirable in the circumstance of clinically evident COPD. There is no defined threshold for a degree of COPD that would preclude open repair; it is worth emphasizing that there is a linear correlation between the degree of COPD and the risk of aneurysm rupture. Anecdotally in the years before the availability of EVAR, we have performed open aneurysm repair on patients with oxygen-dependent COPD (generally through a flank approach) and have had such patients do well. We insist that patients be free of tobacco for a month before open operation. A current serum creatinine level and GFR calculation is an important consideration, especially in patients who will require a suprarenal clamp and/or renal artery reconstruction. Converting a patient with CKD to dialysis-dependent renal failure with either open or endovascular repair is clearly a devastating complication and a death sentence for the patient. It is commonplace to encounter patients with complex AAA who have either a single functioning kidney or flow-limiting renal vascular occlusive disease. Such factors will figure prominently in operative planning as reviewed later.

The long and extensively studied history of objective parameters of cardiac risk stratification began in 1976 with the description by Boucher et al. of the dipyridamole thallium nuclear stress test to predict and prevent postoperative cardiac ischemic complications or cardiac-related death. Over the past 40 years, multiple clinical and imaging parameters have been utilized for cardiac risk stratification, and American Heart Association (AHA) guidelines advise when to apply nuclear stress testing and/or cardiac catheterization in the preoperative assessment of patients about to undergo open AAA repair. There also exists Level 1 evidence that aggressive detection and treatment of coronary artery disease before open vascular surgery produces no better outcome than optimal medical management of associated coronary artery disease. Our approach is generally consistent with the AHA guidelines and begins with a careful clinical history relative to known or previously treated coronary artery disease and the patient's exercise tolerance with respect to precipitating symptoms of exertional dyspnea or chest pain. Irrespective of seemingly benign clinical risk stratification, we maintain a low threshold to obtain cardiac functional studies (nuclear stress testing) especially in elderly patients or those with other factors such as arthritis, which might limit functional capacity. It is to be emphasized that such stress testing is not simplistically considered as "positive or negative." Rather, such functional cardiac studies are to be considered in a quantitative fashion, and if ischemic potential is identified, cardiology consultation is certainly indicated for a further discussion about the desirability for cardiac catheterization and especially to ensure optimization of an antiischemic medical regimen. In current practice, it is uncommon to go to the extent of cardiac catheterization and/or coronary angioplasty/stenting to prepare a patient for open aneurysm repair.

GENERAL PRINCIPLES OF OPEN REPAIR AND OPERATIVE PLANNING

Regardless of the various technical approaches for open repair or the proximal extent of the aneurysm, certain principles apply to ensure good results. With respect to aneurysm extent, a juxta- or pararenal aneurysm is one wherein there is insufficient neck length to permit infrarenal cross-clamp application and proximal anastomosis. A suprarenal aneurysm involves one or both renal arteries arising directly from the aneurysm and, of course, implies that separate renal artery reconstruction might be needed. A type 4 thoracoabdominal aneurysm, or total abdominal aneurysm, is one where the aneurysm extends to or slightly above the level of the celiac axis. First, a careful and precise operative plan, dictated by high-quality, fine-cut CTA imaging, is a sine qua non. The analogy to deriving a precise plan for endovascular repair extends also to open surgery. The extent of proximal and distal repair, location of suture lines and proximal cross-clamp application, and the desirability (or lack thereof) of concomitant renal/visceral artery repair are all determined by review of the preoperative CT scan. The site of proximal cross-clamp application is selected not only to allow complete resection of the aneurysm, but also specifically to avoid aortic wall fracture and/or atheromatous embolization; such information is dictated by the CTA and not by "feeling for a soft spot." We routinely use soft-jawed clamps, which have less potential for tearing a diseased aorta.

Successful open repair relies on the principles of an expeditious and bloodless operation with minimization of cross-clamp times and blood turnover. Broad surgical exposure, which absolutely requires fixed self-retaining retractor systems, is essential. Although it has been recognized throughout the history of aortic surgery that minimal blood turnover and cross-clamp times are strongly correlated with success, less emphasis has been given to performing an expeditious operation. Patients are best served with a perfect 4-hour operation, as opposed to a perfect 8-hour operation. In the era of cardiac risk stratification evolution, we performed a retrospective study of variables predictive of significant cardiopulmonary complications. The one independent variable that significantly predicted such complications was an operation that exceeded 5 hours in length. Related to this is a practical consideration to keep the repair simple in extent. To that end, we have a strong preference for tube graft reconstruction, and it is entirely appropriate to ignore minor degrees of iliac occlusive and/or aneurysmal disease. We conducted a long-term follow-up study, which indicated that subsequent iliac aneurysm repair was uncommon after tube graft reconstruction for AAA.

A vital consideration in successful open repair is the selection or determination of surgical approach best suited to a particular patient and particular aneurysm extent (Box 1). Over time, the majority of open AAA repairs were performed with a midline transperitoneal approach, familiar to the majority of vascular surgeons as an extension of their general surgery training and experience. Two variables have somewhat changed the paradigm over the past 25 years. First, master aortic surgeon, Dr. Melvin Williams at Johns Hopkins, reintroduced the advantages and facility of a left flank approach for abdominal aneurysm surgery in the 1990s; this method was originally described by Charles Rob of Rochester. Second, with the successful application of endovascular repair for most infrarenal aneurysms, open surgical repair has essentially become the preferred technique of more complicated AAAs, involving at least part of the visceral aortic segment. Related to that consideration, a surgical approach that enables continuous exposure of the entire visceral aortic segment is the preferred operation for most, if not all, such

BOX 1 Considerations for Different Surgical Approaches

Transperitoneal Approach

- Redo aortic surgery
- Explant of infected aortic graft
- Repair aortoenteric fistula
- Distal right renal artery reconstruction
- Bilateral transaortic renal endarterectomy

Left Flank Retroperitoneal Approach

- Decreased risk of prolonged ileus
- Proximal aortic lesions
- Ease of exposure for repair of complex lesions
- Exposure of large AAAs
- Hostile abdomen
- Horseshoe kidney
- Abdominal wall stoma
- Morbid obesity

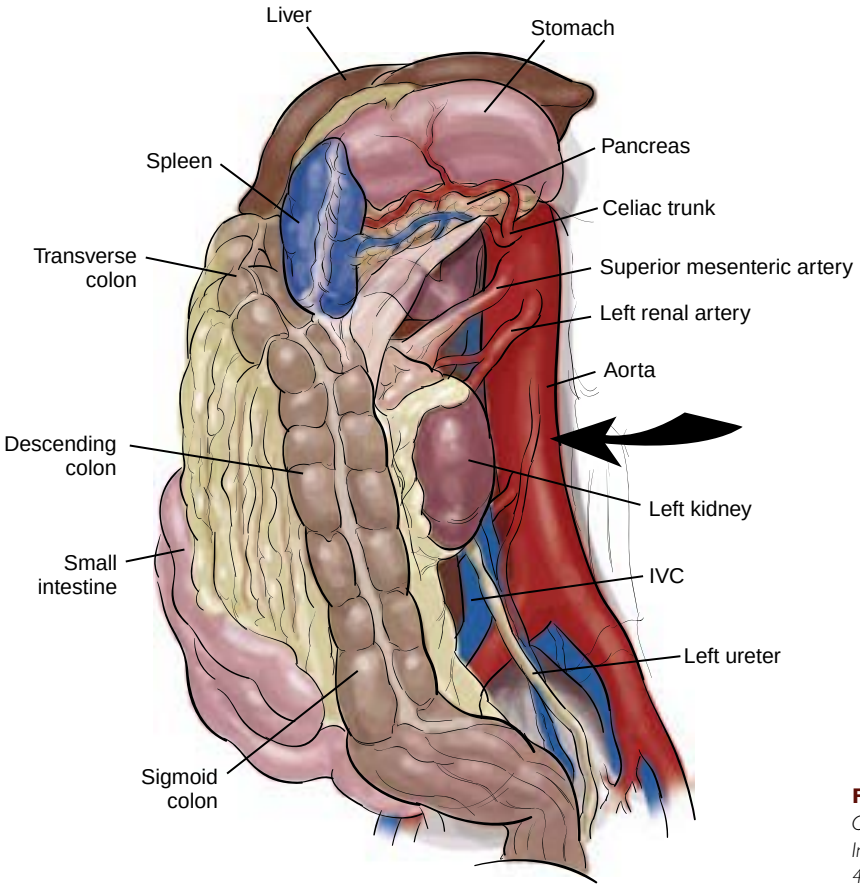


FIG. 1 **Left-sided medial visceral rotation.** *(From Aylwin C, Jenkins M. Abdominal Aortic Trauma, Iliac and Visceral Vessel Injuries. In Rasmussen TE, Tai NRM:* Rich's Vascular Trauma, *4th Edition, Philadelphia: Elsevier; 2022, 212–225.)*

complex aortic lesions. Note that we refer to this method collectively as a "left flank approach," as it has been our observation that there is much confusion about what is referred to as a "left retroperitoneal approach." The latter can, in fact, be performed at a variety of levels with respect to the intercostal spaces and is dictated by the proximal extent of the aneurysm and, importantly, patient body habitus. In addition to these considerations, vascular surgeons are familiar with other considerations that might dictate a left flank approach, such as a hostile abdomen, abdominal wall stoma, horseshoe kidney, and obesity. The evidence base with respect to the advantages of a left retroperitoneal approach would indicate that the only objective benefit is less disturbance of gastrointestinal function; while this is indeed true, it does not consider the facility of a left flank approach for more complex abdominal aneurysms, as previously noted. We have performed a strictly extraperitoneal approach by resection of a portion of the 11th rib and reflecting the peritoneal envelope right and medially. Again, dependent on body habitus, this method can afford adequate exposure for a pararenal aneurysm but has definite limitations for more proximal lesions. Accordingly, an 8th or 9th interspace thoracoabdominal incision with division of the solid portion of the costal margin has become our preferred approach for most aneurysms that require open operation in contemporary practice. It has also been our observation that the "morbidity" of such thoracoabdominal incisions is unfounded myth, as if entering the pleural cavity and partly dividing the left hemidiaphragm well away from the phrenic nerve is some major escalation of operative insult for the patient. While it is possible to keep the abdominal portion of such an incision entirely extraperitoneal, this is neither necessary nor desirable, as it is time consuming and bloody to peel the peritoneum off the undersurface of the left hemidiaphragm. For most aneurysm cases, the left-sided medial visceral rotation includes sweeping the left kidney out of its bed. Alternatively, in circumstances such as a retroaortic left renal vein or when this same incision is used for visceral segment endarterectomy or antegrade mesenteric bypass, the left kidney is left in situ (Fig. 1).

TECHNICAL DETAILS OF OPERATION

Midline Transperitoneal Approach and Its Variations

While our preference is for a left flank approach for the majority of complex abdominal aneurysms, as stated above, it is certainly true that the midline anterior approach is adequate for the majority of pararenal aneurysms, again after consideration of the patient's body habitus. We do not agree that a midline anterior approach is mandatory for some of the specific considerations that have previously been championed, such as a patient who requires reconstruction of the right renal artery or a right common iliac level anastomosis. Indeed, with appropriate patient positioning an aortobifemoral distal reconstruction can be performed in conjunction with a left flank approach. When the surgeon selects a midline anterior approach, familiarity with the variations and extensions of this operative incision is mandatory for the safe conduct of operation. These extensions include, in order of increasing application, wide mobilization of the left renal vein by ligation and division of its branches, extending proximal exposure by performance of a right-sided medial visceral rotation maneuver, and supraceliac clamp application through the lesser sac. The technique of midline transperitoneal exposure of the aorta follows a series of routinely performed steps in the following order: (1) mobilization of the entire omentum, transverse colon, and its mesentery superiorly, (2) division of the ligament of Treitz, (3) ligation and division of the inferior mesenteric vein and the peritoneum on the caudal border of the pancreas, which will allow superior retraction of the pancreas, and (4) evisceration of the small bowel

onto the right upper abdomen (although this step can be omitted in some patients in favor of simply packing the small bowel in the right side of the abdomen before placing the self-retaining retractor). We eschew division of the left renal vein because this maneuver entails at least transient left kidney dysfunction. Furthermore, after ligation of the adrenal, gonadal, and left renal lumbar vein, the left renal vein can be broadly mobilized and retracted superiorly or inferiorly to gain adequate exposure. We nearly always surround the aorta with an umbilical tape to ensure that the cross-clamp provides secure control.

Perhaps the only circumstance where we plan supraceliac clamp application from a midline transperitoneal approach is redo aortic surgery for graft infection and/or aortoenteric fistula. However, this cross-clamp scheme can be life-saving in the circumstance of operative misadventure in elective surgery or proximal control in the setting of ruptured AAA. Not only is this maneuver inconvenient in terms of working on both sides of the transverse mesocolon, but it can be quite difficult in mesomorphic individuals. The important technical steps of this maneuver are division of the ligament tethering the left lobe of the liver, entering the lesser sac, ensuring the orientation of the esophagus with an indwelling nasogastric tube, and dissecting off the fleshy portion of the diaphragmatic crura, which of course lies anterior to the aorta at this point. The surgeon works cephalad to the point where the median arcuate ligament crosses the aorta anteriorly. When a cross-clamp is applied at this level, the surgeon should endeavor to move it to a more distal location once the pararenal aorta is totally dissected out and secured.

The right-sided medial visceral rotation maneuver to extend exposure of the pararenal aorta and lower visceral aortic segment is not often utilized and is likely unfamiliar to many vascular surgeons. If this maneuver is needed, the patient would have been better served by a left flank approach. However, this maneuver can be life-saving in the circumstance of intraoperative complications or can greatly facilitate a graft reconstruction of the right renal artery. The technical steps of this maneuver involve extending the midline posterior peritoneal incision around the right paracolic gutter and, thus, mobilizing the entire right colon in continuity with the duodenum. This shifts the axis of orientation of the superior mesenteric artery (SMA) and the root of the mesentery from a 45-degree angle toward the right lower quadrant to a 90-degree angle where all of the abdominal viscera are now reflected and eviscerated onto the patient's chest. Sharp dissection of the neurosplanchnic tissue at the origin of the SMA, sometimes supplemented by sharp incision of the anchoring tendons of the diaphragmatic crura on either side of the aorta, will permit clamp application at or even cephalad to the SMA. This exposure can be utilized for combined aortic graft replacement in conjunction with bilateral transaortic renal endarterectomy.

Left Flank Approach

For the treatment of complex AAAs, as opposed to extent 1-3 TAAA, an 8th or 9th interspace thoracoabdominal incision will typically suffice. As previously noted, this is our strong preference for most lesions, although the retroperitoneal, extrapleural approach with partial resection of the 11th rib will suffice in patients of appropriate body habitus and pararenal aneurysm. The differentiating feature between the two incisions is division of the solid portion of the costal margin with partial lateral division of some of the left hemidiaphragm. Thereafter, the technical steps of operation are identical.

The patient is positioned in a right lateral decubitus position, but it is unnecessary and undesirable to have most of the chest in full lateral position. The hips are then rotated such that they are nearly flat, especially if an aortobifemoral reconstruction is contemplated. The incision extends about halfway posterior on the incident rib and posterior shingling, or division of the rib, is unnecessary. The costal margin is divided, and the internal mammary vessel secured. At this point, the left hemidiaphragm is divided laterally and posteriorly for a distance of about 6 inches, and this easily preserves phrenic innervation to the left hemidiaphragm. Now, the self-retaining retractor system is placed, and the field is set up in a totally infradiaphragmatic orientation. The left-sided medial visceral rotation maneuver is carried out by elevating the left kidney out of its bed after incising Gerota's fascia. Inferiorly, the left ureter is identified, swept medially, and protected with laparotomy pads when blades of the self-retaining retractor system are placed upon it. Fracture of the splenic capsule is commonplace, and there should be no hesitation to remove the spleen.

As the field is set up, the left kidney and the entire viscera are packed away to the right side of the abdominal cavity without the need for evisceration. The next step in the procedure is to identify the left renal artery, coursing just cephalad to the left renal lumbar vein, which is divided. The left renal artery is now dissected back to its aortic origin; in circumstances of very large aneurysms, it is common to find that the left renal artery origin is tucked at or even under the median arcuate ligament as it courses from the anterior aspect of the aorta to insert posteriorly on the bony elements. A right angle clamp is placed under the median arcuate ligament, which is then divided with the Bovie apparatus beginning the exposure of the visceral aortic segment. The left crus of the diaphragm is divided until the posterior mediastinum is encountered. Now, dissecting medially, the origins of the visceral vessels are circumferentially dissected out and the supraceliac aorta is encircled with a vessel tape (Fig. 2). Deliberately discerning the origin of the right renal artery is usually possible in pararenal or even suprarenal aneurysms; this is not advisable in the case of extent four thoracoabdominal aneurysms. Such complete dissection of the visceral aortic segment may be a necessity depending on the proximal extent of the aneurysm.

From the left renal artery origin, the posterolateral aspect of the aneurysm neck and the aneurysm is dissected free of retroperitoneal tissue, and ligation and division of the inferior mesenteric artery may be desirable to facilitate exposure of the aortic bifurcation. The iliac arteries are not circumferentially dissected and are nearly always controlled with intraluminal balloons. The proximal cross-clamp location, as dictated by preoperative imaging studies, can be supraceliac, between the celiac and SMA, or above one or both renal arteries. Sometimes an immediately infrarenal neck can be severely angulated in the case of large aneurysms and the surgeon may encounter a circumstance where an infrarenal clamp will not suffice. If the left renal artery originates from aneurysmal tissue, which requires resection or harbors a tight ostial stenosis, a side-arm left aortorenal bypass is performed with such a graft constructed before cross-clamp application. Installation of 4°C renal preservation solution directly into the renal arteries is used when a suprarenal or supravisceral clamp is applied. After cross-clamp application and

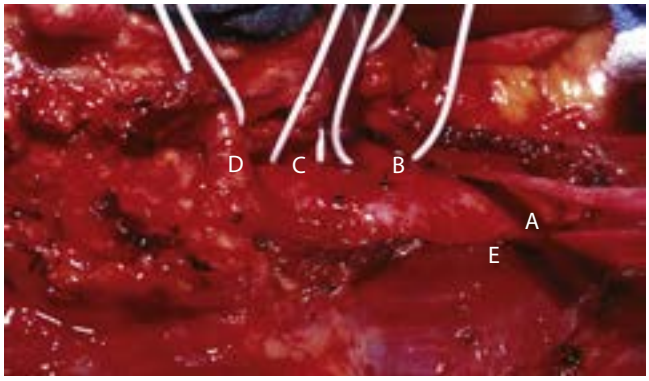


FIG. 2 Exposure of the visceral aortic segment with umbilical tape encircling the lower descending thoracic aorta *(A)*, white vessel loops around the celiac *(B)*, SMA *(C)*, and left renal artery with the left kidney rotated anteromedially *(D)*. Also visible is the left crus of the diaphragm, which is incised to facilitate exposure of the posterior mediastinum, allowing dissection of the visceral aortic branches *(E)*.

opening of the aneurysm, 12 French Foley balloon catheters are used to control iliac back-bleeding and the lumbar vessels are oversewn. The management of the proximal aortic cuff will vary with individual patient anatomy.

In circumstances where the graft can be sewn to an infrarenal aortic cuff, we strongly prefer circumferential division of the aorta for a more precise performance of the proximal anastomosis. However, when the aneurysm extends more proximally and the aortic cuff aortotomy becomes more beveled, the posterior wall of the aorta is left intact and the caudal border of the right renal artery ostium becomes the starting point for an oblique anastomosis, the posterior wall of which is performed in Creech fashion. In circumstances of significant ostial stenoses of the right renal artery or SMA, concomitant button eversion endarterectomy or, more preferably, direct ostial balloon expandable stenting is performed (Fig. 3). This adjunct can also be used at the ostium of the right renal artery if there is any question that the suture line has compromised same. The surgeon's goal should be to complete the proximal anastomosis with a clamp time of 20 to 30 minutes, and with renal cold preservation, major postoperative disturbance of renal function should be rare. Following completion of this proximal anastomosis, left renal artery reconstruction is completed in circumstances where the anatomy dictates. Polytetrafluoroethylene (PTFE) graft is preferred for this reconstruction for ease of handling, as opposed to attempting a Carrel button reimplantation. This left aortorenal graft does need to be carefully planned both in terms of length and orientation from the main aortic graft to prevent kinking and occlusion of the reconstruction when the left kidney is returned to its anatomic position. As previously noted, the distal reconstruction is almost always to the aortic bifurcation, although individual iliac anastomoses can certainly be performed through this approach if necessary. Similarly, tunneling for an aortobifemoral graft is accomplished without difficulty by extending the abdominal incision more inferiorly and rotating the operating table to the left.

SPECIAL CONSIDERATIONS IN OPEN REPAIR OF RUPTURED AAA

As in elective repair, vital information is gleaned from the preoperative CT scan with respect to the important considerations of the potential for endovascular repair versus the need for open operation. Clearly, factors such as the operating room environment and experience of the surgeon will also strongly influence this decision. Presuming that the patient will be treated with open operation, the same algorithm of which surgical approach to apply and the likely site of proximal aortic cross-clamp application must be decided. Also influencing this decision is the topography of rupture as displayed on the CT scan. If, for example, the retroperitoneal hematoma is inferior and/or on the right side of the abdomen, a left flank approach can be utilized with the expectation that rapid proximal aortic control

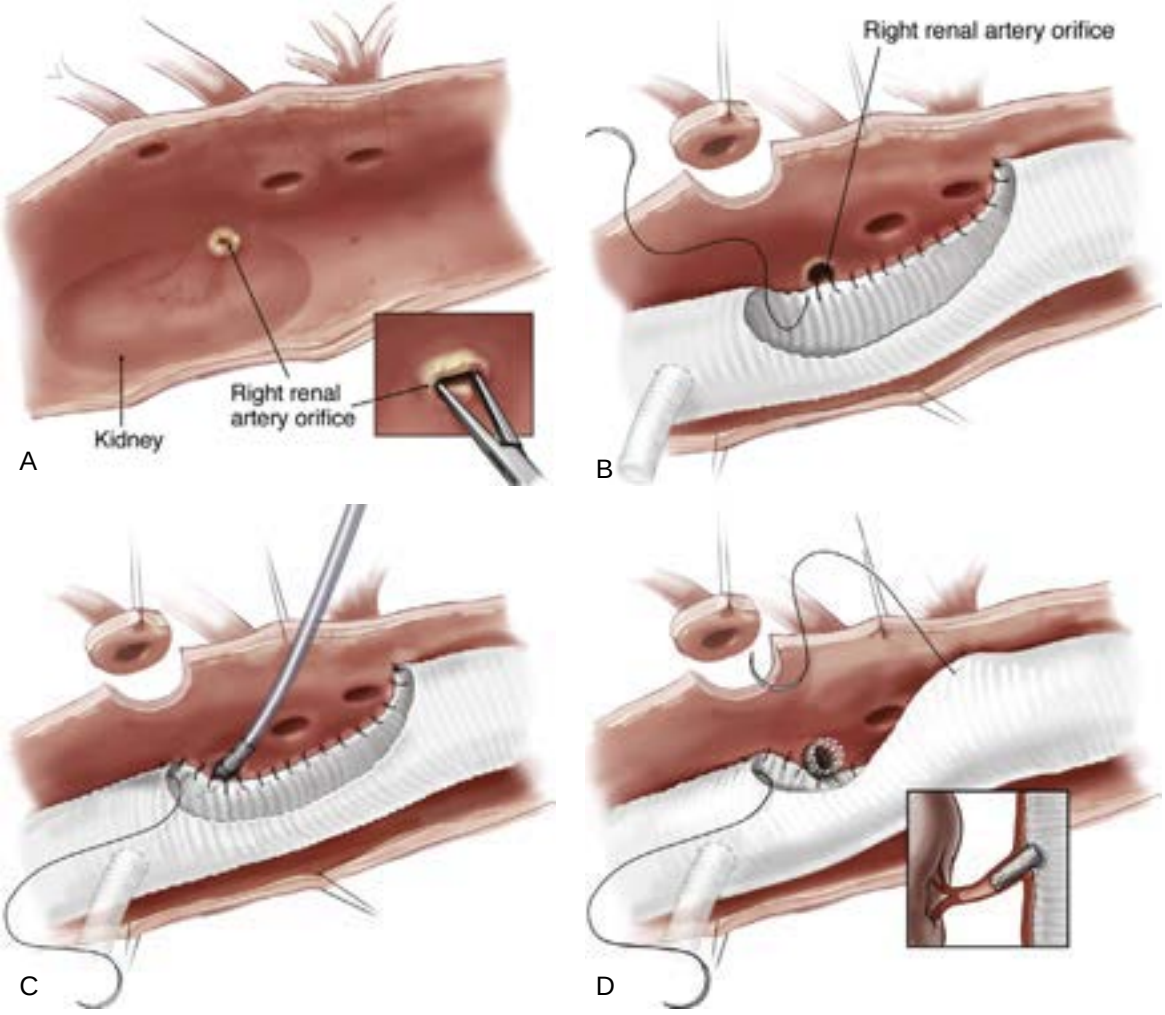


FIG. 3 Direct ostial balloon expandable stenting of the right renal artery in circumstances of significant ostial stenoses of the right renal artery (or SMA). *(From Patel R, Conrad MF, Paruchuri V, Kwolek CJ, Cambria RP. Balloon expandable stents facilitate right renal artery reconstruction during complex open aortic aneurysm repair.* J Vasc Surg. *2010;51:310–315.)*

in clean surgical planes can be anticipated. Alternatively, if the CT scan displays rupture or hematoma along the course where a left flank approach would proceed, the disaster of entering the rupture before proximal control can occur. In this situation, the patient is best served by a more proximal thoracoabdominal incision to facilitate supradiaphragmatic aortic control of the lower descending aorta. That being said, and depending on the clinical condition of the patient, most vascular surgeons would assume that the most rapid control would be that achieved with a midline transperitoneal approach, and we agree with this if the aneurysm is infrarenal or pararenal in extent. Dissecting the supraceliac aorta, as previously detailed, is a very useful adjunct in the clinical circumstance of a ruptured aneurysm being treated through a midline transperitoneal approach. Irrespective of the actual site of rupture, the retroperitoneal hematoma frequently surrounds the aneurysm neck and sets the stage for potential injury of the left renal vein in the hurried attempt to obtain proximal control. Blunt dissection in the hematoma of the aortic neck can be a helpful adjunct to ascertain a position for cross-clamp application. If hemorrhage occurs, the supraceliac clamp can be applied until the aneurysm neck and pararenal aorta are dissected out in the hopes of repositioning the clamp below the visceral vessels. We do not administer heparin in circumstances of ruptured aneurysms. However, after the iliac arteries are balloon-occluded with Foley catheters, regional heparin can be used to fill the iliac vessels and prevent thrombosis. Blood and fresh-frozen plasma must be administered concomitantly, and diffuse coagulopathy can be anticipated with either prolonged operation, excessive blood loss, or long cross-clamp times. Every attempt should be made to complete a tube graft type of reconstruction, yet adequate lower extremity circulation must be verified. If hemostasis in the retroperitoneum is not secure, packing of the abdomen with an anticipated return to the operating room within 24 to 48 hours after correction of coagulopathy is a very reasonable approach. In addition, this affords the surgeon the opportunity for a second look for left colon ischemia, which occurs frequently after treatment of ruptured AAA.

TREATMENT OUTCOMES WITH OPEN AAA REPAIR

The widespread commercial availability of fenestrated stent grafts has made a minimally invasive endovascular approach to complex AAA repair possible. As previously mentioned, while the degree of surgical insult is certainly greater with an open repair versus an endovascular one, the outcomes with open repair of complex AAA are such that we prefer this approach in select patients. Predictors of perioperative mortality in all patients undergoing AAA repair include CAD and the amount of intraoperative blood transfusion required. Predictors of cardiac complications include preoperative CHF, COPD, renal insufficiency, and intraoperative blood transfusion. COPD, the amount of intraoperative blood transfusion, and preoperative creatinine are also predictive of both renal and respiratory complications after AAA repair. The data available within the Vascular Study Group of New England (VSGNE) show that the long-term survival of the patients who underwent open repair of complex AAA from 2003 to 2011 was 91% at 1 year and 71% at 5 years, which was not significantly different from the long-term survival of patients undergoing routine open infrarenal AAA repair.

Data from a recently published multicenter, randomized trial showed that long-term survival was similar among patients who underwent endovascular repair and those who underwent open repair. While there was a difference in survival advantage seen early with endovascular repair, a late survival advantage was seen with open repair, and ultimately no difference was observed after 8 years postoperatively.

While endovascular technology continues to advance, long-term durability and/or device-specific complication rates are not yet fully elucidated. There is, therefore, a continued role for open surgical repair of AAA in a select patient population with anatomy that is not amenable to endovascular techniques.

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Endovascular Treatment of Abdominal Aortic Aneurysms

Richard P. Cambria, MD, and Scott G. Prushik, MD

Abdominal aortic aneurysm (AAA) is defined as a 50% increase in diameter of a given blood vessel compared with the baseline diameter. There is a strong male predominance, with a male-to-female ratio of 6:1. AAA is fairly common, affecting 15% of men over age 65 and accounting for approximately 15,000 deaths annually in the United States. The average rate of growth of an AAA is approximately 3 mm/yr. Smoking increases the average annual growth by 20% and also increases the risk of rupture twofold. Multiple trials have established that an AAA should be repaired once it reaches a threshold of 5.5 cm in men and 5 cm in women.

Endovascular aneurysm repair (EVAR) was first performed in 1990 by Juan Parodi in Buenos Aires. The first EVAR was performed using a stainless steel bare-metal stent sutured to a Dacron graft, which was then mounted on a large angioplasty balloon and crimped inside a large sheath. The graft was then inserted and deployed through an open exposure in the common femoral artery. This successful first procedure paved the way for the current era of EVAR.

In the 30 years since EVAR was first introduced, the techniques and devices have been refined and improved. In 2003 EVAR surpassed open aneurysm repair as the preferred method, and currently approximately 80% of AAAs are repaired using an endovascular technique. EVAR has been shown to have a lower perioperative mortality rate, shorter hospital length of stay, and lower rates of early complications.

Several randomized controlled trials have compared endovascular and open aneurysm repair. These include the EVAR 1 trial, the DREAM trial, and the OVER trial. The results of the 3 trials are consistent and lead to similar conclusions. First, EVAR has lower periprocedural and 30-day morbidity and mortality rates compared with open aneurysm repair. Second, the short-term survival advantage of EVAR diminishes with time, and there are equal mortality rates between the techniques at 2 years and beyond. Finally, EVAR

is associated with higher long-term device-related complications as compared with open aneurysm repair. Therefore, the planning, accuracy of deployment, and long-term follow-up with imaging are important in achieving a good long-term result.

PREOPERATIVE PLANNING

Precise preoperative planning is essential for short- and long-term outcomes after EVAR. Procedural success depends on several factors: adequate iliofemoral access for device delivery, adequate proximal seal zone below the renal arteries, adequate distal seal between the graft limbs and the iliac arteries, and adequate length of overlap between components of the graft. To assess the patient's anatomy before the procedure, a computed tomography (CT) angiogram with fine cuts (<2.5 mm) is a necessity. The axial, coronal, and sagittal images should be reviewed, along with three-dimensional (3D) reconstructions to perform precise measurements. There are several commercially available third-party software programs that can be used to create these reconstructed images. These programs include Terarecon, M2S, 3mensio, and Intellix. These reconstructions show detailed images of the aortic lumen, branches, and aortic wall. The software can be used to generate a centerline through the aorta into both external iliac arteries, allowing for precise measurement of the distances between branch vessels to make an accurate plan in terms of the type and size of device. The length of the main body and corresponding iliac limbs are dictated by these careful centerline measurements performed using 3D reconstructions. The CT angiogram is also used to carefully inspect the aortic neck morphology in terms of calcification, mural thrombus, and diameter. It is also important to carefully assess the iliofemoral access to safely introduce and deploy the endovascular device.

ASSESSING ACCESS VESSELS

Current endovascular technology requires bilateral access for device delivery, with the most common site of entry being the common femoral arteries. It is important to assess the iliofemoral vessels for patency, diameter, calcification, thrombus, and tortuosity. If there is significant common femoral disease, an endarterectomy may be required to facilitate placement of the delivery sheath. Luminal diameter should be carefully measured to ensure that it is sufficient for placement of the device sheath safely. Iliac stenosis can be managed with angioplasty before device sheath placement. Patients with small external iliac vessels may require the creation of an iliac conduit through a retroperitoneal incision using a 10-mm Dacron graft on the distal common iliac artery. Alternatively, an endoconduit can be performed by placing a 10-mm covered stent graft followed by angioplasty. Tortuous iliac arteries are generally straightened with the use of a stiff guidewire; however, severe tortuosity may preclude safe delivery of the device.

PROXIMAL AORTIC SEAL

Achieving appropriate proximal seal between the endovascular device and the aorta depends on adequate apposition between the graft and nonaneurysmal aorta. The minimum length required for adequate seal varies between 10 and 15 mm depending on the device (Table 1). Adequate seal is assessed by measuring the aortic diameter below the level of the lowest renal artery and in 5-mm increments caudally to assess for a conical neck. The seal zone should be assessed for angulation relative to the adjacent aorta, calcification, and mural thrombus. It is important to perform these measurements in centerline, perpendicular to the wall of the aorta to ensure adequate graft sizing. If measurements are made on axial CT angiography without taking into account the centerline, the aortic neck diameter can be overestimated, leading to oversizing of the endograft and fabric infolding, resulting in possible type Ia endoleak. The proximal endograft is then oversized approximately 10% to 20% relative to the diameter of the aortic and the seal zone.

DISTAL ILIAC AND JUNCTIONAL SEAL

A nonaneurysmal distal seal zone is required in the common iliac artery for adequate distal fixation. The current devices require either 10 or 15 mm of length for adequate seal. If the common iliac artery is aneurysmal and adequate seal cannot be achieved, the graft may be landed in the external iliac artery. If the graft is sealing in the external iliac artery, the internal iliac artery must be embolized either before or as part of the aneurysm repair to prevent endoleak. In patients for whom it is important to preserve blood flow to one or both of the internal iliac arteries, Gore offers a commercially available iliac branch endograft that places a second bifurcated component into the external and internal iliac arteries to preserve pelvic flow. Iliac artery diameter measurements should be taken perpendicular to the wall of the artery, again taking advantage of the 3D reconstruction software and using the centerline measurement. Iliac limbs should be oversized between 10% and 20% just as in the proximal aortic fixation. Junctional seal should be maximized between components, generally about 3 cm of overlap, depending on the device. Once the device is placed, angioplasty should be performed on the overlap zone to prevent type III endoleak.

PATIENT SELECTION

As mentioned previously, the major selection criteria for EVAR are anatomic factors that can be used to predict outcomes. These include the diameter of the aortic neck, the length of the neck, angulation, and the distal iliac seal zone. There are currently 6 commercially available endovascular aneurysm devices that are approved by the Food and Drug Administration in the United States (Fig. 1). These current devices recommend a neck length between 10 and 15 mm and angulation between 45 and 60 degrees. One exception to the neck angulation is the Aorfix device, which allows for neck angulation up to 90 degrees. Generally, neck diameters up to 32 mm can be accommodated by current grafts.

Adherence to the instructions for use is vital to good short- and long-term outcomes. In general, vascular surgeons have had low rates of adherence to the instructions for use. It has been shown that nonadherence leads to a higher rate of endoleak and corresponding AAA sac diameter growth at 5 years. This puts patients at risk for rupture and requires a higher intervention rate. Therefore, patients who have anatomy that is not suitable for endovascular repair should be offered open surgical repair or fenestrated EVAR.

PROCEDURAL STEPS

Arterial Access

Open Femoral Access

Either a vertical or oblique skin incision is made overlying the common femoral pulse just below the inguinal ligament. The vertical incision includes the advantage of getting additional exposure to the iliac and femoral vessels if necessary; however, the oblique incision is favored by many surgeons due to a lower incidence of wound complications. The common femoral artery is dissected distal to the inguinal ligament and controlled with vessel loops. An 18-gauge access needle is then inserted into a disease-free portion of the artery, and a 0.035 starter wire is advanced into the proximal aorta. A short 6Fr sheath is placed over the wire and into the common femoral artery. A stiff wire, either an Amplatz or Lunderquist wire, is inserted into the descending thoracic aorta. A pigtail catheter with multiple 1-cm markers is introduced on the contralateral side in place just above the renal arteries. The patient is then systemically heparinized.

Percutaneous Femoral Access

Percutaneous access for EVAR has increased in popularity over the past 10 years. This approach has the advantage of shorter procedure time, less postoperative pain, and decreased risk of wound complications. Disadvantages of this approach include increased hospital

TABLE 1 Characteristics of Currently Available Endovascular Devices

Device	Graft /Stent Material	Treatable Aortic Neck Diameter (mm)	Main Body Diameter (mm)	Delivery System Size Main Body/Limb (Fr)	IFU Neck Length/Angle	Iliac Treatment Diameter (mm)	Distal Iliac Fixation Length (mm)	Proximal Fixation	Design Features
Excluder	ePTFE/ Nitinol	19–32	23–35	16–20/12–15	≥15 mm and ≤60 degrees	8–25	≥10	Infrarenal	Repositionable proximal delivery system to achieve accurate proximal landing zone
Zenith Flex	Woven polyester/ stainless steel	18–32	22–36	21/14–16	≥15 mm and ≤60 degrees	7.5–20	>10	Suprarenal	Partial proximal repositioning; shortened Z-stents inhibit kinking
Endurant II	Woven polyester/ nitinol	19–32	23–36	18/14–16	≥10 mm and ≤60 degrees or ≥15 mm and ≤75 degrees	8–25	≥15	Suprarenal	Approved for treatment of 10 mm proximal aortic neck
AFX	ePTFE/ cobalt chromium alloy	18–32	25–34	19/9	≥15 mm and ≤60 degrees	10–23	≥15	Infrarenal or Suprarenal	Unibody device provides anatomic fixation on aortic bifurcation
Ovation	ePTFE/ nitinol	16–30	20–34	14–15/12–15	≥10 mm and ≤60 degrees or <10 mm and ≤45 degrees	8–25	≥10	Suprarenal	Smallest delivery sheath; proximal sealing ring with Polymer
Aorfix	Woven polyester/ nitinol	19–29	24–36	22/20	≥15 mm and ≤90 degrees	9–19	≥15	Infrarenal	Ability to treat aortic necks with severe angulation

ePTFE, Expanded polytetrafluoroethylene.

costs and occasional urgent conversion to open access and arterial repair. We recommend routine use of ultrasound guidance with percutaneous access to help identify an area on the anterior wall of the common femoral artery that is free of atherosclerotic plaque. A small transverse stab incision is made with an 11 blade just below the probe. The tract is then dilated above the artery using blunt dissection with a hemostat. A micropuncture needle is then inserted into the common femoral artery under ultrasound guidance, followed by the micropuncture wire and sheath. At this point arteriography is performed to ensure adequate positioning of the arterial access in the common femoral artery before upsizing the sheath. If satisfied with the access site, a 0.035 guidewire is placed, followed by a 6Fr sheath. Next, the sheath is removed, the Perclose Proglide is placed over the wire, and the wire is removed. The first Proglide is deployed in the 10 o'clock position, and the sutures are clamped with a straight snap. The 0.035 wire is replaced, the Proglide is removed, and manual pressure is held while the next Proglide device is placed over the wire. The wire is again removed, and the sutures are deployed in the 2 o'clock position. The sutures are then clamped with a curved snap and the wire is again replaced. After the Proglide is removed, manual pressure is held, and an 8Fr sheath is placed for hemostasis. This is repeated on the contralateral side. The patient is then systemically heparinized. On the ipsilateral side, the wire is exchanged for either an Amplatz or a Lunderquist wire to facilitate the placement of a large sheath. A marker pigtail catheter is placed just above the renal arteries on the contralateral side.

Device Deployment

We will describe the steps here for the deployment of a bifurcated modular graft because this is the most commonly used device. After bilateral open or percutaneous femoral access is performed, a floppy Glidewire is placed into the proximal thoracic aorta and exchanged over a catheter for a stiff wire, either Amplatz or Lunderquist. It is important always to visualize the tip of the stiff wire in the aortic arch to minimize inadvertent placement in the arch vessels, increasing the risk of stroke. A pigtail catheter is then placed through the contralateral side and placed just above the level of the renal arteries

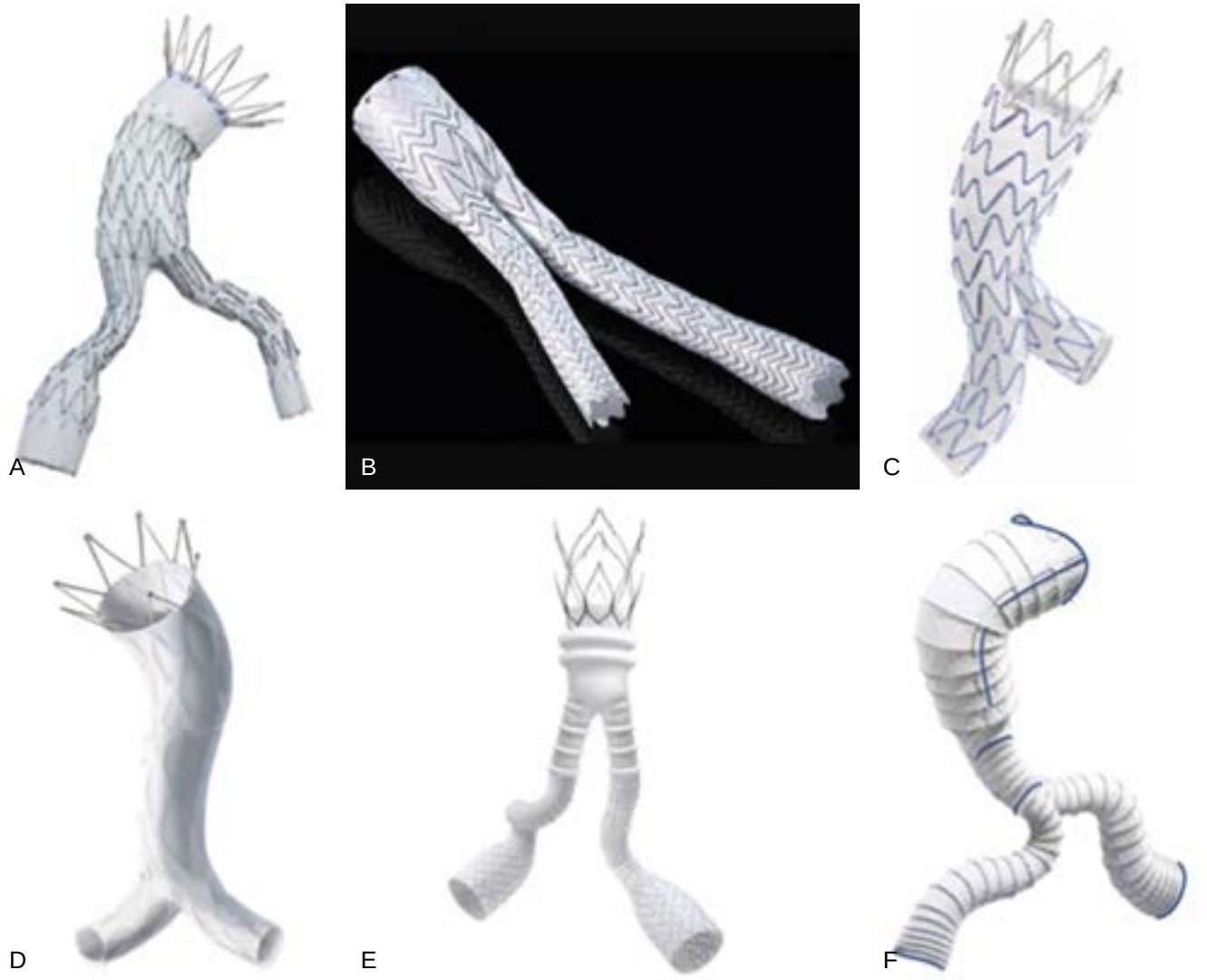


FIG. 1 Commercially available endografts. **(A)** Cook Zenith Flex. **(B)** Gore Excluder. **(C)** Medtronic Endurant II. **(D)** Endologix AFX. **(E)** Endologix Ovation. **(F)** Lombard Aorfix. *(From Brinster CJ, Sternbergh WC. Endovascular aneurysm repair techniques. In: Sidawy AN, Perler BA, eds.* Rutherford's Vascular Surgery and Endovascular Therapy. *9th ed. Philadelphia: Elsevier, 2019.)*

generally at about the L1 vertebral body. If there is a question about iliac occlusive disease or about the length of main body needed, an angiogram can be obtained now to make length measurements. However, usually, the main body is inserted through the ipsilateral side in the undeployed position, and angiography is performed to confirm the position of the renal arteries.

To properly deploy the main body, the contralateral gate should be oriented under fluoroscopy before insertion. The orientation should be confirmed as the device is being advanced to avoid the gait opening in a difficult position to cannulate. Once the undeployed graft is placed in the pararenal aorta, angiography is performed to confirm the position of the lowest renal artery, which is then marked on the screen. Initial deployment should begin about 1 cm above the renal arteries, and, as the graft is deployed, it is slowly pulled down below the lowest renal artery. After the proximal landing zone is established, the deployment continues until the contralateral gate is open. At this point, the bare-metal suprarenal stent is deployed for the devices that have it.

The next step is cannulation of the contralateral gate. This is generally performed using a Glidewire and catheter. It is important to confirm that the wire indeed has passed through the contralateral gate. This can be done by either placing a pigtail into the main body to ensure that it spins easily because it will be constrained behind the graft if not through the gate or by inflating an angioplasty balloon at the level of the contralateral gate and spinning the gantry to confirm its position within the gait. Once this is done, a stiff wire is placed, and the gantry is moved to 20-degree left anterior oblique for the right common iliac artery or right anterior oblique for the left common iliac artery. Angiography is then performed using the marker catheter to measure the length from the distal graft to the iliac bifurcation. The appropriate limb is then inserted with the least minimal overlap between device components and landed just above the takeoff of the internal iliac artery. At this point, the ipsilateral limb is fully deployed, and, if necessary and depending on the device, an ipsilateral iliac limb extension is advanced and deployed in a similar manner to the contralateral limb.

Once the graft is fully deployed, a compliant balloon may be used for gentle angioplasty of the aortic neck, device overlap zones, and distal seal. It is important not to be overly aggressive with angioplasty so as not to cause proximal aortic or iliac artery rupture. After this, completion angiography is performed. The angiographic catheter is placed in the pararenal aorta, and the following should be carefully

inspected on the angiogram: patency of the renal and internal iliac arteries, position of the proximal seal zone, flow through the graft and iliac arteries bilaterally, and inspection for endoleak.

Once the surgeon is satisfied with the result, femoral closure is performed. If open access was performed, the wires and sheaths are removed, the arteries are clamped, and repair is performed transversely with 5-0 Prolene suture. If percutaneous access was used, the sheath is removed, while leaving the wires in place to maintain access, and the Proglide device sutures are cinched down. Once adequate hemostasis is obtained, the wires can be safely removed.

Follow-up

Patients return to the office for follow-up at 1 month after surgery, at which time a CT angiography of the abdomen and pelvis is performed, which serves as the baseline study. Repeat CT angiography is performed at 1 year after surgery. Presence or absence of endoleak and aortic sac regression are determined by CT angiography, and follow-up is performed annually. Patients with shrinking aneurysm sacs and no evidence of endoleak can be safely managed with yearly duplex ultrasound scanning. Patients with enlarging sacs or endoleaks are best monitored with yearly CT angiography.

COMPLICATIONS

Endoleak

Endoleak is defined as persistent blood flow in the aneurysm sac after EVAR. This results in continued pressurization of the aneurysm sac, which places the patient at continued risk of aneurysm growth and ultimately rupture. Endoleaks can be classified in to one of five categories (Fig. 2), which help to determine the best course of treatment.

Type I Endoleak

Type I endoleak (Fig. 3) occurs as a result of an incomplete seal at either the proximal aortic sealing zone (Type Ia) or the distal iliac seal zone (Type Ib). This results in continued pressurization of the aneurysm sac, leading to sac growth. Type I endoleak is generally encountered at the time of stent graft placement or shortly thereafter, although it can be encountered at any time. Because this pressurization and aneurysm growth leads to continued risk of rupture, treatment of type I endoleak is mandatory. Proximal, Type Ia endoleak can be treated with angioplasty with a compliant balloon, proximal extension cuff if there is adequate length below the renal arteries, placement of a Palmaz stent, or with the use of the Aptus Endovascular Repair System. Treatment of type Ib endoleak can be done by deploying an iliac limb extension with embolization of the internal iliac artery as necessary.

Type II Endoleak

Type II endoleak (Fig. 4) is defined as persistent sac filling from back-bleeding side branches such as the inferior mesenteric artery, lumbar arteries, or middle sacral artery. Type II endoleak is relatively common and seen in between 10% and 20% of patients on CT angiogram after EVAR. Generally, there is a benign course with as many as 80% spontaneously resolving within 6 to 12 months of stent graft placement. It has been shown in multiple studies that the risk of aneurysm rupture due to type II endoleak is small. Therefore, treatment is only performed if there is documented sac enlargement. Treatment is generally performed through endovascular means using coil embolization or Onyx Liquid Embolic System (ethylene-vinyl alcohol copolymer). This embolization can be performed through a transarterial approach via the superior mesenteric artery or internal iliac arteries. It can also be performed from the iliac arteries and directly accessing the aneurysm sac from behind the iliac limb. If transarterial embolization is unsuccessful embolization can be attempted via either a translumbar or transcaval approach. If embolization is unsuccessful by all means and the sac continues to grow operative intervention can be performed by explant of the graft and open repair or direct ligation of back-bleeding vessels.

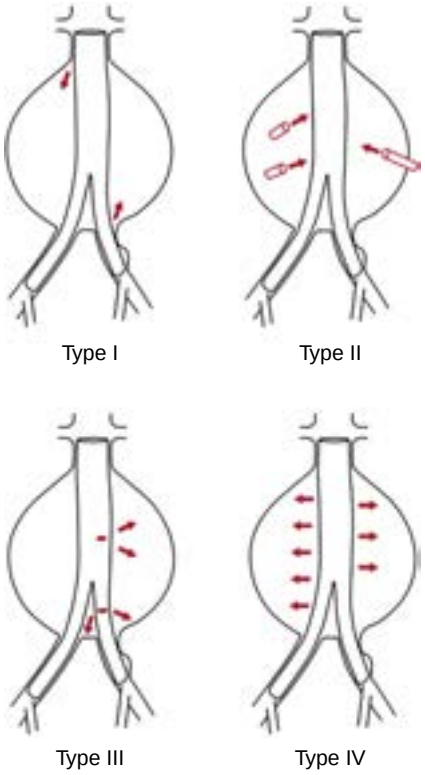


FIG. 2 Type I to IV endoleaks. Type I endoleak originates from an incomplete seal at the proximal (type Ia) and distal (type Ib) seal zones of the endograft. Type II endoleak results from back-bleeding from patent branch vessels of the abdominal aorta including the inferior mesenteric artery and lumbar arteries. Type III endoleak originates from tears in the graft fabric and from junctional leaks between graft components. Type IV endoleak results from porosity in the graft fabric.



FIG. 3 Type Ia (proximal) endoleak originating from the superior seal zone of an endograft.

Type III Endoleak

A type III endoleak (Fig. 5) occurs when there is a tear in the fabric of the graft or flow between separate components of the graft. This

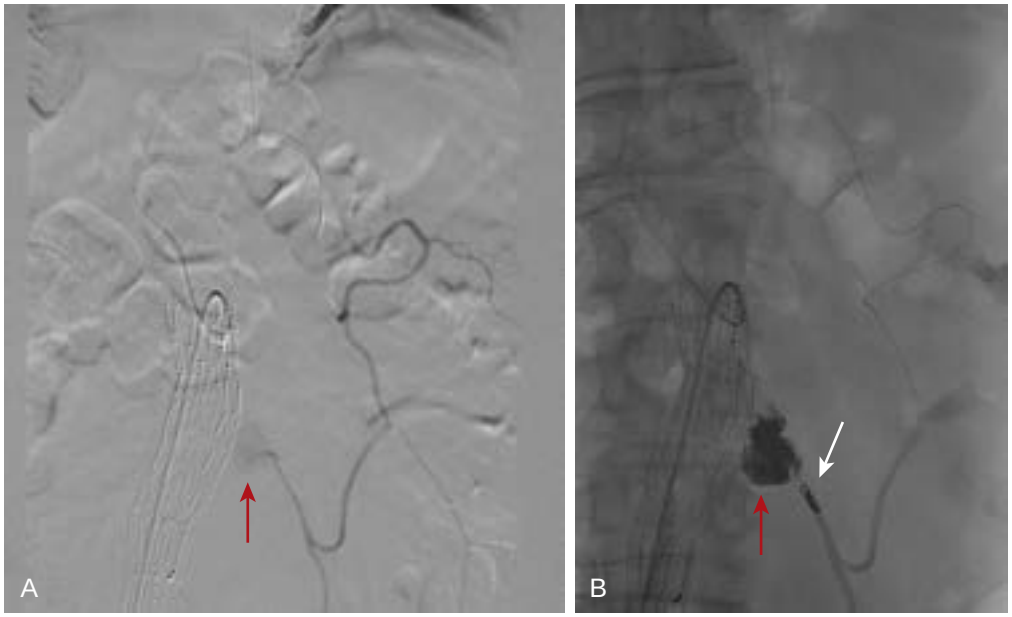


FIG. 4 Type II endoleak from the inferior mesenteric artery. **(A)** Angiography performed via selective catheter placement in the superior mesenteric artery demonstrates a blush at the ostium of the inferior mesenteric artery *(red arrow)* feeding an enlarging abdominal aortic aneurysm sac. **(B)** Coil embolization of the endoleak with Onyx glue *(red arrow)* and coil embolization *(white arrow)* of the inferior mesenteric artery.

leads to continued pressurization and sac enlargement increasing the risk of rupture as in type I endoleak. Therefore, treatment of type III endoleak is again mandatory. Treatment involves placement of a cuff or a new limb to bridge the gap between separated components. Treatment may require relining the graft with a new stent graft, which is generally performed using an aorto uni-iliac device along with a femoral-femoral bypass and coil embolization of the contralateral common iliac artery.

Type IV Endoleak

Type IV endoleak is related to flow through the graft due to the porosity of the fabric. It is rare to encounter this type of endoleak with the current generation of stent grafts. Typically, no treatment is necessary, and the endoleak resolves as the graft interstices thrombose.

Type V Endoleak

This type of endoleak is referred to as *endotension* and is defined as sac enlargement without an identifiable endoleak on imaging studies. There are several proposed theories behind type V endoleak. One theory is that the flow into the aneurysm sac is so slow that it cannot be detected with current imaging techniques. Another theory postulates that pressure is transmitted across thrombus in the aneurysm sac maintaining sac pressure. Regardless of the mechanism, continued sac pressurization leads to ongoing risk of rupture. Close follow-up is recommended to determine the rate of growth and the necessity of repair. Repair is performed through relining with a new graft or with explant and open repair.

Graft Limb Occlusion

Occlusion of one graft limb occurs in about 3% of patients and usually occurs in the first 6 months after EVAR. It is more common with aortoiliac occlusive disease, a small distal aorta, or tortuous iliac arteries. It was more common in stent grafts with unsupported limbs; however, in the current generation of stent grafts, with supported limbs, lower limb occlusion rates have been noted. Most patients with limb occlusion present with buttock, thigh, or calf claudication. Rest pain or acute limb ischemia occur but are less common. Several approaches have been used to treat limb thrombosis including thrombolysis, angioplasty, and stent placement to straighten out kinks. Open surgical approaches include femoral-femoral bypass, axillary-femoral bypass, axillary-bifemoral bypass, or surgical thrombectomy.

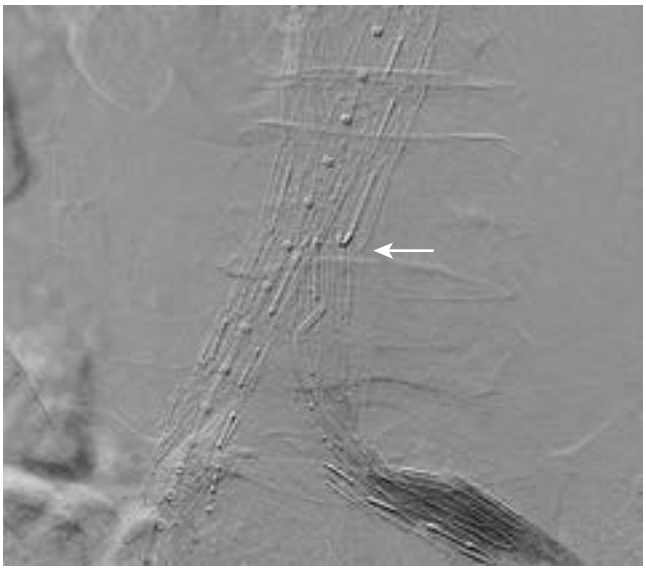


FIG. 5 Type III endoleak from separation of the limb from the main body of the graft *(arrow)*.

Ischemic Complications

Ischemic complications after EVAR stem from one of several mechanisms, including direct vessel occlusion, atheroembolization during manipulation and device deployment, and inadequate collateralization of the mesenteric and pelvic circulation. Pelvic ischemia can present as buttock claudication, buttock necrosis, spinal cord ischemia, colon ischemia, and erectile dysfunction. Pelvic ischemia can occur frequently after EVAR, especially sexual dysfunction and buttock claudication, which should be discussed with the patient

during the consent process. It generally occurs after embolization of one or both internal iliac arteries for the treatment of common iliac artery aneurysm. Buttock claudication can occur in more than 50% of patients with unilateral internal iliac artery embolization and more than 60% with bilateral internal iliac artery embolization. Erectile dysfunction occurs in 17% of patients with unilateral internal iliac artery embolization and 24% with bilateral embolization. Although the incidence of buttock claudication is relatively high, approximately two-thirds of patients report resolution of symptoms within 1 year of EVAR. Although mesenteric ischemia has a high mortality rate after aneurysm repair, it is seen in less than 2% of endovascular procedures. Spinal cord ischemia is an extremely rare event after endovascular AAA repair and has been reported in less than 0.5% of cases.

Renal Artery Occlusion

Renal artery occlusion either occurs from coverage of the origin of the artery by the graft or through embolization. Upward movement of the graft after deployment is uncommon. Usually, renal artery coverage is a complication that occurs as a result of deploying the graft too high, either from misjudging the location of the fabric relative to the radiopaque markers on the graft or due to parallax if there is improper gantry position. If coverage is detected on the completion angiogram, attempts should be made to salvage the kidney. If there is some flow identified over the top of the graft, this can usually be accomplished by placing a stent into the renal artery orifice, which is easiest from a left brachial approach. If the renal artery cannot be visualized and a wire cannot pass, it is sometimes possible to pull the graft down slightly to make a small channel for the wire. This can be accomplished with gentle traction downward with a compliant balloon inflated in the main body or with a wire snared up and over, "flossing" the graft to allow for traction. If all of these techniques fail, open splenorenal or hepatorenal bypass may be necessary. Embolization to the renal arteries can present with early or delayed renal insufficiency. This is especially true when there is thrombus in the aortic neck and a graft with suprarenal fixation is used.

Suggested Readings

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Management of Ruptured Abdominal Aortic Aneurysms

David P. Stonko, MD, MS, and Caitlin W. Hicks, MD, MS

INTRODUCTION

Ruptured abdominal aortic aneurysm (rAAA) is a surgical emergency associated with high morbidity and mortality. Time to diagnosis, appropriate referral, and expeditious time to operation are crucial to achieving favorable outcomes. However, early detection and prevention provide the best treatment.

Risk factors for aortic rupture include smoking, which is the greatest risk factor for development of AAA, size, rapid growth, tenderness, chronic obstructive pulmonary disease, family history, peripheral artery disease, genetic predilection, and female sex. Although female sex is associated with an increased risk of rupture compared with male sex, females are less likely to have an AAA than men. Males 50 years of age and older who have smoked more than 100 cigarettes in their lifetime have a high rate of AAA and should be screened with a one-time abdominal ultrasound examination, which is reimbursed by Medicare.

Not all AAAs will be detected early, and some will progress to rupture. Historically rAAA has been associated with in-hospital mortality as high as 40% to 50%. Despite advances in critical care, transfer protocols, and centralization of care, this figure was stable across numerous studies for over 40 years. However, in 1994 the first endovascular aortic aneurysm repair (EVAR) for rupture was performed, which over the last 20 years has resulted in a paradigm shift toward endovascular management of rAAA. Since the introduction of EVAR, studies have shown an improvement in rAAA in-hospital mortality, with current estimates as low as 20%. Despite this encouraging improvement, there has been no proven mortality benefit for EVAR versus open repair for a rAAA in the long term.

PRESENTATION, DIAGNOSIS, AND INITIAL MANAGEMENT

Most AAAs are fusiform and are usually not associated with pain or other symptoms before rupture. The onset of abdominal or back pain portends impending or ongoing rupture, and these patients should be regarded as such, especially in the setting of a known AAA. Classically, patients with rAAA also present with a pulsatile abdominal mass and shock physiology including hypotension and tachycardia. However, most patients with rAAA do not actually present with the complete triad of signs and symptoms, and a high clinical suspicion of aortic pathology is necessary.

Several broadly held misconceptions exist about the diagnosis and natural history of rAAA. In the absence of other pathology, patients with rAAA will likely have a normal lower extremity pulse examination, may or may not have an abdominal bruit or thrill, and, though mortality for rAAA is high, death may not occur immediately as the rupture is often contained initially by the retroperitoneum (RP). The rAAA may take several hours to evolve to uncontained rupture and death.

The initial evaluation of a patient with a suspected rAAA should follow the typical airway, breathing, and circulation (ABC) protocol. Immediate management should focus on obtaining adequate venous and arterial access, cardiac monitoring, laboratory analysis including type and screen, and blood product preparation. As discussed in detail later, patients with rAAA should not be intubated until they are in the operating room, and the focus should be on initial blood pressure and heart rate control (SBP < 120, HR < 80) to reduce circulatory impulse

and slow the progression of rupture. If the patient is hypertensive, impulse control should be established with a short-acting agent such as esmolol or labetalol. This is particularly important in patients with a contained rupture. Fluid and vasopressor support should be limited to maintain impulse control, prevent further rupture or aortic tearing, and limit additional blood loss. This is contrary to the treatment of most patients presenting with hypotension, but it is critical in the management of rAAA. Once aortic control is obtained in the operating room, the transfusion strategy can be augmented as described later.

In practice, patients presenting with abdominal or back pain and vital sign changes will usually undergo computed tomography angiography (CTA) for diagnosis. Given the efficiency of CTA in the modern era, cross-sectional imaging should be obtained whenever possible to facilitate endovascular operative planning for treatment of rAAA and rule out other pathology. Many other conditions would likely be on the differential for patients presenting with rAAA, including perforated viscus, gastric or small bowel ulcer, hepatobiliary pathology, cardiac pathology, nephrolithiasis, pancreatitis, and other vascular etiologies such as aortic dissection. Prior studies have shown that CTA does not delay time to the operating room and can determine anatomic suitability for EVAR (Box 1). Conventional transabdominal ultrasound, although useful for screening AAA, is not sensitive for rupture and does not provide the anatomic information necessary to provide objective measurements to determine anatomic suitability for EVAR.

Time to hemorrhage control and aortic balloon occlusion is of the utmost importance when treating a patient with rAAA. No other vascular pathology carries the same consequences of delay. If the diagnosis is made and the facility can provide definitive management, then they should proceed accordingly. However, if the facility is unable to provide definitive care, then transfer should be arranged expeditiously. Prior studies have shown that transfer of patients with rAAA from smaller hospitals to those with aortic centers did not increase mortality and possibly improved it. This pattern held, even when the same surgeons were performing the procedure across both hospitals. If the patient is to be transferred, initial critical care management as described earlier should be started in parallel. CT imaging can also be transferred electronically to support preparation on the part of the receiving institution, surgical team, and operating room staff.

ENDOVASCULAR VERSUS OPEN REPAIR

Four large randomized clinical trials comparing EVAR versus open rAAA repair have been conducted to date: NOTTINGHAM, IMPROVE, ECAR, and AJAX. None of these trials demonstrated a survival advantage for EVAR over open surgery in the long term, though EVAR has been shown to have lower in-hospital morbidity and mortality. EVAR, however, has been associated with a higher rate of postoperative abdominal compartment syndrome (ACS) than open rAAA repair, likely because the hematoma from the rupture is not evacuated (discussed later).

Because of the improved in-hospital mortality and lower morbidity associated with EVAR, many centers have adopted an EVAR-first strategy for the treatment of rAAA patients. Typical anatomic requirements can be assessed with preoperative CTA. If the aneurysm neck is too short or too angulated for EVAR (see Box 1), then open repair may be necessary. In addition, if renal perfusion cannot be maintained with an endovascular approach, then open repair should be used. It is not appropriate to sacrifice the renal arteries to perform EVAR and thereby commit the patient to hemodialysis. The fluid shifts after EVAR related to the hemorrhage and resuscitation are substantial, and rAAA outcomes in hemodialysis patients are poor.

There are currently several devices approved by the US Food and Drug Administration for endovascular repair of an infrarenal AAA. Data and outcomes measures on each of these devices vary, but approximately 50% to 75% of all rAAAs are anatomically amenable to EVAR. It is possible to use EVAR outside the officially approved Instructions for Use (IFU). This technique may temporize rAAA patients who are poor candidates for open rAAA repair, but the long-term outcomes of an off-IFU EVAR application are marginal. In the future, as more sophisticated devices covering larger anatomic variability become available, the number of patients who will be anatomically suitable for EVAR is expected to increase.

BOX 1 Typical Anatomic Requirements for EVAR for Ruptured AAA

- Aortic neck diameter less than 32 mm
- Aortic neck angulation less than 60 degrees
- Limited aortic thrombus and calcification (relative)
- Parallel wall and undilated aortic neck length at least 15 mm below the lowest renal artery
- Appropriate-size iliac arteries without excessive tortuosity or occlusion, and at least a 10-mm seal zone

TECHNIQUE

Operating Room Preparation and Retrograde Balloon Occlusion of the Aorta

Regardless of whether an endovascular or open repair approach is planned, the initial operative management of a patient with rAAA is the same. The patient should be prepped and draped widely, including the bilateral groins and abdomen at a minimum. In general, all preparation of the patient, including intravenous access, arterial lines, and sterile preparation, should be performed before induction of anesthesia. This is important because for patients at the extent of their physiologic reserve, loss of preload with induction can result in cardiovascular collapse. Close discussion with anesthesia about the patient's hemodynamic status and the surgical plan is important.

Once adequate access is obtained, balloon occlusion of the aorta should be established. Local anesthesia should be used when possible for this step to allow for aortic control before induction of general anesthesia. Percutaneous common femoral artery (CFA) access should be obtained using ultrasound guidance, followed by stiff wire placement into the thoracic aorta, a 12Fr sheath, and an occlusion balloon. Pre-placement of closure devices may be done at this time or at the end of the case depending on patient stability, body habitus, and other clinical factors.

Occasionally, iliac vessel access may be difficult. The goal is to build a stable platform for sheath placement. The iliac arteries can be navigated with a guidewire followed by a straight or angle-tipped catheter and then exchanged for a stiff wire once aortic cannulation is obtained. The stiff wire will often straighten tortuous iliac arteries, making placement of a large-bore sheath more feasible. The goal of access and sheath placement is to maneuver the sheath through the iliac arteries without creating a dissection or other injury. For patients with extensive atherosclerotic disease, the iliac may need to be stented after straightening (crack and pave), allowing the graft to seal within the stent.

Once sheath access is obtained, the aortic occlusion balloon should be rapidly introduced to a level just proximal to the rupture. This allows for hemodynamic stabilization by both occluding flow into the rupture and increasing afterload. Once the balloon is up, progression toward definitive EVAR or open repair can follow.

Endovascular Repair

Once the aortic occlusion balloon is in place, diagnostic imaging can be obtained to identify the takeoff of the renal arteries. The next step in EVAR repair is deployment of the main body of the stent graft. After obtaining contralateral access, there are two main approaches to this: (1) fully deploy the main body; deflate the aortic occlusion

balloon and insert it into the stent graft; and then reinflate it at the proximal edge of the stent graft to maintain hemodynamic control during gate cannulation or (2) deploy the main body; remove the balloon; and then proceed with gate cannulation in the usual fashion because there is often sufficient seal with the main body in place. Gate cannulation can be the most time-consuming step of the case. It is important to have all necessary wires and catheters available nearby to avoid delays. Once the main body is deployed and the gate is cannulated, one may proceed with managing the distal segments. Here, either an aortouniiliac with femoral-femoral bypass or a bi-iliac stent graft may be used. The distal landing zone of the stent should be beyond the involved portion of the aneurysm but also beyond any substantially diseased portion of the iliac arteries. This will commonly be to the takeoff of the internal iliac artery, but it may need to be extended in certain circumstances, as discussed later.

The AJAX randomized clinical trial used aortouniiliac grafts for the management of EVAR. An aortouniiliac graft, when compared with the more standard bi-iliac stent graft, has the advantage of an easier learning curve and rapid hemorrhage control because contralateral gate cannulation is not necessary. However, the aortouniiliac configuration adds time for the femoral-femoral bypass and is associated with an increased surgical infection risk because of the need for open bilateral femoral artery exposure and presence of a prosthetic bypass graft. If attempting to place a bifurcated stent graft and gate cannulation is not possible, the bifurcated device can be converted to an aortouniiliac configuration in which the contralateral common iliac artery (CIA) is embolized and a femoral-femoral bypass is subsequently performed. Bilateral groin cutdowns and tunnelling are more likely to require general anesthesia, and this consideration may affect operative planning; however, a transition to general anesthesia after hemorrhage control is obtained is possible and may be necessary for other reasons, such as tenuous respiratory status and the need for large-volume resuscitation.

Once the EVAR is deployed in its entirety, gentle balloon angioplasty is used at the distal fixation zones and all areas of device component overlap. Proximal angioplasty should be performed with caution as it can cause recurrent rupture in the setting of a fragile aorta. A postdeployment angiogram should then be performed to assess for endoleak. Special attention should be paid for type 1 endoleaks, which should be addressed before leaving the operating room. For type 1a endoleaks, it may be necessary to perform a gentle balloon angioplasty of the proximal seal zone. If the endoleak persists, deployment of aortic cuffs or endoanchors to create an adequate proximal seal may be necessary. For rAAAs with a type 1a endoleak, no more than two attempts at ballooning the proximal seal zone should be made. In the event of a rupture with ballooning or manipulation, the balloon should be immediately advanced above the site of rupture and reinflated, with conversion to open repair to follow. In cases in which a proximal extension will violate the renal or visceral arteries, a chimney or snorkel technique to maintain renovisceral perfusion may be used. For type 1b endoleaks, it may be necessary to sacrifice the hypogastric artery to get a good seal distally. In these cases, the hypogastric artery should be coiled before covering to prevent the formation of a type 2 endoleak. Ideally, the patient would have at least one hypogastric artery preserved at the end of the case to maintain pelvic perfusion. For type 3 endoleaks, balloon angioplasty of the overlapping graft components should be performed. Type 2 endoleaks are less critical to address and can usually be followed with serial imaging to assess whether they result in aortic sac enlargement long-term.

No patient with a rAAA should leave the operating room with a type 1 endoleak. If a type 1a or 1b endoleak persists despite the maneuvers described, conversion to open repair may be necessary. Conversion is required in 1% to 2% of cases in most series but confers a significant in-hospital mortality disadvantage compared with successful EVAR.

At the end of the case following successful EVAR deployment, it is important to maintain a high index of suspicion for iliac artery injury. Iliac artery injuries are more common in emergent EVAR compared with elective EVAR, and they are more frequent in women compared with men because of the relatively smaller diameter of the iliac arteries. Often an iliac artery injury is masked throughout the case because the large sheaths tamponade it. Therefore, an exchange-length stiff wire should be maintained across access to both iliac arteries as the sheaths are removed. Ideally, the dilators are reinserted into the sheaths before removal to facilitate easy replacement if necessary. The sheaths should be removed one at a time, and attention should be paid to confirm no hemodynamic changes or bleeding before removing the wire. If an iliac injury is suspected, the sheath should be reinserted over the maintained wire on the offending side to provide tamponade, and a stent graft should ultimately be placed to cover the injury.

Consideration should be given to prophylactic exploratory laparotomy for decompression to avoid ACS following EVAR, as discussed later. EVAR has higher rates of ACS than open rAAA repair, likely because intraperitoneal or RP decompression is not routinely performed. Prophylactic exploratory laparotomy is particularly important in patients with intraperitoneal free rupture, regardless of repair approach. If the hematoma is limited to the RP, this may not be needed unless there are signs of femoral nerve compression.

There are variable practice patterns for heparin dosing and reversal during endovascular repair of rAAA. These range from no anticoagulation at all, to using heparin only after aortic control, to giving heparin at a half dose. At our institution, we administer heparin after the aortic occlusion balloon is placed. Heparin is initially dosed at approximately 80 units/kg to maintain an activated clotting time (ACT) >250 until case completion using point-of-care ACT measurements in the operating room.

Open Repair

The two main approaches to open rAAA repair are the transperitoneal (TP) or RP approaches. In general, the initial operative steps via both exposures are similar. If the aortic occlusion balloon is working well, the general principle is to get distal control first and then obtain supraceliac aortic control. However, if the aortic occlusion balloon is not working well, proximal (supraceliac) aortic control should be obtained before obtaining distal control. Once both proximal and distal control are achieved, the renal arteries are dissected, and the proximal clamp is moved down to the infrarenal or suprarenal position, depending on aneurysm anatomy.

If the RP approach for open rAAA repair is chosen, then a bump or sandbag should be placed underneath the left flank to allow the left chest to rest at 60 degrees and the pelvis at 45 degrees. A curvilinear incision is made extending from the left tenth intercostal space (plus or minus one depending on the level of the patient's renal arteries) down to the midpoint between the umbilicus and the pubis. The abdominal wall muscles are divided sequentially down to the peritoneum. Entry into the peritoneum is avoided. As the RP is entered, a hematoma will likely be encountered. The peritoneal contents are reflected to the patient's right side in a progressive fashion to expose the left psoas muscle and the aorta. Once the aorta is visible, a retractor is set in place. Assuming the aortic occlusion balloon is working well, both common iliac arteries should be dissected circumferentially for a short course, taking care not to injure the common iliac veins in the process. Obtaining bilateral common iliac artery control allows for aortic repair using either a straight tube or a bifurcated graft, depending on the patient and aneurysm anatomy.

Once distal control is obtained, supraceliac aortic control can then be obtained by moving proximally along the aorta to the level of the left crus. From here, the left crus can be partially divided, and an aortic cross-clamp can be placed. Following placement of the cross-clamp, the aortic occlusion balloon should be deflated.

Once both proximal and distal controls are obtained, the renal arteries should be identified and dissected. The aortic cross-clamp

should then be moved to the lowest level possible that still allows for proximal control. For most AAAs, this will be just above or just below the renal arteries. Prolonged placement of a supraceliac clamp should be avoided whenever possible as this is associated with substantially higher morbidity and mortality because of visceral ischemia. Once the proximal clamp location is revised and both the proximal and distal clamps are in place, the aortic sac can then be opened, and the aorta can be repaired in usual standard fashion.

Figure 1 represents the post–open repair of the ruptured juxtarenal AAA shown in Figure 2 at 30 days postoperatively. This was completed via the RP approach.

If the TP approach for open rAAA repair is chosen, the patient should be prepped and draped widely in the supine position. A generous laparotomy from xiphoid to pubis should be created. Distal and proximal control is sequentially obtained in the order discussed earlier.



FIG. 1 Postoperative CT scans with IV contrast, arterial phase images, from 30 days after open rAAA repair. **(A)** Representative axial cut demonstrating open rAAA repair and sequela of prior rupture. **(B)** Representative sagittal cut of the same repair. There is no sign of ongoing hemorrhage and the repair is intact.



FIG. 2 CT scans with intravenous contrast, arterial phase images. **(A)** Representative axial cut demonstrating a 10.4-cm rAAA with signs of rupture, including a large left retroperitoneal hematoma. **(B)** Representative sagittal cut of the same rAAA, demonstrating a nearly 90-degree neck angulation that precludes the use of endovascular aneurysm repair.

To expose the infrarenal aorta from the TP approach, the transverse colon is lifted cephalad, and the small bowel is swept to the right. The peritoneum is incised, and the ligament of Treitz is taken down to allow for full mobilization of the duodenum to the right. This maneuver exposes the anterior surface of the infrarenal aorta. From here, the aorta can be traced distally to the bifurcation, allowing for rapid identification and control of the bilateral common iliac arteries.

Supraceliac control can be obtained quickly from the TP approach by mobilizing the left lateral lobe of the liver, retracting the liver to the patient's right, and incising the gastrohepatic ligament. If not already done, the esophagus should be intubated with a nasogastric

or orogastric tube, identified, and retracted to the left. The right crus is then divided to expose the supraceliac aorta. From here, a clamp is placed on the supraceliac aorta, and the occlusion balloon is deflated and removed. Once the renal arteries are visualized, the proximal clamp should be moved distally as quickly as possible to perfuse the viscera. Finally, the sac is opened, and repair continues in standard fashion.

As with EVAR, heparinization protocols for open repair of rAAA vary by institution. We usually obtain proximal and distal aortic control and then administer heparin at a dose of 80 units/kg to maintain an ACT >250 during the remainder of the case, similar to EVAR.

Regardless of whether the RP or TP approach is used, one important intraoperative consideration is whether the inferior mesenteric artery (IMA) will be re-implanted. The watershed area of the IMA, which primarily affects the sigmoid colon, is teleologically affected by hypotension and ligation. Although there are no prospective clinical trials defining precisely when to re-implant the IMA, generally, if there is weak back-bleeding from the IMA, the patient has a history of prior colon surgery without intact collaterals, or the sigmoid colon appears ischemic, then re-implantation should be pursued. Figure 3 depicts an open repair with IMA re-implantation.

Another consideration during aortic cross-clamping and dissection in open rAAA repair is the avoidance of major venous injury. Aortocaval fistula also presents a serious challenge. This should be suspected if, when a controlled aortic aneurysm sac is entered, brisk dark bleeding is found from the right-side wall of the aneurysm sac. Sponge sticks on the inferior vena cava can help temporize this, and the aortocaval fistula should be repaired using large bites of nonabsorbable suture through the inside of the aortic wall.

COMPLICATIONS

Complication rates are substantially higher for rAAA repair compared with elective repair. The estimated major complication rates for open and endovascular rAAA repair are 50% to 80% and 40% to 60%, respectively. The most common major systemic complications include acute kidney injury (40%–75%), respiratory failure (40%), myocardial infarction (25%) and sepsis (15%).

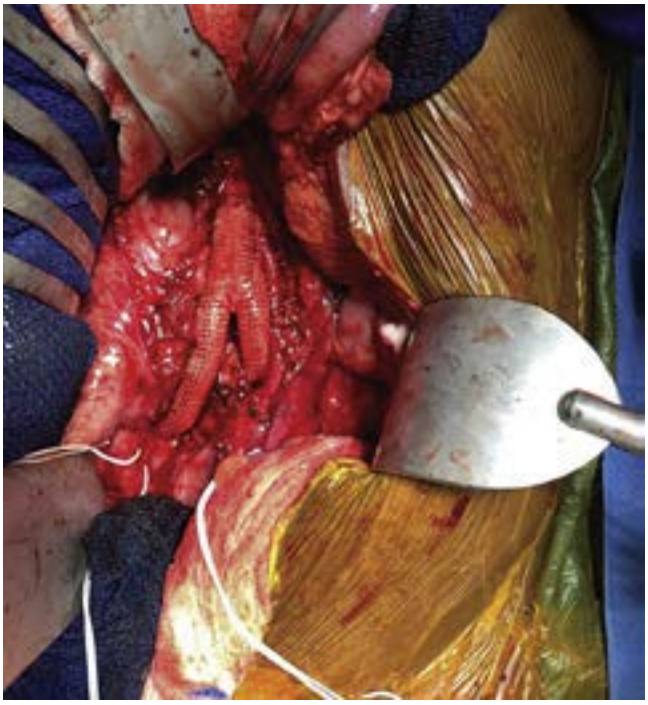


FIG. 3 Intraoperative image of open ruptured abdominal aortic aneurysm repair with inferior mesenteric artery re-implantation performed because of concern for sigmoid colon ischemia.

Bowel ischemia or ischemic colitis is six times more common after rAAA repair compared with patients who undergo elective surgery for AAA without rupture. This is partly a result of patient age, which tends to be higher for patients presenting with rupture, and ligation or coverage of the IMA in the setting of rupture with concomitant hypotension and shock. Hypotension alone is enough to cause bowel ischemia in some patients, and iatrogenic occlusion of the hypogastric artery during rAAA repair can exacerbate the effect. A high index of suspicion is required to diagnose bowel ischemia after rAAA repair. Large loose bowel movements immediately after surgery, bloody bowel movements, and persistent postoperative leukocytosis should all raise suspicion for ischemia. In any patient with suspected bowel ischemia, the initial diagnostic modality of choice is a flexible sigmoidoscopy. Subsequent management depends on the severity of the ischemia. Mild or moderate ischemia is treated with bowel rest, broad-spectrum intravenous antibiotics, and serial abdominal examinations. Severe ischemia (or mild ischemia with progression of symptoms despite optimal medical management) requires a return to the operating room for an exploratory laparotomy and likely bowel resection.

Abdominal compartment syndrome (ACS) also increases morbidity and mortality of rAAA and occurs when relaxed bladder pressure is sustained greater than 20 mm Hg and is associated with organ dysfunction. Increasing intraabdominal pressure and rising plateau or driving pressures may be useful adjuncts for making an early diagnosis. ACS has been linked to massive transfusion, coagulopathy, and use of an aortic occlusion balloon. It is more common after EVAR than open rAAA repair, occurring in up to approximately 20% of EVAR and 10% of open rAAA repair patients. The higher risk of ACS after EVAR is usually the result of an unevacuated intraperitoneal hematoma coupled with large resuscitative volumes leading to visceral and interstitial edema. Together, this impairs venous return and increases renal dysfunction.

ACS is also possible after open rAAA repair. This can be related to an unevacuated intraperitoneal hematoma if the RP approach was used and/or large resuscitative volumes leading to visceral and interstitial edema similar to post-EVAR ACS. If an intraperitoneal hematoma is present and the RP approach is used, the peritoneum should be incised at the end of the case to evacuate the peritoneum. Alternatively, once the RP incision is closed, a separate laparotomy may be performed. The TP approach has a built-in laparotomy that allows for easier evacuation, assessment of abdominal wall laxity, and the possibility of leaving the patient open temporarily without an additional incision. As discussed earlier, RP hematomas are fundamentally different than intraperitoneal hematomas as they are part of a separate compartment. They may, however, cause femoral nerve compression, which also requires evacuation associated with symptoms.

Access complications occur in approximately 15% to 25% of EVARs and can be dealt with via a myriad open and endovascular techniques. As discussed earlier, diseased or tortuous iliac arteries may be difficult to navigate, and intraoperative injury may require iliac stent placement after the large-bore sheaths are removed. Maintaining wire access, replacing the dilator in the sheath before removal, and being prepared with stents in several sizes can help avoid catastrophe. Acute thrombosis or occlusion of an EVAR limb or the native iliac arteries should raise suspicion for a kinked or stenotic graft limb or an undetected iliac injury such as a dissection. Depending on the etiology of the problem, this can usually be treated with femoral cutdown and embolectomy, femoral-femoral bypass, or extension of the iliac stent graft.

Acute kidney injury and renal failure are also common complications of rAAA repair, occurring in 40% to 75% of cases, and are associated with ACS. Acute kidney injury is related to preoperative systemic hypotension coupled with proximal aortic cross-clamping, both of which cause renal hypoperfusion. The risk of acute kidney injury can be reduced by decreasing the proximal aortic cross-clamp (and/or

balloon occlusion) time, and transfusing to maintain a hemoglobin above 8 g/dL throughout the case. Contrast agents used in EVAR may also contribute to acute kidney injury, but the magnitude of this impact is not well known. As many as 23% of patients presenting with rAAA who survive surgery will require hemodialysis in the early postoperative period, but this is usually (>90%) temporary as long as the renal artery origins are preserved during the repair. Renal failure, however, is an independent risk factor for all-cause 10-year mortality.

FOLLOW-UP

In the long term, complications of EVAR include endoleaks, device migration, limb occlusion, and recurrent rupture. Current guidelines recommend that patients who undergo treatment with EVAR be surveilled at 1 month, 6 months, and 12 months postoperatively with a CTA, however the 6-month CTA can be eliminated if the 1-month scan is not concerning for endoleak or other pathology. If there is no evidence of endoleak, sac enlargement, or stent graft disruption on the 12-month CTA, ongoing surveillance with annual duplex ultrasound examination is reasonable. If future ultrasound examinations are suspicious for endoleak or sac enlargement, then further evaluation with CTA should be pursued. Patients treated with open rAAA repair should undergo a baseline CT within 12 months of the initial repair. Both open and EVAR patients should also undergo CTA every 5 years following repair to detect noncontiguous aortic disease.

CONCLUSION

Ruptured abdominal aortic aneurysm is one of the most serious anatomic diseases encountered by surgeons. Despite improvements in screening algorithms, surveillance protocols, multidisciplinary aortic care centers, and critical care, morbidity and mortality associated with rAAA remain high. Early diagnosis is key, and a high threshold of suspicion and broad differential diagnosis in older adult patients with a history of smoking who present with abdominal pain is necessary. Once the diagnosis of rAAA is made, time to aortic occlusion and definitive repair is of the utmost importance. If necessary, patients should be expediently transferred to a facility with capabilities for both open and definitive endovascular repair. Although large clinical trials have not yielded a long-term mortality benefit for EVAR over open rAAA repair, most institutions are moving toward EVAR-first protocols when anatomically possible because of the lower in-hospital morbidity and mortality associated with EVAR compared with open repair. Expanded use of new endovascular techniques and devices may provide an avenue for improvements in long-term survival and complications in the future.

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Management of Abdominal Aortic Aneurysm with Concomitant Nonvascular Abdominal Pathology

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GENERAL CONSIDERATIONS

Abdominal aortic aneurysm (AAA) is a relatively common, potentially life-threatening condition with an overall reported incidence of 5 to 10 cases per 100,000, with complications such as dissection and rupture leading to 15,000 deaths annually.

Associated AAA risk factors such as age, smoking, hypertension, and atherosclerosis not only increase the risk of aortic pathology but are also associated with nonvascular issues such as biliary tract, associated malignancies, and congenital and inflammatory conditions. The nearly universal application of high-resolution scanning in the workup of the AAA patient has shown that coincident nonvascular pathology is not a rare situation, with reported incidences between 7% and 29%.

The management of this complex clinical dilemma still remains controversial and a matter of debate due to the low number of reported patients and the obvious inability to conduct randomized studies. The danger of increased hemodynamic stress as well as the theoretical risk of graft infection remain the main arguments against combined procedures. Alternatively, the postlaparotomy AAA rupture rate of 3% to 10% with sizable aneurysms, as well as the potential of progression of coincident malignant disease, must be taken into consideration with any staged procedure.

Although open aortic aneurysm repair still has a place in appropriate patients, endovascular aneurysm repair (EVAR) is rapidly replacing it as the preferred method in the management of the aneurysm patient. This endovascular method has many potential advantages in the treatment of patients with concomitant disease including

decreased physiologic stress, lack of peritoneal cavity derangement, as well as the ability to shorten the time between staged procedures.

An appropriate and organized approach to these complex patients is to divide the discussion of possible treatment paradigms between the emergent and elective clinical situation.

ELECTIVE AORTIC ANEURYSM WITH ASYMPTOMATIC ABDOMINAL DISEASE

As previously stated, with the almost universal application of high-resolution scanning in the workup of elective AAA patients, the discovery of concomitant nonvascular abdominal pathology is increasingly common. The most common findings reported in the literature include cholelithiasis, gastrointestinal (GI) and genitourinary (GU) malignancies, solid organ tumors, Meckel's diverticulum, and abnormalities of the appendix.

CHOLELITHIASIS

Cholelithiasis is a common disorder occurring in approximately 10% to 15% of the general population. This is mainly a benign entity with only 2% to 3% of patients in the general population becoming symptomatic and, of those, only 3% to 5% develop complicated disease. Interestingly, the incidence of cholelithiasis seems to be higher in the AAA patient with reported rates of 13% to 20%.

The reported incidence of postoperative cholecystitis following open aneurysm repair has been reported to be 0.3% to 18%, but of note, another particular advantage of EVAR is that this rate does not seem to be increased following endovascular repair (0.2%–1.6%). The historic bias toward simultaneous surgery in these patients came out of the fear of postoperative biliary complications and predated the endovascular, laparoscopic, endoscopic, and interventional era. The obvious concern with the combined procedures emanate from the opening of the biliary tract with a known culture positive rate of 14% and risk of subsequent graft infection. As stated, new less-invasive treatment modalities in the management of biliary and aneurysm disease have led to a general consensus away from simultaneous surgery in these patients. Postoperative symptomatic cholelithiasis as well as choledocholithiasis can now be adequately and safely managed with new modalities without the need for another laparotomy.

GASTROINTESTINAL MALIGNANCIES

In the population presenting with an AAA, the concomitant presence of GI pathology is not uncommon with reported rates of 8% to 14%. Colorectal cancer is the most commonly associated lesion with occurrence rates as high as 2%.

When faced with this complex dilemma, the surgeon must choose between a staged or combined procedure. An aneurysm-first procedure obviates the postlaparotomy rupture risk; however, it can significantly delay the treatment of a neoplastic lesion leading to upstaging as well as potential complications such as obstruction, bleeding, and perforation. Conversely, a combined procedure exposes the patient to increased hemodynamic stress as well as the potential of graft infection with rates reported by Oriel as high as 2%.

Time-honored surgical principles direct the surgeon to treat the most pressing condition first. In the patient with a colorectal cancer-threatening complication and an asymptomatic AAA, the colectomy should be done first followed by aneurysm repair in 4 to 6 weeks, preferably by EVAR or retroperitoneal technique. Conversely, in the patient with a larger aneurysm (>5 cm) and a tumor unlikely to obstruct, the aneurysm should be treated first. In the unusual case where the patient presents with concomitant life-threatening GI and aneurysmal disease, a combined procedure is a reasonable consideration. In the conduct of this complex undertaking, meticulous surgical technique is mandatory avoiding inordinate blood loss, prolonged operative times, and graft contamination. Adequate broad-spectrum antibiotics are essential. The aneurysm repair should be done first, preferably with the use of autogenous, cryopreserved, or antibiotic impregnated grafts as well as the consideration of IMA implantation in cases of rectosigmoid pathology. Adequate coverage of the graft is essential with the possible use of an omental pedicle. The bowel resection follows, beginning with adequate packing and isolation of the periaortic retroperitoneum using antibiotic-soaked laparotomy pads. Finally, serious consideration of the liberal use of the Hartman's procedure should be entertained, especially when there are concerns of collateral colonic blood supply.

The rapid evolution and widespread application of EVAR provides many advantages in this complex subset of patients, including lower physiologic stress as well as significantly reduced delay between staged procedures. Currently, in the properly selected patient who is an endovascular candidate, consensus leans toward a staged EVAR first, followed relatively quickly (12–14 days) by GI resection. In preparing for the EVAR as the first procedure, particularly where subsequent left or sigmoid colon resection is anticipated, it is essential to assess the adequacy of the colonic blood supply as the procedure requires coverage of the IMA. In a patient with a patent IMA and inadequate SMA/IMA collateral support, open aneurysm repair with IMA implantation, either staged or combined, may be the best option.

Renal Cancer

The coincident occurrence of aneurysms and renal cancer (0.1%–3%) is increasingly reported with the current use of high-resolution scanning. As with GI malignancies, the management should be guided by AAA size, location of the cancer, and the extent of the malignant disease.

A simultaneous approach to both lesions has been reported to have acceptable results and obviates the complication of postlaparotomy aneurysm rupture as well as tumor growth. As the upper urinary tract is usually sterile, the risk of subsequent graft infection is extremely low. Renal failure is the most common complication, and thus it is important to assess preoperative renal function, the need for suprarenal aortic clamping, and overall technical difficulties that may lead to increased blood loss in the combined procedure. In cases where conditions may lead to significant renal insult, a staged procedure may be more appropriate allowing time for renal recovery between the next operation.

When performing a combined operation, patients with a left renal lesion should be approached retroperitoneally if possible, and right-sided lesions will need a midline procedure. There have been several recent reports in the literature discussing the use of a hybrid simultaneous approach combining laparoscopic nephrectomy and EVAR with good results in well-selected patients. In the patient where a staged approach is most appropriate, EVAR followed by a laparoscopic or open nephrectomy is the most reasonable treatment.

Bladder Cancer

Although minimal data exist on the coexistence of bladder cancer and aneurysm disease, Grego reported an incidence of nearly 3% in his series of patients. Although several series have reported excellent clinical outcomes with simultaneous procedures, it must be remembered that the lower GU tract is frequently not sterile and such an approach is accompanied by the practical risk of aortic graft infection. As this risk is substantially mitigated by EVAR, along with a reduction in physiologic insult, a staged EVAR as the first approach is the best option in appropriately selected patients.

Prostate Cancer

Prostate cancer and aortic aneurysms occur in the same population of older men, with some studies reporting a 100-times incidence of aneurysms in patients with prostate cancer. Although several less-invasive therapies exist in the management of prostate cancer that simplify the treatment algorithm in the patient with combined disease,

radical prostatectomy remains the mainstay therapy at the current time. As in the management of bladder cancer, combined surgery series have reported acceptable results with the previously described risks remaining. Given this, the application of mainstream, less-invasive treatments such as EVAR and robotic procedures in a staged or hybrid combined approach seems to provide a more reasonable strategy despite the paucity of data.

Solid Organ Tumors

Many reports exist documenting the successful resection of solid organ lesions at the time of aneurysm repair. Given the sterility of the lesions, synchronous treatment is reasonable assuming the patient can tolerate the physiologic insult. Despite this, in the endovascular candidate, a staged EVAR-first approach is the most reasonable course in management.

Appendix and Meckel's Diverticulum

Due to the associated risk of aortic graft infection and their mostly benign natural history, incidental appendectomy or Meckel's resection are inappropriate in asymptomatic patients during open aneurysm repair. In such patients found to have chronic inflammation or an uncomplicated tumor, many authors also feel a staged approach with laparoscopic resection following aneurysm repair is the safest therapy with a very low risk of second laparotomy. In the most unusual case of acute or complicated GI disease, a staged approach with intestinal resection preceding aneurysm repair should be undertaken once the peritoneal inflammation is resolved. However, if one is dealing with simultaneous life-threatening clinical entities during open surgery, a combined repair is probably the only option employing all of the risk-mitigating tools used with the combined colorectal operation. In the endovascular candidate faced with simultaneous life-threatening lesions, a combined hybrid approach of EVAR and laparoscopic resection is probably the best strategy.

EMERGENT AAA REPAIR AND CONCOMITANT DISEASE

Ruptured AAA is a catastrophic clinical event with high operative mortality (30%–50%) even with expedient and expert management. Whether the procedure is open or EVAR, the patient suffers significant physiologic insult often leading to cardiac, renal, hepatic, and mesenteric ischemia, and activation of a significant inflammatory response, often leading to multiple system organ failure (MSOF) and periodic abdominal compartment problems. The addition of another procedure to this process is imprudent and ill-advised. In the rare circumstance in which the patient has another coexistent, intraabdominal, life-threatening process, a simultaneous procedure may have to be considered with significant increased mortality. The patient with a symptomatic aortic aneurysm is, by definition, unstable and in the process of developing rupture. The same decision calculus applies in these patients as stated in the rupture patient.

Emergent Laparotomy for Abdominal Pathology with Incidental AAA

Consistent with previous statements, the immediate life-threatening process should be treated first followed by a staged aneurysm repair, preferably EVAR, in patients with concerning large aneurysms after recovering from the first procedure. In the very rare case when the intraabdominal emergency is met with an aneurysm mandating immediate repair in a patient not a candidate for an endovascular approach, a combined procedure must be considered.

In the patient explored for the presumed acute abdomen with negative findings except a sizable AAA, it is reasonable to assume that the aneurysm is symptomatic, and intraoperative vascular surgical consultation should be obtained.

Elective Laparotomy for Abdominal Pathology with an Incidental Asymptomatic AAA

As stated previously, in the modern-day workup for abdominal disease, the surprise discovery of an incidental AAA is extremely rare. However, when confronted with this situation, it is best to proceed with the planned abdominal procedure. In patients with large aneurysms (>5 cm), staged repair should follow as soon as reasonably possible.

SUMMARY

1. Avoid synchronous surgery if possible.
2. Treat the most life-threatening procedure first.
3. Emergent AAA repair takes priority over any type of intraabdominal disease.
4. Incidental sizable aneurysms (>5 cm) found during laparotomy for nonvascular disease should be treated as early as possible in the post-op period, preferably by EVAR.
5. Nonemergent nonvascular pathology found during AAA repair should be managed later in a staged manner.
6. In the unusual case where both the AAA and the intraabdominal pathology present as synchronous life-threatening issues, a combined procedure must be entertained. During the conduct of this risky procedure, meticulous surgical technique applying all known graft infection-mitigating strategies should be applied
7. In the conduct of the staged or synchronous procedure, one should enlist the least physiologically taxing and minimally invasive procedures, including EVAR and laparoscopic and robotic technologies.

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Management of Thoracic and Thoracoabdominal Aortic Aneurysms

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INTRODUCTION

Descending thoracic aortic aneurysms (DTAAs) and thoracoabdominal aortic aneurysms (TAAAs) are uncommon when compared with isolated infrarenal abdominal aortic aneurysms (AAAs), accounting for only 2% to 5% of all aortic aneurysms. DTAAs are defined as those that involve the thoracic aorta between the origin of the left subclavian artery (LSA) and the diaphragmatic hiatus, whereas TAAAs can involve varying degrees of the visceral aortic segment along with the thoracic and infrarenal aorta. TAAAs are classified by anatomical definitions as devised by Dr. Stanley Crawford (Fig. 1).

Although pathologies of the abdominal aorta are commonly degenerative in nature, those affecting the thoracic and visceral aorta include a more diverse range of predisposing conditions, such as connective tissue disorders (Marfan syndrome, Loeys-Dietz syndrome, etc.), dissections, aortitis, and trauma. Open repair of DTAA and TAAAs, first described in 1952 by Bahnson and later simplified by Dr. Crawford, was initially plagued by increased morbidity and mortality rates as a result of renovisceral and spinal cord complications. Although adjuncts have been developed to decrease the incidence of these devastating complications at high-volume centers, these aneurysms continue to pose technical challenges to cardiac and vascular surgeons. The advent of thoracic endovascular aortic repair (TEVAR) has further diminished the morbidity associated with surgical repair. TEVAR is a well-established modality for the treatment of degenerative aneurysms of the thoracic aorta and traumatic transections; however, its utilization in patients with connective tissue disorders and for both acute and chronic dissections continue to be the subject of ongoing study. Endovascular repair of TAAA is now performed across the world using branched and fenestrated devices, although these devices remain under clinical trials in the United States.

INDICATIONS FOR SURGERY

In a study on the natural history of thoracic aneurysms, a 30% 5-year rupture risk was observed when aneurysm size exceeded 6 cm. Rupture risk was negligible in aneurysms less than 5 cm and equivalent to morbidity risk of surgical repair at the 5- to 6-cm range. Given these findings, ≥6 cm has been accepted as the size threshold to consider elective repair in acceptable risk patients for TAAA patients and >5.5 cm for isolated TAA. As aneurysms of the thoracic aorta become larger, they also begin to expand at more accelerated rates. This increased expansion has been found to correlate with higher rupture rates. As such, patients presenting with aneurysm growth rates ≥10 mm per year should also be considered for surgical repair. Additional risk factors for rupture have been identified and include increasing patient age, female gender, chronic pain, history of chronic obstructive pulmonary disease (COPD), compression of surrounding structures, and development of a dissection within a degenerative aneurysm. Chronic type B aortic dissections and presence of connective tissue disorders have been found to be independent risk factors for rupture proclivity at smaller aneurysm sizes. In these settings, the size threshold to consider surgical repair is reduced to 5 cm. Furthermore, these populations tend to present at younger ages compared with patients with degenerative aneurysms, potentially resulting in better comorbidity profiles and decreased operative risk.

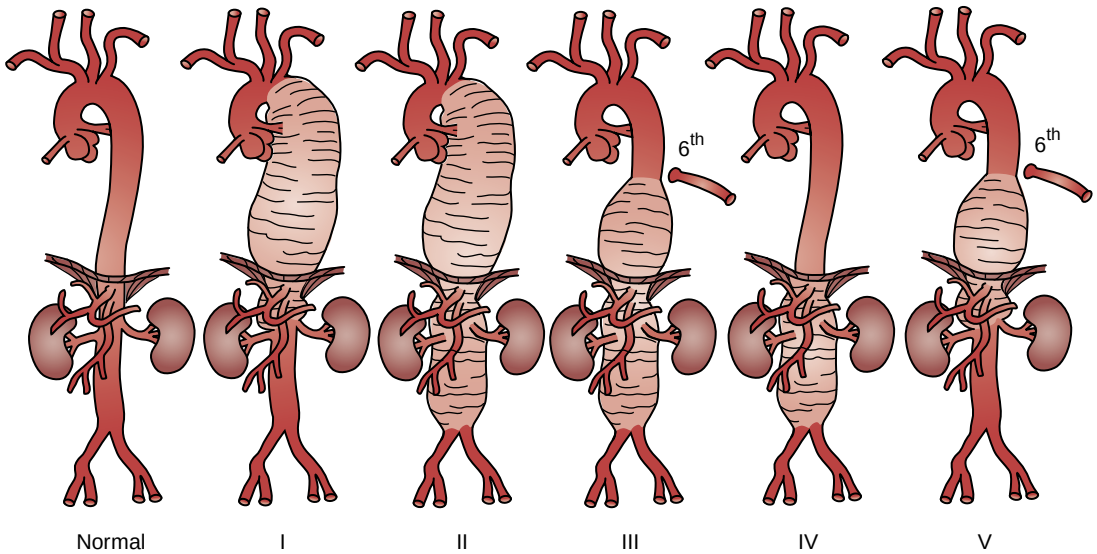


FIG. 1 Crawford classification of thoracoabdominal aortic aneurysms, types I-V. Type I, distal from origin of left subclavian artery to above renal arteries. Type II, distal from the left subclavian artery to the infrarenal aorta. Type III, from the sixth intercostal space to the infrarenal aorta. Type IV, from the 13th intercostal space to the aortic bifurcation. Type V, below the sixth intercostal space to the renal arteries. *(From Cronenwett JL, Johnston KW.* Rutherford's Vascular Surgery, *7th Edition, Philadelphia: Elsevier; 2010, Figure 131-8).*

PATIENT SELECTION AND PREOPERATIVE RISK ASSESSMENT

The approach and extent of operative repair required for DTAA and TAAAs varies greatly depending on the Crawford classification; however, consistent themes exist regarding clinical variables that influence both overall morbidity and ischemic spinal cord injury (SCI). Each patient's associated comorbid conditions, particularly those affecting cardiac, renal, and pulmonary function, require an accurate assessment to appropriately steer operative decision making. Aortic aneurysms are considered markers of coronary atherosclerotic disease, and because a majority of patients possess additional atherosclerotic risk factors, preoperative cardiac testing is mandatory in the elective setting. Echocardiography, either transthoracic or transesophageal, should be utilized to rule out valvular or ventricular dysfunction that may result in hemodynamic compromise from increased cardiac afterload following aortic cross-clamping. Additionally, nuclear stress testing can identify major areas of myocardium potentially at risk for significant ischemia. In patients with abnormal noninvasive workup, further evaluation via cardiac catheterization should be considered as both a definitive diagnostic and potentially therapeutic intervention. Nonreversible ischemic cardiomyopathy resulting in significantly decreased left ventricular function generally precludes open surgical repair.

A baseline serum creatinine is commonly used to assess renal function. If renal dysfunction is noted by elevated serum creatinine levels, patients may benefit from preoperative renal revascularization via percutaneous stenting, or by surgical bypass or endarterectomy at the time of aneurysm repair. Up to 15% of TAAA patients present with significant renal insufficiency, defined as a serum creatinine ≥1.8 mg/dL, and this has been shown to correlate with perioperative renal failure and mortality. Patients with renal insufficiency requiring extensive repairs, especially those with type II, type III, or type V TAAAs, have relative contraindications to open repair given the strong correlation with poor outcomes in these populations. Indeed, acute renal failure can have devastating effects on many other systems, such as fluid overload and electrolyte disturbances promoting malignant arrhythmias. Whether or not endovascular approaches to TAAA can reduce the burden of acute kidney injury (AKI) versus open repair remains unanswered. The requisite need for contrast-enhanced CT angiography after complex endovascular repair is a relative contraindication for such technology, as the patient cannot have proper imaging to determine presence of endoleak.

Patients with aneurysms involving large portions of the thoracic aorta, DTAAs, and type I–III TAAAs should undergo preoperative pulmonary function tests. These patients often require single-lung ventilation and, without the necessary pulmonary reserve, may not tolerate such technique. An FEV1 of >1.0 L or a PCO_2 of <45 mm Hg generally represents appropriate pulmonary function to accept single-lung ventilation. Patients who fail to meet these criteria should undergo aggressive medical therapy with subsequent reevaluation or evaluation for possible endovascular repair. Patient age in and of itself is not a contraindication to open repair; however, overall functional status should be evaluated as part of the preoperative risk assessment. Previous series have shown that the elderly with appropriate functional status have acceptable perioperative morbidity and mortality rates. Patients with overall fragility should probably not be offered open surgical repair, although they may be candidates for endovascular repair or hybrid procedures depending on their anatomy.

Along with the previous physiologic assessments, patients being considered for endovascular repairs have independent anatomical criteria that must be assessed. High quality imaging is necessary to ensure that there are appropriate proximal and distal seal zones to prevent endoleaks that may result in late aneurysm rupture. Patients with thoracic aneurysms may have extreme tortuosity of the aorta that prohibits the delivery and accurate placement of a stent-graft. For branched and fenestrated repair of TAAA, ostial disease of the renal and visceral vessels can complicate cannulation for stent graft placement. Likewise, TAAA also commonly requires larger diameter devices compared with isolated infrarenal AAA, making femoral and iliac artery access evaluation a priority. Patients with diffuse iliofemoral disease may not allow for passage of the larger sheaths necessary to deliver the stent-graft. Inadequate evaluation of the iliofemoral access can result in disastrous complications resulting from iliac artery disruption or avulsion. The presence of difficult access can be circumvented by utilizing iliac conduits, which are further described later in the chapter.

Standard central venous access and invasive hemodynamic monitoring should be employed for all cases, including the use of pulmonary artery catheter placement when indicated. Double-lumen intubation is often necessary to provide single-lung ventilation for aneurysms with extensive thoracic components. Systemic hypothermia can be avoided by using fluid warmers along with passive external warming after completion of aortic reconstruction. Washed red blood cells (Cell-Saver) and transfusion of banked packed red blood cells (PRBC) and fresh-frozen plasma (FFP) should be applied liberally as opposed to large volume crystalloid infusions. Given the extensive nature of the reconstructions and long graft surfaces, platelet consumption is common, and platelets should be administered to prevent significant thrombocytopenia.

STRATEGIES FOR THORACIC AND THORACOABDOMINAL AORTIC RECONSTRUCTION

Two surgical techniques that are commonly utilized to repair DTAA and TAAAs are the "clamp-and-sew" technique versus the use of distal aortic perfusion through a left heart bypass (LHB) circuit. Each technique has been found to be efficacious and is often surgeon- and center-dependent. Both techniques are often paired with other adjuncts to decrease complications related to spinal cord, visceral, and renal ischemia. Operative technique variations and ongoing research have been centered on preventing the dreaded complications of renal failure and SCI. The judicious application of adjuncts for organ protection have been supported by the literature and include cerebrospinal fluid (CSF) drainage, intercostal revascularization, renal hypothermic perfusion, and distal aortic perfusion.

Organ Protection Adjuncts

SCI following DTAA or TAAA repair is the most feared morbid complication after DTAA and TAAA reconstruction. Placement of spinal drains to allow CSF drainage has been the best studied and widely accepted strategy employed to prevent paraplegia following thoracic aortic surgery. Early studies suggested that proximal aortic cross-clamping results in elevated CSF pressures that may compromise perfusion of the spinal cord. Preoperative placement of drainage catheters to allow efflux of CSF during the perioperative period functions to preserve spinal cord circulation. In a randomized trial comparing type I and II TAAAs with and without CSF drainage, paraplegia rates were reduced from 13.0% to 2.6% with the utilization of CSF drainage. Both patient populations had similar aortic cross-clamp times, LHB use, and intercostal artery revascularizations. An 80% overall risk reduction of postoperative SCI complications was observed with CSF drainage in patients undergoing type I and II TAAA repair in this series. Our institution favors the use of CSF drainage in conjunction with monitoring of motor-evoked potentials (MEP) and distal aortic perfusion via LHB. In patients felt to be at increased risk of paraplegia, digital subtracted angiography (DSA) of the thoracic aorta may be performed preoperatively to identify the artery of Adamkiewicz for revascularization if mandated by intraoperative findings. MEPs are monitored during aortic cross-clamping,

and the decision to revascularize intercostal arteries is made based on the loss of MEPs, clinical inspection of patent intercostals, or as dictated by preoperative DSA imaging of the artery of Adamkiewicz. Other adjuncts include epidural cooling to decrease neuronal energy requirement and continuous infusion of naloxone as a free radical scavenger and inhibitor of excitatory amino acids.

Cold renal perfusion has been well established as an adjunct to minimize ischemic injury to the kidneys during open TAAA repair. Perfusion catheters are placed into the renal orifices, and cold renal preservation fluid is used to flush the kidneys followed by continuous infusion. At our institution, we use 1-L bags of normal saline with 500 mg of methylprednisolone added and then placed on ice. Preservation of renal function is paramount to successful outcomes, as evident from a study that found postoperative renal failure to result in an eightfold increase in mortality risk ([OR 7.8]; 95% CI, 3.4–17.9; P <0.01).

Operative Technique

A double lumen endotracheal tube is often necessary for single lung ventilation for patients with type I-III TAAA to facilitate exposure to the thoracic aorta and inferior pulmonary vein for partial LHB. In patients with type IV TAAA, LHB is not often necessary and the chest not opened widely enough to require single lung ventilation. For all patients with DTAA and TAAA, the patient is positioned in a modified right lateral decubitus position, with the left chest rolled upward between 70 to 90 degrees and the pelvis rotated only approximately 30 degrees. The patient is placed on an adjustable beanbag to support the position and an axillary roll is placed to protect the brachial plexus. The rib spaces are then identified and counted to mark the proper intercostal space for the necessary exposure (Fig. 2). The patient is then widely prepped and draped to include the left chest, left flank, and both groins.

The Johns Hopkins approach employs a thoraco-retroperitoneal approach to all TAAA repairs to minimize the convective fluid and temperature losses incurred by an open peritoneum. The transversalis muscle is identified at the costal margin and the fibers are split

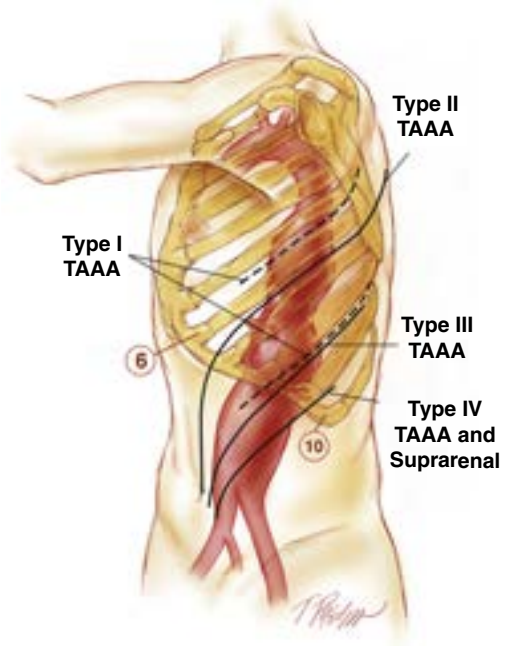


FIG. 2 Incisions based on patient anatomy and aneurysm classification. For type I thoracoabdominal aortic aneurysm (TAAA) repair, two separate thoracotomies are made through a single skin incision.

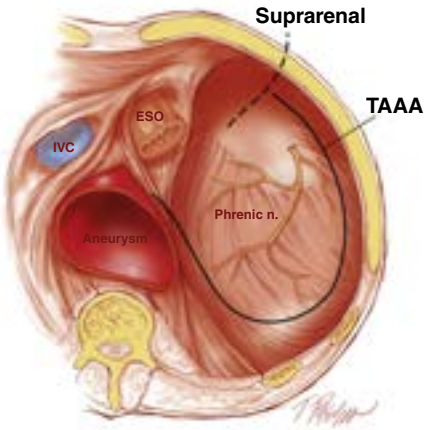


FIG. 3 For TAAA repair, the diaphragm is taken down in a circumferential fashion to avoid injury to the phrenic nerve branches and allow normal diaphragm function postoperatively. In patients with suprarenal abdominal aortic aneurysms in which the DTA does not require exposure, a partial division of the diaphragm can be used as part of left flank approach.

to identify the peritoneal sac. This is then bluntly swept medially out of the left retroperitoneal space. The anterior abdominal wall is then divided with electrocautery to the distal extent of the incision. Blunt mobilization of the retroperitoneum is continued medially to expose the left psoas muscle, where the left common iliac artery is often identified. The left ureter is commonly then found on the back of the peritoneal sac and at this point a static self-retaining retraction system is placed. Of note, for type I TAAA, we recommend the use of two separate thoracotomies at the 5th and 8th interspace, through a single skin incision, as depicted in Figure 2. This allows for sufficient exposure to the proximal DTA while also allowing diaphragm mobilization and identification of visceral branches for distal clamp location. The left renal artery is then identified to further guide the remainder of the visceral dissection. A prominent left lumbar vein is normally encountered coursing along the left aorta as it empties into the left renal vein. This structure can be ligated and divided to allow for safe medial retraction of the left kidney. The diaphragm can be mobilized in a circumferential fashion to further expose the DTA and suprarenal aorta (Fig. 3). We do not endorse radial division of the diaphragm as this sacrifices branches of the phrenic nerve that may predispose to pulmonary complications postoperatively. Once the left kidney and retroperitoneum have been completely mobilized, they can be safely retracted to provide complete exposure to the thoracic and abdominal aorta. For type I and II TAAA and proximal DTAA, the left vagus nerve is identified crossing the distal aortic arch and giving rise to the left recurrent laryngeal nerve as it courses around the arch at the ligamentum arteriosum. If the anatomy dictates a proximal clamp between the left common carotid artery and LSA, the ligamentum arteriosum is usually ligated and divided.

If LHB is to be utilized for distal aortic perfusion for type I–III TAAAs, the left inferior pulmonary ligament is taken down to expose the left inferior pulmonary vein. A purse-string 4-0 polypropylene suture is then placed, before sharply performing a venotomy to place a 24 Fr venous cannula. An 8-mm Dacron graft is then sewn in an end-to-side fashion onto the left common femoral or left iliac artery to avoid leg ischemia from direct cannulation that may confound MEP monitoring. Distal aortic perfusion is then initiated along with moderate hypothermia at 32°C to 34°C. Sequential aortic cross-clamping is then utilized to isolate the proximal DTA while the proximal anastomosis is performed, followed by the lower thoracic aorta if intercostal revascularization via an inclusion patch

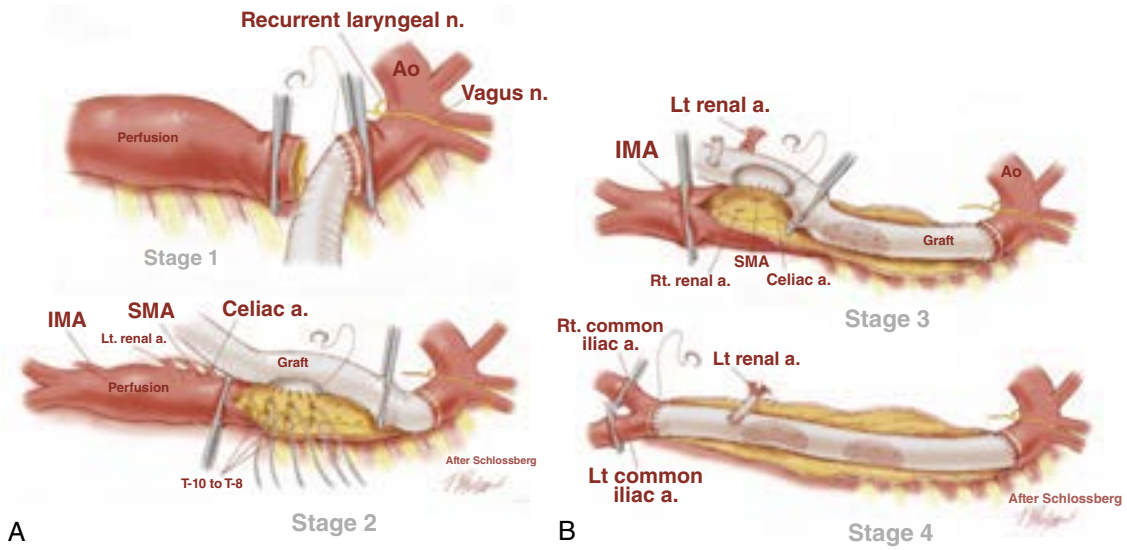


FIG. 4 **(A)** To minimize the risk of end-organ ischemic complications, we advocate for distal aortic perfusion and sequential aortic cross-clamping. The first stage includes proximal aortic cross-clamping with a distal clamp on the DTA to allow for completion of the proximal anastomosis. Next, the graft is clamped while a supraceliac clamp is placed distally to allow for either intercostal reimplantation or ligation. Balloon occluders can be placed to temporarily control intercostal arteries to be reimplanted. **(B)** The next clamp is placed on the infrarenal aorta to allow for reconstruction of the visceral segment. This is accomplished with either a Crawford visceral inclusion patch to revascularize the right renal, superior mesenteric, and celiac arteries; or, in the case of patients with connective tissue disorders, with separate bypass grafts to each vessel to reduce the risk of patch aneurysms in the follow-up period. Finally, clamps are placed on bilateral common iliac arteries for the distal anastomosis and reimplantation of the left renal artery. We prefer aortorenal bypass to a Carrel patch so as not to cause thinning of the artery or kinking if a renal endarterectomy is necessary. *IMA,* Inferior mesenteric artery; *SMA,* superior mesenteric artery.

anastomosis is to be done, then the abdominal aorta during visceral revascularization, and finally the iliac vessels for the distal anastomosis (Fig. 4). Before placing the initial cross-clamp, it should be emphasized to the anesthesia team to maintain lower systolic blood pressures to avoid complications from the increased afterload created from the aortic cross-clamp. Our institution strives to maintain bypass circuit flows of 2.0 to 3.5 L/minute to provide 60 to 80 mm Hg for distal pressures. Once the visceral reconstruction has begun, the rewarming process is started.

For the aortic reconstruction, after appropriate exposure and proximal and distal control, the aorta is entered posterior to the left renal artery and the aortotomy extended as necessary. Figure 4 demonstrates the sequence of steps utilized to perform the aortic reconstruction for a type II TAAA. Depending on the type of DTAA or TAAA and the anatomy of the patient, the sequence of clamping and anastomotic sites can be modified. During the visceral revascularization, cold renal perfusion is maintained as described earlier. The patient body temperature should be monitored during cold renal perfusion to avoid excessive hypothermia that can result in heart arrhythmias or poor myocardial performance. We advocate for left aortorenal bypass versus direct Carrel patch of the left renal artery as this prevents thinning of the artery and potential for kinking if a renal endarterectomy is to be performed. Furthermore, the left renal bypass graft can be constructed onto the main conduit before cross-clamping to avoid unnecessary additional renal ischemia. The distal anastomosis is then completed at the appropriate level based on the patient's anatomy. The aneurysm sac should be closed over the reconstruction if possible. The retractors are then released and the retroperitoneal contents returned to their appropriate position.

The thoracoabdominal incision closure is then started with the purpose to secure the chest wall and abdominal musculature to promote return to baseline function. A large axiom drain is routinely placed in the left retroperitoneal space that can be brought through the abdominal wall. The diaphragm is then reconstructed with interrupted figure-of-eight 0-silk sutures. The final several centimeters of the lateral diaphragm can be closed following the chest closure and can be done from the abdomen. For type I–III TAAAs, pleural chest tubes are placed to drain any effusions resulting from the chest dissection and proximal suture line. The rib interspaces are reapproximated using #2 looped absorbable sutures, and any residual cartilaginous joint at the costal margin is excised to provide stabilization and prevent overriding of the adjacent ribs. The chest and abdominal musculature is then closed in multiple layers along with the subcutaneous tissues and skin.

Outcomes

Postoperative outcomes following DTAA and TAAA repair are dependent upon the level of disease. Patients with DTAA are more prone to neurologic complications, whereas those undergoing TAAA repair are more susceptible to renal failure. As mentioned before, the evolution of adjuncts for end organ protection has made a considerable impact on patient mortality and significant morbidity. Likewise, the acuity at the time of patient presentation also affects patient outcomes, as those who present with need for emergent repair have a higher incidence of morbidity and mortality.

A review of our experience with 300 patients undergoing open TAAA repair or open DTAA demonstrated a perioperative mortality rate of 7.5%. Furthermore, our rate for SCI was only 2.5% with the judicious use of LHB for distal aortic perfusion, moderate hypothermia, CFS drainage, and selective use of intercostal revascularization based on MEP monitoring. Acute renal failure, using the definition of many clinical series that is more than double the baseline creatinine or an absolute value >3.0 mg/dL, occurred in 12.5% of patients with dialysis dependence in only 2% to 3%. However, in most of this subset of patients, they returned to their baseline renal function over the course of their follow-up. These findings are comparable to and have been replicated by other large-volume studies at centers of excellence.

Postoperative renal function is most affected in those patients whose aneurysm pathology require prolonged renal ischemia, such as type II–IV TAAA. The strongest predictor for postoperative renal failure is preoperative renal insufficiency, especially in those patients with a glomerular filtration rate <40 mL/min. While the utilization of cold renal perfusion and other adjuncts has led to a decrease in the incidence of postoperative renal failure, it has not been quite as a profound resolution as seen with SCI. Other measures to improve postoperative renal function have included sequential clamping to reduce renal ischemia time and fenoldopam infusions. Despite these maneuvers, most studies have found anywhere between 2% to 9% of patients require hemodialysis for postoperative renal failure. Following 2286 open TAAA repairs, Coselli et al. observed that hemodialysis was needed in 5.6% of all patients, with the incidence increasing to 8.3% in those with type II TAAA. Postoperative renal failure has repeatedly been observed to be a predictor of perioperative mortality. Patients who develop postoperative renal failure have been found to have a tenfold increase in risk of mortality.

ENDOVASCULAR MANAGEMENT OF DTAA AND TAAA

TEVAR has emerged as the preferred treatment of descending thoracic aortic pathologies as an alternative to the significant morbidity and mortality associated with traditional open repair. TEVAR offers decreased operative risk by minimizing aortic manipulation, hemodynamic shifts resulting from large volume hemorrhage, and complications associated with LHB. Open thoracic repair is indicated for patients with aneurysm or dissection secondary to connective tissue disorders, wherein these disorders were exclusion criteria, so the safety and efficacy of TEVAR has not been proven. Endovascular repair of TAAA is performed under clinical trials in the United States using branched and fenestrated technology (FBEVAR), but the results are encouraging as centers develop experience and expertise in device selection and placement.

Preoperative Planning

High-resolution imaging is imperative for all patients being considered for TEVAR and FBEVAR. The tortuous nature of the thoracoabdominal aorta and potential for involvement of the distal aortic arch mandate precise preoperative planning to prevent immediate treatment failures. Computed tomography angiography (CTA) is the most commonly used diagnostic test for patients with suspected aortic pathology. Of the many benefits of CTA, perhaps most important are the multiple reconstructions that can be created from the original images vital for preoperative planning. A classification system has been created to better define proximal seal zones based on anatomic landmarks (Fig. 5). The distal seal zone is typically proximal to the celiac axis for TEVAR, but FBEVAR will extend to the distal aorta or iliac vessels.

The location of the proximal seal zone dictates the potential need for additional interventions. Pathologies involving the proximal DTA or distal arch may require coverage of the LSA. The most recent literature suggests that patients undergoing LSA coverage have improved outcomes with preservation of flow to the LSA. This can be done either in a staged approach with a carotid-subclavian bypass or transposition, or at the time of TEVAR with creation of a fenestration to the LSA. Patients who mandate preservation of flow to the LSA include prior left internal mammary-coronary bypass, dominant left vertebral artery, incomplete circle of Willis, and presence of a functioning left upper extremity arteriovenous fistula or graft. Another critical element of preoperative planning is evaluation of the access vessels for delivery of the device, particularly the iliofemoral system. Although the evolution of devices has resulted in lower profile delivery systems, absence of appropriate access is a contraindication to TEVAR. An alternative to circumvent poor access vessels is to create an iliac or aortic conduit. Inadequate access vessel evaluation can lead to catastrophic consequences, including dissection, perforation, or frank rupture, which can result in patient mortality.

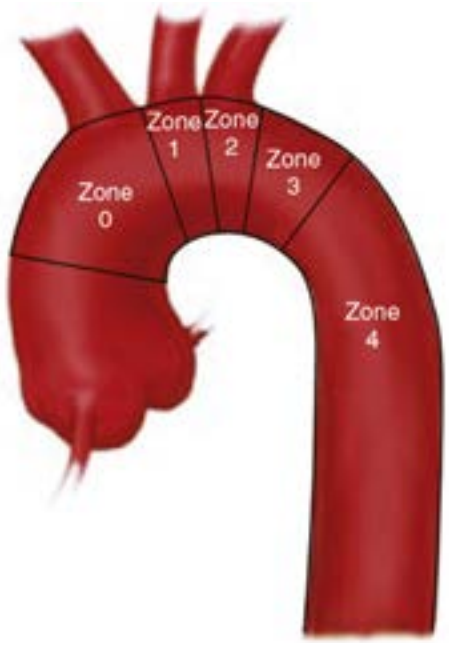


FIG. 5 Depiction of the proximal seal zones depending on patient anatomy. Patients with proximal seal zones between zones 0 to 2 often require debranching procedures to preserve cerebral and upper extremity perfusion. In patients requiring zone 2 proximal seal zone, we recommend staged left subclavian artery (SCA) revascularization for elective cases.

Operative Technique

In our Johns Hopkins approach to TEVAR and BFEVAR, we advocate for preoperative placement of a lumbar drain for CSF drainage to reduce the risk of paraplegia, as well as LSA revascularization. CSF drainage is particularly important in cases where coverage of the entire thoracic aorta is planned or the patient has previously undergone prior AAA repair. We recommend the drain be placed preoperatively as rapid placement of a lumber drain after the onset of neurologic deficit is not practical in most settings. Furthermore, it has been our experience that a limited time frame of 1 to 2 hours exists to initiate CSF drainage before irreversible ischemia to the spinal cord occurs. As such, delaying CSF drainage until the completion of the procedure and reversal of general anesthesia may place the patient at unnecessary risk. Additionally, the LSA should not be covered by the stent graft in the absence of a first-stage revascularization. For elective procedures, it is our practice to admit patients in advance of TEVAR to undergo either LSA-carotid transposition or bypass. While our preference is for LSA transposition, LSA-carotid bypass may be necessary for situations unsuitable for transposition, such as prohibitive distance between the LSA and left carotid or an early takeoff of the left vertebral artery just distal to the LSA origin. Following a recovery period of 2 or 3 days, they return to the operating room for TEVAR during the same hospitalization.

The patient is placed in a supine position, and bilateral groins and abdomen are prepped and draped. General anesthetic is commonly utilized in these patients; however, the advent of percutaneous closure devices has resulted in the possibly of local anesthetic and

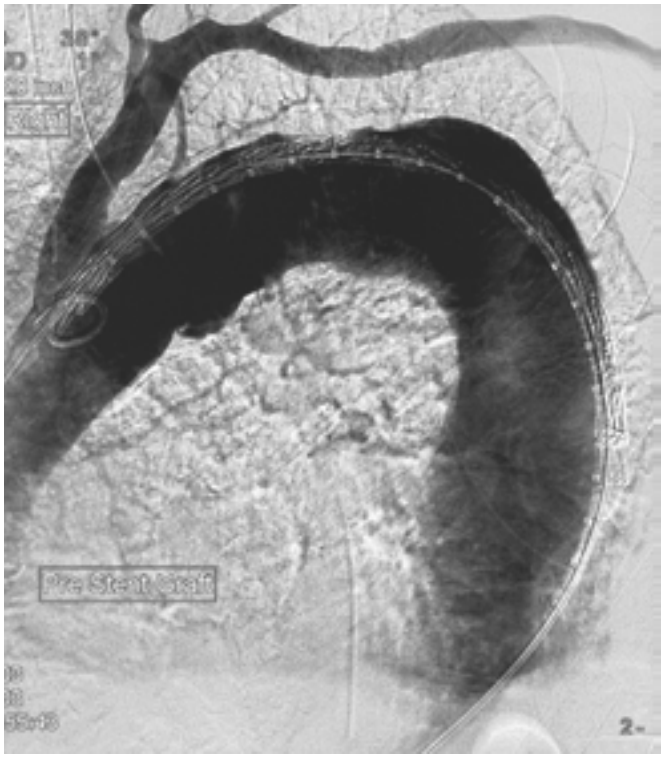


FIG. 6 During TEVAR, thoracic aortography is used to confirm the device is appropriately positioned in the proximal DTA before device deployment. In this angiogram, the undeployed device is located directly under the left subclavian artery origin.

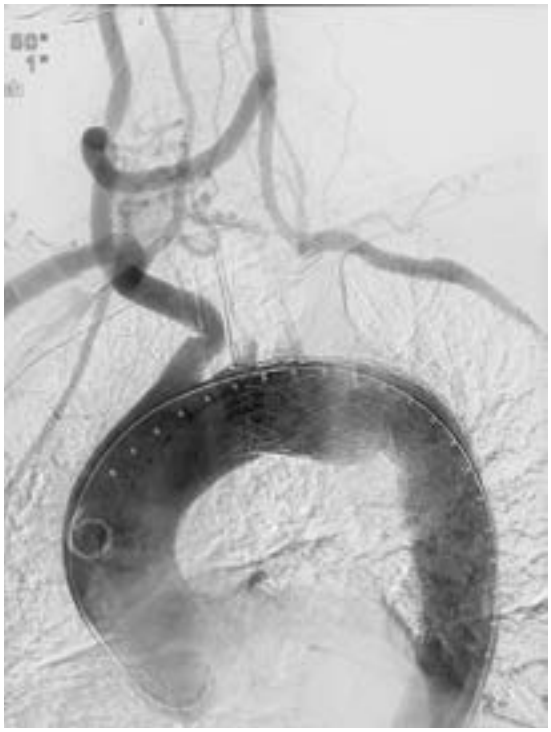


FIG. 7 Completion angiography is used to confirm stent graft placement and exclusion of the aneurysm sac. In this case, due to involvement of the aortic arch in the aneurysm pathology, a zone 1 proximal seal was required. The completion angiogram demonstrates patency of the preoperative debranching with a carotid-carotid bypass and left carotid-subclavian transposition.

moderate sedation for patients felt to be a prohibitive risk for general anesthesia based on cardiopulmonary comorbidities. Another option for high-risk patients includes epidural anesthesia.

Following the surgical exposure of the CFA for delivery of the device, the patient is systemically heparinized. An angiographic pigtail catheter is then introduced over a guidewire through the 5Fr sheath and into the thoracic aorta. The device is then introduced through the exposed CFA over a stiff wire to the approximate position of the pathology. Aortic arch or thoracic aorta angiography is then performed utilizing DSA to delineate the aortic anatomy and determine the appropriate positioning of the stent graft (Fig. 6). Following deployment of the stent graft, a large-diameter compliant balloon can be utilized for improved fixation of the stent graft to the aortic wall at the proximal and distal landing zones or at sites of overlap if multiple devices are deployed (Fig. 7).

It is critical to monitor the withdrawal of the access sheath while concurrently monitoring the patient's hemodynamics to evaluate for any signs of access vessel disruption. If there are any indications of iatrogenic access injury manifest usually abrupt hypotension with sheath removal, the sheath can be reinserted over the stiff wire to obturate the injury. In instances where the sheath cannot be replaced, the large-diameter compliant balloon can be placed proximal to the site of injury to occlude the aorta and provide vascular control. Depending on the degree of vessel injury, repair options include a flank incision to access the retroperitoneum for reconstruction of the vessel in cases of frank disruption versus endovascular covered stent placement for less severe injuries.

BFEVAR usually requires additional transaxillary access for insertion of stent grafts through the branches or fenestrations of the aortic device and antegrade into the visceral and renal vessels. Operator skill and experience in transaxillary access and direct cannulation of the aortic branch vessels is critical. Tortuosity of the target vessels, angulation cephalad of the target, or ostial disease can greatly complicate stable cannulation of the vessels to allow delivery of the bridging stents from the FBEVAR aortic device into the target vessel.

Outcomes

The application of endovascular therapies for pathologies of the thoracic aorta was pioneered by Dake et al. in 1994. Their initial series of 13 patients undergoing TEVAR demonstrated 100% technical success in the absence of mortality and paraplegia. This initial report was followed by the first long-term outcomes as part of the midterm follow-up results of the Gore TAG trial. The trial compared 191 patients undergoing TEVAR for DTAA to 94 patients who received traditional, open surgical repair. Their findings demonstrated that patients undergoing TEVAR had decreased rates of aneurysm-related mortality (2.8% vs. 11.7%, $P = 0.008$) but similar rate of all-cause mortality (68% vs. 67%, $P = 0.433$) at 5-year follow-up. TEVAR was also associated with lower rates of major adverse events during the first postoperative year (42% vs. 77%, $P < 0.001$). However, 3.6% of TEVAR patients were subjected to secondary interventions, and 21% were found to have endoleaks or persistent communication between the previously sealed aorta and the aneurysm sac. During the follow-up period, there were no reported ruptures or stent graft collapse, and only one incidence of significant stent graft migration. Trials utilizing additional devices have since been performed and again were found to be at least comparable to, if not superior to, open surgical repair (Table 1). Walsh et al. published a meta-analysis

TABLE 1 Summary of Outcomes Among the Three Multicenter Regulatory Trials Comparing TEVAR to Open Surgical Repair

	Gore TAG	Cook TX2	Medtronic Talent	Open Repair	Johns Hopkins Hospital
Patients	140	160	195	353	90
Mean age (yr)	71	72	70	68	67
Mortality	1.5%	1.9%	2.1%	7.1%	3.3%
SCI (paraplegia/paraparesis)	2.8%	5.6%	8.7%	13.0%	1%
Stroke	3.5%	2.5%	3.6%	6.7%	1%
1-year reinterventions	2.1%	4.4%	10.7%	3.7%	–
Aneurysm-related survival	83%	91.6%	83.9%	82%	–

of 17 studies and found significant reductions in mortality and major neurologic complication rates when comparing TEVAR to open surgical repair. Although prospective, randomized trials comparing TEVAR to open surgical repair are lacking, most mid- and long-term follow-up data suggest that TEVAR is superior to traditional open surgical repair in regard to perioperative mortality and SCI. TEVAR is particularly of benefit in patients felt to be unfit for open surgical repair due to preexisting comorbidities or baseline functional status.

Endovascular repair of TAAA was first described by Chuter et al. at University of California, San Francisco, in 2001. Since then, there have been advances made in endovascular technique including snorkel, sandwich, surgeon-modified endografts, and fenestrated and branched endografts (Figs. 8 and 9). These techniques have allowed for the treatment of high-risk patients with complex anatomy. The US Food and Drug Administration first approved the use of fenestrated endografts (FEVAR) in 2012 for juxtarenal AAAs. During the last 2 decades, endovascular repair of TAAA has shifted from physician modified stent grafts to manufactured off-the-shelf and custom-made endografts. Various nonrandomized studies looking at the outcomes of endovascular versus open repair of TAAA, have demonstrated lower morbidity, shorter length of stay in the hospital, and improved aneurysm related mortality (Table 2).

TABLE 2 Comparison of Endovascular and Open TAAA Repair

Endovascular TAAA Repair						
Author/Year	**Midfield Crawford Extent/No.**	**Mean Age**	**30-Day Mortality (%)**	**SCI**	**Paraplegia (%)**	**Dialysis (%)**
Tenorio Mayo Clinic (2020)	I–III (240)	72	3	N = 25 (10%)	6	2
Eagleton Cleveland Clinic (2016)	II–III (354)	74	4.8	II (21) III (10) N = 31 (8.8)	4	2.8
Verhoeven Nuremburg (2015)	I–III (115) IV (41) V (10)	69	7.8	N =15 (9.0%)	1.2	1.8
Open TAAA Repair						
Author/Year	**Midfield Crawford Extent/No.**	**Mean Age**	**30-Day Mortality (%)**	**SCI**	**Paraplegia (%)**	**Dialysis (%)**
Geisbusch German Registry (2019)	Total = 1422	67	23.9	–	4.9	31.6
Hicks Johns Hopkins (2017)	I–III (66) IV (71)	62	6.6	–	1.5	2.4
Coselli Baylor (2016)	I–III (2640) IV (669)	67	4.9	I (71) II (147) III (71) IV (27)	2.9	2.5

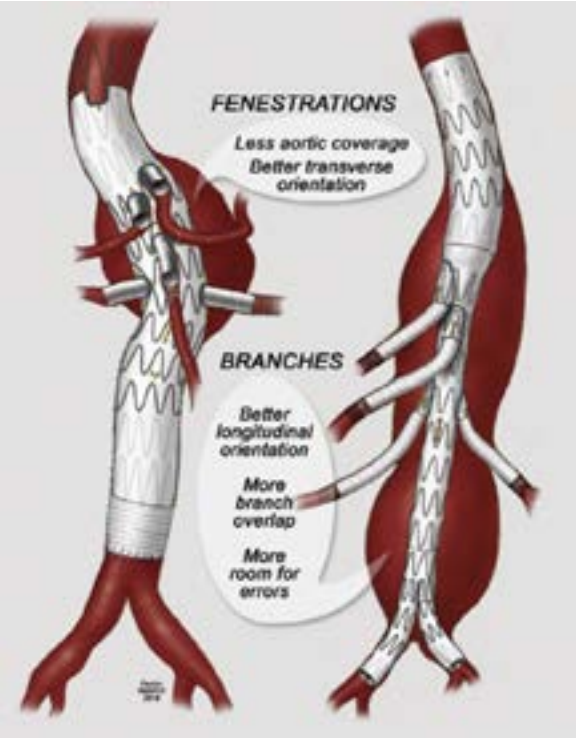


FIG. 8 Configuration of fenestrated and branched aortic endovascular devices for repair of TAAA. *(From Oderich GS, Ribeiro M, Reis de Souza L, et al. Endovascular repair of thoracoabdominal aortic aneurysms using fenestrated and branched endografts,* J Thorac Cardiovasc Surg. *2017;153:S32–41).*



FIG. 9 Three-dimensional surface and volume rendered reconstruction of CTA imaging of branched endovascular device for repair of an 8.2-cm type II TAAA.

Suggested Readings

Arnaoutakis DJ, Arnaoutakis GJ, Beaulieu RJ, et al. Results of adjunctive spinal drainage and/or left subclavian artery bypass in thoracic endovascular aortic repair. *Ann Vasc Surg*. 2014;28:65–73.

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Management of Acute Aortic Dissections

Karen M. Kim, MD, MS, and Thomas E. MacGillivray, MD

Acute aortic dissection is the most common catastrophe of the human aorta. With a reported incidence of 3 out of 100,000 patients each year, aortic dissection is a deadly disease with an early mortality of 1% to 2% per hour. Without appropriate treatment, the 2-week mortality of aortic dissections involving the ascending aorta is approximately 90%. Although the presentation may be classic, symptoms can be nonspecific and can occur in patients with no evident risk factors. Misdiagnosis leading to even a slight delay in treatment is associated with increased mortality; therefore, proper diagnosis and expeditious therapy are essential for improved survival. Patients with aortic dissections require lifelong medical management and surveillance with regular imaging to monitor for aneurysmal degeneration or complications that can occur after open or endovascular repair of aortic dissection.

PRESENTATION AND DIAGNOSIS

Aortic dissection results from a sudden intimal disruption that leads to the pressurized propagation of blood flow through a "false lumen" within the media of the aorta. Circulatory collapse and death can occur within seconds due to aortic rupture, frequently misdiagnosed as a massive myocardial infarction. The classic presentation is sudden, severe, "10/10," "tearing," or "ripping" chest pain radiating to the back between the scapulae. Occasionally, patients will present with little or no pain. Afflicted patients often appear listless and possess a sense of impending doom.

Preferential blood flow in the false lumen, as opposed to the "true lumen," can disrupt and occlude branching vessels of the aorta, resulting in decreased blood flow to an organ ("malperfusion") and even end-organ ischemia with pathophysiologic compromise

("malperfusion syndrome"). A new neurologic deficit or a pulseless extremity can distract the unsuspecting clinician. Electrocardiogram (ECG) changes or a new diastolic murmur can occur from retrograde dissection into the coronary arteries or the aortic valve resulting in myocardial ischemia or congestive heart failure. Acute paralysis, abdominal pain, renal insufficiency, and syncope are all well-recognized atypical presentations of acute dissection. Difficult-to-control hypertension can be a risk factor as well as a presenting sign in patients with aortic dissection. Hypotension and shock are concerning signs of tamponade, cardiac dysfunction, or ongoing hemorrhage. A high index of suspicion for aortic dissection is imperative for any patient with asymmetric pulses or differential blood pressures in the extremities.

High-resolution contrast-enhanced computed tomographic angiography (CTA) has replaced conventional aortography as the gold standard diagnostic study to confirm or exclude the diagnosis of acute aortic dissection. CTA has a diagnostic sensitivity and specificity of 90% to 100% and is readily available in most hospitals. False positive diagnoses can occur due to artifactual lines resulting from mistiming of contrast boluses or inappropriate gating with the cardiac cycle. Although scans limited to the thoracic aorta can confirm the diagnosis, it is recommended to scan the entire aorta and iliofemoral vessels to assess for subclinical malperfusion and to assist in planning the surgical or endovascular intervention.

Transesophageal echocardiography (TEE) can be a valuable tool to diagnose and manage patients with acute aortic dissection. Although TEE does require special expertise, it can rapidly assess for tamponade, valvular dysfunction, and cardiac wall motion abnormalities, particularly in the hemodynamically unstable patient transported directly to the operating room. Magnetic resonance imaging (MRI), conventional aortography, and coronary angiography have a very limited role in the acute management of aortic dissection patients.

Historically, "acute" dissections are those present for 14 days or less, whereas "chronic" dissections describe those present for greater than 2 weeks. Recently, the nomenclature has been modified to include "hyperacute" (<24 hours), "acute" (between 24 hours and 14 days), "subacute" (15–90 days), and "chronic" (>90 days) phases based on time from the initial presentation.

Intramural hematoma (IMH) comprises approximately 10% to 20% of patients who present with the clinical picture of acute aortic dissection. It consists of hemorrhage within the media of the aortic wall, usually without identifiable intimal disruption. Radiographically, IMH appears as a high-attenuation crescentic or circumferential thickening of the aorta on noncontrast imaging, with absence of blood flow through a false lumen on contrast imaging (sometimes inappropriately referred to as dissection with thrombosed false lumen). IMH may result from a microscopic intimal tear, hemorrhage of the vasa vasorum, or a penetrating aortic ulcer. Although it is a matter of discussion and debate, acute IMH is usually managed similarly to acute aortic dissection.

CLASSIFICATION

Acute aortic dissection can manifest in several different anatomic patterns that have different therapeutic and prognostic implications. The two main classification schemes in use worldwide to describe aortic dissection are the DeBakey and Stanford systems (Fig. 1). The DeBakey system categorizes the dissection based on the origin of the intimal tear and the extent of the dissection. Aortic dissections involving the ascending, arch, and descending aorta are DeBakey type I. Dissections confined only to the ascending aorta are DeBakey type II. Aortic dissections that originate and propagate distal to the left subclavian artery are DeBakey type III, with IIIa limited to the descending thoracic aorta and IIIb extending below the diaphragm.

The Stanford classification system divides dissections into two categories: those that involve the ascending aorta (Stanford type A, or DeBakey types I and II) and those that involve the descending thoracic aorta (Stanford type B, or DeBakey type III), regardless of the site of primary intimal tear. The aortic arch is not straightforwardly addressed in the Stanford classification, and dissections involving this area are sometimes referred to as type B (by North American surgical consensus, described later) or as "non-A-non-B" (by European surgical consensus).

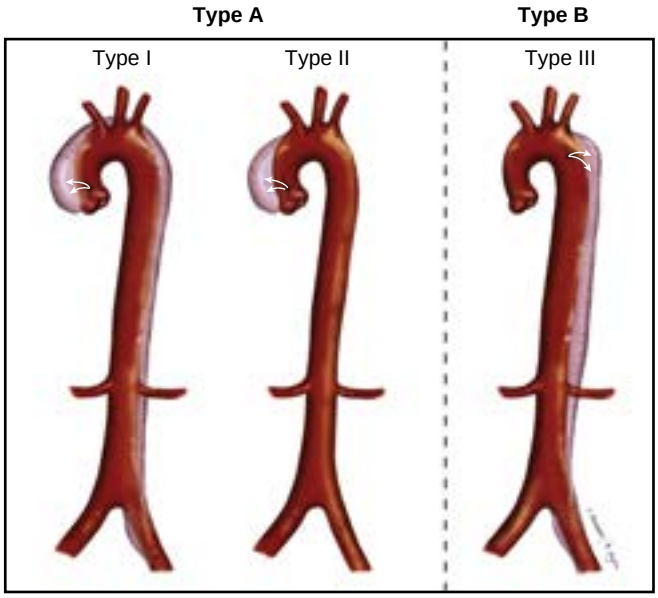


FIG. 1 Anatomy and classification of aortic dissection: DeBakey and Stanford systems. **DeBakey Classification**: Type I dissection originates in the ascending aorta and extends at least to the aortic arch and typically to the descending aorta (and beyond). Type II dissection only in the ascending aorta. Type III dissection originates in the descending aorta, usually just distal to the left subclavian artery, and extends distally. **Stanford Classification**: Type A dissection involves the ascending aorta (with or without extension into the descending aorta). Type B dissection does not involve the ascending aorta (includes arch dissection) *(From Braverman AC, Thompson R, Sanchez L. Diseases of the aorta. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds.* Braunwald's Heart Disease. *9th ed. Philadelphia: Elsevier. 2012.)*

Recently, the Society of Thoracic Surgeons (STS) and the Society of Vascular Surgeons (SVS) created a new classification system that combines the "A" and "B" of the Stanford classification with endovascular aortic zones to communicate, in greater detail, anatomic features of the dissection that may affect planning for endovascular therapies. In the SVS/STS classification system, type A dissections encompass those with an intimal tear in the ascending aorta and proximal arch including the innominate artery ostium (zone 0), and type B dissections encompass those with an intimal tear in any portion of the aorta distal to that (zones 1 and beyond). In this system, dissections involving the arch are more clearly defined. Type I dissections (as in the letter "I," not the Roman numeral) are those with an unidentified intimal tear. For type A and I dissections, the distal extent of the dissection (d) by endovascular zone is denoted with a subscript (e.g., type A_d or I_d). For type B dissections, both the proximal extent (p) and the distal extent (d) by endovascular zone are denoted with subscripts (e.g., type $B_{p,d}$) (Fig. 2). For example, a type B dissection with an entry tear just beyond the left subclavian artery with retrograde extension of the false lumen to the origin of the left common carotid artery (i.e., zone 1) and antegrade extension to the renal arteries (i.e., zone 8) would be denoted as type $B_{1,8}$.

Acute type B dissections are further classified as "complicated," "uncomplicated," or "high risk" (Box 1). Complicated type B dissections include approximately 20% of patients with rupture or

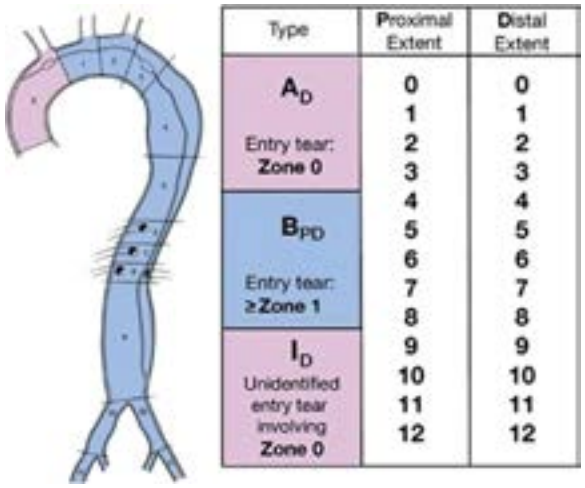


FIG. 2 STS/SVS aortic dissection classification system. *(Modified from Lombardi JV, Hughes GC, Appoo JJ, et al., Society for Vascular Surgery (SVS) and Society of Thoracic Surgeons (STS) reporting standards for type B aortic dissections.* Ann Thorac Surg. *2020;109:959–981.)*

BOX 1 Characterization of "Uncomplicated," "High Risk," and "Complicated" Aortic Dissections

Uncomplicated

No rupture
No malperfusion
No high-risk features

High risk

Refractory pain
Refractory hypertension
Bloody pleural effusion
Aortic diameter >40 mm
Radiographic only malperfusion
Entry tear: lesser curve location
False lumen diameter >22 mm

Complicated

Rupture
Malperfusion

Modified from Lombardi JV, Hughes GC, Appoo JJ, et al. Society for Vascular Surgery (SVS) and Society of Thoracic Surgeons (STS) reporting standards for type B aortic dissections. *Ann Thorac Surg.* 2020;109:959–981.

malperfusion syndrome for whom open surgical or endovascular therapy is indicated. Uncomplicated type B dissections are effectively managed with optimal medical therapy, while patients who have acute type B dissections with high-risk features may benefit from endovascular therapy to reduce short- and long-term morbidity and mortality.

MANAGEMENT

Initial Management

Once the diagnosis of acute aortic dissection, whether type A or type B, is suspected, invasive hemodynamic monitoring and aggressive antiimpulse therapy should be instituted without delay. A radial arterial monitoring cannula should be placed in the upper extremity with the best pulse and blood pressure, as a limb with a barely palpable pulse or lower blood pressure may indicate malperfusion. Intravenous β-blockade should be the medication of first choice to decrease the aortic dP/dT by titrating the infusion to a goal heart rate of 60 to 70 beats per minute and a systolic blood pressure of 100 to 120 mm Hg. Once adequate beta-blockade is achieved, vasodilators (nitroprusside, nicardipine, clevidipine, etc.) can be added to further control hypertension. Initial blood pressure control with vasodilators like nitroprusside or hydralazine should be avoided. Although vasodilators will lower the blood pressure, they can increase the dP/dT and shear forces in the aorta, thereby increasing the risk of rupture. Acute type A dissection patients with a diastolic murmur or TEE evidence of significant aortic valve regurgitation should not be managed with β-blockers because of the high risk of exacerbating congestive heart failure.

Acute aortic dissection can be a very dynamic disease with a rapidly evolving clinical course. Patients diagnosed with hyperacute/acute type A aortic dissection should be emergently transferred to a cardiac surgical center for immediate surgical repair. Unnecessary testing or optimizing medical therapy should not be allowed to delay definitive surgical repair. Even patients with coronary, cerebral, visceral, renal, and/or extremity malperfusion should be managed with central aortic reconstruction as a first step, which will frequently correct the malperfusion syndrome. Recently, some centers have had success with initial endovascular stabilization of visceral malperfusion syndromes before surgical repair of the ascending aorta due to the high risk of mortality in this group of patients. Nonoperative management, though it carries high risk of mortality, may be appropriate when faced with very high-risk patients, especially those with advanced coronary, pulmonary, and renal disease.

Management of Acute Type A Dissections

Acute Stanford type A dissections account for greater than 60% of all dissections and are surgical emergencies requiring immediate operation. The goal of surgical therapy for acute type A aortic dissection is to prevent imminent death from aortic rupture (causing exsanguination or tamponade), acute aortic insufficiency, or malperfusion of the coronary, cerebral, and systemic circulations. The principal technique to accomplish these goals is to resect the primary intimal tear in the ascending aorta by replacing the ascending aorta with a tube interposition graft, thus reestablishing blood flow in the true lumen of the aorta. Resuspension of the aortic valve is often needed to reestablish competence of the aortic valve after retrograde extension of the dissection has disrupted one or more of the aortic valve commissures.

Invasive arterial and central venous pressure monitoring are helpful for the induction and conduct of general anesthesia. Temperature monitoring of the nasopharynx, central venous or pulmonary arterial blood, and bladder can ensure uniform perfusion and cooling. TEE, EEG, and cerebral oximetry are useful adjuncts for monitoring.

As cardiopulmonary bypass is required for ascending aortic replacement, the surgeon must determine the site of arterial cannulation and perfusion. Although historically the common femoral artery was the most common approach for arterial cannulation given its size, easy accessibility, and surgeons' familiarity, recent studies have shown that the right axillary or innominate artery, via an 8 or 10 mm Dacron graft anastomosed end-to-side to the artery, is a preferred site for arterial perfusion to avoid retrograde embolic events and to facilitate the use of antegrade cerebral perfusion during circulatory arrest. Some experienced surgeons advocate the use of direct central ascending aortic cannulation with the use of TEE guidance—a potentially challenging approach but one that can be lifesaving in the management of an unstable patient.

Through a median sternotomy, the heart and ascending aorta are readily exposed. The right atrium is easily cannulated for venous drainage to initiate cardiopulmonary bypass. Most aortic surgeons

utilize a period of hypothermic circulatory arrest to perform an open distal aortic anastomosis. During cooling, it is imperative that the surgical, anesthesia, and perfusion teams monitor the patient to ensure uniform perfusion and cooling. Occasionally, cannulation strategies must be altered to manage malperfusion during cardiopulmonary bypass. In situations involving aortic insufficiency and/or coronary malperfusion, the surgeon should be prepared to vent the left ventricle on bypass, cross-clamp the aorta, and meticulously protect the myocardium with retrograde coronary sinus and possibly direct antegrade coronary ostial cardioplegia strategies.

Although there is considerable debate about the optimal temperature for hypothermia and circulatory arrest, the authors achieve moderate hypothermia (temperature between 24°C–27°C) in the nasopharynx before turning off the circulation to the body while employing antegrade or retrograde cerebral perfusion. With the patient in Trendelenburg position, the entire ascending aorta from the sinotubular junction up to the innominate artery, with a bevel including the lesser curve of the aortic arch, is resected. The aortic tissues are extremely fragile, and they should be delicately handled. Without an aortic cross clamp, the aortic arch can be inspected for complex intimal disruptions and to confirm that the brachiocephalic branches are intact and arising from the true lumen. All three layers of the proximal aortic arch are then reconstructed, thereby obliterating the false lumen, which will then allow blood flow through the true lumen once central perfusion is reestablished. Some surgeons reconstitute the aortic wall between two Teflon felt strips and anastomose a Dacron graft to the aortic-felt sandwich (Fig. 3A). The authors prefer to insert a piece of Teflon felt into the false lumen (Fig. 4A) and to then sew the Dacron graft to the reconstituted aorta, buttressed with a strip of Dacron around the adventitia. The authors avoid the use of glues during these operations. Although glues allow for easier tissue handling, they can be destructive to the aorta and promote late pseudoaneurysm formation.

With the distal anastomosis completed, the aortic arch is de-aired, the proximal end of the graft is clamped, and cardiopulmonary bypass is resumed through the Dacron graft to promote true lumen flow (Fig. 3B, C). Generally, aortic arch replacement is not routinely necessary for managing most patients with acute type A aortic dissection. Arch replacement increases the complexity and length of the procedure, which can add to the already high-risk operation. Situations when the aortic arch should be considered for replacement in acute dissection patients include complex intimal disruptions in the arch, arch aneurysms larger than 5 cm, or genetically triggered thoracic aortic diseases (e.g., Marfan, Loeys-Dietz, Ehlers Danlos). Arch replacements should be performed with the use of selective antegrade or retrograde cerebral perfusion, which has been demonstrated to improve outcomes. For patients with large intimal disruptions in the distal arch or proximal descending aorta, antegrade deployment under direct vision of a stent graft, or "frozen elephant trunk" (Fig. 5), can stabilize the distal aorta and reduce the need for early reintervention or can address distal malperfusion.

During rewarming, the aortic root, aortic valve, and proximal ascending aorta are assessed for reconstruction or replacement. The false lumen may extend retrograde into the aortic root but without intimal tear in the sinus segment; in this case, the aortic root can be reconstructed using a "neo-media" technique by obliterating the false lumen with Teflon felt (Fig. 4B,C). Attention is required in patients who present with aortic regurgitation and in those who have complex aortic root dissections approaching the coronary ostia. Aortic regurgitation is the most common cardiac complication associated with acute type A dissection. There are three possible dissection-related mechanisms that can contribute to aortic regurgitation. Acute dilation of the sinotubular junction and root caused by the expanding false lumen can result in incomplete coaptation of the valve cusps. The dissection can also extend into the aortic root, disrupting the commissural posts resulting in prolapse of the valve cusps. Additionally, an aortic flap can itself prolapse through the valve in diastole preventing appropriate valve function. In most patients, the sinotubular junction can be reconstructed, the aortic valve commissures resuspended, and the aortic valve preserved. Situations when composite aortic root replacement with coronary button reimplantation should be considered include patients with aneurysms of the aortic root exceeding 5 cm, complex aortic valve pathology, dissection approaching the coronary ostia, and genetically triggered thoracic aortic diseases. Valve-sparing aortic root replacement should be reserved for highly experienced aortic surgeons in this setting.

Surgical Results with Acute Type A Dissections

According to the International Registry of Acute Aortic Dissection (IRAD) database, the overall surgical mortality of acute type A aortic dissection is 18%. In unstable patients (e.g., preoperative presence of tamponade, shock, congestive heart failure, stroke, coma, myocardial ischemia/infarction, acute renal failure, or mesenteric ischemia), the surgical mortality is greater than 30%. Postoperatively, aortic dissection patients are at risk for coagulopathic bleeding requiring transfusions and reexploration. Transient neurologic dysfunction, stroke, renal insufficiency, acute lung injury, new malperfusion syndromes, multiorgan system failure, and refractory hypertension are some of the possible early postoperative complications requiring intensive care and prolonged hospital care of these complicated patients. There is variability of outcomes reported from different centers, but the fact remains that acute type A aortic dissection is a highly lethal condition which, even when appropriately managed, has a high risk of morbidity and mortality.

Management of Acute Type B Dissections

Historically, the results of open surgical therapy for acute type B dissection had been associated with a higher mortality than with medical therapy. Currently, optimal medical therapy using antiimpulse medications remains the preferred treatment for patients with uncomplicated type B dissection. Approximately 20% of patients with acute type B dissections are complicated by rupture or malperfusion and have a high risk of death without intervention. Thoracic endovascular aortic repair (TEVAR) with stent grafts has largely replaced open surgery for patients with complicated type B aortic dissection with improved early outcomes. Open surgical repair is reserved for those patients with unsuitable anatomy for TEVAR and for those with genetically triggered aortic diseases. Whether TEVAR of uncomplicated type B dissection with high-risk features proves to be superior to medical management remains to be proven. There are reports that TEVAR improves aortic remodeling over time, which may translate to decreased aortic complications and improved long-term survival.

Thoracic endovascular repair addresses rupture or malperfusion by covering the primary intimal tear and possible large reentry tear(s) in the descending thoracic aorta, thereby restoring blood flow to the true lumen of the aorta and its major branches. Coverage is usually extended from the caudal aspect of the left subclavian artery (LSA) (zone 3) to just proximal to the celiac artery (zone 5) and may extend proximally into zone 2 if the intimal tear is close to or involves the LSA. If TEVAR does not need to be performed emergently, revascularization of the LSA with carotid-subclavian bypass or subclavian-carotid transposition can decrease the risk of vertebrobasilar stroke, left arm ischemia, and paralysis.

TEVAR is most often performed via iliofemoral access, with open exposure or ultrasound and fluoroscopy-guided percutaneous access of the common femoral artery. Systemic heparin is administered to achieve ACT >250 sec. After advancement of a J-wire into the ascending aorta, intravascular ultrasound (IVUS) is used to confirm true lumen access along the entire extent of the wire. IVUS is also helpful in noting the origins of the LSA and celiac axis, a compressed true lumen, and dissection extending into branch vessels. The soft wire is then exchanged for a stiff Lunderquist

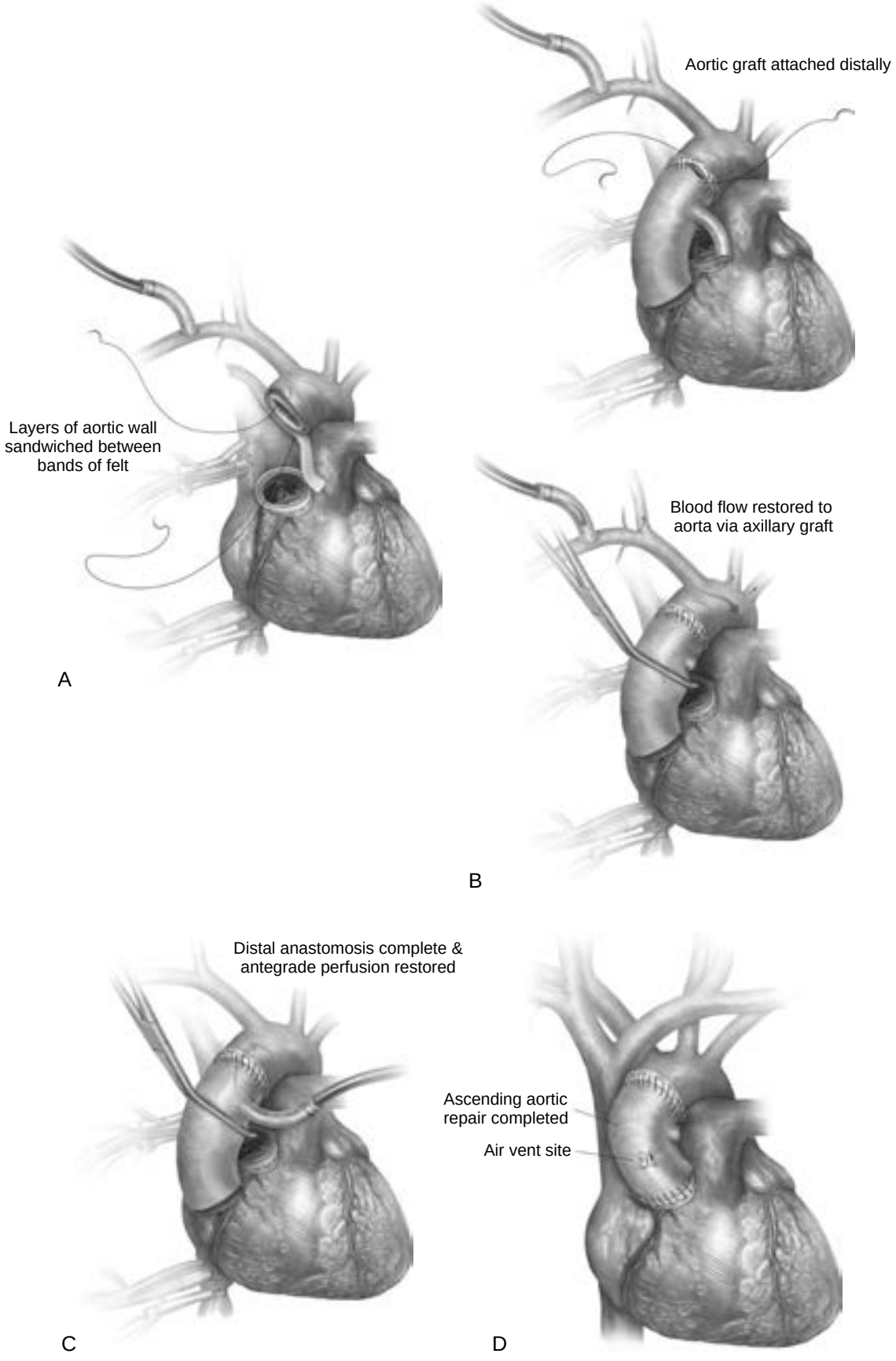


FIG. 3 **(A)** The dissected layers of the proximal and distal aorta reapproximated between layers of Teflon felt. **(B)** The completed distal anastomosis, with the graft clamped proximally, the aortic arch and branches de-aired, and flow restored to the patient's head and body via axillary artery inflow. **(C)** Distal reperfusion reinitiated through a side-arm of the ascending graft. **(D)** The completed procedure, with the dissected ascending aorta removed, the valve resuspended, all air evacuated from the left circulation, and the patient decannulated. *(Modified from Bolman RM 3rd. Acute type A aortic dissection operative techniques.* Thorac Cardiovasc Surg. *2009;14[2]:124–135.)*

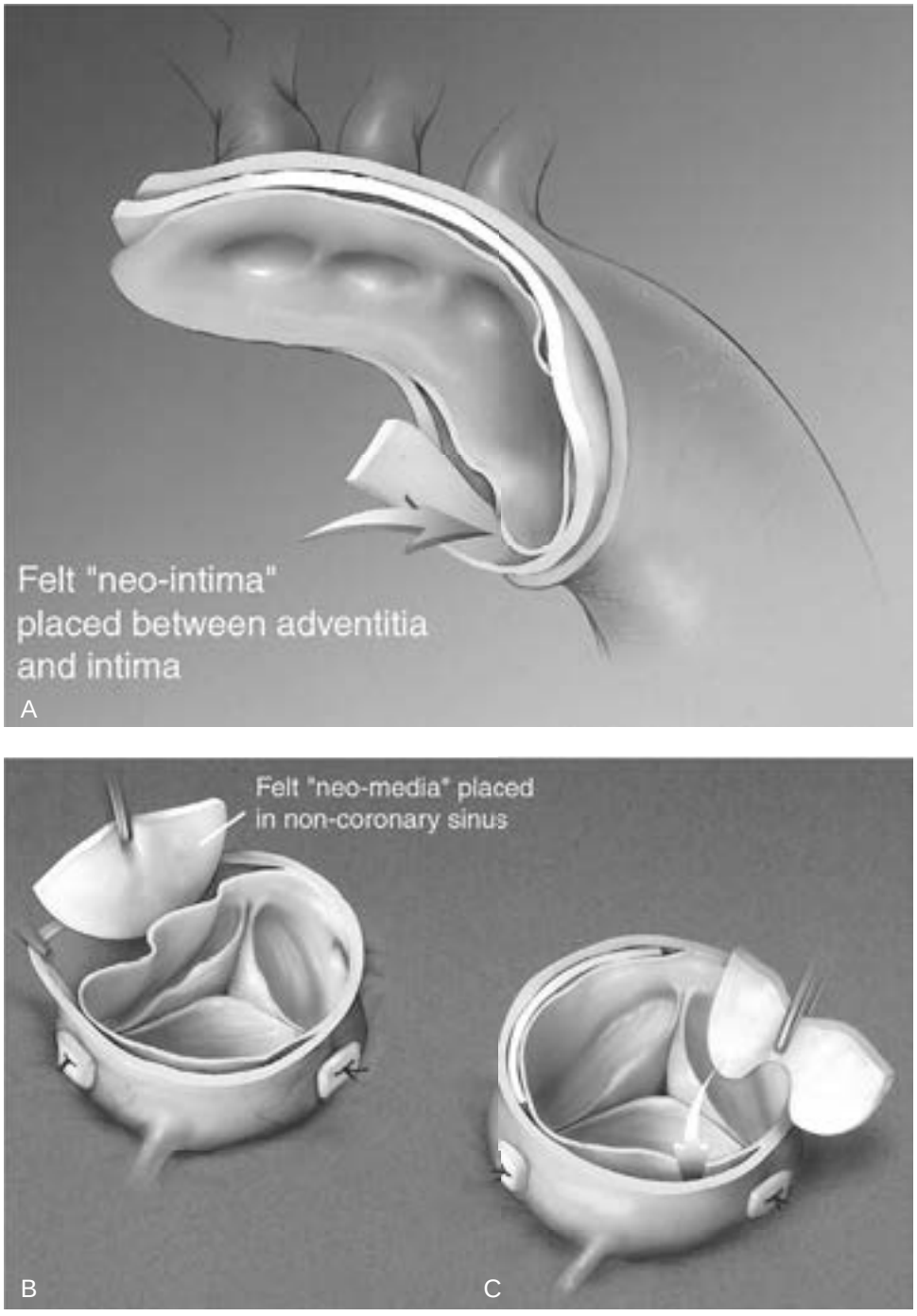


FIG. 4 "Neo-media" felt technique to reconstruct the distal hemiarch **(A)** and aortic root **(B** and **C)**. *(Modified from Bavaria JE, Brinster DR, Gorman RC, et al. Advances in the treatment of acute type A dissection: an integrated approach.* Ann Thorac Surg. *2002;74:S1848–S1852.)*



FIG. 5 Ascending aortic and hemiarch replacement with frozen elephant trunk. *(Modified from Szeto WY. Conventional versus frozen elephant trunk for complex aortic arch pathology: what should we be doing now?* J Thorac Cardiovasc Surg. *2015;149:1294–1295.)*

wire, and a large sheath is advanced into the abdominal aorta. The appropriately sized device is delivered through the sheath, a pigtail catheter is advanced alongside the stent graft (whether through the sheath or from contralateral femoral access), and thoracic aortography in left-anterior-oblique (LAO) projection is performed to delineate the origin of the LSA. The device is positioned with the proximal extent in the desired endovascular zone (zone 2 if coverage of the LSA is planned, zone 3 if not), and with ventilation held, the device is deployed. The delivery system is removed, and subsequent devices are advanced and deployed in similar manner until the desired extent of coverage is achieved. Completion aortography is performed to confirm patency of branch vessels and absence of proximal, distal, and overlap endoleaks. IVUS can be used as well to examine patency of branch vessels and to confirm the absence of retrograde type A dissection. The sheath is removed and the arteriotomy repaired primarily or with percutaneous closure devices. In the early postoperative period after TEVAR, when spinal cord perfusion is vulnerable, the mean arterial pressure should be kept at 80 to 90 mm Hg to decrease risk of paralysis or paraparesis. Once the risk of spinal cord ischemia has abated, lifelong blood pressure control is necessary to reduce long-term morbidity and mortality. Other early complications include stroke, bleeding from major vascular complication, and stent-induced new entry (SINE) tears, while late complications include endoleaks, aneurysmal degeneration of treated or untreated aorta, and infection.

The 5-year survival of patients with chronic type B aortic dissection is 60% to 80%, with many of these patients succumbing from aneurysmal degeneration and rupture.

Suggested Readings

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Carotid Endarterectomy

Bruce A. Perler, MD, MBA

Stroke is one of the most important healthcare problems in the United States and throughout the Western world in terms of mortality, morbidity, and cost. Nearly 800,000 new strokes occur each year in the United States, and it is the fifth leading cause of death and the most frequent cause of long-term disability in this country. More than 80% of strokes are ischemic, and atherosclerosis of the extracranial carotid arteries is the most common preventable cause of ischemic stroke. It is therefore not surprising that carotid endarterectomy (CEA) has been the most frequently performed open vascular surgical operation in the United States.

CLINICAL PRESENTATION

In formulating a treatment plan for the patient with carotid artery disease, the two most critical issues have been the patient's clinical status and the degree of stenosis in the internal carotid arteries. Today, however, especially among patients with asymptomatic disease, we are recognizing that the composition of the plaque is predictive of future ischemic events and therefore is a relevant consideration in selecting patients for CEA. The vast majority of individuals with significant carotid artery disease are completely asymptomatic, and most are identified by the presence of a bruit in the neck. Although the cervical bruit is the only physical finding suggestive of carotid artery disease, it cannot be overemphasized that it is an insensitive and very nonspecific finding. Among individuals with a cervical bruit, no more than 30% to 50% will be found to have a clinically significant stenosis in the ipsilateral internal carotid artery (ICA). Conversely, among individuals with

high-grade carotid stenoses, a bruit will be found in no more than 20% to 50% on the affected side.

A minority of patients with significant carotid artery disease may be identified after presenting with a transient ischemic attack (TIA). A TIA is defined as an abrupt interruption of focal neurologic function, and usually with very rapid resolution. Symptoms consistent with a TIA include weakness, paralysis, numbness or paresthesias of an arm and/or leg on one side of the body (hemiparesis or hemianesthesia), difficulty speaking or finding words (aphasia or dysphasia), or acute loss of vision in one eye or a part of the eye (amaurosis fugax). An exceedingly uncommon but important manifestation of a TIA is the so called *limb-shaking TIA,* which typically occurs in individuals with very severe or pre-occlusive stenoses or those with carotid occlusions and are often confused with seizures. The average duration of a TIA is about 14 minutes, but most last less than 5 minutes, and more than 80% resolve within 2 hours. In other words, if symptoms have lasted longer than 2 hours, it is likely that the patient is in the process of evolving a completed stroke. To be considered a TIA, the symptoms must completely resolve within 24 hours. Formerly, if symptoms lasted longer than 24 hours but resolved within 48 hours, the presentation was considered a *reversible ischemic neurologic deficit* (RIND), although this terminology is falling out of favor. Finally, if symptoms persist and if there is evidence of an infarct on cerebral imaging, the patient has manifested a stroke. It should be noted that several recent large population-based studies have demonstrated that no more than 10% to 35% of individuals who suffered an ischemic stroke actually experienced a recognized TIA before the stroke occurred. Crescendo TIAs refers to a clinical scenario in which the patient is experiencing repeated neurologic events, often at increased frequency, with complete symptomatic resolution between attacks. A *stroke-in-evolution* refers to patients who manifest ongoing symptoms that often worsen over a short period, ultimately culminating in a completed stroke.

The differentiation of patients into the proper clinical class is critical because the risk of subsequent stroke and thus the threshold for and risk of CEA one would be willing to accept will depend on the clinical status. For example, among asymptomatic patients with a significant internal carotid stenosis, the risk of stroke over the next 5 years is approximately 10% to 15%, although recent improvements in medical management may have reduced the incidence somewhat. On the other hand, among patients who have experienced a TIA, the incidence of stroke is approximately 25% within the first year, and most of those strokes occur early, within the first few weeks or months after the TIA with a decreasing incidence over time. The 5-year incidence of stroke among individuals who have experienced a TIA is 35% to 45%. Finally, among individuals who have experienced an ischemic stroke secondary to carotid artery disease, the 5-year stroke incidence is roughly 50%, and nearly 50% of those second strokes may be fatal.

Imaging Studies

Carotid duplex ultrasound has emerged as the diagnostic modality of choice for evaluating patients with suspected carotid disease. Duplex evaluation provides both anatomic B-mode ultrasound imaging information about the composition of the plaque and degree of stenosis, as well as an assessment of flow velocities (spectral analysis) that allows one to more precisely predict the degree of stenosis in the carotid arteries. In the hands of experienced sonographers, it is more than 90% accurate in depicting significant carotid stenoses when compared with contrast angiography. As noted earlier, among patients with asymptomatic ICA stenoses, it is not only the severity of the stenosis but also the character of the plaque that should influence the decision to perform a CEA; specifically, plaque that appears echolucent on imaging may have a higher risk of subsequent ischemic events than more echogenic plaque. Duplex ultrasound is more sensitive than contrast angiography in identifying the potentially vulnerable or unstable carotid plaque and therefore the patient who will most benefit from performance of CEA.

When further anatomic information is required, for example in assessing a potentially high bifurcation or unusual lesion or when previous duplex scans provide conflicting information, magnetic resonance angiography (MRA) or computed tomography arteriography (CTA) may be obtained. On occasion, MRA may overestimate the degree of stenosis. CTA can provide more anatomic information than MRA, but it does require contrast administration.

In light of its invasiveness, risks, and costs, contrast arteriography is very infrequently performed today before CEA. In addition to its role in carotid artery stenting, it might play a role if there are ongoing concerns about the underlying anatomy such as a high carotid bifurcation, before reoperative CEA, to assess vertebrobasilar insufficiency, or to identify possible intracerebral arterial disease.

In the symptomatic patient, computed tomography (CT) or magnetic resonance imaging (MRI) should be obtained to assess for cerebral infarction and its extent. MRI is more accurate in the early hours after a stroke. Previous studies have demonstrated that as many as 10% of asymptomatic patients and 30% of patients who have experienced TIAs will have evidence of cerebral infarctions on CT or MRI studies. The presence of so-called "silent strokes" on imaging is associated with an increased risk of subsequent stroke among patients with clinically asymptomatic carotid stenoses.

INDICATIONS FOR CEA

The indications for CEA have been established by level 1 evidence derived from several randomized prospective clinical trials (Table 1). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated a clear benefit of CEA plus best medical management compared with best medical management alone for symptomatic patients with high-grade (70%–99%) carotid stenoses. The same year, the European Carotid Surgery Trial (ECST) demonstrated a similar but smaller benefit in symptomatic patients with 70% to 99% stenoses. Analysis of a second cohort of symptomatic patients with moderate (50%–69%) stenoses in the NASCET trial demonstrated a smaller but statistically significant benefit as well. Therefore, CEA is indicated in acceptable operative risk symptomatic patients with a > 50% ICA stenosis. One exception are symptomatic patients with a < 50% stenosis caused by a carotid web. This is a condition seen primarily in relatively young women, and it is felt to be a variant of fibromuscular disease. They have been found to develop thrombi behind the intimal web, which then embolize to the brain and cause recurrent strokes. Antiplatelet therapy has been much less effective than in arteriosclerotic disease, and CEA has resolved these episodes (Fig. 1).

The Asymptomatic Carotid Atherosclerosis Study (ACAS) demonstrated a significant benefit of CEA plus best medical management compared with best medical management alone for patients

TABLE 1 Carotid Endarterectomy: Randomized Trials

Trial	Indication	CVA/Death	Risk Reduction	*P*
NASCET	Sx: > 70%	5.8%	16.5%/2 years	< 0.001
	Sx: 50%–69%	6.7%	10.1%/5 years	< 0.05
ECST	Sx: 70%–99%	7.5%	9.6%/3 years	< 0.01
ACAS	Asx: > 60%	2.3%	5.9%/5 years	0.004
ACST	Asx: > 60%	3.1%	5.4%/5 years	< 0.0001

ACAS, Asymptomatic Carotid Atherosclerosis Study; *ACST,* Asymptomatic Carotid Surgery Trial; *Asx,* asymptomatic; *CVA,* cerebrovascular accident; *ECST,* European Carotid Surgery Trial; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *Sx,* symptomatic.

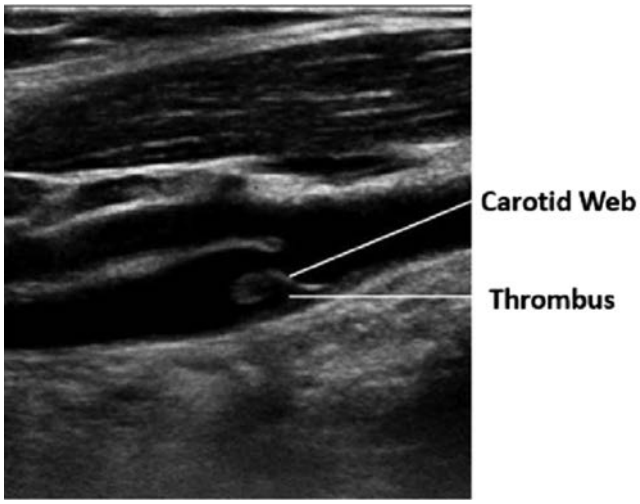


FIG. 1 **Duplex ultrasound image of a carotid web.** *(From Sidawy AN, Perler BA, eds. Rutherford's Textbook of Vascular Surgery & Endovascular Therapy. Elsevier; 2019.)*

with asymptomatic stenoses of 60% to 99%. These findings have been confirmed in the Asymptomatic Carotid Surgery Trial (ACST) in Europe.

The most recent published clinical practice guidelines of the Society for Vascular Surgery recommend CEA and optimal medical therapy for patients with symptomatic disease (stroke or TIA) and a ≥ 50% internal carotid stenosis, and state that CEA should be "considered" for asymptomatic patients with a ≥ 70% internal carotid stenosis, assuming the patient has a reasonable life expectancy (3–5 years) and that the operation can be performed with a stroke/death rate of < 3%. These recommendations mirror earlier guidelines from the American Heart Association (AHA). Specifically, the AHA recommends CEA for patients who have experienced a TIA or stroke within 6 months and ipsilateral 70% to 99% internal carotid stenoses if the surgeon has a perioperative stroke/death rate of ≤ 6%. For symptomatic patients with a 50% to 69% ipsilateral internal carotid stenosis, CEA is recommended after consideration of patient-specific factors such as age, comorbidity, and severity of symptoms. For asymptomatic patients, the AHA recommends CEA for patients with a 60% to 99% stenosis if the surgeon's perioperative stroke/death rate is ≤ 3%.

Despite this level 1 evidence, the role of CEA in the management of patients with asymptomatic carotid disease has been recently challenged. This argument is predicated upon the observation that the natural history of asymptomatic carotid disease in contemporary practice is better than what was observed in the medically managed patients in the randomized trials because of recent improvements in medical management and especially the use of statins. However, it is also true that the outcome of CEA today is superior to what was observed in the trials as well, in part because of the same improvements in medical management and especially statins (see later). Therefore, the author believes that there is no conclusive evidence to dismiss the findings of the ACAS and ACST investigations, and the recommendations for CEA in the currently published guidelines remain appropriate. The ongoing CREST-2 trial is designed to address this issue.

CEA: OPERATIVE TECHNIQUE

Anesthesia

CEA may be performed under general anesthesia, regional anesthesia with deep or superficial cervical block, and even pure local anesthesia. Although early reports suggested a reduced length of stay associated with CEA performed under regional anesthesia, comparable lengths of stay are routinely documented today among patients who undergo operations under general anesthesia. The majority of studies comparing the two techniques have reported improved perioperative cardiac stability with regional anesthesia, but this does not necessarily result in a reduced incidence of myocardial infarction. Disadvantages of regional anesthesia include potential patient discomfort or anxiety, risk of seizure or allergic reaction, anxiety for the operating surgeon, and compromise of technique.

Patient Positioning

Careful positioning of the patient is important to ensure patient comfort and adequate operative exposure. Positioning begins with placing a roll behind the scapula to achieve some extension of the neck. A padded ring is placed under the head to prevent neck injury from hyperextension. If general anesthesia is employed, the endotracheal tube should be taped to the corner of the mouth opposite to the surgical field. If local or regional anesthesia is used, a Mayo stand is placed over the patient's head to suspend the surgical drapes away from the patient's face to prevent sensations of claustrophobia.

Skin Incision

The standard incision used is a longitudinal incision parallel to the medial border of the sternocleidomastoid muscle. The upper portion of the incision is angled posterior to the earlobe if cephalad exposure above the angle of the jaw is required. An alternative incision is to place the incision transversely in an appropriately located skin crease, usually 1 to 2 cm inferior to the angle of the jaw (Fig. 2). This incision provides excellent postoperative cosmesis. However, if the transverse incision is made in a suboptimal location, it may be more difficult to obtain more cephalad and/or caudal exposure in the wound.

Operative Exposure

Meticulous surgical technique is paramount to a successful operation. Manipulation of the carotid artery should be minimized as intraoperative embolization can result from careless handling. The dissection is begun by dividing the platysma and mobilizing the medial border of the sternocleidomastoid muscle. The external jugular vein lies deep to the platysma and should be sought out in this plane to avoid injury or in the event it is needed for patching. It is



FIG. 2 **Longitudinal and transverse carotid incisions.** *(From Sidawy AN, Perler BA, eds. Rutherford's Textbook of Vascular Surgery & Endovascular Therapy. Elsevier; 2019.)*

more commonly encountered with an oblique skin crease incision than with a longitudinal incision. The other structure located at this level is the greater auricular nerve; injury to this nerve leads to numbness of the earlobe. The carotid sheath is entered, and the medial border of the internal jugular vein is dissected. The facial vein is identified crossing medially in the base of the wound and divided; sometimes it has an early bifurcation or trifurcation, and multiple branches need to be ligated. The internal jugular vein is then retracted laterally. The vagus nerve is identified at this point in the carotid sheath, usually located posteriorly between the internal jugular vein and the carotid artery, although in a minority of patients it may lie anteriorly. The common carotid artery (CCA) is controlled circumferentially with an umbilical tape and Rummel tourniquet if a shunt is to be used. At this point, the ansa cervicalis nerve should be identified; it usually lies medial to the distal CCA. Identifying this nerve facilitates safe dissection of the carotid bifurcation and avoids injury to the hypoglossal nerve that crosses medially from a superior to inferior location. The superior thyroid artery is identified coming off the medial border of the carotid bifurcation or proximal external carotid artery (ECA) and is controlled with a tie or vessel loop. The ECA and ICA are encircled with vessel loops, making certain to control the latter beyond the disease process. During the dissection of the carotid bifurcation and its branches, one should avoid dissecting in the crotch of the carotid bifurcation to avoid injuring the carotid body because this can result in hemodynamic instability and troublesome bleeding. If hemodynamic instability results, the carotid body can be injected gently with 1% lidocaine.

Before clamping, the patient is administered 70 to 100 units/kg of heparin, and it is allowed to circulate for 3 minutes. The ICA is clamped first to prevent embolization that can result when the CCA or ECA is clamped. Care should be taken to make sure the ICA is clamped on a normal portion of the artery distal to the plaque.

If local anesthesia or intraoperative electroencephalography (EEG) is employed for selective shunting, a test clamp on the distal ICA should be applied for at least 3 minutes to check for changes in the neurologic examination or EEG pattern. If such changes occur, the artery should be unclamped to allow for reperfusion before reclamping and opening the carotid bifurcation. This is because opening the bifurcation and placing a shunt may take 2 to 3 minutes and should not be performed while the brain is already ischemic. However, unclamping the ICA introduces the potential for embolization from a disrupted plaque.

If carotid stump pressure is to be measured, clamps are placed on the CCA and ECA, and a needle connected to a pressure line is placed into the distal CCA artery below the carotid bifurcation. A stump pressure > 50 mm Hg is generally indicative of adequate perfusion, but this is not foolproof. Clamping the CCA and placing the needle into the artery does introduce the potential for embolization.

Conventional Endarterectomy

The conventional technique for CEA consists of a vertical arteriotomy and today, closure with a patch angioplasty. The arteriotomy is begun in the CCA and continued through the carotid bifurcation into the ICA. One should avoid making the incision too close to the flow divider at the ECA origin because this can distort the anatomy and make the closure more difficult. If a shunt is used, it is first placed in the distal ICA and back bled before the proximal end is placed into the CCA. Two commonly used shunts are the Pruitt-Inahara and the Javid shunts. A third shunt, preferred by the author, is a simple vinyl tube. Because this shunt lies entirely within the artery, it allows the surgeon to almost completely finish closing the arteriotomy before the shunt is removed. Its small diameter allows atraumatic placement in even small ICAs, while its short length offers less resistance to blood flow such that physiologic flow in the ICA is maintained (Fig. 3).

The endarterectomy is begun in the CCA in the plane between the media and the adventitia. The proximal endpoint in the distal



FIG. 3 Exposure of the common, internal, and external carotid arteries with the author's shunt within the vessel. *(From Sidawy AN and Perler BA, eds. Rutherford's Textbook of Vascular Surgery & Endovascular Therapy. Elsevier; 2019.)*

CCA is established, and the plaque is trimmed at that location in a beveled manner. The endarterectomy is continued into the orifice of the ECA, first with a Freer elevator and then with a fine clamp that is passed up into the external carotid artery in the plane of the endarterectomy. The vessel loop on the ECA is released transiently while the plaque is everted from within the ECA. The endpoint of the plaque is inspected: an ideal endpoint has a gradually tapering, feathered endpoint.

The endarterectomy is then continued up into the ICA. A technically perfect endpoint in the ICA is absolutely critical to avoid perioperative stroke and recurrent stenosis. It is virtually always possible to achieve a satisfactory endpoint in the ICA, although this may require special maneuvers to expose the distal ICA with extension of the arteriotomy to facilitate extraction of a long endarterectomy specimen. Tacking sutures at the distal endpoint should be avoided unless absolutely necessary; these are associated with increased perioperative stroke and are indicative of a problematic endpoint. The endarterectomy should be terminated in normal ICA with a gradual, tapered transition to normal intima (Fig. 4). This is best accomplished by pulling the plaque transversely away from the



FIG. 4 Typical carotid endarterectomy plaque. Note the tapered endpoints from the internal and external carotid arteries.

artery with lateral traction. One should avoid pulling out or down on the plaque, which is more likely to result in a step-off that can be difficult to correct.

The preponderance of evidence indicates that the arteriotomy should be closed with a patch. A variety of patch materials are available for use, including autologous vein, polytetrafluoroethylene (PTFE), woven polyester (Dacron), and bovine pericardium. The author prefers Dacron and running 6-0 polypropylene suture. The vessels are bled, and then the endarterectomy site is vigorously irrigated with heparinized saline and inspected again for debris or intimal flaps before the arteriotomy is finally closed. The clamp on the ICA is briefly released to fill the vessel with blood. It is then replaced while the clamps on the CCA and ECA are released so any remaining air or debris will be flushed up the territory of the ECA rather than the ICA. At this point, the ICA clamp is removed.

Eversion Endarterectomy

Eversion endarterectomy represents an excellent alternative technique. The ICA is amputated obliquely at the carotid bifurcation, and the adventitia is rolled back until normal intima is encountered at the distal endpoint. Residual plaque in the common and/or external carotid arteries is endarterectomized, and the ICA is reanastomosed to the CCA with 6-0 polypropylene suture. The advantages of this technique are that the anastomosis can be performed rapidly and is not prone to restenosis; therefore, patching is not required. The disadvantages are that a more extensive dissection is sometimes necessary to mobilize the vessels during the eversion, the procedure does not lend itself readily to shunting (although shunting is not precluded by this technique), and it can be difficult to visualize the endpoint in the ICA after the plaque has been removed; the artery tends to retract as soon as the plaque pulls away from the adventitia, and it can be difficult to expose and reinspect this area of the artery (Fig. 5).

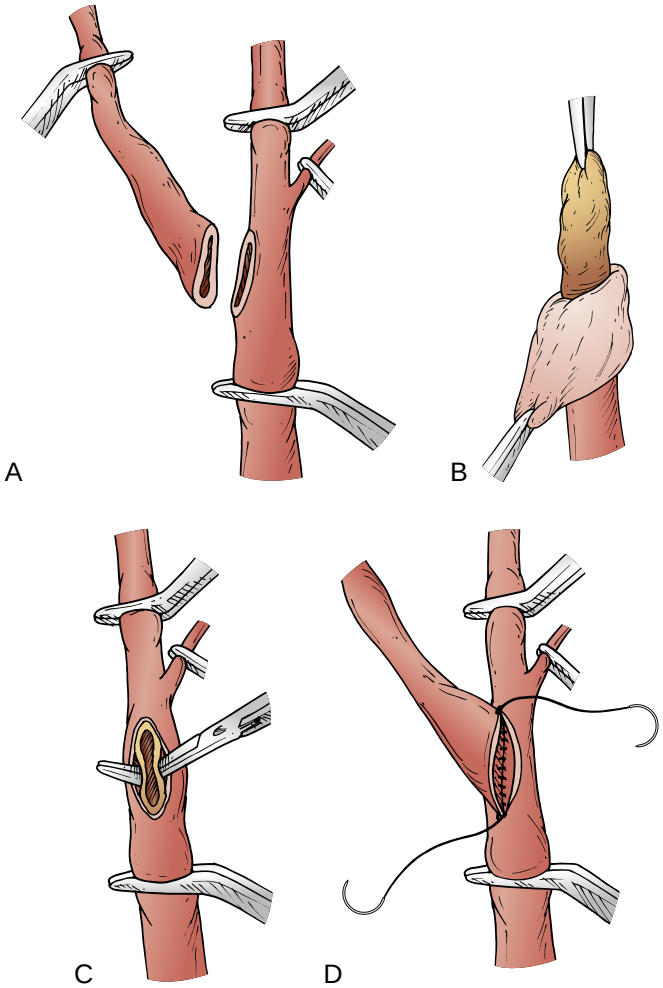


FIG. 5 Eversion endarterectomy. **(A)** Internal carotid artery transected at the bifurcation. **(B)** Adventitia teased back off the internal carotid plaque. **(C)** Plaque endarterectomized from the common carotid artery and origin of the external carotid artery. **(D)** Reanastomoses of the internal carotid artery to the bifurcation. *(Modified from Saratzis N, Saratzis A, Milaras S, et al. Eversion carotid endarterectomy illustrated: tips and tricks of the procedure.* Surg Rounds. *2006;29(8):382–389.)*

Cerebral Protection and Monitoring

One of the longstanding debated issues related to the performance of CEA concerns the use of intravascular shunts: the routine nonuse of shunts, selective use of shunts, and routine use of shunts. The simplest way to perform CEA is to just clamp the carotid bifurcation and perform CEA without a shunt, and there are published series that document excellent results of CEA without shunts. However, all of these studies demonstrate at least a small incidence of stroke, and the etiology of the stroke is intraoperative cerebral ischemia during carotid artery clamping in at least some cases.

Alternatively, some routinely shunt in all cases of CEA, and excellent results have been reported in several large series. However, all of these studies document an incidence of stroke, and the cause of the stroke was attributed to technical problems related to the use of the shunt in some of these cases.

A third option is to shunt selectively. Several techniques have been utilized to identify the patient who truly needs a shunt. In the patient who is under general anesthesia, these include intraoperative measurement of carotid "stump pressure" after the common and external carotid arteries have been clamped, intraoperative neurologic monitoring of the patient's EEG or somatosensory evoked potentials (SSEP), measurement of middle cerebral artery (MCA) flow by transcranial Doppler (TCD) ultrasound, and monitoring of cerebral oximetry. The most accurate method is to perform CEA under regional anesthesia whereby the selection of patients for shunting is based on alterations in the neurologic examination that develop after the carotid artery is clamped.

Completion Studies

Although there are several potential etiologies of perioperative stroke among patients who undergo CEA, a preventable cause is thromboembolism or carotid artery thrombosis resulting from technical imperfection in the carotid artery repair. To minimize this risk, intraoperative completion studies have been utilized including continuous wave Doppler ultrasound, duplex ultrasound, and intraoperative angiography.

Continuous wave Doppler analysis is a purely qualitative method by which an experienced operator can identify areas of stenosis by the high pitch associated with a stenosis. However, it is insensitive to small intimal flaps or more subtle stenoses, and it is quite operator dependent. Duplex ultrasound is a much more sensitive tool that provides detailed anatomic imaging and real-time physiologic information regarding blood flow through the carotid vessels, and it is the author's preference. However, although the ICA endpoint should be directly visualized before closing the arteriotomy, the CCA clamp site is a relatively blind spot. Duplex examination allows one to rule out unsuspected plaque injury, which can then be repaired before completing the arteriotomy closure (Fig. 6). The data yielded from duplex examination are somewhat operator dependent, and there can be technical limitations with placing the Doppler probe in the wound to achieve an adequate examination. Intraoperative angiography has been considered the "gold standard" of completion studies.

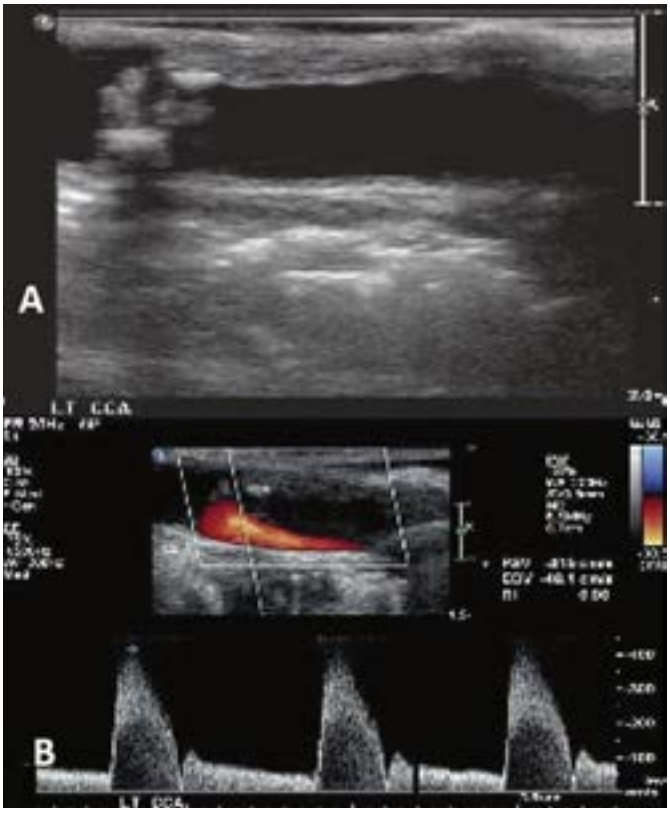


FIG. 6 **(A)** Completion duplex ultrasound image of a common carotid artery demonstrating a clamp injury after restoration of flow following carotid endarterectomy performed by the author. **(B)** Elevated flow velocities at the site of the clamp injury.

BOX 1 Options to Facilitate High Carotid Exposure

Nasotracheal intubation
Division of posterior belly of digastric muscle
Resection of styloid process
Anterior subluxation of mandible
Vertical osteotomy ramus of mandible

EXPOSURE FOR HIGH LESIONS

There are several methods to gain additional cephalad exposure of the high carotid bifurcation (Box 1). The easiest of these, and the initial approach, is to start the operation with nasotracheal intubation. With the patient's mouth closed, the vertical ramus of the mandible is displaced anteriorly 1 to 2 cm compared with when the mouth is open with an oral endotracheal tube. The additional few millimeters of distal ICA exposure afforded by this maneuver will often be the difference in achieving a suitable endarterectomy endpoint in the distal ICA. The next step to enhance distal exposure is to divide the posterior belly of the digastric muscle. This muscle takes the same diagonal course through the wound as the hypoglossal nerve, but it is located superficial to the nerve. Therefore, this nerve should be carefully identified and protected before the muscle is divided. Two other nerves that can be injured high in the neck are the spinal accessory nerve, which enters the tendinous portion of the sternocleidomastoid muscle, usually in the upper third of the muscle, and the glossopharyngeal nerve, which lies deep to the digastric muscle.

The next maneuver that can be extremely effective at gaining cephalad exposure is resection of the styloid process. The insertions of the muscles on the styloid process are excised, and it is carefully resected with a rongeur. This maneuver will permit exposure of the ICA all the way to the skull base.

There are two other options for improving distal exposure of the high bifurcation, both of which require preoperative planning and coordination with the oral or plastic surgeon. Anterior subluxation of the mandible requires placing the mandible in temporary intermaxillary fixation. An even more aggressive approach utilizes a complete vertical osteotomy through the vertical ramus of the mandible, with separation of the mandible to expose the ICA.

PERIOPERATIVE MEDICAL MANAGEMENT

In addition to risk factor control, the patient should be on an antiplatelet mediation (aspirin or clopidogrel) at the time of the CEA. Furthermore, there is compelling evidence that all patients undergoing CEA should be on a statin medication. In the author's series of nearly 1600 CEAs, the 30-day rate of stroke and death was significantly lower among patients taking a statin medication at the time of operation compared with nonusers. Specifically, in multivariate analysis, there was a threefold reduction in stroke and a fivefold reduction in mortality at 30 days among patients undergoing CEA while on statin medications. The perioperative benefits of statins have now been confirmed in multiple other published studies. There was also a trend toward a lower rate of perioperative myocardial infarction among statin users. The author prefers a continuous infusion of low-molecular-weight dextran for the first 24 hours postoperatively or until hospital discharge. Antiplatelet and statin therapy should be continued long-term in the CEA patient.

RESULTS

Perioperative mortality has become exceedingly uncommon following CEA, averaging < 1%, and generally around 0.5% today. Cardiac disease is the most common cause. The incidence of perioperative stroke ranges from 1% to 5% in contemporary practice and correlates directly with the clinical indication for operation. The perioperative stroke incidence should be no more than 1% to 2% among asymptomatic patients and ranges from 2% to 6% among symptomatic patients.

Carotid artery disease is an excellent marker for underlying coronary artery disease, and perioperative myocardial infarction occurs in 2% to 4% of patients in practice today. Systemic blood pressure instability is seen in at least 60% of patients following CEA and generally resolves within 4 to 8 hours in most patients, although it often requires close hemodynamic monitoring and aggressive pharmacologic treatment. The incidence of postoperative bleeding requiring reexploration is 1% to 4%. Wound infections are extremely uncommon following CEA and have been reported in < 1% of cases.

One of the most frequent complications of CEA is cranial nerve injury. This relates to the anatomic location of these nerves with respect to the carotid arteries. The incidence ranges from 5% to 17% in reported series (Table 2). The majority of these injuries result from traction or minor trauma, and they are quite transitory, often resolving in a few days or weeks.

Recurrent Carotid Stenosis

The incidence of a recurrent stenosis has been estimated to range from 5% to 22% of patients in several published institutional series, although only approximately 3% of these lesions were symptomatic. Within the first 36 months after CEA, recurrent stenosis usually results from intimal hyperplasia. Evidence from serial duplex evaluations suggests that at least some of these lesions regress with time, and in part, this may be responsible for some variability in

TABLE 2 Incidence of Cranial Nerve Injury

Nerve	Incidence (%)
Hypoglossal	4.4–17.5
Recurrent laryngeal	1.5–15
Superior laryngeal	1.8–4.5
Marginal mandibular	1.1–3.1
Glossopharyngeal	0.2–1.5
Spinal accessory	<1.0

the reported rates of recurrent stenosis. An occasional "recurrent" stenosis in fact represents residual arteriosclerotic disease after the endarterectomy. Lesions that develop more than a few years after CEA usually result from progressive or new arteriosclerotic disease. Recurrent stenoses develop more frequently in women, in patients who continue to smoke, and in hypercholesterolemic, diabetic, and hypertensive individuals. It has also been suggested that intraoperative injury secondary to arterial clamping, the placement of an intraluminal shunt, or the placement of tacking sutures within the vessel may also predispose to early myointimal hyperplasia lesions. As noted earlier, there is compelling evidence that closure of the arteriotomy with a patch will reduce the incidence of recurrent stenosis, although the optimal patch material remains to be identified.

Reoperative CEA

Reoperative CEA presents additional challenges with the dissection and reconstruction that can increase the risk compared with a primary procedure, but excellent results can be achieved in this situation with careful planning and technique. There are no prospective randomized trials to support repeat CEA, but most available evidence supports treating symptomatic and very-high-grade asymptomatic recurrent stenoses.

Suggested Readings

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Management of Recurrent Carotid Artery Stenosis

Sarah E. Deery, MD, MPH, and Ying Wei Lum, MD

INTRODUCTION

Carotid endarterectomy (CEA) is the gold standard treatment for high-grade symptomatic and asymptomatic carotid artery stenosis and reduces the risk of stroke and death compared with best medical therapy. It is a safe and durable procedure with minimal morbidity and mortality when performed by qualified practitioners on appropriate surgical candidates. Carotid artery stenting (CAS), including transfemoral carotid artery stenting (TF-CAS) and transcarotid artery revascularization (TCAR), has been introduced as an alternative to CEA, particularly in high-risk patients. Following both CEA and CAS, carotid artery surveillance imaging shows that a minority of patients will develop a recurrent narrowing of the carotid artery at or adjacent to the site of revascularization. A luminal diameter narrowing of 50% or greater on duplex ultrasonography, corresponding to a 75% or greater stenosis in the cross-sectional area, is the most commonly used criteria to define carotid restenosis. Restenosis after carotid revascularization has been reported to range from 5% to 20%, depending on the definition used to characterize restenosis and the duration of follow-up. This chapter aims to discuss the risk factors, pathogenesis, morbidity, and management of carotid artery restenosis.

INCIDENCE AND PRESENTATION OF RECURRENT CAROTID STENOSIS

The incidence of recurrent carotid stenosis following CEA varies widely in the literature based on the method and time interval of surveillance. Follow-up prospective data collection from the Asymptomatic Carotid Atherosclerosis Study (ACAS) using Doppler ultrasound surveillance has shown an incidence of recurrent carotid stenosis post-CEA of 4.1% in the early postoperative period (<3 months), 7.6% from 3 to 18 months, and 1.9% from 18 to 60 months. Data from other studies have also shown that the average rates of recurrent carotid stenosis after CEA can be estimated to be 10% at 1 year, 3% in 2 years, 2% after 3 years, and 1% after 5 years.

Recurrent stenosis after CAS, or in-stent restenosis (ISR) also has an incidence ranging from 5% to 20%. Although ISR puts patients at increased risk of cerebrovascular events, the neointimal hyperplastic reaction seems to be associated with a reduced risk of distal embolization as compared with the initial native lesion. Several clinical trials have looked into the risk of stroke secondary to ISR. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)

showed an increased risk of stroke at 5 years in patients who develop severe (>70%) carotid artery ISR. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) also showed similar results, with more than 70% ISR after CAS placing patients at increased risk of stroke. However, multiple other studies including the Stent Protected Angioplasty versus Carotid Endarterectomy Trial (SPACE) showed that there was no associated increased risk of cerebrovascular ischemia in patients who develop ISR at 2 years.

Most patients with restenosis are asymptomatic, and recurrent stenosis is discovered on routine postoperative surveillance following carotid revascularization. However, between 8% and 25% of patients present with symptomatic neurologic events (i.e., transient ischemic attack or stroke). The rate of asymptomatic restenosis in patients that are lost to follow-up is of course unknown. While the vast majority of restenosis is identified in asymptomatic patients, recurrent carotid post-CEA does increase the risk of cerebrovascular ischemia secondary to flow obstruction and thromboembolism. The risk of ipsilateral stroke after CEA is at its highest within the first 2 years after the operation, and the risk decreases over time after 2 years. This can be explained by the relatively higher incidence of recurrent carotid restenosis during that time frame, which increases the risk of ipsilateral stroke. In fact, up to 50% of ipsilateral symptomatic strokes can be attributed to recurrent carotid stenosis after CEA. Not surprisingly, as the incidence of recurrent carotid stenosis decreases over time, so does the risk of developing symptomatic ipsilateral stroke beyond 2 years postoperatively.

RISK FACTORS FOR RECURRENT CAROTID STENOSIS

Several risk factors have been associated with recurrent carotid stenosis after CEA, namely those associated with native carotid artery disease and other atherosclerotic conditions, including continued smoking, diabetes, hypertension, hyperlipidemia, and end-stage renal disease (Box 1). Technical considerations also impact risk for recurrent carotid stenosis. The carotid artery can be reconstructed by primary closure or with patch angioplasty. There is clear and overwhelming evidence showing the superiority of patch angioplasty over primary closure in reducing the rate of recurrent stenosis. ACAS showed a restenosis rate of 4.6% with patch angioplasty versus 16.9% with primary closure. CREST showed a similar reduction in restenosis but no difference in stroke rate. A Cochrane systematic review of 2335 carotid endarterectomies in 2187 patients showed a 59% reduction in carotid restenosis and 27% reduction in serious adverse events. Some surgeons preferentially use the eversion endarterectomy technique when performing CEA, during which the internal carotid artery is transected at the level of the carotid bulb and the distal segment of the internal carotid artery is everted and the plaque peeled away, leaving the endarterectomy bed behind. The Eversion Carotid Endarterectomy versus the Standard Trial compared restenosis rates between standard CEA with patch angioplasty and the eversion technique and showed similar rates in both techniques. In light of overwhelming evidence from multiple studies in factor of conventional CEA with patch angioplasty or eversion endarterectomy over primary closure alone, the Society for Vascular Surgery (SVS) recommends these techniques over standard endarterectomy with primary closure in their Clinical Practice Guidelines.

BOX 1 Risk Factors Associated with Recurrent Carotid Stenosis After Carotid Endarterectomy

- Female sex
- Smoking
- Diabetes
- Hypertension
- Hyperlipidemia
- End-stage renal disease
- Primary closure of carotid artery without patch angioplasty
- Small internal carotid artery diameter
- Previous ipsilateral carotid surgery

BOX 2 Risk Factors Associated with In-Stent Restenosis After Carotid Stenting

- Female sex
- Smoking
- Diabetes
- Hypertension
- Hyperlipidemia
- End-stage renal disease
- Residual stenosis after index procedure
- Use of balloon expandable stents
- Stent subexpansion
- Deployment of multiple stents

ISR after CAS has been attributed to the same risk factors for atherosclerosis as for recurrent stenosis after CEA (Box 2). Technical factors related to ISR include residual stenosis on completion angiography, use of a balloon expandable stent, stent subexpansion, and the deployment of multiple stents. Carotid stents come in two main categories: open-cell stent and closed-cell stent. Open-cell stents are designed to keep adjacent segments of the stent detached from one another. This design allows for better conformational change and adaptability to the vessel anatomy, but with less plaque coverage and more tissue prolapse. Closed-cell stents, on the other hand, are designed with a higher density of interconnections due to more bridging of the adjacent segments. Closed-cell stents offer more plaque coverage but have reduced conformability and apposition to the vessel wall. No long-term study, up to now, has shown a difference in restenosis rate between the two styles of stents.

PATHOGENESIS OF RECURRENT CAROTID STENOSIS

Very early restenosis following CEA is often secondary to an incomplete endarterectomy or technical defect from surgery. Iatrogenic injuries to the blood vessels (i.e., trauma from forceps, vascular clamps, and intravascular shunts) can lead to immediate restenosis or thrombosis, but can also speed up the focal reactive process and increase later development of restenosis. Improper surgical techniques can also contribute to recurrent stenosis (i.e., residual atheroma postendarterectomy, myointimal flap, patch irregularities, and irregular bends and kinks to the blood vessel after reconstruction), particularly in the early postoperative period.

Intimal hyperplasia from a hyperplastic reaction in the endarterectomy bed is the primary cause of recurrent carotid stenosis occurring between 30 days and 2 years after CEA. After 2 years, luminal narrowing is secondary to progressive atherosclerosis, which occurs throughout the artery and is not necessarily confined to the endarterectomy bed. Interestingly, patients who undergo CEA for asymptomatic carotid stenosis have been observed to have a higher risk of developing carotid restenosis at 1 year compared with patients who undergo CEA for symptomatic disease (i.e., TIA). This observation can be explained by the difference in atherosclerotic plaque content in asymptomatic compared with symptomatic patients. Asymptomatic patients tend to have stable plaques that have low macrophage levels, small or absent lipid core, and low levels of matrix metalloproteinase. On the other hand, inflamed plaques with high levels of macrophages, leukocytes, and lipid-rich cores have high levels of matrix metalloproteinase activity, which leads to expansive remodeling of the media and adventitia and less restenosis.

TABLE I Different Patterns of Carotid In-Stent Restenosis

Type	Description and Characteristics of ISR Lesion
I (Focal end-stent group)	Lesions are ≤10 mm long and are positioned at the proximal or distal margin (but not both) of the stent. Lesions ≤10 mm long at both ends of the stent are defined as type I, multifocal end-stent.
II (Focal intra-stent group)	Lesions are ≤10 mm long and are confined to within the stent(s) without extending outside the margins. Two or more discrete lesions ≤10 mm long located within the stent are defined as type II, multifocal intra-stent.
III (Diffuse intra-stent group)	Lesions are >10 mm long and are confined to within the stent(s) without extending outside the margins.
IV (Diffuse proliferative group)	Lesions are >10 mm long and extend beyond the margin(s) of the stent(s).
V (Occlusion group)	Lesions have no prograde flow and no lumen is identified.

ISR, In-stent restenosis.

ISR after CAS likely results from neointimal hyperplasia caused by chronic inflammation secondary to endothelial dysfunction and traumatic irritation of the intima. It occurs within 2 years of the index procedure. Following 2 years, recurrent stenosis after CAS is also likely a de novo atherosclerotic lesion. Interestingly, patients who develop recurrent carotid stenosis after CEA have a higher risk of developing ISR if their restenosis is treated with carotid artery balloon angioplasty or stenting, suggesting that some patients have an above-average aggressive hyperplastic response and unfavorable biology that places them at higher risk to develop early restenosis. Carotid ISR is often detected on surveillance duplex ultrasonography and is categorized in a classification pattern that is similar to the one used for the coronary circulation. There are five types of ISR summarized in Table 1 and Figure 1. Notably, type I lesions (focal end-stent) are the most common after CAS and can occur at both the proximal and distal aspect of the stent. Type IV (diffuse proliferative) lesions are often found in patients with diabetes and are associated with subsequent stent failure requiring reintervention.

SURVEILLANCE FOR RECURRENT CAROTID STENOSIS

After Carotid Endarterectomy

It is crucial to have a methodical and timely surveillance imaging schedule after carotid revascularization to assess for ipsilateral restenosis and contralateral progression of preexisting stenosis. In fact, the progression of contralateral stenosis is more common than ipsilateral recurrent stenosis. Duplex ultrasonography is the imaging modality of choice for surveillance after CEA because it is noninvasive, cost effective, and has a sensitivity of 91% and specificity of 87% for detecting a 50% restenosis of the carotid artery. In its best practice guidelines, the SVS recommends surveillance imaging within 30 days postoperatively following CEA. The SVS guidelines also recommend continued surveillance in patients with 50% or greater ipsilateral restenosis or contralateral stenosis, in those who underwent primary closure of the artery after endarterectomy, and in patients with high-risk factors for atherosclerotic disease progression. However, there is no consensus on the timeline and the frequency of surveillance beyond the postoperative period, and this has been the subject of many debates. Because patients are more likely to develop an ipsilateral restenosis within the 2 years after CEA, it is essential to have more frequent duplex surveillance throughout that period. Most patients who develop atherosclerotic disease of the carotid artery have underlying risk factors such as smoking, diabetes, hyperlipidemia, and hypertension that inherently places them in the high-risk patient category. In our practice, we surveil our patients at the 1-month, 6-month, and 1-year marks postoperatively after CEA. The subsequent surveillance schedule is then tailored to the patient's specific needs depending on their risk factors and the data from previous studies about the progression of their disease.

After Carotid Artery Stenting

Surveillance for ISR in patients who underwent CAS is particularly important because the rate of developing restenosis after CAS is higher than after CEA, albeit most ISR are mild to moderate and require no intervention, and only a minority of patients will develop high-grade ISR that will require reintervention. Unlike restenosis after CEA, ISR after CAS can develop many years after the index procedure. A timely surveillance schedule is important to identify hemodynamically significant lesions that need reintervention; however, there is no consensus on the time intervals and duration of surveillance after the procedure. As with CEA, the imaging modality of choice for surveillance after CAS is duplex ultrasonography. Other modalities such as computed tomographic angiography and magnetic resonance angiography can also be used to detect ISR but may overestimate the degree of ISR and may be skewed by stent artifact. Whenever a hemodynamically significant ISR is suspected on noninvasive imaging, it is best to assess the suspected lesion with digital subtraction angiography to get a more accurate estimate of the degree of restenosis.

In our practice, patients who undergo both TF-CAS and TCAR are surveilled in a similar fashion as our patients who undergo CEA. We obtain a duplex ultrasound at the 1-month, 6-month, and 1-year marks. Subsequent surveillance is then tailored according to duplex findings and whether or not there is any progression of disease. It is important to note that the velocity criteria for duplex surveillance post-CAS are different from the velocity criteria used for surveillance post-CEA as the stent itself impacts velocities. A summary of the velocities and corresponding degrees of restenosis post-CEA versus CAS adopted by our vascular laboratory is shown in Table 2. The goal of duplex surveillance imaging is to identify patients who are at risk for hemodynamically significant (>70%–80%) restenosis that may result in a cerebrovascular event if not detected and intervened with in a timely fashion. Patients found to have less than 20% stenosis do not need a rigorous surveillance schedule. Those who have 20% to 50% stenosis need closer surveillance because there are limited data available on the natural progression of such lesions. Patients with 50% to 70% restenosis need duplex surveillance every 6 months to monitor the disease progression into the severe ISR category. When 70% to 80% restenosis is identified, patients should undergo additional axial imaging or the gold standard digital subtraction angiography for intervention planning.

MANAGEMENT OF RECURRENT STENOSIS AFTER CAROTID ENDARTERECTOMY

In the ACAS and NASCET trials, patients who underwent CEA were concurrently treated with best medical therapy. The results

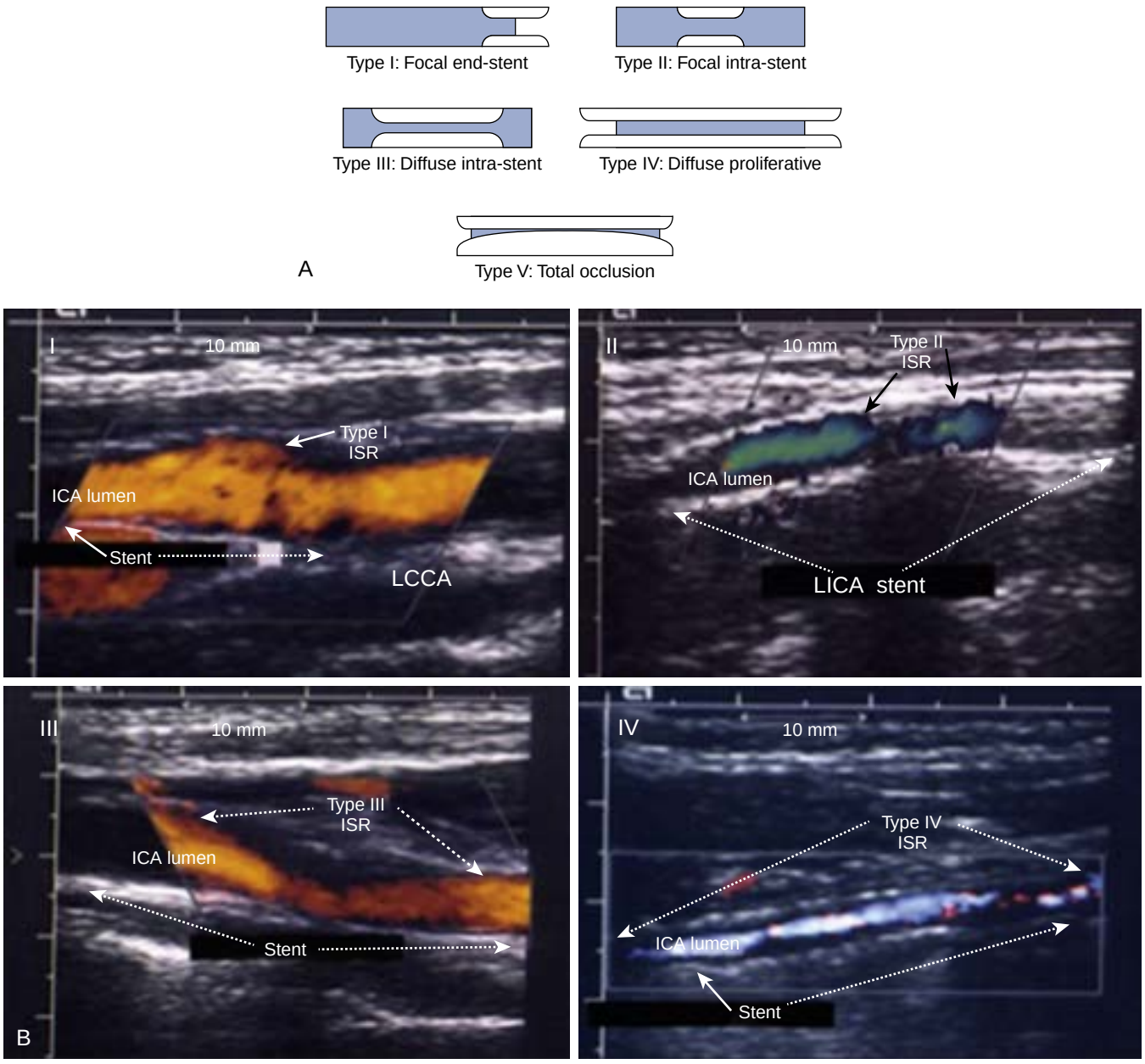


FIG. 1 **(A)** Types I to V carotid in-stent restenosis *(ISR)*. **(B)** Representative B-mode ultrasound images of ISR correspond to types I to IV of post–carotid angioplasty and stenting ISR. *ICA*, Internal carotid artery; *LCCA*, left common carotid artery; *LICA*, left internal carotid artery. *(Modified from Lal BK, et al. Patterns of in-stent restenosis after carotid artery stenting: classification and implications for long-term outcome. J Vasc Surg. 2007;46:833–840.)*

established by these trials reflect the combination of CEA and best medical management. Therefore, it is imperative that all patients be placed on an antiplatelet agent and statin and that their modifiable risk factors are reduced or controlled post-CEA to reduce their risk of recurrent carotid stenosis. Despite best medical management post-CEA, a subset of patients will still develop high-grade restenosis requiring surgical intervention. Reoperative CEA has a higher morbidity rate compared with primary CEA with a periprocedural stroke rate of 7% and a high rate of cranial nerve injury at 19% (compared with ~1% following CEA in a non-reoperative neck).

Symptomatic patients after CEA need a reoperation if their degree of restenosis is 50% or greater. The decision to operate on asymptomatic patients is more complex and requires weighing the risk of operative morbidity against the morbidity of stroke with medical management alone. To justify a reoperation in the asymptomatic population, the benefits of the operation must outweigh the risks of the operation (i.e., stroke, myocardial infarction, cranial nerve injury) and the risks of stroke with medical management alone. The SVS and European Society for Vascular Surgery (ESVS) recommend against a reoperation when the combined stroke and death rate exceeds 6% for patients with symptomatic carotid restenosis and 3% for those with asymptomatic carotid stenosis. In our practice, we initially treat asymptomatic carotid restenosis medically with antiplatelet therapy and high-intensity statin. Surgical intervention is considered in patients who progress to high-grade restenosis despite maximal medical management.

Reoperative CEA is a high-risk operation, and no specific technique has been described to offer superior results over another. Some of the techniques described include endarterectomy alone, patch angioplasty alone without endarterectomy (the patch can be saphenous vein, bovine pericardium, Dacron, or polytetrafluoroethylene [PTFE]), endarterectomy with patch angioplasty, and resection of

TABLE 2 Duplex Ultrasonography Velocity Criteria to Establish the Presence of Recurrent Carotid Stenosis in the Native Carotid Artery Postcarotid Endarterectomy Compared with Established Velocity Criteria to Establish the Presence of In-stent Restenosis After Carotid Artery Stenting

Degree of Stenosis (%)	Native Carotid Artery	Stented Carotid Artery
0–19	PSV <130 cm/s	PSV <150 cm/s and ICA/CCA ratio <2.15
20–49	PSV 130–189 cm/s	PSV 150–219 cm/s
50–79	PSV 190–249 cm/s and EDV <120 cm/s	PSV 220–339 cm/s and ICA/CCA ratio ≥2.7
80–99	PSV ≥250 cm/s and EDV ≥120 cm/s, or ICA/CCA ratio ≥3.2	PSV ≥340 cm/s and ICA/CCA ratio ≥4.5

EDV, End-diastolic velocity; *ICA/CCA*, internal carotid artery/common carotid artery; *PSV*, peak systolic velocity.

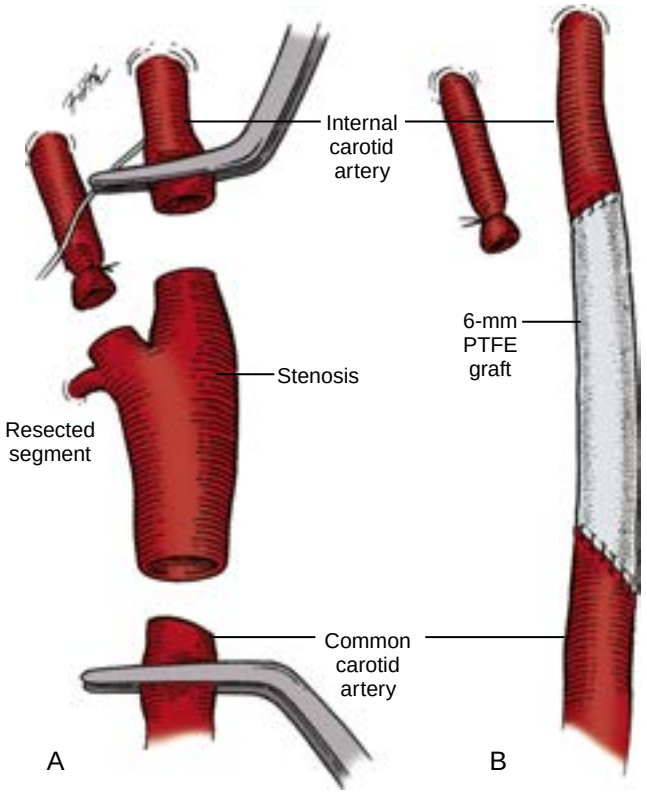


FIG. 2 (A) Resection of a diseased segment of the common and internal carotid arteries with ligation of the external carotid artery. **(B)** Placement of an interposition graft for revascularization of the internal carotid artery circulation, in this case using polytetrafluoroethylene *(PTFE)*. Reversed saphenous vein graft or Dacron additionally may be utilized. This is our preferred technique for management of tertiary recurrent carotid stenosis and for management of recurrent in-stent stenosis when endovascular options are not technically feasible.

the artery with interposition graft (saphenous vein, Dacron, or PTFE; Fig. 2). If performing reoperative CEA in our practice, we attempt excising the previous patch, repeat an endarterectomy, and replace the old patch with Dacron or bovine pericardium. If the repeat endarterectomy is technically not feasible or leaves the artery severely compromised, our approach is to resect the artery and perform an interposition repair with translocated reversed greater saphenous vein graft preferentially. In patients who do not have suitable veins, we use PTFE for an interposition conduit. In patients who develop recurrent stenosis for the second time after a reoperation, we follow a similar algorithm to a first-time restenosis. However, for tertiary carotid interventions, we prefer resection of the involved segment of the artery with interposition graft reconstruction.

An alternative to reoperative CEA is CAS as the first-line management for secondary carotid intervention to avoid dissection in a reoperative field. Older series comparing TF-CAS and CEA for restenosis suggest that neither procedure is associated with superior outcomes. However, TCAR has been developed as an alternative to traditional transfemoral CAS, avoiding the higher risk of periprocedural stroke associated with aortic arch manipulation by wires, catheters, and sheaths. The method of embolic protection utilized is dynamic flow reversal via an external shunt placed between the long introducer sheath in the common carotid artery and a shorter introducer sheath in the femoral vein, containing a filter to capture any debris. Additionally, flow reversal is established before any lesion manipulation, therefore adding an additional area of potential protection over TF-CAS with filter-type embolic protection devices. TCAR was previously indicated only for symptomatic patients with ≥50% stenosis and asymptomatic patients with ≥80% stenosis who were considered high-risk for CEA by the Centers for Medicare and Medicaid Services (CMS), but recently TCAR has been approved for use in standard-risk patients. These medical and anatomic risk factors (Box 3) notably include restenosis after prior CEA, thus automatically making all restenosis patients high-risk for CEA and thus candidates for TCAR even prior to the approval for use in standard-risk patients.

Recent data from the SVS Vascular Quality Initiative TCAR Surveillance Project show higher rates of perioperative stroke and death with TF-CAS compared with TCAR, whereas rates of stroke and death with TCAR were comparable to CEA. Most recently, a series from the Vascular Quality Initiative compared outcomes with reoperative CEA, TF-CAS, and TCAR for restenosis after CEA and found significantly lower odds of in-hospital stroke and transient ischemia attack with TCAR as compared with both redo-CEA and TF-CAS. Given this, and the added potential benefit of being able to avoid reoperative neck surgery with its associated risk, TCAR has become the preferred first-line treatment option in our practice for restenosis after CEA in patients with suitable anatomy.

MANAGEMENT OF RECURRENT STENOSIS AFTER CAROTID ARTERY STENTING

The management of ISR after CAS is a subject of many debates, especially for the asymptomatic patient population. There are no prospective trials that have established time-tested practice guidelines for the management of ISR after CAS. The consensus among most surgeons is that patients who are symptomatic and have an ISR of 50% or more require a reintervention. Patients who are asymptomatic with high-grade ISR of 70% to 80% or more on surveillance duplex should be considered on a case-by-case basis, taking into account the anatomy of their stenotic lesions and their perioperative risk of stroke and death.

Endovascular techniques described to treat ISR after CAS include balloon angioplasty alone, repeat CAS alone, or a combination of repeat carotid artery stent with balloon angioplasty. Balloon angioplasty can be achieved by using a regular angioplasty balloon, a drug-coated balloon, or a cutting balloon. Repeat stenting can be done

BOX 3 CMS Definitions of High Surgical Risk

Physiologic High Risk

- Age ≥ 75
- Congestive heart failure
- Left ventricular ejection fraction ≤ 35%
- Two or more diseased coronary arteries with ≥ 70% stenosis
- Unstable angina
- Myocardial infarction within 6 weeks
- Abnormal stress test
- Need for open heart surgery
- Need for major surgery (including vascular)
- Uncontrolled diabetes
- Severe pulmonary disease
- History of liver failure with elevated prothrombin time

Anatomic High Risk

- Prior head/neck surgery or irradiation
- Spinal immobility
- At risk for wound infection
- Restenosis post-CEA
- Tracheostomy or tracheostoma
- Surgically inaccessible lesion
- Laryngeal palsy, laryngectomy, and/or permanent contralateral cranial nerve injury
- Contralateral carotid artery occlusion
- Severe tandem lesions
- Bilateral carotid artery stenosis requiring treatment
- Dissection

with either a drug-eluting or a regular stent. There are no prospective data that have established one technique to be superior to another. However, because ISR is caused by intimal hyperplasia, some surgeons favor the use of balloon angioplasty with a cutting balloon over regular balloon angioplasty alone because of the reduced rate of recurrent stenosis of 4.2% with a cutting balloon as compared with 15% to 23% with a regular balloon. Figure 3 shows an example of a type II carotid artery ISR treated with angioplasty and stenting that showed improvement on both the completion digital subtraction angiography study and noninvasive duplex study one month postoperatively. Repeat endovascular intervention can be performed via transfemoral access or transcarotid access (TCAR) and should be conducted using embolic protection.

Open surgical techniques (i.e., CEA or carotid artery bypass/interposition grafting with translocated and reversed great saphenous vein, PTFE, or Dacron) can also be used for management of ISR after CAS, especially in cases where there is primary stent thrombosis (Fig. 4), technical failure during stent deployment, heavily calcified lesions that precluded optimal stent apposition to the vessel wall resulting in an inadequate technical result, and preocclusive lesions that cannot be traversed using endovascular methods. The risks of open CEA should also be considered, as some patients who underwent CAS did so as they were at high risk for traditional open surgery, and these risk factors are likely still present. A recent meta-analysis comparing redo CAS (without distinguishing between TF-CAS and TCAR) and CEA for ISR found no differences in perioperative stroke/death, event-free restenosis, or cranial nerve injury. In our practice, we prefer to manage ISR after CAS using angioplasty and/or repeat stenting if the lesion is anatomically amenable to endovascular intervention. We previously reserved open repair for cases where the

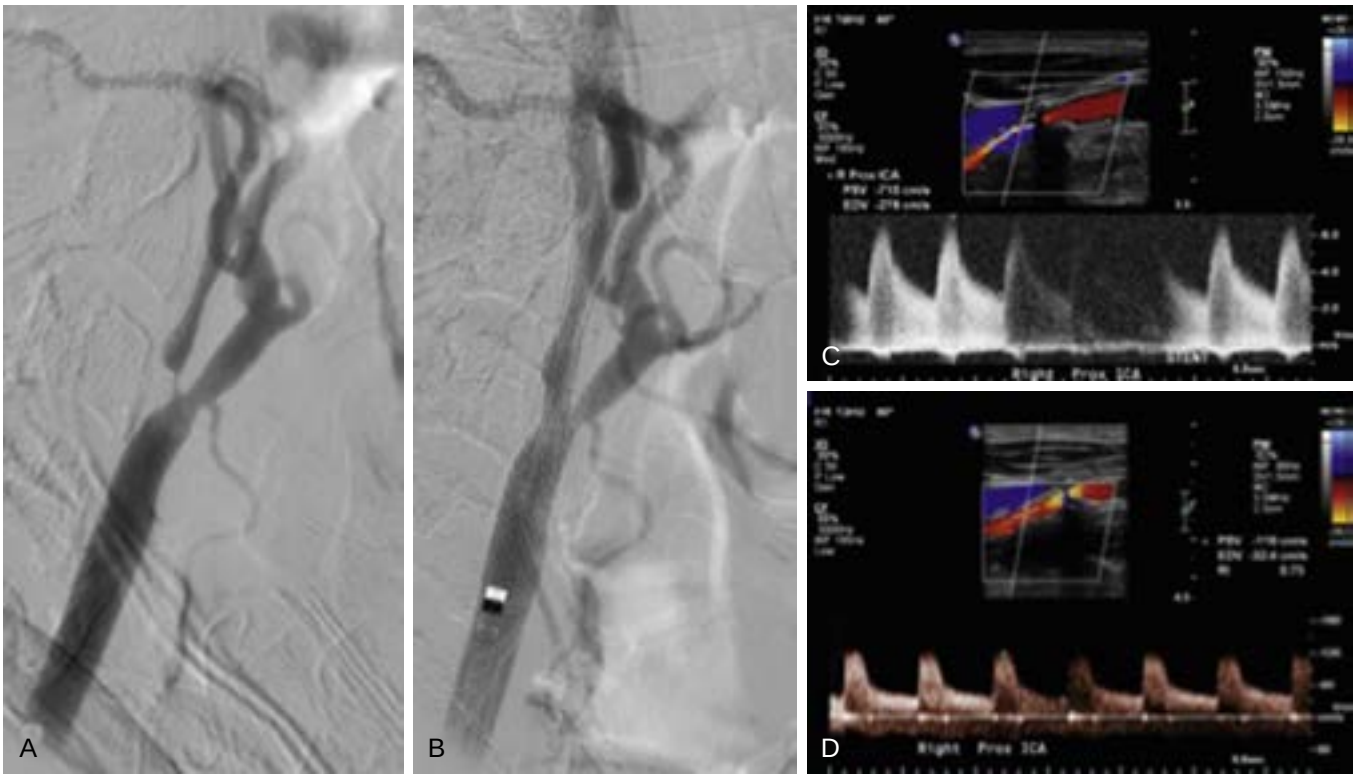


FIG. 3 Focal carotid in-stent restenosis (ISR) in a 78-year-old man with high-grade asymptomatic ISR 6 years after initial carotid angioplasty and stenting. **(A)** Carotid angiography demonstrated a string sign of the proximal internal carotid artery (ICA) with approximately 99% stenosis. **(B)** This restenosis was managed with carotid angioplasty with embolic protection followed by placement of a self-expanding 7 × 30 mm stent. Postprocedural angiogram is demonstrated. **(C)** Preoperative duplex ultrasound demonstrated severe ISR with peak systolic velocity (PSV) of 710, end-diastolic velocity (EDV) of 279, and ICA/common carotid artery (CCA) ratio of 12.2. **(D)** Duplex ultrasound obtained 1 month postoperatively demonstrated PSV of 128, EDV of 33, and ICA/CCA ratio of 2.5.



FIG. 4 Primary stent thrombosis following TCAR, managed with resection of the common and internal carotid arteries and ligation of the chronically occluded external carotid artery, with placement of an interposition graft using Dacron.

patient had a type III or severely calcified aortic arch or excessively tortuous, severely calcified, and/or long-segment stenosis of the internal and/or common carotid artery; however, these patients are often now candidates for TCAR. In patients who do undergo open conversion, we preferentially attempt stent removal with endarterectomy and patch angioplasty and reserve carotid bypass or interposition graft for cases where an endarterectomy endpoint cannot be safely achieved without compromising the integrity of the vessel wall proximal or distal to the endarterectomy bed.

SUMMARY

Symptomatic and asymptomatic carotid artery stenosis are routinely treated with either CEA or CAS. The majority of patients have excellent long-term results. However, a small subset of patients has an aggressive disease biology and tends to develop severe intimal hyperplasia leading to recurrent stenosis of the carotid artery after both CEA and CAS. Routinely scheduled surveillance duplex ultrasonography is the best imaging modality to detect these lesions, such that timely intervention can be offered to the patients to prevent cerebrovascular events. Symptomatic patients who are found to have 50% or greater stenosis on duplex or asymptomatic patients with 70% to 80% or greater stenosis after both CEA and CAS are candidates for reintervention. The procedure of choice for a secondary intervention depends on the patient's functional status, comorbidities, and anatomy of the tandem lesion. All patients should be on maximal medical treatment with an antiplatelet agent and a statin.

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Balloon Angioplasty and Stents in Carotid Artery Occlusive Disease

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BACKGROUND

Nearly 800,000 people suffer a stroke each year in the United States, making it the third leading cause of death in people 65 years of age and older and the leading overall cause of serious, long-term disability. The total cost nationally for stroke-related illnesses is approximately $34 billion per year. The majority of strokes (about 87%) are ischemic in nature. Of those, an estimated 20% to 30% are related to an atheroembolic or thrombotic event caused by carotid occlusive disease.

With the advent of endovascular interventions for other arterial occlusive lesions, carotid artery balloon angioplasty and stenting (CAS) was advocated as an alternative to carotid endarterectomy (CEA) for treatment of carotid atherosclerosis. Although both CAS and CEA can be performed using local anesthesia with similar operative and hospitalization times, CAS offers the advantage of percutaneous groin arterial access and, in the case of transcarotid artery revascularization (TCAR), low risk of postoperative pain, cranial nerve injury, wound infection, and neck hematoma.

In 2010, the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST 1) compared the outcomes of CAS with those of CEA for patients with symptomatic or asymptomatic extracranial carotid stenosis. The trial demonstrated the relative safety of CAS in both symptomatic and asymptomatic patients. However, the data

showed a periprocedural stroke rate for CAS of 4%, with the highest risk for periprocedural stroke being among patients of advanced age (more than 70 years) and with recent (within 2 weeks) neurologic ischemic symptoms. In the CEA arm, the stroke rate was 2.3%. Myocardial infarction (MI) was noted to be more frequent with CEA than with patients undergoing CAS (2.3% vs. 1.1%). However, these are numbers that should be interpreted in light of the fact that patients with a stroke complication were documented to have a worse quality of life than those who had MI.

Interpretation of the results of CREST 1 have been intensely debated and influenced by biases for or against CAS or CEA. Stenting enthusiasts argue that statistical similarity in the primary composite endpoint establishes equipoise for the procedures. In contrast, others question the inclusion of MI as a component of the primary endpoint for procedures that have stroke prevention as their principal objective. They argue for the use of only stroke and death as more appropriate composite endpoints, which significantly favors endarterectomy in CREST 1.

Suffice it to say, CREST 1 has produced valuable level I data comparing CAS with CEA, but the trial did not fulfill the expectation by some of proving undeniably that CAS is better than or even equal to CEA. The CREST 2 trial consists of two independent multicenter, randomized controlled trials of carotid revascularization and intensive medical management versus intensive medical management alone in patients with asymptomatic high-grade carotid stenosis. One trial randomizes patients in a 1:1 ratio to endarterectomy versus no endarterectomy, and another randomizes patients in a 1:1 ratio to carotid stenting with embolic protection versus no stenting. Modern medical management is uniform for all randomized treatment groups and is centrally directed. We are anticipating the results of this trial.

TCAR provides a less-invasive option than CEA and can match the stroke hazard of CEA in standard-risk populations based on the pivotal Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (ROADSTER). The ROADSTER study of high-risk patients undergoing TCAR achieved a 30-day stroke rate of 1.4%, the lowest to date for any prospective trial of endovascular carotid intervention.

BOX 1 Indications for Carotid Stenting According to CMS

- Patients who are at high risk for CEA and who also have symptomatic carotid artery stenosis ≥70%
- Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%
- Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥80%

TCAR is covered by CMS for "High Risk" patients who meet one of the following criteria: greater than 8% stenosis or symptomatic stenosis greater than 50%.

To receive reimbursement for TCAR, the surgeon or hospital must be part of either the ROADSTER (II) trial or VQI registry.

NOTE: Medicare coverage is limited to patients having these indications and to procedures performed using FDA-approved carotid artery stenting systems and embolic protection devices.

BOX 2 Patients at High Risk for CEA According to CMS

1. Congestive heart failure (CHF) class III/IV
2. Left ventricular ejection fraction (LVEF) <30%
3. Unstable angina
4. Contralateral carotid occlusion
5. Recent myocardial infarction (MI)
6. Previous CEA with recurrent stenosis
7. Prior radiation treatment to the neck
8. Other conditions used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II

PREPROCEDURAL CONSIDERATIONS

Preprocedural assessment includes a complete history focused on cardiovascular elements, on symptoms of neurologic or ocular ischemic events related to the carotid circulation, and a history of neck interventions as well as history of neck radiation for the treatment of malignancies. A thorough physical examination with an emphasis on palpation of pulses, auscultation for bruits, and complete neurologic assessment is of utmost importance. The decision about advising for or against CAS is influenced by current Centers for Medicare and Medicaid Services (CMS) guidelines regarding indications for the procedure. These guidelines are listed in Boxes 1 and 2.

Preprocedural imaging should include carotid duplex scan, computed tomographic angiography, and magnetic resonance imaging and angiography (MRI/MRA). These imaging modalities give important information about the presence and hemodynamic significance of carotid occlusive disease, the condition of the brain parenchyma, the presence of additional intracranial or extracranial vascular anomalies (e.g., saccular aneurysms, vascular malformations), and the anatomy of the aortic arch.

Before CAS, patients should begin dual antiplatelet therapy. The authors' regimen consists of clopidogrel 75 mg daily and aspirin 81 mg daily beginning 3 to 5 days before the procedure. In emergency circumstances, when antiplatelet therapy has not been started before the procedure, we use a loading regimen of clopidogrel 600 mg and aspirin 325 mg given at the time of the intervention. In addition, for patients who have been taking antiplatelet therapy on a chronic basis, we typically give a smaller loading dose of clopidogrel 150 to 300 mg immediately after the intervention. If oral administration is not possible, clopidogrel can be given via nasogastric tube; aspirin can be given similarly or per rectum (300 or 600 mg per rectum).

Traditionally, CAS has been performed via a percutaneous transfemoral arterial approach. Assessment of the iliofemoral arterial system along with evaluation of the arch anatomy via computed tomography angiography (CTA) will determine the suitability of this access as a successful platform to deliver the treatment. The presence of an easily palpable femoral pulse strongly suggests that femoral access is suitable. On the contrary, the absence of a femoral pulse should trigger exploring other access options. The presence of a type III or bovine aortic arch, of severe arch atheroma, significant common carotid tortuosity, the presence of significant occlusive disease, as well as prior aortic or cervical arterial procedures complicate the use of the femoral arteries as the access vessel and can potentially increase the risk of cerebral embolization.

The use of TCAR with flow reversal has gained popularity and is now a standard option in most practices. This approach not only facilitates the delivery of the stent under challenging arch and common carotid artery (CCA) anatomy, it adds the benefit of cerebral protection before attempt at crossing the carotid lesion.

TRANSFEMORAL APPROACH FOR CAROTID ANGIOPLASTY

Provided that the patient has suitable aortoiliac and aortic arch anatomy, the transfemoral approach is usually chosen. The patient is placed supine on the angio-table. Topographic fluoroscopic

evaluation of the chest and the neck is performed before prepping to identify objects such as lines, leads, or other previously inserted devices that would interfere with imaging. The range of motion of the C-arm is also evaluated to make sure that it will rotate freely and away from other equipment in the procedural room.

Invasive blood pressure monitoring is obtained. We perform this procedure under strict local anesthesia at the groin access site to afford patient comfort while also being able to assess neurologic function during the procedure. At certain times during CAS, the patient is asked to intermittently squeeze a sound-making device held in the contralateral hand for motor function and to count verbally to assess cognitive function.

To facilitate accurate entry, the chosen femoral artery is accessed under ultrasound guidance with a micropuncture needle that is subsequently exchanged over a microwire for a micropuncture sheath using the Seldinger technique. An arteriogram should be performed through the micropuncture sheath. Inadequacies of the access, if any, should be managed before continuing with the planned intervention.

Once the access is deemed satisfactory, systemic anticoagulation therapy is initiated either with intravenous heparin bolus administration at 100 units per kg or, for those patients where heparin is contraindicated, bivalirudin (Angiomax) at 0.75 mg/kg intravenous bolus, followed by 1.75 mg/kg/hr intravenous infusion. During the procedure, activated clotting times are maintained between 250 and 300 seconds.

A starter J or straight tip wire is advanced just distal to the aortic arch under fluoroscopy. The micropuncture sheath is exchanged for a 90-cm 6Fr sheath, and its tip is advanced to the proximal thoracic aorta. Over the same wire, a 5 or 6Fr pigtail catheter is advanced retrograde through the arch into the proximal ascending aorta. The C-arm is positioned at 35 to 40 degrees in the left anterior oblique orientation and arch aortography is performed via the pigtail catheter using 15 to 20 mL of contrast by either power or hand injection. This imaging should provide sufficient anatomical detail for choosing an appropriate catheter to selectively cannulate the common carotid artery on the side of the pathology.

Typical aortic arch anatomy allows for use of a selective catheter with a simple curve (Berenstein, vertebral; Merit Medical, South Jordan, Utah), while increasingly complex and tortuous aortic arch anatomy requires the use of selective catheters that have either an intermediate curve (H1, Cook Medical; JR4, Cordis) or a complex curve (Simmons, Cook Medical; Vitek, Cook Medical). The pigtail catheter is then exchanged over a guidewire and the chosen catheter is advanced to the previously mapped area of interest. We use a floppy glide wire to select the common carotid with the aid of the catheter. The catheter is advanced to a reasonable purchase but kept proximal to the level of the carotid bulb. The guidewire is then exchanged for a stiffer wire and the 6Fr sheath is advanced either over the catheter or by exchanging the catheter for the sheath introducer to the distal common carotid artery.

If the purchase on the wire is not enough to advance the sheath, angiographic mapping and superselective cannulation of the external carotid artery often provides the required strength to advance the sheath into the common carotid (Fig. 1). Extreme care is given to avoid introduction of microthrombi and tiny air bubbles by frequent wiping of guidewires with Telfa nonadherent strips moistened with heparinized saline and by meticulous flushing of catheters and sheaths with heparinized saline solution.

After successful cannulation of the common carotid artery, a distal filter typically is used for embolic protection. The distal filter, attached to a 0.014-inch wire, is passed through the sheath, carefully maneuvered through the carotid stenosis under fluoroscopic control, and placed in the distal cervical ICA, where it is deployed with removal of its covering sheath. Very tight carotid stenosis that cannot be safely negotiated with the tip of the embolic protection device may require use of a low-profile microcatheter (Prowler; Johnson & Johnson) and steerable microwire (Transcend; Boston Scientific Corp,). Occasionally, predilation of a tight stenosis with a low-profile coronary angioplasty balloon may be necessary to allow subsequent crossing of the lesion with the distal filter. Also, problems imposed by vessel angulation and tortuosity can be resolved with use of a "buddy wire" to slightly straighten the anatomy and facilitate crossing of a lesion by the distal filter, angioplasty catheter, or stent. Furthermore, for situations in which passage of the distal filter is difficult, maneuvers such as having the patient take deep breaths, having the patient turn the head far to one side or the other, or careful manual pressure on the side of the patient's neck by an assistant can be helpful.

The stent is advanced over the wire to cover the carotid lesion. Because most lesions occur near the carotid bulb, tapered stents are better suited to accommodate any size mismatch of the common carotid and the internal carotid (Fig. 2). If a residual stenosis of more than 30% is present after stent placement alone, postdeployment balloon angioplasty is typically done with a balloon that is 5, 5.5, or 6 mm in diameter and 20 mm in length within the confines of

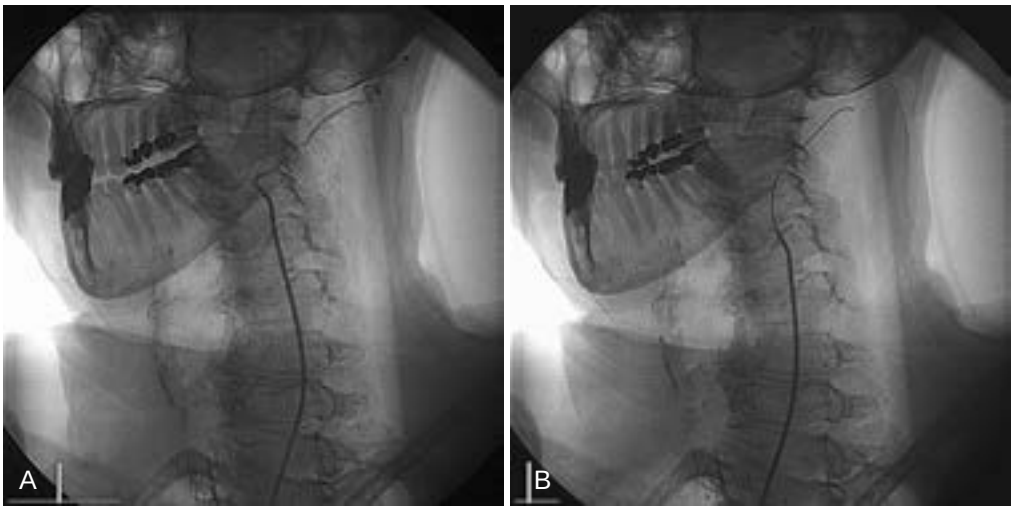


FIG. 1 **(A)** Selective injection to document catheter location in a posterior branch of the external carotid artery before placement of the exchange-length wire used for positioning of the long sheath into the distal common carotid artery. **(B)** Wire placement into the external carotid artery branch through the selective catheter. Inadvertent vessel perforation by the wire could be readily managed with manual compression against the posterior neck muscles.

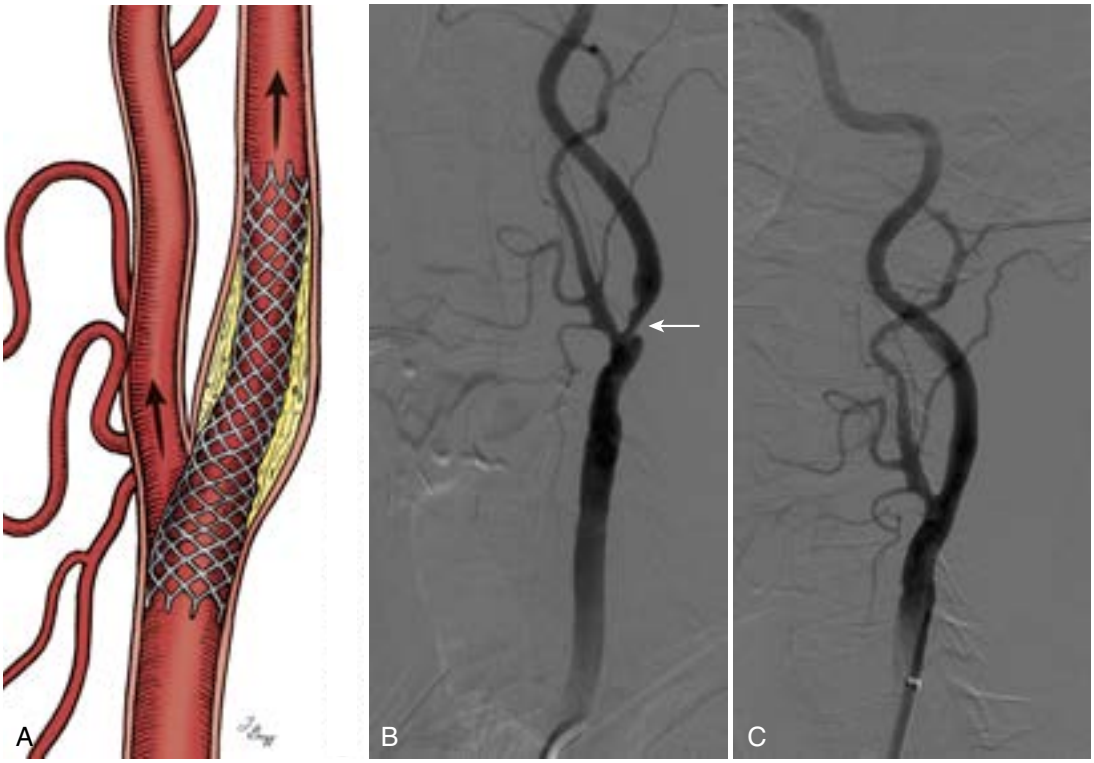


FIG. 2 **(A)** Schematic representation of a stent deployed across the carotid bifurcation to treat a proximal internal carotid artery lesion. Blood flow continues into the external carotid artery through the interstices of the stent. **(B)** Digital subtraction arteriogram (DSA) of a left common carotid injection, lateral neck projection showing a severe stenosis in the proximal internal carotid artery *(arrow)*. **(C)** Completion DSA after placement of a stent across the carotid bifurcation. Note correction of the internal carotid artery stenosis with continued perfusion of the external carotid artery and its branches.
(A courtesy Lydia Gregg, copyright 2010, Johns Hopkins Interventional Neuroradiology.)

the stent. Postdeployment balloon angioplasty is used to achieve an adequate angiographic result, not a perfect one (Fig. 3).

The balloon angioplasty catheters and the carotid stent are passed into position over the wire attached to the distal filter. The same wire is used for passage of a retrieval sheath that captures the filter along with any microemboli that have been trapped during the procedure. After retrieval and removal of the filter and its wire, completion arteriograms of the treated carotid artery and the cerebral territory that it supplies are obtained with injection of contrast through the long sheath. The long sheath is then removed over its dilator and a guidewire to avoid vessel trauma during exit. Systemic anticoagulation therapy is discontinued. After sheath removal, the femoral artery puncture site is sealed with either manual compression or use of a closure device.

TRANSCAROTID APPROACH FOR CAROTID ANGIOPLASTY

This intervention can be divided broadly into three steps: exposure and access of the CCA, the establishment of flow reversal and treatment of lesion, and cessation of flow reversal with closure. We usually employ general anesthesia when performing this approach. Alternatively, a regional block with a local anesthetic may be used.

A distance of 5 cm between the clavicle and the ipsilateral carotid bifurcation and a 6 mm CCA diameter are necessary to establish an ideal platform setup (Fig. 4). The depth of the CCA needs consideration. When a ratio of CCA depth to CCA distance from clavicle to bifurcation exceeds 1, then access with the sheath may prove challenging. If encountering issues with problematic access angles to the CCA, a tunneling technique facilitates a lower angle of access to the CCA. Intraoperatively, depth and length to bifurcation is confirmed with an on-table ultrasound. The vascular sheaths, carotid wires, and the flow reversal system described in this technique are provided by Silk Road Medical. Contralateral percutaneous femoral venous access is obtained, and the venous return sheath (VRS), 8Fr, is inserted and secured to the skin. A venogram is conducted to confirm proper venous placement. A transverse or longitudinal incision is made at the base of the neck, approximately one fingerbreadth above the clavicle, preferably in virgin territory. Dissection is carried through the subcutaneous tissue and platysma. A 3- to 4-cm segment of the CCA is exposed between the clavicular and sternal heads of the sternocleidomastoid muscle (Fig. 5). The patient is systemically heparinized to achieve an activated clotting time of 250 seconds or greater. Further intervention does not proceed until this number is established.

A preclosure stay U-stitch or figure-of-8 stitch with 5-0 Prolene (Ethicon US) is placed at the desired access location on the anterior surface of the CCA. During this process, manipulation of the internal carotid lesion should be avoided before establishing flow reversal. A provided 5F stiff micropuncture set is used, puncturing the artery through the previously placed stitch. The provided micropuncture wire used to access the common carotid artery is premarked to ensure that the lesion is not engaged before flow reversal. The micropuncture sheath is advanced into the common carotid artery at a length of 3 cm. An angiogram through the microsheath with an oblique view helps delineate the bifurcation and lesion location. The provided 0.035 J-wire should be inserted as close as possible to the bifurcation without engaging the lesion. This technique is referred to as the "stop short method." If selecting the ECA due to the need for additional wire purchase, then the provided 0.014

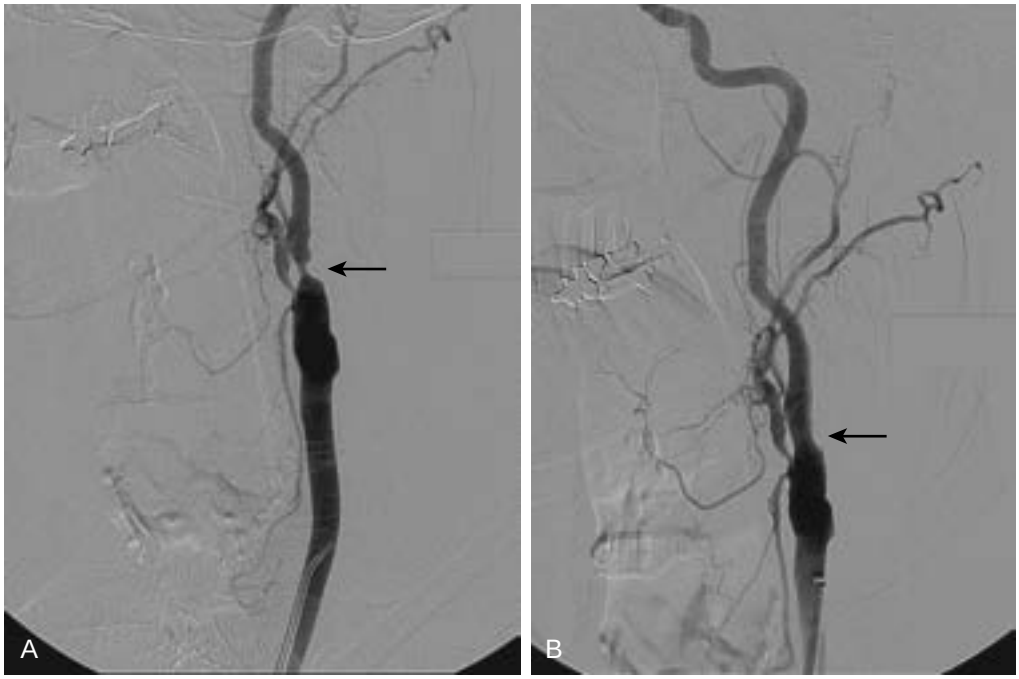


FIG. 3 **(A)** Digital subtraction arteriogram (DSA) of a left common carotid injection, lateral neck projection showing severe stenosis in proximal internal carotid artery *(arrow)*. **(B)** Completion DSA after carotid artery stenting. Notice the residual mild stenosis *(arrow)* at the site of the lesion, which was judged acceptable even though not angiographically perfect.

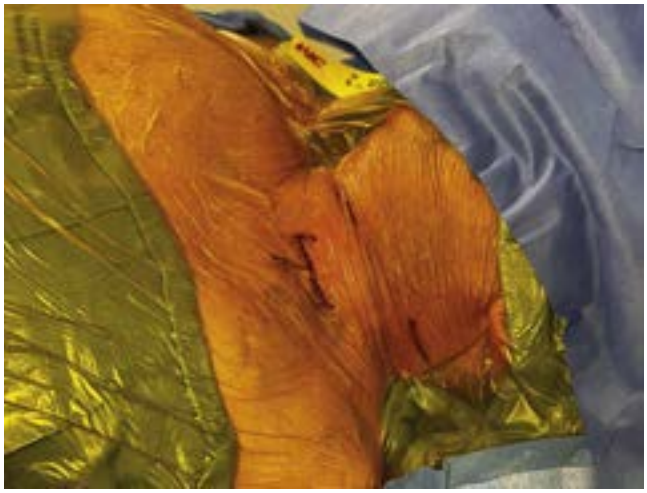


FIG. 4 A distance of 5 cm between the clavicle and the ipsilateral carotid bifurcation and a 6 mm CCA diameter are necessary to establish an ideal platform. These landmarks are identified intraoperatively with the use of ultrasound. *(Courtesy Dr. Rishi Roy, copyright 2021.)*

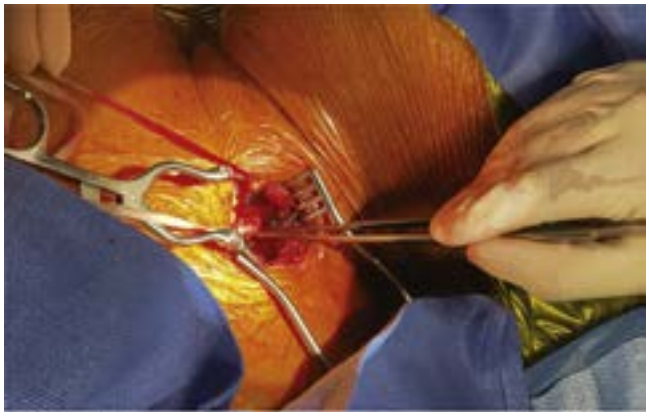


FIG. 5 Exposure of the common carotid at the base of the neck. Dissection is carried deep between the two heads of the sternocleidomastoid muscle to expose 3- to 4-cm segment of the carotid artery. *(Courtesy Dr. Rishi Roy, copyright 2021.)*

microstick wire followed by the sheath are used to select the ECA. Once ECA is selected, the microstick wire is removed and the J-wire is advanced into the ECA. This, again, ensures that the lesion is not engaged before flow reversal. After micropuncture sheath removal, the arterial access sheath (AAS) is advanced to the 2.5-cm marker, a length predetermined by the sheath stopper (Fig. 6). The sheath is sutured to the patient with gentle forward tension. Blood is aspirated, so flushing of heparinized saline through CCA sheath is generally avoided. Slow aspiration avoids ingress of air bubbles through the passive hemostatic valve. Of note, stopcocks are closed.

For the initiation of flow reversal, the flow controller is connected to the AAS. The circuit is prepared by passively allowing a column of blood to fill the line and filter device before connecting to the VRS. Once activated clotting time is confirmed, communication with the team about treatment steps and discussion concerning ideal blood pressure facilitates a smooth intervention. The CCA is occluded. A previously placed clamp, proximal to the arteriotomy, is used for occlusion. The flow controller has two flow settings and allows temporary cessation of flow via a flow stop button (FSB) for contrast injection. Flow reversal is confirmed by two means. The first one consists of stopping the flow to the VRS with the stopcock then clearing the line by injecting heparinized saline into the VRS line. When the stopcock is in the opened position, blood is seen returning in reverse from the flow controller to the VRS. The second way is by performing



FIG. 6 Once access in the common carotid artery is established, the working arterial access sheath is advanced to the 2.5-cm marker, a length predetermined by the sheath stopper. The sheath is sutured to the patient with gentle forward tension. *(Courtesy Dr. Rishi Roy, copyright 2021.)*

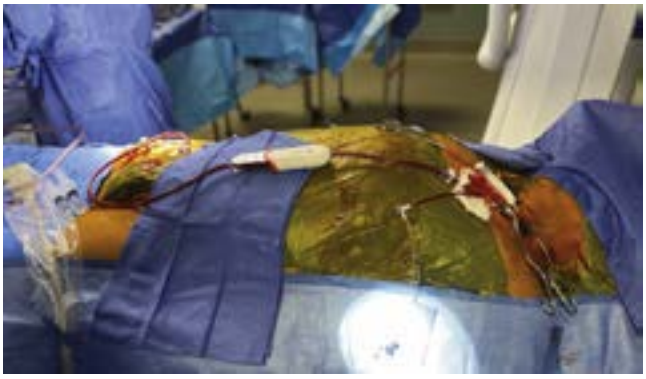


FIG. 7 Depiction of the flow reversal circuit after common carotid arterial access sheath and femoral venous access through the venous return sheath. *(Courtesy Dr. Rishi Roy, copyright 2021.)*

angiograms with a slow, gentle injection of a small volume of contrast to visualize just distal to the lesion while holding the FSB. Releasing the FSB confirms flow reversal within the carotid system (Fig. 7).

Before crossing the lesion, systolic blood pressure should be elevated to optimize flow reversal. Procedural steps are done through the AAS working channel. The ENROUTE transcarotid Neuroprotection System ([NPS] Silk Road Medical has an inner diameter of 8F and an outer diameter of 10F. It is compatible with all US Food and Drug Administration-approved carotid stents, including the ENROUTE transcarotid stent system. The close proximity to the lesion facilitates excellent crossing performance with 1:1 wire torque over a 0.014 wire. The treatment steps typically call for pre-stent ballooning of the stenosis to facilitate stent delivery and deployment at the site of the lesion. Upon completion, antegrade flow is restored by releasing the clamp and disconnecting the flow reversal system from the AAS and VRS. The CCA access sheath is removed, and the previously placed suture is tied for hemostasis. The venous sheath is removed, and hemostasis is achieved by manual compression.

PERIPROCEDURAL MANAGEMENT

Distal embolization is a principal concern with CAS, but the consequences of cerebral embolic events vary widely. Microemboli may produce radiographically apparent lesions on diffusion-weighted MRI scan without clinical evidence of neurologic sequelae. Emboli may also cause clinically significant neurologic deficit, the severity of which depends upon the location and extent of the cerebral tissue that has been rendered ischemic. Therefore, operators who perform CAS must be familiar with the anatomy of the brain and its vasculature so that intracranial cerebral branch vessel occlusion can be readily identified. It is equally important that operators be thoroughly familiar with normal neurologic function and the clinical manifestations of stroke. In addition, dedicated expert neurologic support is essential for a successful carotid stenting program.

Although uncommon, neurologic intolerance to flow reversal during TCAR may occur once the CCA is clamped and is usually manifested by confusion, agitation, or a slow decline in level of consciousness. Maintaining an elevated blood pressure, slowing down the flow reversal, stopping the flow reversal temporarily, converting to general anesthesia to decrease the metabolic demand of the brain and completing the procedure expeditiously are the maneuvers to consider to address this situation. If symptoms persist, aborting flow reversal and completing the procedure using a distal embolic protection is always an option.

Inflation of an angioplasty balloon in the proximal internal carotid artery sometimes provokes bradycardia and hypotension. This issue is addressed with intravenous atropine 0.4 mg either preemptively before balloon predilation or selectively when it occurs. Patients with severe aortic stenosis may be intolerant of even mild bradycardia and hypotension with balloon inflation, and consideration should be given in such patients to using monitored anesthesia and placing a temporary pacemaker before the procedure. Bradycardia and hypotension with carotid balloon angioplasty are rarely seen in patients who have previously undergone CEA, probably because of the denervating effect of surgical dissection near the carotid bulb.

Distal cervical ICA vasospasm is sometimes induced by catheter or wire manipulation or by distal filter or balloon placement. Avoidance of movement of the distal filter once deployed helps minimize vasospasm at the site. Resolution of the vasospasm often occurs spontaneously but can be hastened with transcatheter administration of nitroglycerin (200-μg bolus) into the involved artery.

As mentioned previously, antiplatelet therapy is essential for success of CAS. Dual antiplatelet therapy with clopidogrel (75 mg daily) and aspirin (81 or 325 mg daily) is the current standard. The considerable individual variation in the degree of platelet inhibition provided by antiplatelet therapy is now well known. Also, the impact of clopidogrel or aspirin resistance on long-term stent patency and restenosis rates is being increasingly recognized. Testing for such resistance is commercially available and should be considered preoperatively in all patients when timing allows.

If a patient has less than 20% inhibition on the platelet activity, a higher dosage of medication is warranted. This increase in the target level of inhibition does not translate into higher risk for bleeding. Ticlopidine (250 mg twice daily) can be used in patients who cannot tolerate clopidogrel. If a patient cannot take antiplatelet therapy, carotid stenting should be reconsidered, as the postprocedural stroke risk may then be unacceptably high.

Dual antiplatelet therapy should be continued for at least 3 months after the stent procedure, and daily aspirin should be continued indefinitely thereafter. Glycoprotein IIb-IIIa inhibitors are associated with increased risk of intracranial hemorrhage after carotid stenting, and their role should be confined to the treatment of acute thrombus formation during or immediately after the procedure.

For management of acute in-stent thrombosis, abciximab is administered by giving one-half of the 0.25 mg/kg bolus dose intraarterially near the clot and administering the second half of the bolus dose intravenously over 5 minutes, followed by an intravenous infusion of 10 mcg/min for 12 to 24 hours.

Postprocedural hypotension may accompany periprocedural bradycardia and is usually managed with volume expansion. Moderate bradycardia and mild hypotension, similar to that seen occasionally after CEA related to carotid baroreceptor stimulation, are best treated with fluid supplementation, close observation for any neurologic dysfunction, and occasional use of low-dose vasopressor support.

Control of postprocedural hypertension is important to minimize risk of cerebral hyperperfusion syndrome (CHS). Severe headache associated with hypertension after CAS should heighten suspicion of CHS, which can also present with seizures and focal neurologic deficits. Proper management of CHS entails early diagnosis, invasive monitoring, rapid control of hypertension, anticonvulsant therapy, osmotic diuresis, and neurologic consultation.

FOLLOW-UP

Patients are usually discharged from the hospital on the day after undergoing CAS. Follow-up office visit occurs 4 to 6 weeks after surgery, again 6 months later, and annually thereafter. Follow-up includes a complete neurologic assessment and carotid ultrasound scan examination. Each visit also includes a global cardiovascular evaluation with emphasis on possible coronary, renal, and peripheral arterial occlusive problems. Hypertension and hypercholesterolemia are managed aggressively. Because of the antiinflammatory and plaque stabilization effects, high intensity statin therapy is advised for almost all patients, even in the absence of laboratory evidence of cholesterol abnormalities. Healthy lifestyle habits are encouraged, with emphasis on regular aerobic exercise, dietary discretion, and complete abstinence from tobacco use.

Hemodynamically significant restenosis of carotid stents is not frequent and has been quoted as less than 5%. The application of carotid duplex velocity criteria of native vessels may overestimate the degree of stenosis in postoperative CAS surveillance. We follow the criteria of Stanziale and colleagues who use a peak systolic velocity of 350 cm/s or greater in the stent as a reliable indication of 70% or greater restenosis in a stented carotid artery.

SUMMARY AND PERSPECTIVE

Results of clinical trials have shown that both CAS and CEA are effective procedures for stroke prevention; each has an important place in carotid disease management. Currently, concerns about higher stroke risk with CAS, coupled with reimbursement restrictions and cost-effectiveness issues for asymptomatic CAS, make CEA the more commonly performed procedure. In the authors' practice, CAS is reserved for patients with recurrent stenosis after CEA, a history of neck irradiation or radical neck dissection, lesions located high in the neck (above the level of the C2 cervical vertebra), contralateral vocal cord paralysis, and traumatic dissections with neurologic symptoms in the absence of significant atherosclerotic disease.

Most patients undergoing CEA are at "high risk" based on traditional trial criteria, and only rarely are we compelled to use CAS because of extreme cardiopulmonary risk factors that make surgical treatment prohibitive. CEA should be used with reservation in situations where the risk of periprocedural stroke is higher than usual.

Specific clinical and anatomic factors preclude the use of transfemoral CAS in our practice. Clinical factors include age older than 80 years and recent (within 2 weeks) neurologic ischemic symptoms. Anatomic factors that may prevent CAS include vessel angulation greater than 60 degrees and a severely diseased aortic arch, especially when combined with branch vessel configuration that is hostile for sheath access. It has been proven that use of transcervical access lowers the stroke risk of CAS when compared with transfemoral approach. The 30-day stroke rate of only 1.4% for high-risk patients undergoing TCAR in the pivotal cohort mentioned earlier is worthy of consideration.

Finally, when deciding which procedure and what approach are most appropriate for each patient, skilled vascular surgeons, especially those trained and experienced in both CEA and CAS, bring a unique skill set, ability, and perspective to judging the multiple variables that must be considered carefully to achieve the best outcome for the patient.

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Management of Aneurysms of the Extracranial Carotid and Vertebral Arteries

Virginia L. Wong, MD

Arterial aneurysms involving the extracranial carotid and vertebral arteries are rare, accounting for less than 1% of all peripheral arterial aneurysms. Of the many carotid interventions performed, only 0.1% to 2% are done for extracranial carotid artery aneurysms (ECAAs). Therefore, guidance for treatment of these lesions is based on single-center, retrospective series or literature reviews, rather than large multicenter, randomized trials. Extracranial vertebral artery aneurysm (EVAAs) are even less commonly encountered, and the available experience from case reports and small series provides only limited guidance for clinical management.

EXTRACRANIAL CAROTID ARTERY ANEURYSMS

Etiology

Historically, mycotic aneurysms were the most commonly encountered form of ECAA, associated with locally uncontrolled infection (e.g., peritonsillar abscess, mastoiditis). With increased access to antibiotic therapy, mycotic aneurysms are now unusual. A very low incidence (0.025%–0.85%) of carotid patch infection following carotid endarterectomy (CEA) has been reported. The most common causes of ECAA now are atherosclerotic degeneration and trauma. As with other degenerative peripheral artery aneurysms, weakening of the arterial wall layers is contributory, and most ECAAs of this type are located at the carotid bifurcation or involve the proximal internal carotid artery (ICA). Penetrating trauma, including iatrogenic injury from attempts at central line insertion, are a cause of arterial pseudoaneurysm, most commonly in zone I or II affecting the common carotid artery, though injury can occur at any place where an artery lies in the missile path. Blunt trauma associated with forceful cervical hyperextension or hyperflexion can cause vessel dissection, particularly in zone III near the skull base, with subsequent aneurysmal degeneration of the weakened arterial wall. Iatrogenic endovascular injury during percutaneous interventional procedures can lead to vessel perforation or degenerative aneurysm from intimal dissection anywhere along the traversed arterial distribution. Other etiologies of ECAA include fibromuscular dysplasia, collagen vascular and connective tissue disease, inflammatory disease (e.g., arteritis), radiation injury, cystic medial necrosis, and congenital defects.

Presentation and Diagnosis

Some patients with ECAA may be asymptomatic, their pathology having been identified on high-quality cross-sectional imaging for another indication. The most common presenting symptoms of ECAA are an acute neurologic event (i.e., stroke or transient ischemic attack) affecting nearly half of symptomatic patients. Patients also commonly present with a pulsatile neck mass. Compressive symptoms including vocal hoarseness, dysphagia, facial pain, or cranial nerve palsies may be present. Rupture and hemorrhage may be more common with infection or pseudoaneurysm. Other causes of neck mass include carotid or subclavian artery tortuosity and redundancy, carotid body tumor, cervical malignancy, lymphadenopathy, peritonsillar abscess, and branchial cleft cyst. Diagnostic studies including duplex ultrasound (DUS) and computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) are the most helpful for evaluation as well as for diagnosing alternate pathology (Fig. 1). DUS may be limited in its ability to visualize very proximal or distal disease; however, it remains a good choice for initial evaluation given its cost-effectiveness and low procedural risk. High-quality tomographic studies are mandatory for planning intervention and generally provide all necessary information (Fig. 2).

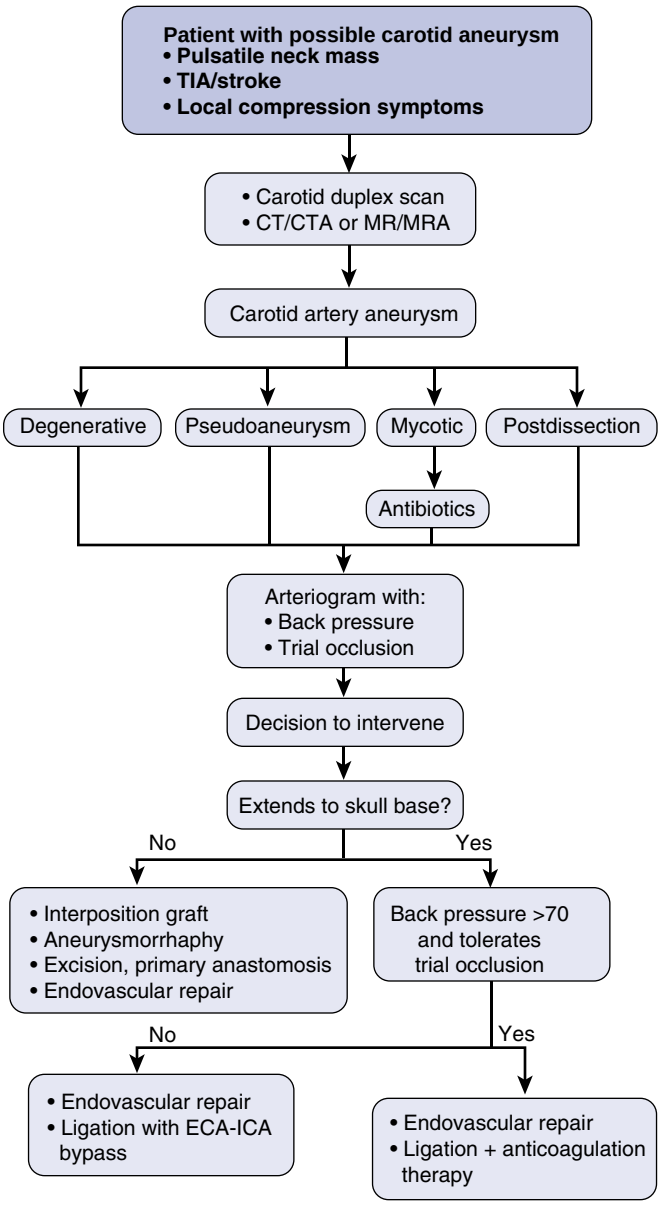


FIG. 1 Algorithm for diagnosis and treatment of carotid aneurysms. *CT,* Computed tomography; *CTA,* computed tomographic angiography; *ECA,* external carotid artery; *ICA,* internal carotid artery; *MR,* magnetic resonance; *MRA,* magnetic resonance angiography; *TIA,* transient ischemic attack. *(Modified from Rothstein J, Goldstone J. Carotid artery aneurysm. In Cronenwett JL, Rutherford RB, eds.* Decision Making in Vascular Surgery. *Orlando: Saunders; 2001:54.)*



FIG. 2 Three-dimensional reconstruction of a CT angiogram of an extracranial carotid artery aneurysm *(arrow)* in a symptomatic patient who presented with dysphagia. *(From Srivastata SD, Eagleton MJ, O'Hara P, et al. Surgical repair of carotid artery aneurysms: a 10-year, single-center experience.* Ann Vasc Surg. *2010;24:100–105.)*

Therefore, traditional catheter angiography is less often required to assess anatomy preoperatively, but it may still be useful for balloon occlusion testing if this information would alter treatment options or the approach to therapy.

Indications for Treatment

The natural history of untreated, asymptomatic ECAAs is not well-known. Although some have reported successful medical management of select ECAAs using antiplatelet or anticoagulant therapy and surveillance imaging, the potentially high rate of embolic neurologic events associated with ECAAs is enough to consider a more aggressive approach in suitable patients with approachable anatomy. Further, there are no established criteria describing which type or size of ECAA would be suitable for noninterventional therapy. Symptomatic patients with neurologic events, compressive complaints, infection, or hemorrhage (rupture) require more urgent treatment.

Preoperative Considerations

Optimal treatment for ECAA will vary depending on the etiology, location, aneurysm morphology, medical suitability for surgery and anesthesia, and prior treatment for other conditions. A thorough history and physical examination will further define some of these characteristics. Consideration for open surgical repair includes cardiovascular and medical fitness, ability to extend and rotate the neck, and availability of suitable conduit or patch material for reconstruction. Access to a very distal ECAA may require unusual maneuvers for exposure or the assistance of a surgeon experienced in skull base procedures. An infectious etiology will require vascularized soft tissue coverage or reconstructive surgery. Consideration for endovascular repair includes availability of interventional expertise and equipment as well as suitable access vessels and anatomy. Endovascular repair may be most appropriate for sterile, nondegenerative ECAA with a low thrombus burden, such as those resulting from trauma or dissection and pseudoaneurysms. Medical unsuitability for surgery or a hostile neck would favor endovascular therapy, if possible. Traditionally, compressive symptoms were principally treated with open surgery; however, symptom relief after endovascular exclusion has been reported.

A morphologic classification of ECAA was proposed by Attigah et al. in a 2009 review of their experience with more than 60 open surgical reconstructions over 24 years, the majority of which were performed for atherosclerotic degeneration (Fig. 3). Although contemporary experience suggests that endovascular treatment may now be suitable or even preferable for some types of ECAA, it is clear that no single reconstruction or treatment is universally suitable for all aneurysm types. Nevertheless, standardizing the anatomic description of ECAA may enhance comparisons between open and endovascular repair for different aneurysm types and extent.

Open Surgical Repair

There are multiple techniques used for open surgical repair of ECAA, the most suitable of which will depend on the etiology, location, and extent of the aneurysm as well as some of the additional factors discussed earlier. Although standard CEA and more limited repair of the carotid arteries may be accomplished under local or regional anesthesia, general endotracheal anesthesia is recommended for the repair of most ECAAs because of the increased operative time required for extensive dissection and arterial reconstruction. Strong consideration should be given to using a shunt or some type of cerebral perfusion monitoring, given longer cross-clamp and hemispheric ischemia times than are typically encountered for standard CEA. Access to the extracranial carotid artery bifurcation is achieved via a longitudinal skin incision along the anterior border of the sternocleidomastoid muscle, a standard approach that is familiar to many surgeons. Proximal extension will be necessary for more proximal common carotid involvement and could require mini- or standard sternotomy if control is needed below the clavicle. The incision is extended cranially behind the ear for exposure of the distal extracranial ICA; division of the posterior belly of the digastric muscle and resection of the styloid process affords improved access to this area. If anticipated in advance, nasotracheal intubation and mandibular subluxation will facilitate distal carotid artery exposure. If the distal ICA is inaccessible for cross-clamping, control can also be obtained with an intraluminal balloon occlusion catheter or shunt. Exposure even more distally can be achieved by partial resection of the mastoid and petrous portion of the temporal bone, achieved with the assistance of an experienced skull base surgeon; however increased morbidity and risk of cranial nerve injury may be associated with these more extreme maneuvers.

Dissection around the aneurysm can be challenging because of the dense inflammatory reaction that often surrounds aneurysmal tissue. Several cranial nerves may be encountered in the field including the vagus and recurrent laryngeal nerve (X), hypoglossal (XII), glossopharyngeal (IX), spinal accessory (XI), and branches of the facial nerve (VII). Expansion of the aneurysm may distort usual anatomic relationships, and nerves may be densely adherent to the aneurysm surface or to surrounding structures. Meticulous dissection is required to identify all structures and protect them from injury. Care should also be taken to manipulate the aneurysm as little as possible during dissection, preventing dislodgement and distal embolism of aneurysm contents. Finally, once dissection and exposure are obtained, systemic heparin is administered to maintain anticoagulation while the carotid artery is cross-clamped and until arterial reconstruction is completed (Fig. 4A).

Primary suture repair is the most straightforward repair technique and may be suitable for focal or very limited pseudoaneurysms, such as those caused by trauma or iatrogenic injury. Interrupted sutures are placed in a transverse manner, as long as

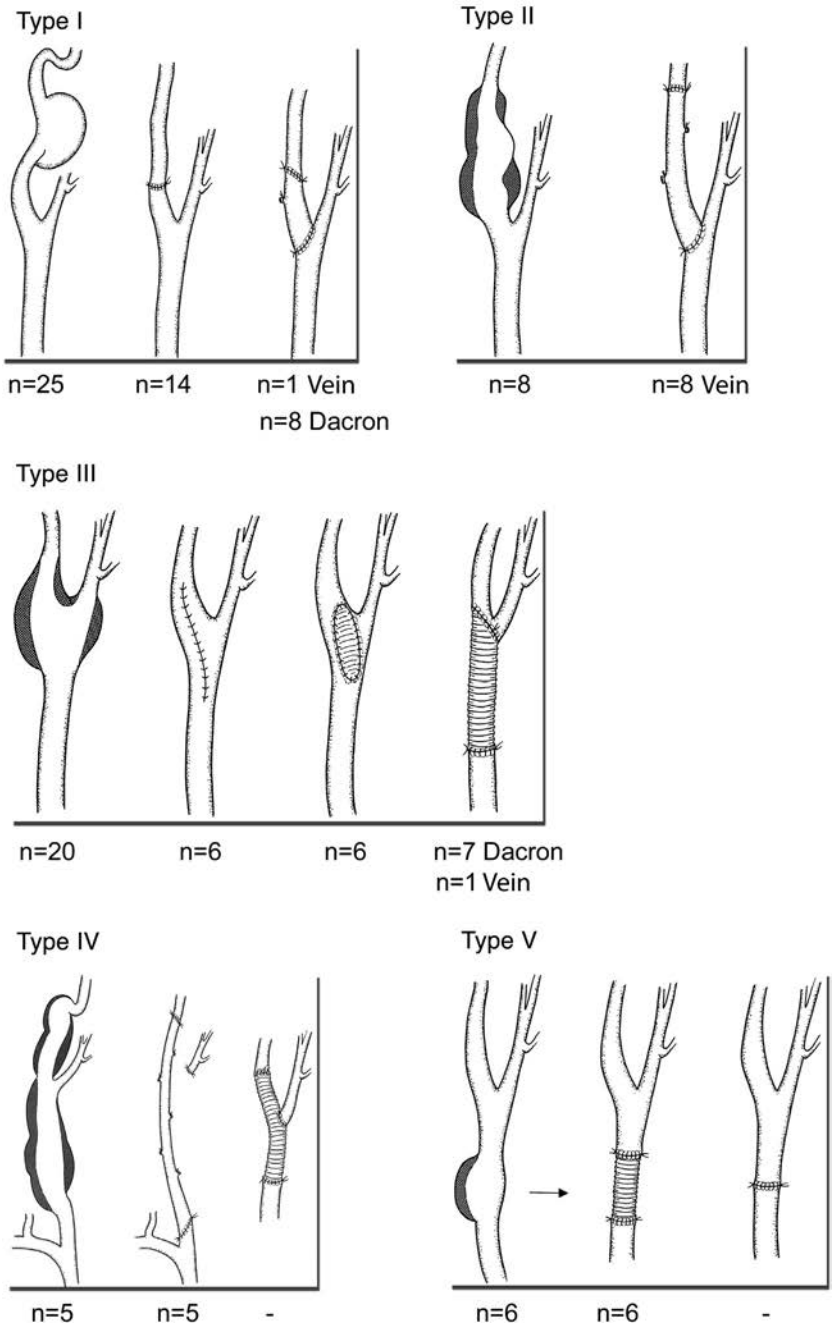


FIG. 3 Morphologic classification of the extracranial carotid aneurysms and possible vessel reconstruction alternatives. Type I: aneurysms of the internal carotid artery distal to the carotid bifurcation. Type II: aneurysm of the internal carotid artery. Type III: aneurysm of the carotid bifurcation. Type IV: aneurysm of the internal carotid artery and the common carotid artery. Type V: aneurysm of the common carotid artery. *(From Attigah N, Kulkens S, Zausig N, et al. Surgical therapy of extracranial carotid artery aneurysms: long-term results over a 24-year period.* Eur J Vasc Endovasc Surg. *2009;37:127–133.)*

this can be accomplished without narrowing the artery. Wider-based pseudoaneurysms or saccular aneurysms whose residual arterial defect account for <50% of the arterial circumference can be repaired with patch angioplasty. Acceptable patches can be constructed of autologous vein (e.g., saphenous), polyester or polytetrafluoroethylene (PTFE) prosthetic, or bovine pericardium (bioprosthetic) materials. If infection is a concern, only autologous material should be used. In cases in which sufficient mobilization of the carotid artery can be achieved, debridement of involved tissue and primary re-anastomosis may be possible (Fig. 4B).

More typically, and for situations in which a greater degree of the artery is involved, resection of the aneurysm and arterial reconstruction by interposition bypass grafting is necessary and would be considered the standard of open surgical repair for most ECAAs. Again, acceptable conduit depends on the circumstances but can include autologous vein or prosthetic materials. If autologous vein is not available, segmental harvest of the superficial femoral artery (SFA) for carotid reconstruction has been described; a chronically occluded SFA can be endarterectomized for use, while a healthy donor artery can be subsequently reconstructed with prosthetic material. The

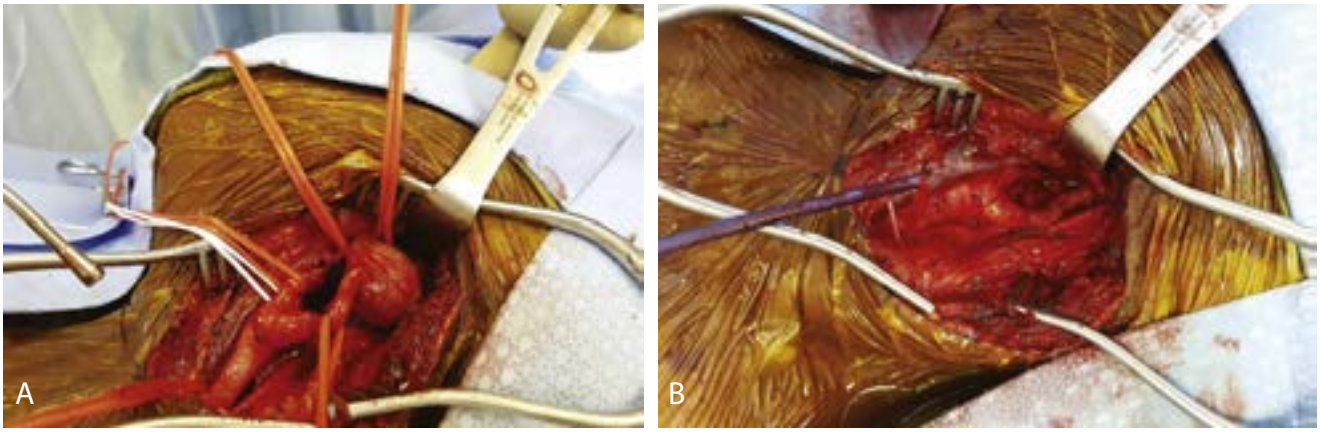


FIG. 4 **(A)** Left extracranial internal carotid artery (ICA) aneurysm; **(B)** Following aneurysm resection and primary ICA re-anastomosis. *(Photos courtesy Vikram Kashyap, MD.)*

external carotid artery (ECA) can typically be ligated without consequence, and division of this artery can provide improved mobility for reconstruction by primary carotid re-anastomosis. Alternatively, the ECA can be ligated distally and the proximal end transposed to the distal ICA (by end-to-end anastomosis) to serve as the "bypass" conduit.

Finally, ICA ligation may be considered, though it is often a choice of last resort given the historically high risk of stroke and mortality associated with this maneuver (in excess of 25%). Ligation may be the only available option in cases of exsanguinating hemorrhage from rupture or when access to the very distal ICA cannot be achieved sufficiently for arterial reconstruction. Patients who may tolerate ligation can be identified by performing a balloon occlusion test preoperatively (if the need for ligation is anticipated before surgery) or by measuring a carotid stump pressure intraoperatively. The balloon occlusion test is performed during preoperative catheter angiography after full heparinization. Balloon occlusion of the ICA distal to the anticipated aneurysm resection point is accomplished for 30 minutes, and the awake patient is monitored for neurologic symptoms. Intraoperatively, a carotid stump pressure is obtained in the heparinized patient by inserting a 20-gauge angiocatheter attached to pressure monitor tubing into the distal ICA and then occluding the common and external carotid artery inflow. A back-pressure measurement of >50 mm Hg suggests that cerebral collaterals are sufficient to allow for ligation of the ipsilateral ICA supply without neurologic sequelae. If either test suggests that a patient will not tolerate ICA ligation and arterial reconstruction is deemed impossible, then extracranial-to-intracranial (EC-IC) bypass should be considered. If ICA ligation is undertaken, therapeutic anticoagulation should be administered postoperatively and continued for at least 3 months to prevent distal embolization of thrombus that forms cranial to the point of ICA ligation (carotid stump syndrome).

Infected ECAAs require additional treatment to include broad-spectrum antibiotic therapy, subsequently tailored to intraoperative culture results; full debridement of all infected and devitalized tissue; and adequate coverage of vascular structures by well-vascularized, healthy tissue. The sternocleidomastoid muscle is readily available for use in most circumstances; however, previously irradiated or extensively operated fields may require myofascial or myocutaneous flaps for proper coverage.

Endovascular Repair

With increasing expertise and improved tools for endovascular therapy, modern series report a greater trend toward use of endovascular techniques for treatment of ECAAs. Many of the same advantages of using endovascular techniques instead of open surgery to treat other vascular conditions have also been reported for ECAA, the most significant benefit being a lower risk of cranial nerve injury. This is particularly the case with very high lesions near the skull base, but endovascular repair may be preferred for nondegenerative ECAAs and pseudoaneurysms. Endovascular treatment should be considered carefully for ECAAs of atherosclerotic etiology as the underlying disease process may result in further arterial degeneration, limiting the potential durability of endovascular treatment.

Endoluminal access to the carotid artery may be obtained from a standard transfemoral arterial approach if access vessel and aortic arch anatomy are suitable. Aortic arch angiography in a left anterior oblique projection is achieved using a multi-sidehole catheter and a power injector to identify the head vessel anatomy, followed by heparinization and advancement of a long arterial sheath into the common carotid artery. Selective carotid and cerebral angiography is then obtained, and a low-profile system is positioned across the carotid artery lesion for intervention. Alternatively, access to the proximal common carotid artery may be achieved by surgical cutdown. In either case, local anesthesia with sedation is usually sufficient unless general anesthesia is required due to hemodynamic instability or other considerations. Use of protection against distal cerebral embolization should be considered the standard of care as it is for stenting of non-aneurysmal carotid pathology. A distal embolic protection device (EPD) should be deployed as early in the procedure as possible. Alternatively, some authors are now reporting the use of transcarotid artery stenting (TCAR) and flow-reversal techniques to achieve embolic protection during endovascular treatment of ECAA.

Successful endovascular exclusion of the aneurysm while maintaining antegrade flow through the ICA can be achieved by placement of a bare metal stent or a covered stent graft across the aneurysm, landing each end of the stent into normal, healthy artery. Bare metal stents alone may be sufficient for exclusion of small aneurysms and more suitable for use in smaller arterial diameters or for treatment of concomitant arterial dissection (Fig. 5). Covered stents will provide more immediate aneurysm exclusion and may be better for traumatic ECAAs or those at imminent risk for rupture or hemorrhage. The external carotid artery will require embolization before coverage by a stent graft to prevent backbleeding into the aneurysm and a type II endoleak. Coil embolization of saccular aneurysms or larger pseudoaneurysms can be undertaken, followed by deployment of a stent to trap the material in place and preserve the antegrade flow lumen. Alternatively, if the aneurysm fails to thrombose after stenting, coil embolization can be performed through the interstices of a previously deployed closed-cell stent, either at the time of stenting or as a secondary procedure.

Post–stent-deployment balloon angioplasty must be undertaken with caution to avoid arterial dissection, and the possibility of



FIG. 5 Digital subtraction angiography of a left internal carotid aneurysm at the skull base with associated weblike stenosis. **(A)** Before treatment by bare metal stent placement. **(B)** After treatment. Note the absence of residual stenosis and presence of a small residual aneurysmal sac, which subsequently closed completely.

transient hypotension and bradycardia during balloon inflation near the carotid bifurcation should be anticipated. The patient's neurologic function is monitored throughout the procedure, and posttreatment completion angiography is obtained to assess for any technical complications. Vessel closure and management of procedural heparin anticoagulation is per routine. Posttreatment antiplatelet or anticoagulant therapy should be considered.

Results of Treatment

ECAA repair by either open or endovascular techniques appears to be effective and with similar early mortality and risk of cerebrovascular events. Although several reviews of the current experience are available, case numbers are too low for subgroup analysis or to describe outcomes of specific techniques (e.g., interposition arterial bypass vs. ECA transposition or bare metal stent-supported coil embolization vs. covered stent graft deployment). Further, these data are unable to establish which modality is more appropriate for a specific circumstance or aneurysm type. The repair technique selected may likely reflect ECAA etiology or anatomic location and extent; therefore, it may not be directly comparable from a retrospective standpoint. Data for late outcomes vary with length of follow-up and are more limited.

A 2015 review by Welleweerd et al. summarized published data for more than 900 patients undergoing open surgery for ECAA repair, finding a pooled 30-day mortality rate of 1.91% and a pooled 30-day stroke rate of 5.16%. A 2020 review of endovascular ECAA repair by Giannopoulos et al. examined more than 150 patients and reported low mortality and cerebrovascular event rates of 2.5% and 4.3%, respectively. A recent review by Galyfos et al. of comparative data from series reporting both open and endovascular ECAA repair found similar outcomes and no differences in this regard between treatment modalities. There do appear to be differences, however, in the risk of cranial nerve injury, as might be expected from our experience with CEA and carotid artery stenting for atherosclerotic disease. The risk of cranial nerve injury is much higher with open ECAA repair (ranging from 0 to 60%) and may be associated with the need for more extensive or distal dissection. Although some percentage of nerve deficits may be transient, it is striking that the rate of cranial nerve injuries in many series of endovascular repair is reported as 0% or very close to that. Few studies offer data on long-term outcomes, though the risk of late stroke also appears to be low after treatment, regardless of modality. Even without large, direct comparisons, outcomes using modern endovascular techniques appear to be acceptable for treatment of some ECAAs and offer many advantages over open surgery.

EXTRACRANIAL VERTEBRAL ARTERY ANEURYSMS

EVAAs are very rare, typically arising from aneurysmal degeneration of a prior intimal dissection or after traumatic injury (both blunt and penetrating). Connective tissue disorders that predispose to aneurysm formation in other arterial beds may be responsible for primary EVAAs. Most patients are asymptomatic, and the diagnosis is made by incidental finding during imaging for another indication. Those with symptoms may complain of persistent ipsilateral head or neck pain, particularly following trauma. EVAA can also result in vertebrobasilar insufficiency or a posterior cerebrovascular event (i.e., stroke or transient ischemic attack). DUS is less helpful for

evaluating EVAAs because it is unable to visualize the artery through its interosseus course (V2 segment) and then more distally through the V3 segment as it approaches the base of the skull. CTA and MRA provide sufficient imaging of EVAAs and their surrounding anatomy, which can be helpful for surveillance and procedural planning.

The natural history of EVAAs is not well described; therefore, the indications for intervention are not clear. Small, asymptomatic EVAAs can likely be safely observed with antiplatelet therapy; however, intervention should be considered for serial enlargement during follow-up or for those with significant thrombus burden that may be at higher risk for embolism. Intervention is recommended for all symptomatic EVAAs.

Open surgical exposure of the vertebral artery can be challenging, depending on the segment of the artery that is affected. The most proximal V1 segment may be approached through a transverse cervical incision, whereby ligation, resection with reconstruction, or transposition onto the carotid artery may be undertaken. Ligation should be well tolerated when the contralateral vertebral artery is normal, and preoperative evaluation of the opposite side by duplex, tomographic imaging, or catheter angiography (including a balloon occlusion test) can be helpful. Access to the V2 segment of the artery is complicated by the bony foramina through which it courses as well as by an associated venous plexus. Exposure of the V3 segment via a posterior approach can provide improved access to the artery near the base of the skull for a distal bypass anastomosis, but this exposure is less familiar to most surgeons and should probably be attempted only by those with considerable experience working in this area.

Given the challenges associated with surgical access to the extracranial vertebral artery, endovascular management of EVAAs is appealing. Endovascular coil embolization can be used as an alternative to open surgical ligation, particularly in cases of traumatic pseudoaneurysm or hemorrhage. Stenting of EVAAs is technically feasible, though tortuosity may preclude the ability to stent safely through some segments of the artery. Unfortunately, high rates of in-stent restenosis have been associated with stenting for vertebral artery occlusive disease; thus, the use of stents for aneurysmal disease should be considered with care, particularly if the contralateral vertebral artery or other posterior fossa collateral flow has been deemed inadequate.

Suggested Readings

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Brachiocephalic Reconstruction

Gregory J. Pearl, MD, and Lauren Beliveau, MD

INTRODUCTION

The most common anatomic configuration of the brachiocephalic vessels off the transverse aortic arch is three separate and discrete branches from proximal to distal: the innominate artery, the left common carotid artery, and the left subclavian artery. The innominate artery gives rise to the right subclavian and right common carotid artery. The most common variant of arch anatomy is the bovine arch. In this variation, the left common carotid artery either shares a common origin with the innominate artery off the arch, or the left common carotid artery arises directly off the innominate artery. Interestingly, this is not the anatomic configuration of a cow's aortic arch, but rather resembles a cow with horns on illustration.

Other common variants include the left vertebral artery arising directly off the arch between the left common carotid and the left subclavian arteries and the aberrant right subclavian artery that arises just distal and posterior to the left subclavian artery, coursing across the midline between the esophagus and anterior spinal ligament to the right upper extremity (Fig. 1). An aberrant right subclavian artery can be associated with dysphagia lusoria as a result of compression from the right subclavian artery on the esophagus.

The brachiocephalic vessels supply the upper extremities as well as the brain, so any disease entity that affects these vessels, either as a result of flow-limiting stenosis or as a source of embolization, may produce serious symptoms that are difficult to correct surgically (Fig. 2). The underlying lesions affecting the great vessels may be a result of and associated with disease arising in the aortic arch or may be secondary to lesions intrinsic to the brachiocephalic vessels themselves. The pathologic entities include atherosclerotic disease, inflammatory arteritides, blunt or penetrating trauma, or a pathologic process involving the ascending or transverse aortic arch such as aortic dissection or aneurysm. Additionally, occlusive or aneurysmal lesions of the subclavian arteries may be associated with arterial thoracic outlet syndrome. Debranching procedures of the brachiocephalic vessels have also become an important adjunct in the endovascular treatment of aortic dissections or aortic aneurysmal disease involving the transverse arch or proximal descending thoracic aorta.

CLINICAL PRESENTATION

The clinical manifestations of lesions involving the brachiocephalic arteries are in large part dependent on the underlying pathogenesis and extent of vessel involvement, such as single-vessel versus multivessel disease, as well as the anatomic location of the culprit lesions. In Berguer's report on brachiocephalic revascularization, he identified an approximately 40% incidence of multivessel involvement of the brachiocephalic arteries.

Atherosclerotic disease involving the arch vessels is not uncommon and in most instances is asymptomatic. At times, the only finding is an otherwise asymptomatic discrepancy in blood pressure in the upper extremities. Symptoms caused by occlusive lesions involving the brachiocephalic vessels may be those typical of carotid artery distribution transient ischemic attack (TIA) or stroke, vertebrobasilar events, or upper-extremity ischemia such as arm fatigue or digital ischemia. Lateralizing hemispheric neurologic events include amaurosis fugax, or transient monocular loss of vision, word-finding difficulty, and weakness or numbness involving one side of the body only.

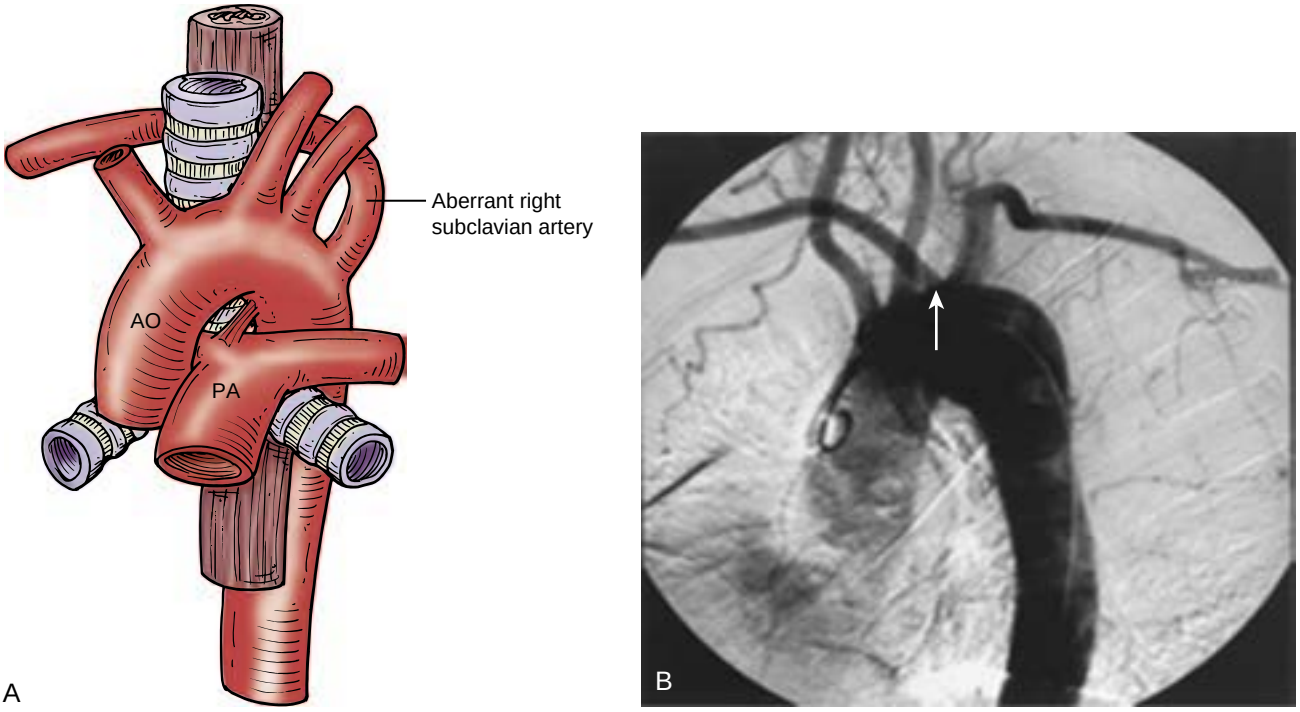


FIG. 1 Illustration **(A)** and digital subtraction arteriogram **(B)** demonstrating the anatomic configuration of an aberrant right subclavian artery *(arrow)*. *AO,* aorta*; PA*, pulmonary artery.



FIG. 2 Digital subtraction angiogram showing multivessel atherosclerosis involving brachiocephalic vessels.

Multivessel occlusive lesions, as seen in patients with advanced atherosclerotic disease or Takayasu arteritis, may produce nonlateralizing neurologic symptoms such as dizziness and visual disturbances secondary to cerebral hypoperfusion. Patients presenting with classic lateralizing hemispheric neurologic events that cannot be attributed to cervical or intracranial carotid disease should undergo aggressive interrogation of the brachiocephalic vessels as a potential source of these symptoms.

Severe occlusive disease in the proximal subclavian arteries may produce flow reversal in the ipsilateral vertebral artery, leading to a condition known as *subclavian steal syndrome*. Flow reversal in the vertebral artery noted on duplex ultrasound examination of the neck is not an uncommon finding and is frequently asymptomatic. However, in the classic clinical picture of subclavian steal, the patient will experience typical symptoms of vertebrobasilar insufficiency associated with arm exercise. These symptoms can include vertigo or "drop attacks" in which the patient suddenly falls to the ground without losing consciousness. Complaints of arm fatigue secondary to proximal subclavian atherosclerotic occlusive disease are uncommon because of the extensive capacity of collateral flow to the upper extremity combined with the decreased physical demands inherent in the atherosclerotic age group and therefore rarely require intervention. However, findings of unilateral digital ischemia as a result of microembolization should lead to a high index of suspicion for the culprit lesion to be located in the proximal subclavian or brachiocephalic vessels (Fig. 3). Interrogation for the source lesion in this setting should not be delayed and should be pursued aggressively because ongoing embolization could potentially lead to extensive distal tissue loss and consequent severe functional impairment.

DIAGNOSTIC EVALUATION

A thorough history and physical examination are paramount in the initial evaluation of these patients. Careful palpation of the carotid and upper-extremity pulses in conjunction with auscultation of the neck, including the parasternal and paraclavicular areas, for the presence of bruits is necessary. Bilateral upper-extremity blood pressure measurements may easily and quickly be performed and yield useful information if a significant discrepancy is discovered. Any significant alteration in the comparison of the quality of pulses, the presence or absence of bruits, or significant upper-extremity blood pressure



FIG. 3 Ulceration in patient with arterial thoracic outlet syndrome.

discrepancies of greater than 20 mm Hg is highly suggestive of hemodynamically significantly subclavian or brachiocephalic disease. Of note, a significant blood pressure discrepancy in the upper extremity in an asymptomatic elderly patient is not uncommon and does not necessarily warrant additional investigation in the absence of symptoms or worrisome physical findings of digital ischemia.

Duplex ultrasound is extremely useful and sensitive in the interrogation of the cervical portion of the carotid arteries. However, it is of more limited use in the assessment of the brachiocephalic vessels because of their intrathoracic location. A diminished carotid pulse noted on palpation in conjunction with altered low velocity and dampened waveforms in the carotid artery at the base of the neck may be indirectly indicative of a hemodynamically significant proximal occlusive lesion that may mandate further investigation depending on the clinical setting. As described earlier, duplex ultrasound can easily detect flow reversal in the cervical part of the vertebral artery, which is suggestive of proximal subclavian occlusive disease. Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) are additional noninvasive imaging modalities that are useful in the assessment of the aortic arch and brachiocephalic vessels. Both modalities require intravenous contrast administration for adequate imaging of these vascular structures. In our experience, MRA tends to be fraught with motion artifact related to the underlying cardiac cycle and respiratory variation, and it also tends to overestimate the degree of stenosis of the occlusive lesions. CTA seems to be better tolerated by patients because a much shorter time is required to complete the study, which obviates the problems associated with claustrophobia seen in many patients undergoing MRA. Multiplanar digital subtraction angiography remains the gold standard imaging modality, and despite its more invasive nature, it remains particularly appropriate in those patients for whom potential endovascular treatment of the brachiocephalic disease is being considered.

TREATMENT

Indication for Treatment

The most frequent indication for the treatment of brachiocephalic disease includes patients whose symptoms can be directly attributed the anatomic location of disease. The symptoms may include lateralizing neurologic hemispheric symptoms, vertebrobasilar insufficiency, or upper-extremity ischemic symptoms. One would expect to identify significant lesions in the common carotid, subclavian, or innominate artery compatible with the lateralizing neurologic clinical presentation of the patient. In patients with nonlateralizing symptoms related to global hypoperfusion, multivessel brachiocephalic involvement, bilateral carotid disease, or tandem lesions should be suspected and confirmed on thorough workup. Classic subclavian steal syndrome with onset of vertebrobasilar symptoms with arm exercise also indicates a need for treatment.

There is a paucity of natural history data to direct decision making in patients with asymptomatic brachiocephalic disease. The rich data from retrospective analyses and subsequent prospective analysis of the risks inherent in severe asymptomatic carotid bifurcation disease do not exist for asymptomatic brachiocephalic disease. General agreement exists that asymptomatic subclavian artery occlusive disease need not be treated other than in the occasional patient who requires normalization of subclavian artery flow to support the use of an internal mammary bypass graft for coronary artery revascularization or in the difficult hemodialysis patient who requires placement of dialysis access in the extremity supplied by the stenotic subclavian artery. In the patient with asymptomatic severe proximal common carotid artery occlusive disease, it seems intuitive that intervention should be considered for a preocclusive or critical stenosis at its origin to preserve patency of the common carotid artery and consequently reduce the long-term risk for stroke. Brachiocephalic reconstruction has also become increasingly used in conjunction with endovascular repair of thoracic aortic dissection or aneurysm.

Before the routine use of endovascular techniques in the cerebrovascular circulation, treatment of tandem carotid disease presented a quandary for the treating physician. In the symptomatic patient, it was often unclear whether the symptoms were related to a carotid bifurcation lesion or to a more proximally located common carotid or innominate lesion. Prioritization of which lesion to treat first could be quite problematic. The currently favored strategy involves a combined approach with open carotid endarterectomy and retrograde angioplasty and stenting of the proximal common carotid artery or innominate lesion. To be clear, the proximal disease only needs intervention for severe, flow-limiting stenosis. Mild or moderate proximal lesions do not need to be treated concomitant to carotid endarterectomy and should simply be observed prospectively. In patients with nonatherosclerotic conditions affecting the brachiocephalic vessels, the indications for treatment should be reserved for the symptomatic patient. In patients with inflammatory arteritis such as Takayasu arteritis, the acute inflammatory phase should be treated medically to quiescence, and intervention should be reserved for resultant fibrotic stenosis in the affected vessels based on symptoms and severity, as is done with atherosclerotic lesions (Fig. 4).

Treatment Options

A number of therapeutic modalities are currently available for the treatment of brachiocephalic disease. The treatment options are categorized into two groups: open surgical reconstruction or endovascular intervention. These two general approaches are not mutually exclusive, and as mentioned previously, certain clinical situations may require combined treatment with both modalities to best treat more complex disease. Open surgical approaches may be further categorized as direct (anatomic) reconstruction and indirect (extraanatomic) reconstruction. The direct approach requires a median sternotomy for treatment of innominate or left common carotid artery lesions or a left posterior lateral thoracotomy for treatment of proximal left subclavian disease. The anatomic reconstruction maintains antegrade laminar flow accomplished through a bypass arising from the ascending aorta to the innominate and/or left common carotid artery. In the setting of isolated focal lesions localized to the innominate artery alone, endarterectomy may provide a suitable treatment option. Open repair may be preferred in suitable

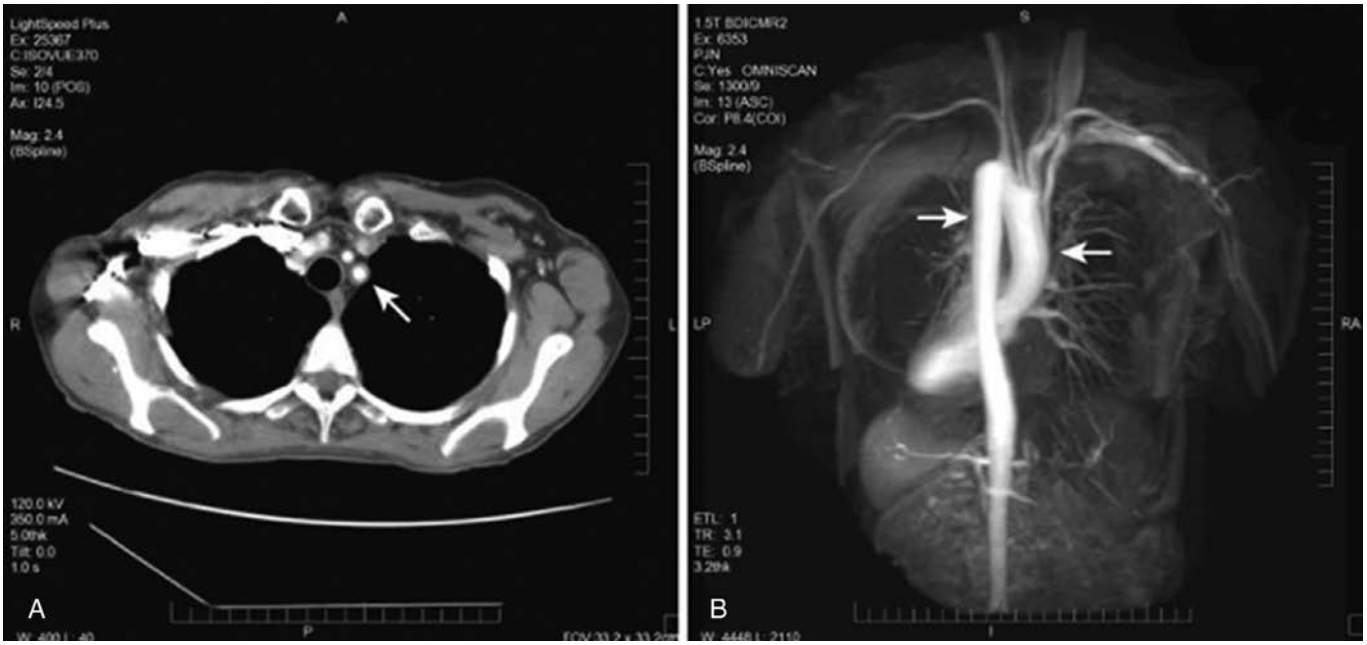


FIG. 4 Axial images from a CT angiogram **(A)** and three-dimensional reconstructed MRA **(B)** of a young woman with Takayasu's arteritis. Note the lucency surrounding the proximal brachiocephalic vessels on the CTA and the double contour of the ascending and descending thoracic aorta demonstrating wall thickening and inflammation.

risk patients with extensive severe calcific atherosclerotic disease at the origin of the vessel to be treated. If severe brachiocephalic disease is identified in a patient being considered for coronary artery bypass grafting, the coronary revascularization may be performed safely concomitant with the brachiocephalic revascularization.

In patients with severe calcific disease in the ascending aorta and aortic arch, in whom cross-clamping the aorta would be impossible or extremely hazardous and construction of a graft anastomosis would be difficult, or in patients deemed to be poor candidates for median sternotomy because of advanced age, prior sternotomy or mediastinal radiotherapy, or multiple comorbidities, the indirect approach is preferable. This procedure is performed through supraclavicular or cervical incisions and involves bypass grafting or arterial transposition. Extraanatomic procedures are very well tolerated, with inherently low morbidity and mortality rates, and excellent long-term patency rates have been reported. The choice between performing a direct or indirect vascular procedure for brachiocephalic disease is also dependent on a number of other anatomic/pathologic factors, including the number of vessels involved, the location and distribution of the occlusive lesions in the involved vessel, the underlying pathogenesis and nature of the symptoms (embolic vs. hypoperfusion), and the status of the other vessels supplying the brain not requiring or amendable to intervention, such as total internal carotid artery occlusion.

Advances in guidewire, angioplasty balloon, and stent design as well as the availability of covered stent grafts, have broadened the applicability of endovascular treatment of severe brachiocephalic disease. As the experience and skill of the interventionalist have grown with the technologic advances and improved device availability, endovascular treatment of fairly complex brachiocephalic disease has gained wider acceptance and use. With appropriate careful technique, excellent outcomes have been achieved with low associated morbidity. As is true for intervention in any vascular bed, close follow-up and regular surveillance is mandatory regardless of the type of intervention performed in the treatment of brachiocephalic disease.

ANATOMIC (DIRECT) REVASCULARIZATION

Endarterectomy

Endarterectomy may be considered for focal atherosclerotic lesions in the innominate artery. This would be performed via median sternotomy. It should not be attempted in patients in whom the lesion is located at the ostium of the vessel because these lesions are an extension of severe atherosclerotic disease in the aortic arch. The calcific atherosclerotic disease involving the aortic arch could make placing a side-biting clamp on the arch just proximal to the takeoff of the innominate artery quite hazardous, and achieving a satisfactory end point of the endarterectomy into the aortic arch would be difficult with the associated risks for embolization, residual flap formation, or dissection. Additionally, innominate artery endarterectomy should not be considered in patients possessing a bovine configuration because this would require temporary disruption of flow into the right and left carotid systems simultaneously. Accomplishing a satisfactory end point in the left common carotid artery may also prove difficult with this anatomy.

Proper endarterectomy for innominate arterial atherosclerotic lesions requires placement of a side-biting clamp across the aortic arch at the level of the takeoff of the innominate artery. This allows extension of the endarterectomy proximally onto the aortic arch itself to remove all of the plaque that arises from the aorta. The endarterectomy is performed through a longitudinal arteriotomy that typically does not require patch closure because of the large caliber of the vessel. Distribution of plaque into the right subclavian and right common carotid artery may require extension of the median sternotomy incision up into the right side of the neck along the anterior border of the sternocleidomastoid muscle. Again, achievement of satisfactory end points with this extent of disease may prove difficult, and bypass from the ascending aorta in these situations is probably more prudent.

Endarterectomy for isolated atherosclerotic lesions in the proximal left common carotid artery and left subclavian artery may be

performed; however, these procedures require a median sternotomy in the case of left common carotid lesions or a left thoracotomy in the setting of left subclavian origin disease, and they are more appropriately treated with extraanatomic approaches, which have proven to be better tolerated with excellent patency rates. An endovascular approach to these lesions (either through an antegrade transfemoral approach or, more commonly, a retrograde cervical approach for left common carotid artery lesions or a retrograde left brachial approach for left subclavian lesions) has been successfully performed with excellent technical success and patency rates. These techniques are discussed more fully later in this chapter.

Bypass Graft

Bypass grafts constructed in an antegrade configuration are performed through a median sternotomy incision, with the origin of the bypass graft arising from the anterolateral aspect of the ascending aorta. Careful palpation of the ascending aorta should be performed to avoid placement of the partially occluding side-biting clamp in an area of significant atherosclerotic disease. Intraoperative epiaortic ultrasound can be used as an adjunct to identify calcium in the ascending aorta. Careful sizing and positioning of the graft is mandatory to avoid kinking or graft compression in the retrosternal space when the sternum is closed. Additionally, the grafts are tunneled posterior to the innominate vein. A bulky graft may cause compression of the innominate vein, leading to left brachiocephalic vein occlusion and left arm swelling postprocedure. Therefore, in the clinical setting in which both the innominate artery and the left common carotid artery are to be bypassed, use of a bifurcated graft should be avoided because of the large volume and bulky nature of these grafts in this limited space.

Following systemic heparinization of 100 units/kg for a goal ACT >250, a partially occluding clamp is applied on the ascending aorta as previously described, and a 10- to 12-mm woven Dacron tube graft is anastomosed to the ascending aorta in an end-to-side fashion with 4-0 Prolene (Ethicon, Piscataway, NJ) suture. The graft is then clamped, tunneled, and distended with blood to assess hemostasis of the suture line and proper length of the graft before trimming. The distal anastomosis to the innominate artery is then performed either in an end-to-end or end-to-side fashion, depending on the clinical situation. When concomitant bypass to the left common carotid artery is required, an 8-mm knitted Dacron graft is taken off the innominate bypass graft in an end-to-side fashion above the thoracic inlet and left brachiocephalic vein to avoid graft kinking or compression. The distal anastomosis to the left common carotid artery may then be performed in an end-to-end or end-to-side configuration with 5-0 Prolene suture—again, depending on the clinical situation. Proximal occlusive lesions of the left subclavian artery are rarely symptomatic; therefore, a "triple bypass" of all three brachiocephalic vessels is rarely, if ever, indicated for occlusive disease. As noted previously, isolated left subclavian disease, when symptomatic, is best treated with endovascular treatment or extraanatomic bypass.

Brachiocephalic reconstruction may be performed safely with excellent outcomes. Multiple series have historically reported 30-day mortality rates of 4% to 7%, perioperative stroke rates ranging from 2% to 5%, and 5-year and 10-year patency rates exceeding 90%. As in the case of patients undergoing carotid endarterectomy, these patients must be followed closely with annual physical examinations and surveillance duplex ultrasound for assessment of graft patency.

EXTRAANATOMIC (INDIRECT) REVASCULARIZATION

Isolated unilateral proximal common carotid artery or proximal subclavian artery lesions are readily treatable with extraanatomic reconstructions. These indirect methods of revascularization are performed through supraclavicular and/or cervical incisions and are better tolerated, with less perioperative morbidity and mortality, and they achieve patency rates similar to those of direct reconstruction. The most common form of revascularization is for construction of a prosthetic bypass between the ipsilateral carotid and subclavian arteries. The prosthetic graft utilized is usually a 7-mm or 8-mm knitted Dacron or polytetrafluoroethylene (PTFE) conduit. For treatment of proximal lesions, the procedure is performed through a single transverse supraclavicular incision at the base of the neck. The clavicular head of the sternocleidomastoid muscle is divided, and the scalene fat pad is reflected cephalad, taking care to identify and protect the phrenic nerve coursing anterior to the anterior scalene muscle. Care should also be taken to preserve the lymphatics at this level. The anterior scalene muscle is then transected off its insertion to the first rib, exposing the underlying subclavian artery. The internal jugular vein is identified at the medial aspect of the supraclavicular incision and is mobilized laterally, exposing the underlying common carotid artery at the base of the neck. Care is taken to identify and protect the vagus nerve, which should be gently retracted laterally with the internal jugular vein. A short tunnel through the scalene fat pad is then made carefully behind the internal jugular vein and the vagus nerve. On the left side, great care should also be taken to avoid injury to the thoracic duct. In this exposure, a short bypass graft is constructed between the proximal common carotid artery and mid-subclavian artery in an end-to-side fashion with 5-0 or 6-0 Prolene sutures. It is not necessary to consider placement of a shunt during cross-clamping of the common carotid artery for performance of a carotid-to-subclavian bypass, and obviously a shunt is not necessary for a subclavian-to–common carotid artery revascularization.

In the performance of a subclavian-to-carotid bypass, it may at times be necessary to perform a concomitant carotid endarterectomy. In this setting, the procedure is performed through a supraclavicular incision at the base of the neck as well as an additional incision higher up the neck along the anterior border of the sternocleidomastoid muscle, as is typically performed in standard carotid exposure for endarterectomy. End-to-side anastomosis to the subclavian artery is constructed, and the bypass graft is then tunneled and brought up distally to the carotid bifurcation to the endarterectomy arteriotomy site with the distal subclavian-to-carotid anastomosis serving as a patch closure. This type of reconstruction is particularly required in situations in which the entire common carotid artery is occluded up to the level of the carotid bifurcation, and internal carotid artery patency has been preserved via retrograde filling through the external carotid artery and its branches. Our preference in the treatment of coexistent focal hemodynamically significant stenosis of the proximal carotid artery with severe carotid bifurcation disease remains performance of retrograde angioplasty and stenting of the proximal common carotid lesion with open carotid endarterectomy and patch angioplasty. The technique for retrograde angioplasty is discussed later in this chapter.

In settings in which the subclavian artery is not suitable for use as inflow for ipsilateral subclavian-to-carotid bypass, a carotid-to-carotid bypass may be considered. The contralateral carotid artery is used as the inflow vessel for revascularization. The common carotid arteries are exposed through bilateral longitudinal incisions at the base of the neck along the anterior border of the sternocleidomastoid muscle. The common carotid arteries are then dissected free and exposed in a standard fashion, and the pharynx is identified medially. A short retropharyngeal tunnel is then made between the pharynx and the anterior spinal ligament with a combination of sharp and blunt digital dissection. It is helpful to have a nasopharyngeal tube or an esophageal temperature probe in place to facilitate palpitation of the pharynx and ensure dissection in the proper plane. The retropharyngeal tunneling facilitates a shorter bypass graft and avoids the possibilities of skin erosion and the feeling of strangulation that sometimes occurs with subcutaneous tunneling of these grafts in the anterior neck. The grafts also pose a cosmetic issue in patients with a very slender neck when tunneled anteriorly. The prosthetic graft utilized is a 7- or 8-mm knitted Dacron or PTFE graft anastomosed in an end-to-side fashion at both common carotid arteries with 5-0 and 6-0 Prolene sutures. The common carotid arteries are not cross-clamped simultaneously; therefore, placement of a shunt is typically not required.

In rare instances, subclavian-subclavian or axillary-axillary bypasses have been utilized to restore pulsatile flow into the subclavian and vertebral arteries for symptomatic vertebral basilar disease, or in the presence of a total occlusion of the innominate artery, they may restore pulsatile flow to the right common carotid artery as well. The subclavian arteries are approached through supraclavicular incisions as described previously. The grafts are constructed in an end-to-side fashion and are tunneled across the suprasternal notch. The axillary-axillary bypass grafts are constructed through bilateral infraclavicular incisions. The pectoralis major muscle is split along the length of its fibers, and the clavipectoral fascia is incised. The axillary vein will be encountered initially during the dissection with the axillary artery located just posterior and slightly superior to the vein. The axillary vein is completely mobilized with ligation and division of multiple side branches to facilitate exposure to the axillary artery. The prosthetic graft is then anastomosed in an end-to-side fashion to the axillary artery and is tunneled subcutaneously across the front of the manubrium sterni. The subclavian-subclavian and axillary-axillary grafts are utilized in high-risk patients, usually those with hostile anatomy that would be encountered with the more standard direct or extraanatomic procedures.

ARTERIAL TRANSPOSITION

Subclavian-carotid or carotid-subclavian transposition has the advantage of avoiding prosthetic material and the small attendant risk of infection. The transposition procedure is more technically challenging than utilization of a bypass because of the requirement of a more extensive dissection and mobilization of the vessels. The dissection requires more retrosternal exposure of the proximal portion of the vessels, and particular attention must be paid to visualization and exposure of the internal mammary and vertebral arteries for transposition of the subclavian artery. The procedures are performed through a transverse supraclavicular incision. The dissection then proceeds along the anterior border or between the heads of the sternocleidomastoid muscle down to the internal jugular vein. The internal jugular vein and vagus nerve are then mobilized and gently retracted laterally, exposing the proximal common carotid artery. The subclavian artery is then exposed after identification and ligation/division of the vertebral vein. The subclavian artery is carefully dissected sharply, with dissection carried proximal to the takeoff of the internal mammary and vertebral arteries. In the subclavian-to-carotid transposition, the proximal subclavian artery is clamped with a Cooley-Darra clamp, transected, and carefully oversewn. Great care must be taken to avoid loss of control of this proximal stump because the stump is placed with tension to facilitate exposure in the upper mediastinum, and loss of this stump into the thoracic cavity before satisfactory suture ligation would be disastrous. The common carotid artery is then cross-clamped proximally and distally, and the subclavian artery is transposed and sewn in an end-to-side fashion with 5-0 or 6-0 Prolene suture. Care is taken to avoid kinking of the vertebral artery with the transposition. The indication and clinical situation requiring a carotid-to-subclavian transposition is much less common but is performed in a nearly identical fashion, with transection and suturing of the common carotid artery in the upper mediastinum and transposition of the common carotid artery to the subclavian artery just beyond the takeoff of the vertebral and internal mammary arteries. Subclavian-to-carotid transposition is our preferred technique in the event that debranching is required in the performance of thoracic aortic endograft treatment for aneurysm or dissection (Fig. 5). Newer techniques for management of the left subclavian artery during treatment of the thoracic aorta incorporate placement of a chimney stent graft in the proximal left subclavian artery or single-branch aortic grafts.

Outcomes for extraanatomic brachiocephalic reconstructions are excellent. Multiple series have shown low incidences of paraprocedural stroke, and 30-day mortality is less than 3%. The 5-year and 10-year patency rates exceed 90% in most series, and the patency rates of arterial transposition approach 100%.



FIG. 5 CTA of follow-up surveillance endovascular thoracic aneurysm repair in which debranching of the left subclavian artery with subclavian to left common carotid artery transposition *(arrow)* had been performed preoperatively.

ENDOVASCULAR TREATMENT

Numerous reports have demonstrated excellent results with open surgical revascularization in the setting of brachiocephalic disease with acceptably low 30-day mortality, stroke, and perioperative stroke as well as achievement of superb long-term patency of the reconstruction. However, as is true for all vascular beds, pursuit of minimally invasive procedures to treat brachiocephalic disease has been inevitable. Early reports of endovascular intervention in the arch vessels consisted mainly of lesions treated with angioplasty alone, and follow-up was limited. These studies revealed that endovascular intervention was feasible, and, as expected, utilization of endovascular techniques has increased with improvements in balloon and stent technology and maturation of technical skills in the treatment of cerebrovascular disease. In skilled hands, excellent outcomes with low morbidity and acceptable patency rates have been demonstrated.

Anatomic considerations are important in the planning of any treatment of brachiocephalic disease, but especially so if endovascular therapy is being considered. The anatomic characteristics of the lesions to be treated are key in the assessment for feasibility of treatment with catheter-based therapy. Endovascular intervention is preferable for stenosis rather than total occlusion and for nonostial, nonulcerative, and minimally calcified concentric lesions. Endovascular treatment is less favorable for severely eccentric lesions and lesions that extend contiguous to or into a major branch vessel, such as the vertebral artery arising off the subclavian artery, the left common carotid artery arising off the innominate artery in the bovine configuration, or minimal separation of the origins of the innominate and left common carotid artery off the arch. These configurations carry the added risk of the compromise of the origin of one vessel in

the treatment of another. Additionally, rotation of the vessel origin around the arch downward toward the ascending aorta for severe atherosclerotic disease affecting the aortic arch may make access and intervention of the brachiocephalic vessels much more challenging, and in these instances, open surgical treatment may be preferable.

INNOMINATE ARTERY INTERVENTIONS

Endovascular treatment of innominate lesions exposes the patient to potential embolization to both the right carotid and right vertebral artery distributions and therefore must be performed with great precision. Documentation of the position of the origins of the right common carotid and right subclavian artery branches in relation to the disease process is imperative. A kissing balloon technique is necessary to treat innominate lesions that extend directly proximate to or into the primary branches and to ensure proper distal stent placement. It is also important to ensure that the origin of the left common carotid artery is not compromised by angioplasty and stenting of a proximal calcific lesion in the innominate artery (Fig. 6).

The innominate artery has the most challenging angulation extending off the aortic arch for cannulation through an antegrade transfemoral approach. Prolonged attempts at cannulation should not be pursued from this approach because of the risk of trauma and consequent embolization from the associated atherosclerotic disease in the aorta. In this situation, a retrograde brachial access may be performed and safe traversal of the innominate lesion accomplished. The innominate lesion may then be treated over the wire placed from the retrograde brachial approach, or the retrograde brachial wire can be snared from below and brought down with a through-and-through technique for greater stability for passage of the sheath and angioplasty system.

For ostial lesions, 1 to 2 mm of the stent should protrude into the aortic lumen. If the angioplasty and stent are being performed through the retrograde right brachial approach, it may be difficult to inject adequate contrast to visualize the exact position of the innominate orifice relative to the aortic arch. It is helpful to have an angiographic pigtail catheter in place for arteriography and facilitation of better imaging. The transfemoral guidewire or angiographic catheter itself can act as a marker as it curves around the arch abutting the innominate orifice. With the brachial approach, the guidewire should be directed into the ascending aorta rather than making the sharp curve into the descending thoracic aorta because this facilitates in-line alignment for deployment of the stent.

The risk of embolization with primary angioplasty and stenting of innominate lesions appears to be low; therefore, the requirement for cerebral protection in these procedures remains unclear. In most instances, the simplest, most straightforward approach without protection is best unless a "high-risk" lesion with a worrisome potential for embolization is to be treated.

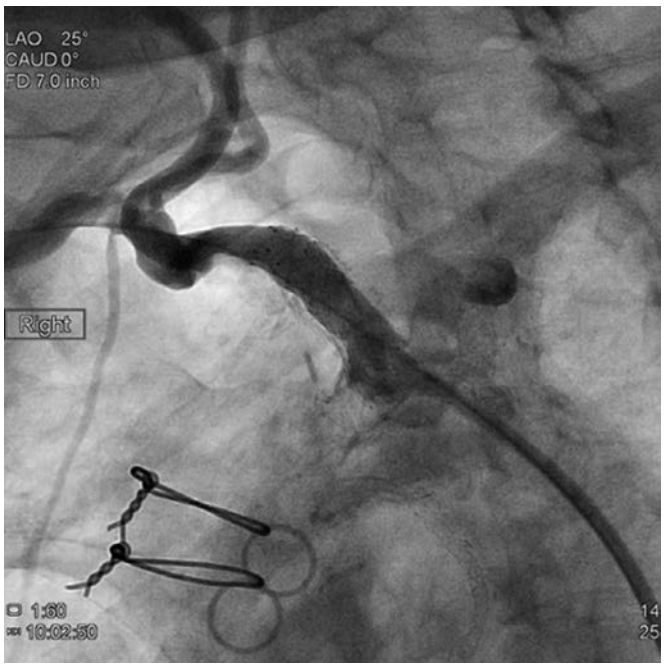


FIG. 6 Innominate artery following percutaneous transluminal angioplasty and stenting. Note the sternal wires from a previous coronary artery bypass, which would have made an open innominate artery revascularization technically challenging.

Left Common Carotid Artery

Endovascular treatment of left common carotid artery lesions at the level of the arch is feasible and safe and may be performed in an antegrade transfemoral approach similar to that described with the innominate artery intervention. In the situation of an angulated takeoff of the left common carotid artery from the arch and when better stability of the angioplasty system is required, a "buddy wire" may be positioned in the external carotid artery to facilitate maintenance of the guidewire and sheath position at the origin of the vessel, as is done in the treatment of more distal carotid disease. A protection device is frequently used with the antegrade transfemoral approach for endovascular interventions on "high-risk" lesions.

More commonly, proximal common carotid lesions are accessed in a retrograde fashion from the distal carotid artery via cervical incision. The carotid branches are thus readily controlled with application of a distal clamp, and cerebral protection is ensured.

Left Subclavian Artery

Antegrade transfemoral access to the left subclavian artery off the arch is the easiest of the three vessels to obtain. After accessing the origin of the vessel, a 0.035 guidewire is passed across the lesion into the distal subclavian artery. The guidewire may then be exchanged for a stiffer wire if deemed necessary. A long 6Fr or 7Fr sheath is then positioned just across the origin of the vessel at the level of disease. Predilation with a 4-mm angioplasty balloon may be necessary to facilitate passage of the stent. Correct sizing of the stent is essential to ensure that the area of disease is covered fully and that the vertebral artery origin is not "jailed." For ostial lesions, the stent should extend 1 to 2 mm into the aortic lumen (Fig. 7).

If the subclavian lesion approaches the origin of the vertebral artery, it may be important to protect the vertebral artery origin. This may be accomplished after placement of a larger sheath into the origin of the subclavian artery and exchange of the 0.035 wire for two separate 0.014 wires—one placed antegrade out into the axillary artery and the other placed antegrade in the vertebral artery. A balloon-expandable stent may be accurately placed over both 0.014 wires immediately at the takeoff of the vertebral artery. In another approach in which both antegrade transfemoral access and retrograde brachial access into the subclavian artery are obtained, the 0.014 wire is placed through the retrograde transbrachial sheath into the vertebral artery, and the angioplasty and stenting are performed across the 0.035 wire from the antegrade transfemoral approach. The retrograde transbrachial sheath also facilitates the imaging of the vertebral artery at the time of the intervention. Embolic protection of the vertebral artery has been described, but its routine use cannot be advocated because of the exceedingly low risk of emboli to the vertebral basilar system during subclavian artery intervention as well as the risk of dissection of the vertebral artery with instrumentation. Again, for emphasis, the simplest, most straightforward approach with the least guidewire and catheter manipulation is generally best.

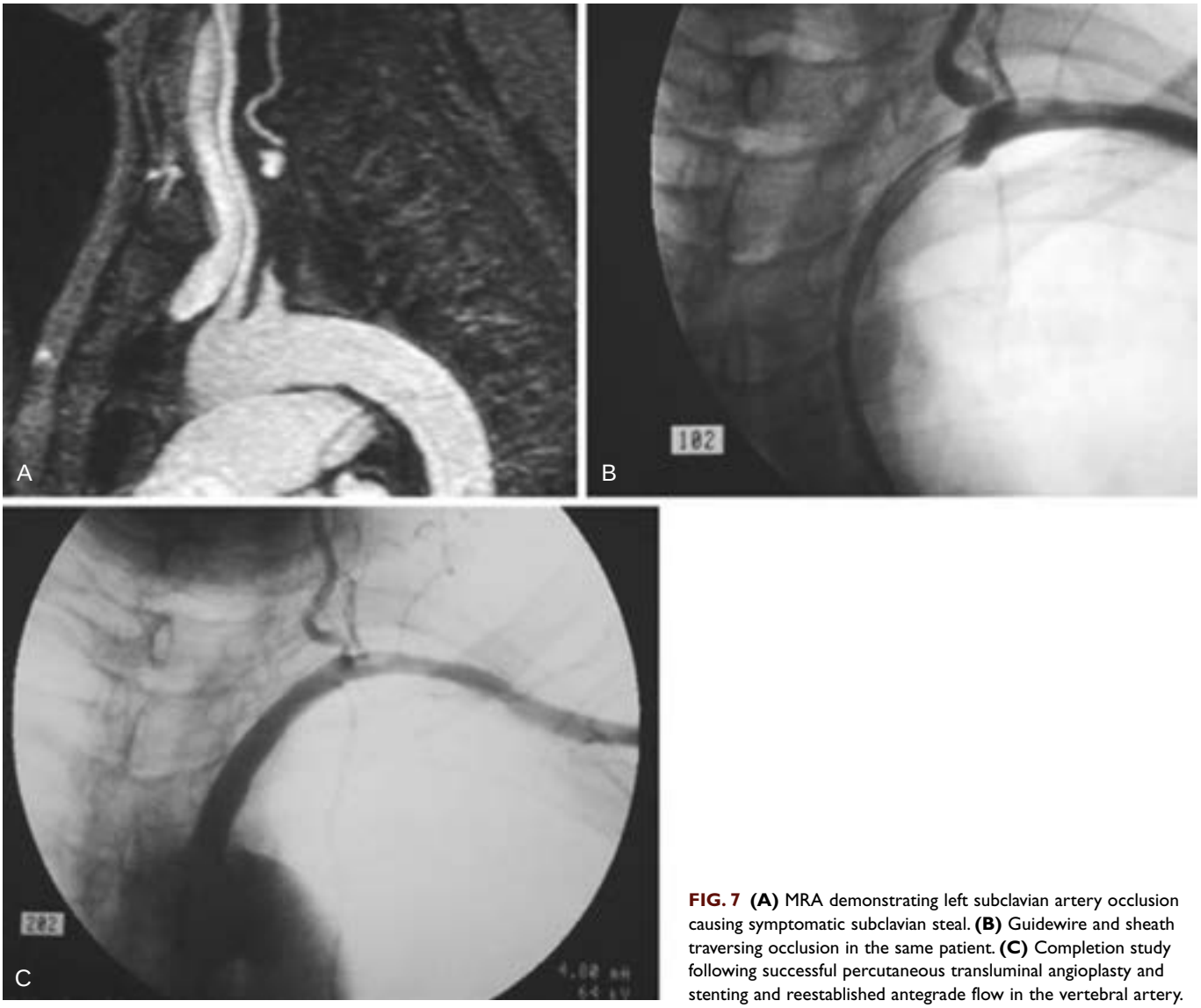


FIG. 7 **(A)** MRA demonstrating left subclavian artery occlusion causing symptomatic subclavian steal. **(B)** Guidewire and sheath traversing occlusion in the same patient. **(C)** Completion study following successful percutaneous transluminal angioplasty and stenting and reestablished antegrade flow in the vertebral artery.

MANAGEMENT OF THE LEFT SUBCLAVIAN ARTERY FOR THORACIC AORTIC ENDOVASCULAR REPAIR

For patients with a thoracic aortic aneurysm or dissection requiring endovascular repair, an adequate proximal seal length of 2 cm is recommended. Seal zone length is determined by preoperative three-dimensional reconstructed CTA. In up to 70% of patients presenting with dissection, the proximal extent of disease involves the left subclavian artery. This means coverage of the left subclavian artery is often required in treatment of these disease processes. In these cases, it is suggested that the left subclavian artery be revascularized before stent graft placement to maintain adequate spinal cord perfusion and prevent left upper extremity claudication or neurologic changes. This can be done via left carotid-to-subclavian bypass with endovascular plug of the left subclavian artery proximal to the vertebral artery or by subclavian-to-carotid transposition, as described earlier. Transposition is preferred if anatomy is favorable. We choose to perform this as a separate procedure if possible so the patient can be evaluated for complications from subclavian revascularization before thoracic aortic stent graft placement.

SUMMARY

The treatment of disease affecting the brachiocephalic vessels is safe, effective, and durable. Younger, low-risk patients are suitable candidates for direct anatomic reconstruction performed through a median sternotomy, particularly those patients with multivessel involvement. The direct anatomic reconstructions include a bypass arising from the ascending aorta or innominate arterial endarterectomy. Older adult patients with multiple comorbidities or patients with prior median sternotomies or a hostile mediastinum from other causes are better treated with an indirect extraanatomic approach or should be considered for endovascular intervention. Extraanatomic surgical reconstructions are performed with various types of prosthetic bypasses or arterial transposition. Endovascular therapy is performed via an antegrade transfemoral approach, a retrograde brachial approach, or, at times, a combination of both. Selection of the mode of treatment in each individual patient is based on various patient, anatomic, or pathologic factors in which one approach may be safer and more effective than another. The requirements for brachiocephalic reconstruction have increased with the ever-expanding treatment of aortic aneurysmal disease and aortic dissection for

the purposes of debranching and expansion of the applicability and appropriateness for endovascular treatment of aortic arch and descending thoracic aortic disease.

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Upper Extremity Arterial Occlusive Disease

Aric Wogsland, MD, Virginia L. Wong, MD, and Vikram S. Kashyap, MD

Upper extremity (UE) arterial occlusive disease and ischemia is much less common than in the lower extremity (LE) and can be caused by a wide variety of etiologies. Due to extensive arterial collateralization around the shoulder and elbow, patients may remain asymptomatic despite significant chronic arterial obstruction. Although rare, ischemic symptoms of the hand and arm are poorly tolerated and can lead to significant loss of function and disability. Therefore, diagnosis and management of UE ischemia can be considerably more challenging than for LE disease.

ETIOLOGY

A wide variety of disease states may lead to UE ischemia (Box 1). Atherosclerosis and inflammatory arteritis tend to affect larger, more proximal vessels, including the innominate and axillosubclavian arteries. Digital and smaller forearm arterial disease is commonly seen in renal failure, diabetes, and with connective tissue disorders. Embolism and trauma commonly affect the brachial artery. Iatrogenic manipulation, such as for arterial catheterization or hemodialysis access procedures, may exacerbate the effects of underlying arterial disease and precipitate new ischemic symptoms.

Systemic Disease

In the United States, atherosclerosis is the most common cause of subclavian artery obstruction, affecting the left side more frequently than the right side. Patients usually have associated risk factors (e.g., hyperlipidemia, hypertension, smoking, diabetes) and/or manifestations of atherosclerotic disease in other arterial beds (e.g., peripheral artery disease, coronary artery disease). Takayasu's arteritis, a form of inflammatory arteritis, is typically described in younger women and frequently affects the supra-aortic trunk vessels. Temporal or giant cell arteritis (GCA), generally found in patients greater than 60 years of age, affects the axillary to brachial arteries, as well as the superficial temporal and ophthalmic arteries. Both diseases are associated with systemic inflammation, though many patients with GCA may manifest a much more indolent and less-well identified inflammatory phase than those with Takayasu's disease. The inflammatory phase can be characterized by fever, fatigue, generalized myalgia, and arthralgia, accompanied by elevated erythrocyte sedimentation rate (ESR). Both inflammatory diseases produce characteristic smooth, tapering arterial stenosis that differs in angiographic appearance from the irregular, heterogenous plaque typically seen with atherosclerotic disease (Fig. 1). Superficial temporal artery biopsy may provide definitive diagnosis in cases of GCA.

Occlusive disease of the more distal upper extremity arteries is associated with a number of autoimmune, inflammatory, and rheumatologic conditions. Scleroderma, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), lupus, and rheumatoid arthritis are associated with small vessel disease, affecting palmar and digital arteries (Fig. 2). Thromboangiitis obliterans (Buerger's disease) affects small distal arteries and is strongly associated with ongoing tobacco use.

Embolism

Embolism is a frequent cause of acute upper extremity ischemia. Cardiac emboli secondary to arrhythmia is most common, with the majority of emboli lodging at the brachial artery terminus or more proximally at the origin of the deep brachial artery (Fig. 3). Other sources include proximal arterial aneurysm, ulcerated atherosclerotic plaque, and paradoxical embolus from deep venous thrombosis through a ventricular septal defect. Multiple emboli affecting smaller, more distal arteries should prompt evaluation for a proximal arterial source, especially in the absence of cardiac arrhythmia. Subclavian artery aneurysm or ulcerative lesion secondary to thoracic outlet obstruction can be a source of distal emboli (Fig. 4). Repetitive compression of the subclavian artery by myofascial and/or osseous structures at the thoracic outlet leads to poststenotic dilation and deposition of mural thrombus. Posttraumatic and infectious arterial aneurysms at any level can also result in embolization.

Trauma

Blunt and penetrating trauma involving the upper extremity can cause ischemia by multiple mechanisms, including arterial traction, intimal dissection, transection, and thrombosis. Iatrogenic pseudoaneurysm and thrombosis after brachial artery manipulation (e.g., arterial lines, interventional procedures) are complications that may not be recognized immediately due to the rich arterial collateral supply around the elbow. Effort-induced fatigue (i.e., arm "claudication") may develop later.

Repetitive trauma can also cause arterial injury. Hypothenar hammer syndrome, which affects the terminal portion of the ulnar

BOX 1 Causes of Upper Extremity Ischemia

Vasospasm
- Raynaud's disease
- Medication-induced vasopressors, β-blockers
- Ergot poisoning

Intrinsic Arterial Disease
- Atherosclerosis
- Radiation arteritis
- Azotemic arteriopathy
- Spontaneous dissection
- Fibromuscular dysplasia

Inflammatory Diseases
- Connective tissue disorders
- Buerger's disease
- Takayasu's arteritis
- Temporal (giant cell) arteritis
- Hypersensitivity angiitis

Noninflammatory Medical Disease
- Thrombophilic states
- Myeloproliferative disorders
- Cold injury
- Hepatitis-associated vasculitis
- Cryoglobulinemia
- Vinyl chloride exposure

Embolism
- Cardiac (most common)
- Proximal aneurysm
- Arterial thoracic outlet syndrome
- Atheroembolism
- Paradoxic embolus (with accompanying septal defect)

Trauma
- Iatrogenic
- Blunt arterial injury
- Penetrating arterial injury
- Hypothenar hammer syndrome
- Vibration



FIG. 1 Right upper extremity angiogram of a 57-year-old woman with temporal arteritis showing a classic, smooth, tapering stenosis in the proximal brachial artery. The patient's primary presenting complaint was forearm effort fatigue.

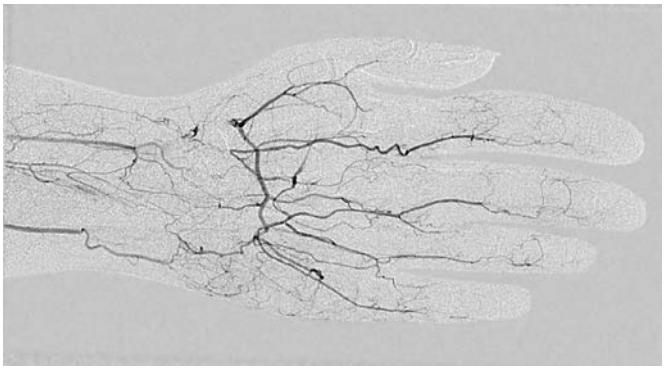


FIG. 2 Left-hand angiogram of a patient with scleroderma and small artery occlusive disease, producing multiple occlusions of the distal forearm, palmar, and digital arteries. The patient presented with severe Raynaud's syndrome and nonhealing fingertip ulcerations.

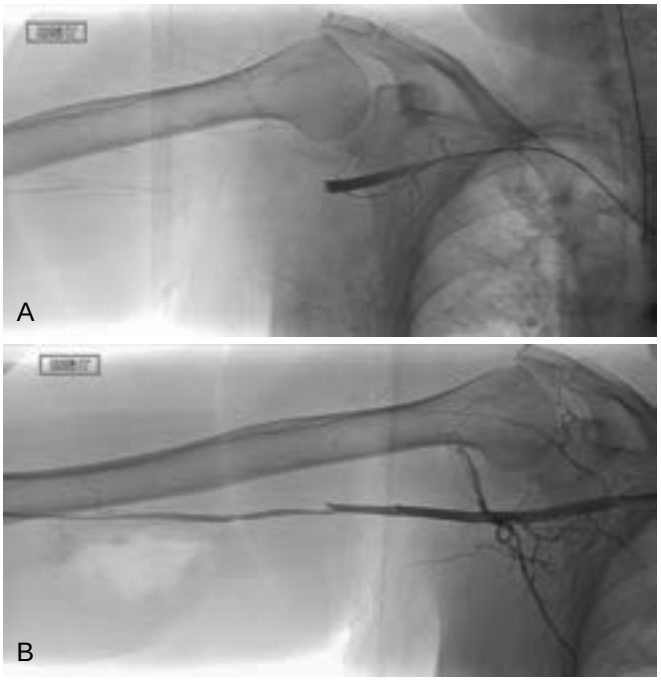


FIG. 3 **(A)** Embolic occlusion of the right axillobrachial artery secondary to atrial fibrillation. **(B)** Completion angiogram following surgical embolectomy.

artery in Guyon's tunnel (formed by the pisiform, the hook of hamate, and the transverse carpal ligament), results from repeatedly striking objects with the base of the palm. This can lead to segmental ulnar artery occlusion or aneurysm formation with subsequent digital artery embolism (Fig. 5). Vibration-induced digital artery injury has also been described from prolonged use of heavy tools such as jackhammers and chain saws.

EVALUATION

History and Physical Examination

A detailed history and physical examination are essential for diagnosing the correct etiology of upper extremity arterial disease. Symptoms may include digital color change, coolness, numbness, weakness, effort-induced fatigue (arm "claudication"), digital ischemic rest pain, and tissue loss (nonhealing digital ulcer or frank

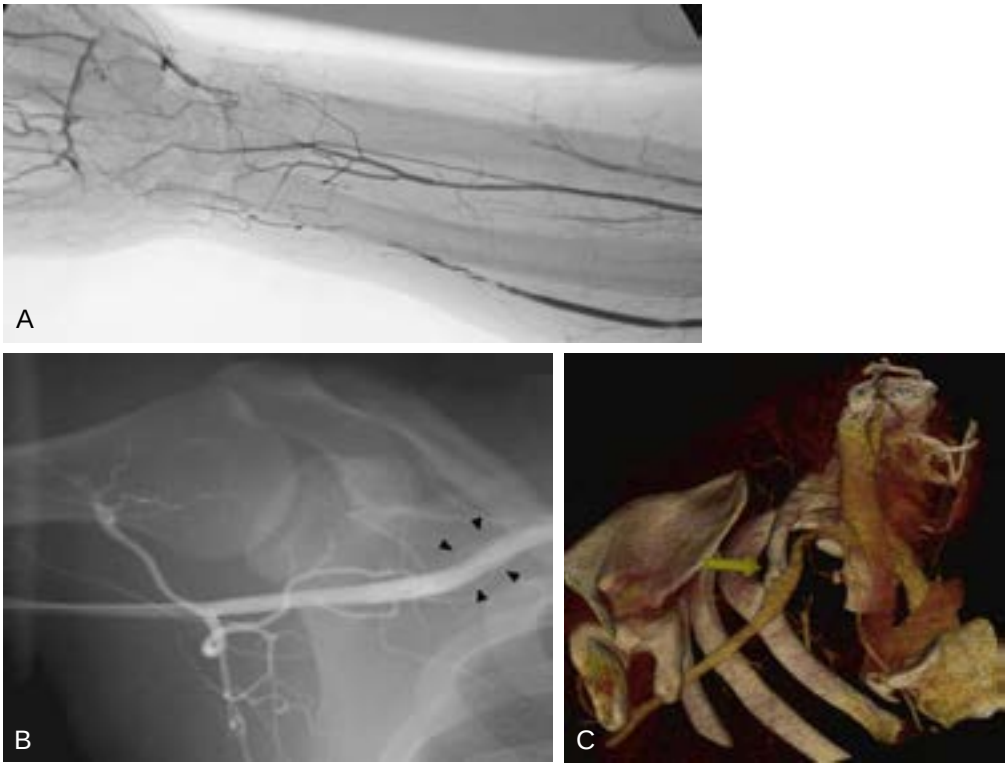


FIG. 4 **(A)** Right upper extremity angiogram in a 28-year-old, showing embolic shower to right forearm and hand arteries. **(B)** Right subclavian artery aneurysm with mural thrombus *(arrowheads)*. **(C)** Three-dimensional reconstruction of CT angiogram showing right subclavian artery pressed downward by overlying clavicle (removed from image for arterial visualization) onto bony exostosis between first and second ribs *(arrow)*.

gangrene). Raynaud's phenomenon may represent benign vasospasm, but it can also manifest secondary to fixed occlusive lesions, which must be ruled out. Involvement of the larger, more proximal arteries typically causes effort-induced fatigue. Digital tissue loss is nearly always associated with small vessel disease, with or without more proximal involvement. Patients who experience posterior circulation symptoms (e.g., dizziness, ataxia, diplopia) during prolonged use of the UE, may have subclavian steal syndrome. This is caused by siphoning of arterial flow away from the posterior cerebrum (via the vertebral artery) to provide antegrade flow to the ipsilateral UE in the face of an obstructing proximal subclavian artery (can also be innominate artery, if on the right side) lesion. Patients who have had coronary revascularization using the right or left internal mammary artery (i.e., RIMA or LIMA) may experience angina with use of the UE, as arterial flow is stolen away from the coronary bypass graft. Atherosclerotic risk factors, occupational activities, personal or family history of autoimmune or connective tissue disorders, and history of upper extremity arterial intervention or trauma should be investigated. Renal failure and vascular procedures for hemodialysis access should be noted.

A complete examination of the neck and upper extremities should be performed, documenting pulses at superficial temporal, common carotid, subclavian, axillary, brachial, radial, and ulnar locations on both sides. Diminished or absent pulses indicate significant stenosis or occlusion proximal to that location; symmetric disease may suggest a systemic condition. Auscultation over the proximal arteries for bruit and inspection of hands and digits for color, temperature, trophic changes, and tissue loss are important. Electrocardiogram and echocardiogram can diagnose arrhythmia and atrioventricular thrombus, which predispose to cardioembolism. Chest and cervical spine radiographs evaluate for cervical ribs or osseous anomalies causing arterial thoracic outlet obstruction. Computed tomography (CT) or magnetic resonance imaging (MRI) may be necessary to identify non-bony myofascial or ligamentous arterial entrapment. Serum studies for ESR, autoimmune markers (rheumatoid factor, antinuclear antibody, complement levels), hypercoagulable disorder (factor V Leiden, prothrombin gene mutation, antithrombin III, protein C and S deficiencies, antiphospholipid antibody, and hyperhomocysteinemia) may be helpful.

Noninvasive Vascular Evaluation

Evaluation in the noninvasive Vascular Laboratory should be undertaken in all patients with suspected UE arterial disease. Bilateral arm blood pressure measurement, segmental arterial limb pressures, wrist-brachial index (WBI), absolute digit pressures, digital plethysmography, and directed arterial duplex are useful for objective identification of upper extremity arterial disease and for quantifying the degree of ischemia. A blood pressure difference >20 mm Hg between right and left brachial arteries suggests unilateral axillosubclavian arterial disease. Diminishment of >15 mm Hg between ipsilateral arm segments suggests intervening hemodynamically significant arterial disease. Absolute resting digit pressure <50 mm Hg suggests significant ischemia. As with LE testing, arterial calcification due to diabetes or longstanding renal failure may result in falsely elevated pressures. Provocative positional testing can be helpful in diagnosing arterial thoracic outlet syndrome. Cold-induced digital waveform dampening in the face of normal WBI is helpful in diagnosing Raynaud's phenomenon and for ruling out more proximal fixed arterial lesions. Directed arterial duplex can provide detailed anatomic information for more peripheral lesions but is less useful for evaluation of intrathoracic lesions due to lack of sufficient visualization. Arterial duplex evaluation of the vertebral arteries can readily identify bidirectional or retrograde vertebral artery flow, which indicates stenosis or occlusion of the ipsilateral subclavian artery, proximal to the vertebral artery origin.

Advanced Imaging

Computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are important noninvasive modalities

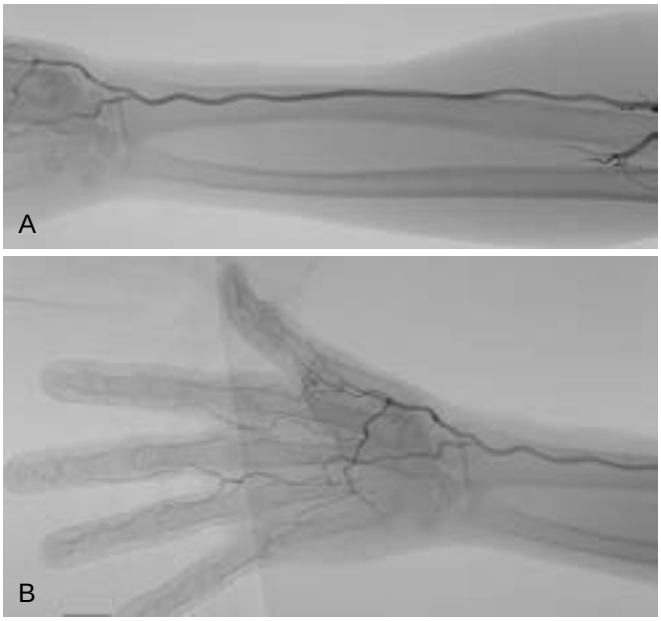


FIG. 5 Angiogram showing right ulnar artery occlusion in a 59-year-old retired millwright. Palmar and digital arterial supply is from the radial distribution. Hypothenar hammer syndrome is suspected.

for evaluating upper extremity arterial supply and the surrounding tissues. Aortic arch and large proximal artery visualization is excellent, while three-dimensional reconstruction and other postprocessing techniques are valuable for identification of thoracic outlet obstruction and planning surgical release or revascularization of these lesions (Fig. 6). Smaller forearm and hand arteries are less well visualized with tomographic imaging. Catheter angiography still provides the most detailed evaluation of the forearm, palmar, and digital arteries and may be necessary for preoperative planning. Heavily calcified arteries, metallic stents or operative clips, implanted vascular device leads or central venous catheters, and orthopedic hardware may produce significant artifact, obscuring diagnostic detail with any radiographic imaging modality. Risk of contrast-induced nephropathy must be considered when using CTA in patients with severe renal dysfunction. Risk of nephrogenic systemic fibrosis (NSF) may be a consideration with use of MRA in end-stage renal disease (ESRD) patients.

Catheter angiography remains a standard diagnostic imaging modality for UE arterial evaluation at any level and may also offer the opportunity for simultaneous endovascular treatment of selected lesions. Higher-quality images of smaller forearm and palmar arteries can be obtained with selective administration of contrast into the distal brachial artery. Provocative or diagnostic maneuvers such as catheter-directed vasodilator administration, pull-back intra-arterial pressure measurement, and angiogram with compression of flow through a patent ipsilateral arteriovenous access (evaluation for dialysis access-induced steal) can be performed during catheter angiography. Evaluation of the aorta and proximal upper extremity arteries requires aortic arch catheterization, usually from a transfemoral approach, while focal evaluation of distal brachial and forearm arteries can also be accomplished by antegrade or retrograde brachial arterial catheterization proximal to the level of suspected disease.

MANAGEMENT

Medical therapy represents the first line of treatment for many patients with UE arterial disease and is the preferred management during the acute phase of inflammatory arteritis. Surgery and intervention is generally recommended for patients with acute traumatic or embolic events, or for those with debilitating symptoms or significant ischemia. Endovascular techniques provide an opportunity for less-invasive treatment and have become the preferred option for focal proximal lesions that would otherwise require thoracotomy or sternotomy for direct access. Catheter-directed thrombolysis may be effective for acute small vessel thrombosis. However, the utility and durability of endovascular treatment is limited for more extensive and more distal arterial lesions, where surgical reconstruction is preferred.

Medical Therapy

For atherosclerosis, risk factor modification is indicated for all patients, including abstinence from tobacco and the use of lipid-lowering and antiplatelet therapy. Complete tobacco cessation is mandatory for a diagnosis of thromboangiitis obliterans (Buerger's disease), the symptoms of which may be improved simply by abstinence; however, the disease cannot be controlled in the face of continued tobacco exposure. Cold avoidance and calcium channel blockade with nifedipine may be useful for treatment of Raynaud's symptoms. The acute inflammatory stage of Takayasu's disease and GCA is treated with corticosteroids or other antiinflammatory agents such as cyclophosphamide, methotrexate, azathioprine, infliximab, or mycophenolate mofetil. Interdisciplinary management with rheumatology and other medical specialties is helpful. If possible, interventional treatment with endovascular or surgical techniques should be avoided during the acute inflammatory stage, due to poor results and high restenosis rates.

Endovascular Therapy

Endovascular therapy is particularly suited for short, focal obstructive lesions in the innominate, subclavian, and axillobrachial arteries. A transfemoral approach allows for antegrade aortography and selective UE angiography through a long, supportive sheath. Retrograde access from the ipsilateral brachial artery is another common approach and affords the most direct access to orificial supraaortic trunk lesions. However, retrograde passage of large sheaths for the delivery of interventional devices may be limited by brachial artery diameter and may require preemptive surgical exposure (i.e., cutdown) to repair the access site following sheath decannulation and avoid access site complications. Intraprocedural and postoperative anticoagulation management and monitoring for hand ischemia and median nerve compression symptoms caused by brachial sheath hematoma are routine. In 2019, Madden and colleagues evaluated brachial artery complications associated with percutaneous access for endovascular interventions. They reported a 10% complication rate, including the need for surgical exploration for bleeding and thrombosis. The incidence of complications increased with larger sheath diameters: 5.4% for 5Fr, 12.4% for 6Fr, and 12.5% for 7Fr. The liberal use of open surgical exposure and primary arterial repair is recommended when using the brachial artery for access, especially when larger sheath access is anticipated.

Once wire access across the lesion has been achieved, balloon angioplasty alone may provide sufficient treatment. Self-expanding bare metal stents are used for significant residual stenosis (>20% luminal diameter stenosis or persistent pressure gradient >20 mm Hg), immediate elastic recoil, or dissection following angioplasty. Balloon-expandable stents are useful for treatment of focal calcific lesions at the innominate, carotid, or left subclavian artery orifice, where obstruction is due to spillover aortic plaque; these lesions typically require higher radial force and precise stent deployment for treatment (Fig. 7). Covered stents can be used to treat traumatic arterial pseudoaneurysm or for rupture following balloon angioplasty. Care should be taken to avoid using balloon-expandable stents in areas where they may become easily deformed by UE movement, such as through the midsubclavian artery at the thoracic outlet or in the axillary artery. Even repeated compression of self-expanding stents in these locations can result in stent fracture. However, stenting



FIG. 6 **(A)** MRA of the aortic arch and supra-aortic vessels. **(B)** Coronal reconstruction CT angiogram demonstrating aberrant right subclavian artery origin from distal posterior aortic arch, beyond innominate and left common carotid artery origins.

lesions in this area may be considered once surgical decompression of the thoracic outlet has been achieved and is a common adjunctive procedure for treatment of thoracic outlet syndrome. Following stent therapy, antiplatelet agents are routinely administered.

While open surgical balloon catheter thromboembolectomy provides the most rapid restoration of arterial flow in patients with severe, acute ischemia due to thrombosis or embolism, access to smaller arteries of the hand and digits is not possible in this manner. Catheter-directed thrombolysis can be very useful for thrombosis of distal forearm, palmar, and digital arteries. The transfemoral approach is preferred, using a long, supportive sheath for delivery of the thrombolytic agent via an infusion wire or catheter advanced into the thrombus, or positioned to allow the agent access to affected vessels. Continuous thrombolytic infusion is continued, monitoring for signs of hemorrhage and for a decrease in serum fibrinogen level. Angiography through the existing catheter takes place at intervals to assess thrombolytic progress or adjust catheter position for maximum gain. Therapy is complete when an acceptable clinical or angiographic result is obtained or is terminated when no further progress is made or if bleeding or a critical drop in serum fibrinogen occurs. Risk of bleeding complications increases with duration of therapy and total amount of lytic agent delivered. Forearm or hand fasciotomy may be required for release of compartment syndrome following revascularization in patients with severe ischemia lasting more than 6 hours or in those who exhibit compromised neuromotor function.

Surgical Therapy

Exposure techniques, revascularization options, and procedural success vary depending on the etiology and extent of arterial disease, as well as the anatomic location of the lesion.

Operative Exposure of the Subclavian Artery

Due to the oblique and posterior course of the aortic arch, different approaches are needed to access the proximal right or left subclavian artery. The origin of the right subclavian artery is best exposed

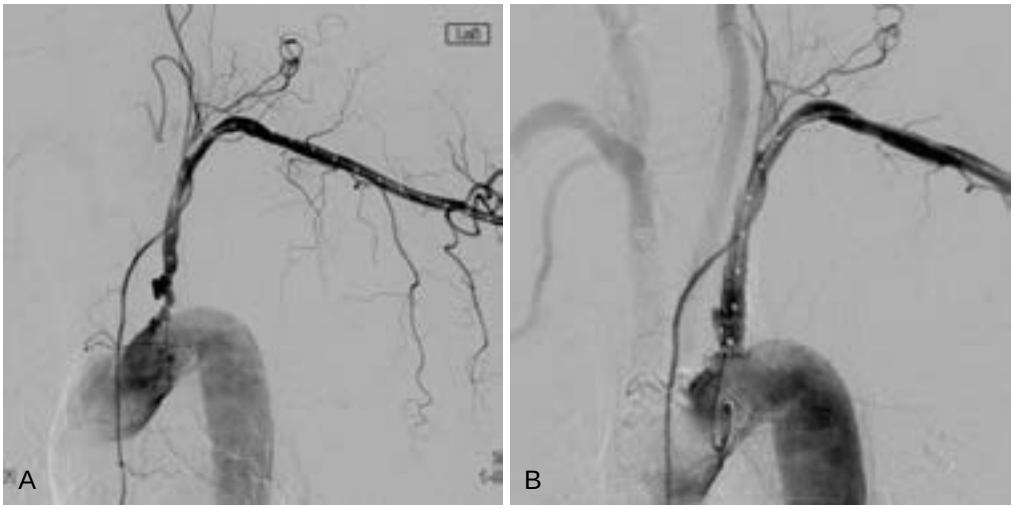


FIG. 7 **(A)** Aortogram from retrograde left brachial artery approach showing orifical subclavian artery stenosis. **(B)** Aortogram following deployment of a balloon-expandable bare metal stent across the lesion.

through a median sternotomy. Mobilization of the overlying left brachiocephalic vein allows complete visualization of the innominate artery and its bifurcation into the right subclavian and common carotid arteries. Cervical extension of the incision allows access to the right carotid sheath. Care must be taken to avoid injury to the right recurrent laryngeal nerve, which courses inferiorly around the proximal right subclavian artery and ascends medially between the esophagus and trachea. The preferred approach to the more posteriorly positioned left subclavian artery origin is through a left lateral thoracotomy, sited between the 4th and 5th ribs. Following entry into the pleural cavity, inferior retraction of the left upper lobe will reveal the aortic arch, visible through the mediastinal pleura. The vagus nerve passes anterolateral to the left subclavian artery, and the thoracic duct lies posteromedial to the artery. Care must be taken to avoid injury to either of these important structures. Given the development of endovascular techniques that provide good treatment results for orifical subclavian artery lesions, the morbidity associated with direct open surgical approach can often be avoided. Limited exposure of either the right or left proximal subclavian artery can be achieved via a supraclavicular cervical incision and is useful for the revascularization procedures described later.

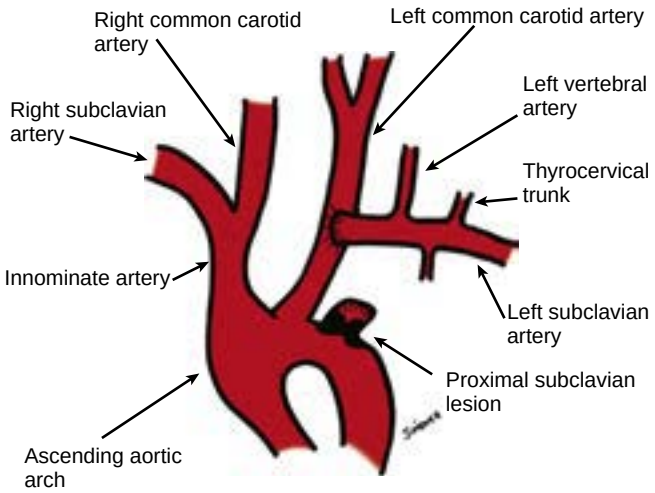


FIG. 8 Left subclavian artery transition.

Surgical Reconstruction for Proximal Subclavian Artery Lesions

Carotid-subclavian artery bypass and subclavian artery transposition have both been described extensively for operative treatment of proximal subclavian artery obstruction, with 75% to 90% patency at 5 years and acceptable morbidity. Preoperative evaluation should include carotid duplex to determine whether common carotid and/or bifurcation disease also requires treatment and to evaluate the vertebral arteries. Advantages of transposition include completely autogenous reconstruction and the need to perform only one anastomosis. Bypass avoids the need to obtain very proximal subclavian artery control deep in the incision and is better suited for extensive lesions beyond the orifice. Bypass is also preferred for preservation of a patent internal mammary artery to coronary artery bypass graft.

Subclavian Artery Transposition

The patient is placed in a supine position, with the head turned away from the operative side. A small roll placed under the shoulders helps provide better neck extension. A short, transverse cervical incision is made 2 cm above the clavicle and parallel to it, from the sternoclavicular joint toward the midclavicle. The platysma is divided, and then the clavicular head of the sternocleidomastoid muscle is divided for better visualization. The scalene fat pad is mobilized superiorly, exposing the anterior scalene. The phrenic nerve, which runs from lateral to medial across the anterior scalene on its way into the chest, must be identified and preserved. The anterior scalene is divided from its attachment to the first rib. The internal jugular vein is mobilized and retracted laterally to allow access to the common carotid artery. The vagus nerve should be identified and preserved. On the left, the thoracic duct may require ligation; injury will cause serious lymphatic leak. The subclavian artery is skeletonized, obtaining control of the thyrocervical trunk, vertebral, and internal mammary arteries. Following heparinization, branch vessels are occluded first to prevent embolism. The subclavian artery is clamped and divided as far proximal as possible. The proximal arterial stump is then secured with stay sutures and immediately oversewn to avoid retraction of the artery back into the chest before secure closure can be achieved. The common carotid artery is clamped. Shunting is usually not required so long as the carotid artery bifurcation remains open. The common carotid artery is opened longitudinally on its posterolateral surface, and end-to-side anastomosis is performed between the transected subclavian artery and the common carotid artery (Fig. 8). If the subclavian artery is too short to reach, mobilization of the common carotid artery may

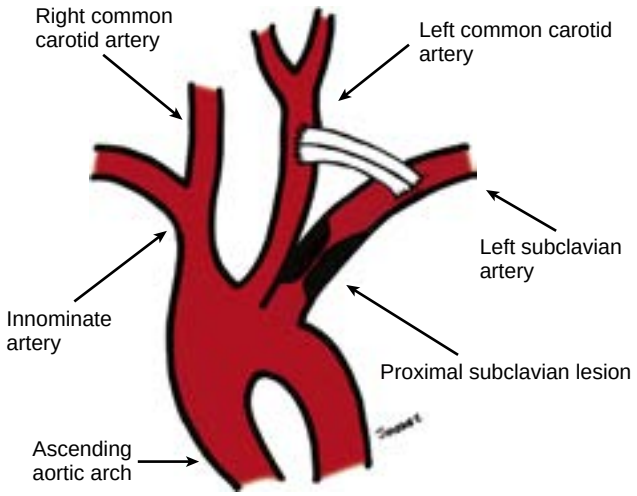


FIG. 9 Carotid-subclavian bypass.

bring it farther laterally. Division of the internal mammary artery may provide more length as well. The incision is closed over a closed suction drain, left in place for 24 hours. The drain is removed when sanguineous and/or lymphatic drainage has diminished.

Carotid-Subclavian Bypass

Patient positioning and exposure is as discussed earlier for subclavian artery transposition. For bypass, only a short segment of the subclavian artery needs to be exposed. The usual site is just distal to the thyrocervical trunk. As such, most of the dissection takes place lateral to the clavicular head of the sternocleidomastoid muscle. Phrenic nerve injury is more common with this more lateral approach, and a concerted effort to identify this structure early in the dissection is required. A short polytetrafluoroethylene (PTFE) graft is tunneled beneath the internal jugular vein, and end-to-side anastomosis is performed to the common carotid and subclavian arteries (Fig. 9). Beveling the carotid end of the graft 20 to 30 degrees is necessary to direct the bypass graft downward toward the subclavian artery.

Axillary Artery

Occlusive lesions of the axillary artery are rare. Exposure may be required for trauma or for proximal anastomosis of an axillofemoral bypass. The ipsilateral arm is abducted onto an arm board. An infraclavicular incision is made two fingerbreadths below the midclavicle and extended to the deltopectoral groove. Fibers of the pectoralis major muscle are split, and the underlying clavipectoral fascia is opened. The pectoralis minor muscle is divided at its tendinous insertion onto the acromion for better visualization. The axillary vein lies slightly anterior and inferior to the artery; overlying venous branches may require division for full exposure of the artery. Care must be taken to avoid transection of the lateral pectoral nerves, which may lead to postoperative pectoralis muscle atrophy.

Surgical revascularization of the axillary artery for occlusive disease is required infrequently. Carotid-axillary, carotid-brachial, subclavian-brachial, and axillobrachial bypasses have been described and may be required for extensive subclavian artery lesions, trauma, or revascularization of failed, less-extensive bypasses. Autogenous vein appears to be the preferred conduit in this location, likely due to the length of graft required for revascularization.

Brachial Artery

For access to the brachial artery, the ipsilateral arm is abducted onto an arm board or table. Exposure can be achieved through a longitudinal incision made anywhere along the bicipital groove on the medial limb, between the biceps and triceps muscles. The basilic vein will be medial and superficial to the brachial sheath. The median nerve lies immediately adjacent to the brachial artery and is usually encountered first upon opening the brachial sheath. Care must be taken with the use of traction and cautery to avoid injury to this large sensorimotor nerve. Mobilization over several centimeters will allow enough slack for gentle vessel loop retraction of the nerve away from the underlying brachial artery. Crossing branches from paired brachial veins may require division for full exposure of the artery. Exposure of the terminal branchial artery and its bifurcation into radial and common ulnar interosseous arteries can be achieved by extension of the arm incision onto the anterior forearm in "lazy S" fashion so as to avoid longitudinal scar contracture across the antecubital crease. Division of the bicipital aponeurosis is necessary to achieve contiguous exposure of the artery across the antecubital space. A number of patients (estimated at 10%–25%) have a radial artery origin much more proximally in the limb (so-called brachioradial artery variant), which may be located anywhere between the axillary artery and the brachial artery terminus. This artery is usually encountered as a smaller caliber, more superficial vessel, which is not in immediate proximity to the median nerve. The identification of two arterial structures at the antecubital crease or in the distal arm on preoperative or intraoperative duplex raises the suspicion for this variant. It is the most commonly identified upper extremity arterial variation, distinct from the rare superficial brachial artery or truly duplicated brachial artery variations. Definitive identification of variant radial artery anatomy requires complete duplex ultrasound visualization (from origin to wrist), extensive proximal exposure for direct visualization, or angiography; however, persistence of a radial pulse at the wrist following brachial artery cross-clamping should help confirm anatomy.

For localized brachial artery trauma or for catheter retrieval of thromboembolic material, exposure and mobilization of a relatively short distance of the brachial artery will suffice. Control of the uninvolved proximal and distal artery should be obtained. Primary suture repair or reanastomosis can be considered if adequate length and sufficient vessel circumference remain following debridement of devitalized tissue. Patch angioplasty or interposition graft may be required for repair or bypass of more extensive lesions. Saphenous vein is the preferred conduit for brachial artery bypass, due to size match and improved patency over prosthetic material. Only autologous material should be used in infected or contaminated fields. Penetrating or extensive blunt trauma may also be associated with nerve injury; detailed sensory and motor examinations should be performed before and after revascularization.

Radial and Ulnar Arteries

Exposure of the radial artery in the forearm is achieved via a longitudinal incision oriented along a line extending from the antecubital crease to the styloid process of the radius. The fascia is opened along the medial border of the brachioradialis muscle. Proximally, the artery lies beneath the muscle. More distally, the artery lies deep to the antebrachial fascia, between the brachioradialis and flexor carpi radialis tendons. At the wrist, the radial artery is quite superficial, lying just beneath the antebrachial fascia and medial to the radius. Exposure of the ulnar artery in the forearm is achieved by following a plane between the flexor carpi ulnaris and flexor digitorum superficialis muscles. In the midforearm, the artery lies beneath the flexor carpi ulnaris muscle and adjacent to the ulnar nerve. Distally, the artery lies just beneath the antebrachial fascia. Bypass to the forearm arteries is rarely used and is most often required for trauma or neglected embolic occlusion.

RESULTS OF TREATMENT

Open surgical bypass has long been the preferred option for extensive or more distal arterial disease. In 1993, Mesh et al. performed 95 upper extremity arterial bypass procedures over a 15-year period with an overall 5-year patency of 63%. Autogenous conduit

demonstrated superior patency at all anatomic sites compared with prosthetic material (71% vs. 38%). All far distal forearm prosthetic grafts failed within 1 year. A series by Spinelli and colleagues from 2009 reported on 23 upper extremity bypasses performed over a 10-year period, primarily in patients with critical limb ischemia. They achieved 83% primary 3-year patency, using autogenous conduit in more than 80% of cases. Thus, the surgical literature supports using arterial bypass with autogenous conduit.

With regard to less extensive and more proximal lesions, Ziomek and colleagues reported that prosthetic graft is the conduit of choice for short-length carotid-subclavian bypasses, with superior long-term patency than for autogenous vein bypass (94% vs. 58% at 5 years). However, they and others conclude that subclavian transposition may yield slightly better results then bypass. Systematic review in 2002 by Cina et al. found higher mean 1-year patency and symptomatic freedom rates associated with transposition (98% and 99%) compared with bypass (84% and 88%).

In 2007, AbuRahma et al. compared results of endovascular therapy using subclavian artery balloon angioplasty/stenting with those from carotid-subclavian bypass for symptomatic lesions. Over a 10-year period, 121 patients were treated with balloon angioplasty/stenting, while 51 patients were treated with surgical bypass. There was no difference in survival between the two groups. Primary patency at 1 year was 93% for angioplasty/stenting and 100% for bypass. Superior primary patency was noted at 5 years in the surgery group (96%), compared with the endovascular group (70%), though in higher risk or older patients, endovascular therapy may be quite acceptable.

SUMMARY

Upper extremity arterial occlusive disease and ischemia are less common than in the lower extremity, but when symptomatic, it can cause significant disability. The etiology is diverse and may include systemic conditions, necessitating a thorough clinical evaluation before deciding upon a treatment strategy. Medical management is useful for optimizing and controlling systemic disease. Endovascular therapy is acceptable as an effective, less-invasive treatment option, particularly for less extensive or intrathoracic lesions. Surgical revascularization remains the standard therapy for more extensive lesions and for more distal disease, with acceptable results for most upper extremity bypass procedures.

Suggested Readings

AbuRahma AF, Bates MC, Stone PA, et al. Angioplasty and stenting versus carotid-subclavian bypass for the treatment of isolated subclavian artery disease. *Endovasc Ther*. 2007;14:698–704.

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Aortoiliac Occlusive Disease

Maryam Ali Khan, MD, Claire Janssen, MD, and Mahmoud B. Malas, MD, MHS

INTRODUCTION

Peripheral arterial occlusive disease (PAOD) affects an estimated 4.3% of the population in the United States and is anticipated to increase in prevalence with a growing aging population. Atherosclerosis is the most frequent cause of aortoiliac occlusive disease. Risk factors include age, smoking, gender, race, ethnicity, diabetes, hypertension, dyslipidemia, a family history of PAOD, chronic kidney disease, and hyperhomocysteinemia. Cigarette smoking, the strongest risk factor, has been found to have a dose-related relationship with the development and severity of PAOD. The prevalence of PAOD increases with age older than 40 years, with prevalence increasing to 15% in those older than 70 years and almost 25% in patients older than 80 years. PAOD generally affects men more than women, although some studies have shown higher disease prevalence in women. Notably, at any given age, the rate of PAOD among African Americans is almost double that of non-Hispanic whites. Although nonatherosclerotic causes of aortoiliac occlusive disease including trauma, radiation-induced aortoiliac occlusive disease, cystic adventitial disease, iliac endofibrosis, and a congenital persistent sciatic artery can present similarly, they will not be discussed herein.

The presenting symptoms of PAOD depend on the location(s) and severity of the distribution. Commonly asymptomatic, it is discovered incidentally in most cases. However, symptoms may range from claudication (i.e., activity-induced pain) to critical limb-threatening ischemia (CLTI) characterized by the presence of PAOD in conjunction with rest pain, or tissue loss (gangrene, or lower limb ulceration). Ankle-brachial indices are a reliable physiologic screening modality and correlate with disease progression (normal ≥0.9). Patients with CLTI are at high risk for limb amputation at an estimated rate of 10% to 20% within 1 year of diagnosis. But only an estimated 10% of the asymptomatic patients are expected to progress to CLTI. On the contrary, cardiovascular morbidity (e.g., stroke and myocardial infarction) and mortality risks remain high. All-cause mortality and cardiovascular mortality in patients with PAOD are slightly higher in symptomatic patients (5-year risk of 24% and 7.7%, respectively) than asymptomatic patients (5-year risk of 19% and 7.3%, respectively). However, patients presenting with gangrene have a 5-year risk of all-cause mortality over 50%.

Three major patterns of arterial disease have been described. *Inflow disease* refers to lesions that limit blood flow to the common femoral artery. *Outflow disease* consists of occlusive lesions in the lower extremity arterial tree below the inguinal ligament. Last is a combination of inflow and outflow disease. Aortoiliac occlusive disease (AIOD) is primarily an inflow disorder; however, it can be associated with a more progressive disease pattern. In this chapter, we will focus attention on PAOD affecting the aortoiliac distribution.

DIAGNOSTIC EVALUATION

History and Physical Examination

A thorough history with identification of atherosclerosis risk factors is paramount as the risk-factor modification is a cornerstone of treatment for PAOD. Symptoms of aortoiliac disease are typified by hip, buttock, thigh, and or leg claudication, leg muscle atrophy, male impotence or erectile dysfunction, and absent or diminished femoral pulses. When the constellation of proximal claudication, leg muscle atrophy, erectile dysfunction, and absent femoral pulses is present, it is described as Leriche syndrome, defined by René Leriche in 1948. *Pseudoclaudication* is pain that is position-dependent, not

stereotypically associated with activity, and can occur in the absence of activity. It is imperative to differentiate pseudoclaudication from true PAOD symptoms. Causes of pseudoclaudication include musculoskeletal issues (e.g., spinal stenosis, radiculopathy) or neurogenic issues (e.g., sciatic nerve impingement or diabetic neuropathy). Vascular claudication is characterized by intermittent pain that is exacerbated by walking, is relieved by rest, and is reproducible at a similar distance or effort for each patient. The severity of claudication is inversely related to the distance traveled, and the involvement of certain muscle groups can help with disease localization. Aortoiliac illness often presents as proximal claudication in the hip, buttock, and thigh; however, individuals with multisegmental disease may also present with distal calf or rest discomfort. Meanwhile, neurogenic claudication is characterized as deep aching or burning postural pain that originates in the back or buttocks and is exacerbated by walking or prolonged standing and alleviated by stooping, sitting, or leaning forward. One way to differentiate neurogenic from vascular claudication is the fact that neurogenic claudication often requires sitting to relieve the pain, while vascular claudication usually only requires stopping. Once confirmed that the patient's symptoms are caused by vascular insufficiency, it is important to quantify the severity of claudication and whether it is lifestyle limiting to potentially drive an appropriate intervention. In many cases, clinical history and thorough physical examination are sufficient for the diagnosis of aortoiliac occlusive disease. Absent palpable pulses in the entire limb or both limbs from the level of the common femoral artery down to the foot help confirm the unilateral or bilateral inflow level of PAOD, respectively. Except in the event of acute or subacute ischemia such as embolization, chronic aortoiliac illness alone is rarely responsible for ischemic rest pain or tissue loss. This is caused by a rich collateral network robust enough to supply the lower extremities with sufficient resting tissue perfusion. When rest pain or tissue loss is present, the disease is usually diffuse at multilevels and includes both inflow and outflow vessels.

Physiologic Testing

The ankle-brachial index (ABI) and Doppler studies serve as the best initial physiologic test for the evaluation of PAOD. With a compatible history, ABIs less than 0.9 are diagnostic of PAOD and can correlate with the severity of the disease. In general, with progressively more levels of occlusive disease (e.g., aortoiliac plus femoropopliteal plus tibial occlusive disease), the severity is increased and, consequently, the ABI will be lower. ABIs 0.7 to 0.9 indicate mild arterial disease, and patients are usually asymptomatic. ABIs 0.4 to 0.6 indicate moderate disease, and patients usually experience claudication. ABIs less than 0.4 indicate severe disease, and patients can present with rest pain or tissue loss. In cases with clear symptoms of arterial claudication but with palpable pulses on physical examination and normal ABI at rest, an exercise ABI could confirm the diagnosis of PAOD. A significant decrease in ABI with exercise by walking on the treadmill with 12.5% grade at 2 miles per hour for 5 minutes or until symptoms occur is diagnostic. In cases of severe calcification, ABI can be falsely elevated, and toe pressure will be a more accurate test. This is seen in diabetic and/or hemodialysis patients in whom calcification spares the digital arteries. Duplex ultrasonography (DUS) or segmental limb pressures combined with ABIs give a more complete picture of the level and extent of disease. DUS shows a significant increase in velocity in blood flow in the area of focal stenosis in the vessels. It can also confirm complete occlusion. DUS is limited by echo-shadowing from severe calcification in the vessels and obese patients.

Imaging

Computed tomography angiography (CTA), magnetic resonance angiography (MRA), and/or conventional arteriography can be used to delineate the extent and severity of the aortoiliac segment disease. Although conventional contrast angiography is considered the gold standard for PAOD, CTA has largely supplanted it as the diagnostic modality of choice. Compared with conventional angiography, CTA gives better contrast resolution and provides three-dimensional views of the aortoiliac segment, but it does not allow assessment of live flow through the segment. An arterial duplex/ABI and cross-sectional imaging with CTA is sufficient for initial evaluation. Additional information obtained regarding anatomic classification of the lesion and calcification can further aid in the selection of a treatment strategy.

MEDICAL TREATMENT

Medical management is the cornerstone of the treatment of PAOD, to reduce cardiovascular morbidity and mortality. Stepwise management beginning with risk-factor modification includes cessation of tobacco use, initiation of antiplatelet therapy (e.g., aspirin and/or clopidogrel), initiation of HMG-CoA reductase inhibitors (i.e., statins), and management of other cardiovascular and PAOD risk factors (diabetes and hypertension). Further medical therapy can include cilostazol, a phosphodiesterase inhibitor, to provide symptomatic improvement in exercise tolerance and walking distance in patients with claudication.

The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) trial, a randomized controlled trial comparing supervised exercise therapy with endovascular treatment of aortoiliac disease, showed that the supervised exercise therapy group had more improvement in short-term walking performance than the group undergoing endovascular intervention. In general, walking exercise is recommended three to four times a week for a duration of 30 to 45 minutes for at least 12 weeks and can lead to an improvement in walking distance by approximately 180 meters. The Centers for Medicare and Medicaid Services (CMS) recently approved coverage for a supervised exercise program as a risk factor modification for patients with well-documented PAOD. Medical management is imperative for all patients with PAOD, if for no other reason than to improve overall cardiovascular health.

Decision Making for Intervention

The need for intervention is best assessed on a case-by-case basis, taking into account the severity of occlusive disease, the severity of symptoms, and the overall condition of the patient. In many cases, the risk-to-benefit ratio favors endovascular therapy, particularly in the treatment of aortic occlusive disease.

The optimal technique of revascularization for a patient with claudication is determined by balancing the risks of the specific intervention with the degree and duration of improvement that may be predicted from the intervention. Percutaneous intervention has been found to be safe and effective in patients with claudication and proximal lesions who failed medical management and an exercise program. Patients with multisegmental disease usually present with critical limb-threatening ischemia and should undergo open or endovascular revascularization to fix the inflow in addition to outflow disease to prevent limb loss. Interventions include an endovascular approach, an open surgical strategy, or a combined endovascular and open (hybrid approach). Considerations for intervention selection will be described later in this chapter.

ENDOVASCULAR TREATMENT

The 2007 Inter-Society Consensus for the Management of Peripheral Artery Disease guideline (TASC II) provided a framework to aid in choosing an endovascular or open surgical approach for specific anatomic aortoiliac occlusive lesions (Fig. 1). The guidelines recommend endovascular therapy for short, simple type A and type B lesions. Insufficient evidence concerning TASC C lesions precludes the definitive recommendation of one modality over the other, but surgery is preferred for more extensive and complex type C

Type A lesions

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (≤3 cm) stenosis of EIA

Type B lesions

- Short (≤3 cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totaling 3-10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac of CFA

Type C lesions

- Bilateral CIA occlusions
- Bilateral EIA stenoses 3-10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

Type D lesions

- Infrarenal aortoiliac occlusion
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral occlusion of EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

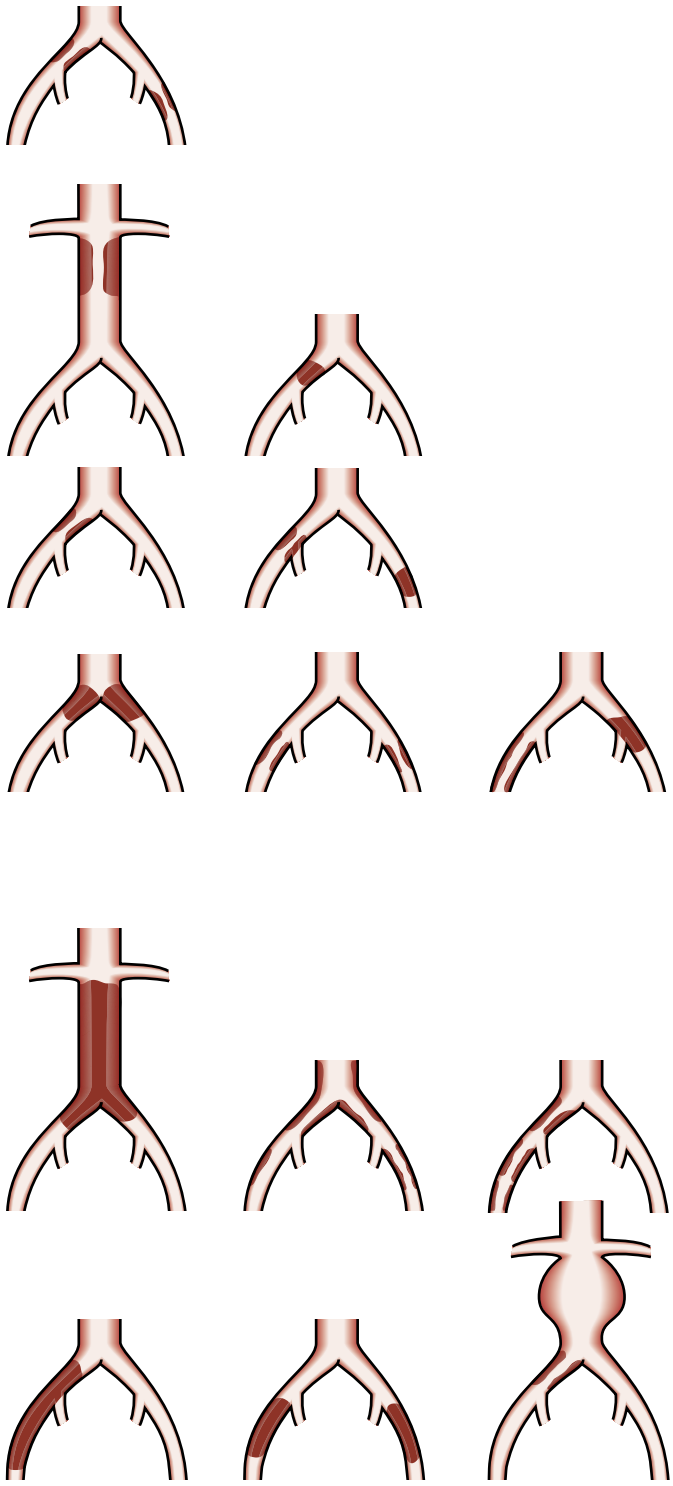


FIG. 1 Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *AAA,* Abdominal aortic aneurysm; *CFA,* common femoral artery; *CIA,* common iliac artery; *EIA,* external iliac artery.

and D lesions. Recently, however, an endovascular-first strategy is being increasingly employed with success because of the advent of improved imaging, techniques, and endovascular devices. Relative contraindications for aortoiliac angioplasty and stenting include circumferential calcification of more than 1-mm thickness because of the risk of rupture. Stent choice is influenced by the physician's expertise, vessel tortuosity, and other lesion characteristics.

Endovascular intervention involves the following steps:

1. Establishing arterial access
2. Diagnostic arteriogram and identification of the culprit lesion(s)
3. Crossing the lesion(s)
4. Balloon angioplasty (PTA) with stenting
5. Completion arteriogram to assess the result
6. Successful closure of the arterial access site

Establishing Arterial Access

The anatomic site for access is dictated by the anticipated site(s) of intervention and can be assessed with noninvasive imaging DUS and CTA for the most favorable access site(s). Aortoiliac lesions can be approached via a percutaneous or open exposure of the ipsilateral and/or contralateral common femoral artery (e.g., unilateral or bilateral access) or the brachial artery. The distribution and extent of disease will dictate the access site(s). Using DUS to guide the access is the standard of care today because several studies have shown improved safety by reducing the risk of access site hematoma and pseudoaneurysms. After access with a "micropuncture" small-caliber access needle and 0.018 wire and microsheath, arterial access is secured by switching to 5Fr sheath over an 0.035-inch guidewire. An Omniflush catheter is used for diagnostic arteriography (Fig. 2).

Diagnostic Arteriogram and Identification of the Culprit Lesion(s)

Anteroposterior and oblique images are obtained of the aortoiliac and common femoral bifurcations. Arteriography of the lower extremities is obtained. In cases of frank occlusions, the flush catheter should be positioned to fill the collateral network to opacify the distal extent of occlusion and reconstituted vessels. Careful review of the diagnostic arteriogram identifies the culprit lesion(s). A 50% or more diameter reduction or a pressure drop of 15 to 20 mm Hg across the stenosis defies a hemodynamically significant lesion. It is critical to measure pull-back pressure with a single-hole catheter across mild or moderate angiographic lesions because the degree of stenosis can be underestimated on iliac angiography because of the tortuosity of the vessels and eccentricity of the disease within the lumen. The patient should then receive a bolus of 80 to 100 units/kg of systemic heparin. In the case of CIA occlusion, contralateral flush catheter placement can allow access to protect the contralateral CIA from damage during an ipsilateral intervention. Meanwhile, a contralateral approach for the external iliac artery is recommended.



FIG. 2 Diagnostic angiogram showing complete occlusion of the left common iliac artery and bilateral external iliac arteries.

Crossing the Lesion(s)

Stenoses and occlusions are approached differently. In cases of stenoses, a steerable tip, angled, hydrophilic guidewire is chosen. The wire is steered through the stenosis. After traversal, an exchange or support catheter is advanced over the wire through the stenosis. The wire is then removed, and a small contrast injection is done to confirm a successful true lumen location. A transbrachial approach reduces the risk of aortic dissection when the femoral approach is unsuccessful.

Crossing an occlusion can be accomplished with several techniques. An angled support catheter in combination with a straight, stiff hydrophilic wire can be used to attempt luminal traversal. If the occlusion is successfully crossed, the position is confirmed with a small contrast injection. The wire is then exchanged for a non-hydrophilic, stiff support wire. If unsuccessful with this approach, a subintimal traversal is attempted. This involves passing a hydrophilic angled guidewire into the subintimal plane with reentry at the distal end of the occlusion back into the luminal space. Inability to reenter luminally can be facilitated by the use of a reentry catheter (e.g., Outback [Cordis] or Pioneer [Philips Volcano]). This approach can be done as antegrade interventions (e.g., unilateral iliac disease approached via the contralateral groin or brachial approach) of the iliac system or as retrograde from the ipsilateral common femoral artery. The outback catheter requires critical orientation to direct a reentry needle into the true lumen of the vessel past the occlusion. This is accomplished with two angiographic views at 90-degree angulations. The Pioneer catheter has an adjunct of intravascular ultrasonography (IVUS) to help guide the reentry needle into the true lumen. These techniques are more complex and require advanced endovascular skills.

Balloon Angioplasty with Stenting

Balloon angioplasty is performed with a balloon diameter that approximates the normal diameter of the reference vessel. The length of the balloon should approximate the length of the diseased segment with care to avoid angioplasty in the normal adjacent artery. In general, balloon angioplasty is performed slowly and deliberately. This affords the best angiographic result and minimizes the potential risk for dissection, perforation, or embolism. Overall, angioplasty is most successful for short, eccentric, calcified focal lesions. After angioplasty, contrast injection is performed to assess the result. Suboptimal angioplasty results (e.g., elastic recoil, dissection, or residual stenosis) should prompt stent placement. In general, PTA alone is rarely used today in the aortoiliac vessels because data on increased durability with additional stenting are very convincing. PTA is usually performed to prepare the vessels for stenting in cases with severe lesions. PTA is also performed after placement of a self-expanding stent (SES) for modeling the stent to the vessel wall. Balloon expandable stents (BES) are preferred for the common iliac arteries because they have more radial force that can help expand high-resistant orifical lesions. They also have the advantage of more accurate placement. They should be sized to fit the nominal diameter of the reference vessel. Aggressive oversizing is avoided with BESs. SESs are usually made from nitinol, making them more flexible than BESs. Thus they are preferred for the external iliac arteries because of vessel mobility and significant tortuosity. They are also more deliverable from the contralateral side above the aortic bifurcation. These stents should not be oversized by more than 10% to the reference vessel diameter to avoid harming the normal artery. SESs deploy less accurately than BESs and tend to migrate distally during deployment. Thus deployment should be done carefully under fluoroscopic guidance with magnification views to allow for micro-adjustment. If ostial common iliac disease and/or distal aortic disease with the common iliac disease are identified, a "kissing" stent technique is used (Fig. 3). Even in the case of a unilateral lesion, simultaneous balloon dilation at the source of each CIA is recommended to protect the contralateral CIA from dissection, plaque dislodgement, or



FIG. 3 "Kissing" stent technique.

embolization. Both balloon-expandable and self-expanding stents have been used for kissing stents. In the common iliac arteries, covered BESs are preferred over bare metal BESs, specifically for TASC C or TASC D lesions to minimize the risk of iatrogenic perforation and arteriovenous fistulas. Otherwise, bare-metal stents and covered stents have equivalent results in the common iliac arteries. In principle, covered stents should minimize in-stent restenosis by keeping the diseased segment out of circulation; nevertheless, experimental results show that they may cause greater neointimal outgrowth at the end of the stent-graft compared with bare stents. Calcium burden in the aortoiliac system can be challenging. Aggressive balloon angioplasty in calcified vessels risks vessel perforation. Therefore, in highly calcified lesions worrisome for the risk of perforation, either balloon-expandable covered stents (e.g., Gore VBX stent) or self-expanding covered stents (e.g., Gore Viabahn stent) are used. The majority of arterial ruptures occur during angioplasty or stenting of small, highly calcified external iliac arteries. Patients generally experience considerable flank or back pain when the artery ruptures because most of these cases are conducted under local anesthesia. Another complication of intervention is iliac dissection, which can continue proximally or distally. Overdilation of a small, calcified artery is the most common cause of dissection in these interventions. Intraoperative identification of dissection is imperative, and treatment of flow-limiting blockage consists of stent extension.

Technical success is defined as less than 20% residual stenosis and a systolic pressure gradient of less than 10 mm Hg. The translesional pressure gradient measurement should be used to determine the success of the angioplasty/stenting.

Closure of the Arterial Access Site(s)

The most common complications associated with endovascular interventions involve the arterial access site. Appropriate patient selection for percutaneous versus open surgical access is paramount for a successful intervention. Percutaneous closure devices are available to the interventionalist to assist with closure. The optimal choice of the closure device is dependent on operator familiarity, the size of the access sheath, and the state of the access vessel. Instructions for use, indications, and contraindications must be followed for each device. In patients who are not candidates for the use of percutaneous closure devices, manual pressure may be used for access site management and may be appropriate in certain situations (e.g., brachial artery access, highly scarred groin, densely calcific access artery). However, recent studies have shown that vascular closure devices are associated with fewer complications including hematomas and pseudoaneurysms. Additional benefits may include earlier ambulation after a procedure, reducing the length of stay in the hospital or outpatient interventional suite.

Results

Balloon angioplasty remains an option for isolated, short-segment iliac disease up to 7 to 10 mm. Primary stenting, however, has become the most common approach for the majority of lesions because of its improved long-term primary patency. Primary patency varies based on the TASC classification, with the worst primary patency observed with TASC C lesions at 65%. Stenting of TASC types A and B common iliac lesions achieve patency similar to that of open surgical reconstruction. The prospective, randomized Covered versus Balloon Expandable Stent Trial (COBEST) concluded that covered BESs have less incidence of restenosis, less incidence of stent occlusion, and therefore better long-term patency rates than bare metal BESs in aortoiliac occlusive disease, particularly in TASC C and TASC D lesions at 5-year posthoc analysis (Fig. 4). However, the number of patients at risk in this trial was very small. Recent meta-analysis, however, has corroborated this finding with a significantly higher primary patency of 92% with the covered stent compared with 75% in noncovered stents. Perioperative mortality is less than 1%, and morbidity ranges from 5% to 20%. External iliac disease is a strong predictor of reduced primary and primary assisted patency rates. Additionally, female gender, renal insufficiency, and CLI have been associated with worse outcomes.

Covered Endovascular Reconstruction of the Aortic Bifurcation

Covered endovascular reconstruction of the aortic bifurcation (CERAB) is an evolving technique proposed to treat extensive disease involving aortic bifurcation through reconstruction using three covered BESs. Typically, a kissing stent technique has been employed; however, recent studies have shown that this configuration has the potential to cause flow disturbances leading to neointimal hyperplasia, thrombosis, and restenosis.

Technique

To begin, two introducer sheaths are inserted into the common femoral arteries. Depending on the features of the lesion, the lesion

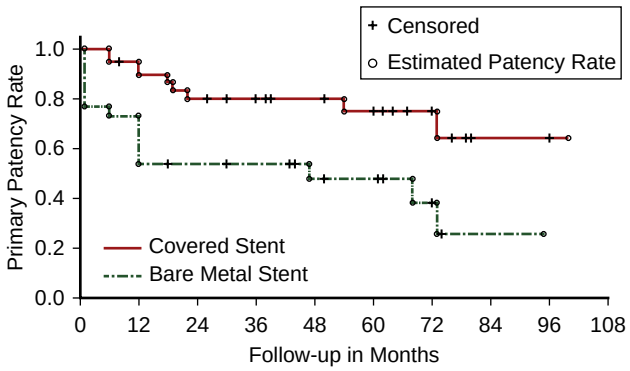


FIG. 4 Primary patency in Inter-Society Consensus for the Management of Peripheral Arterial Disease C/D lesions after balloon-expandable covered stents versus bare metal stents.

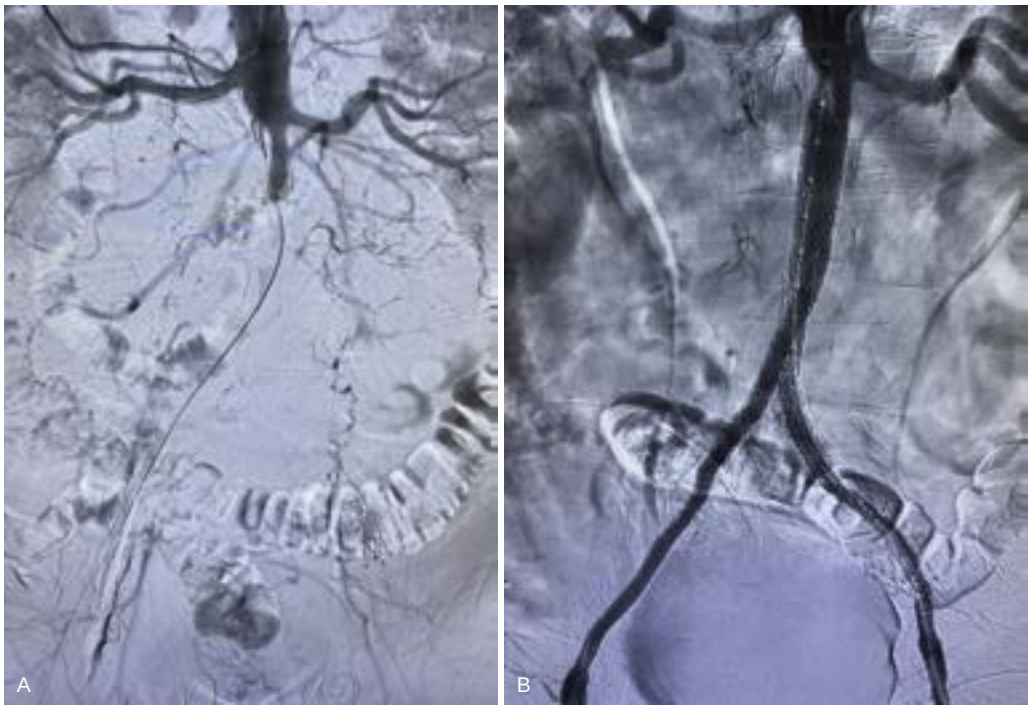


FIG. 5 Covered endovascular reconstruction of aortic bifurcation (CERAB) before device deployment. **(A)** Aortic angiography showing complete occlusion of the aorta and bilateral common, external, and internal iliac arteries. A prior failed stent is seen in the left external iliac artery. Large lumbar arteries collateralize the flow back to the left internal iliac artery and later to the deep femoral artery to reconstitute the common and superficial femoral. **(B)** Complex techniques involved a reentry device to enter the aorta just below the renal glands with access from left the common femoral artery after crossing the occlusion in a subintimal fashion. It was not possible to cross/reenter from the right side, so transbrachial access was performed to cross the right common iliac artery in an antegrade fashion, and the wire was then snared in the right external iliac artery retrograde from the right femoral artery. Once we had bilateral wire access into the true aortic lumen, a 16-mm cover stent was placed in the aorta, and two 8-mm cover balloon expandable stents were placed in the common iliac arteries extending 2 cm into the aortic stent. Additional self-expanding stents were placed in the bilateral external iliac arteries. This is a final completion angiography showing wide-open vessels. *(Courtesy Dr. Mahmoud Malas)*

is traversed endoluminally or subintimally. A 9Fr introducer sheath is placed above the proximal border of the aortic lesion after predilation. Then, in the distal aorta, a 12-mm balloon-expandable polytetrafluoroethylene-coated stent is placed. To promote canalization, the distal end of the stent is positioned roughly 15 to 20 mm above the bifurcation. To achieve complete apposition to the aortic wall, this stent is flared proximally with a balloon suited to the natural diameter of the distal aorta, generally 16 mm. This results in a funnel-shaped stent with a distal section 12 mm in diameter. Following that, two iliac covered stents, generally 8 mm in diameter, are placed in the conic segment of the aortic stent and concurrently inflated. When distal extension may be necessary, internal iliac artery preservation using a bare-metal stent is attempted to prevent buttock claudication and erectile dysfunction. As with standard endovascular procedures, statin treatment and dual antiplatelet therapy for at least 6 months are recommended (Fig. 5).

Results

Early results of this technique have been promising, with primary patency at 1 year and 3 years of 86% and 82%, respectively. Primary assisted patency is 91% and 89% at 1 year and 3 years, while secondary patency is 97% at both 1 year and 3 years. Additionally, limb salvage rate is 98% and 97% at 1 year and 3 years of follow-up.

SURGICAL TREATMENT

Open surgical revascularization is broadly categorized into *anatomic* versus *extraanatomic* revascularization procedures. For the aortoiliac segment, anatomic revascularization refers to aortofemoral, inline iliofemoral bypass, or aortoiliac endarterectomy.

Extraanatomic bypass refers to any bypass graft, autologous or not, that is implanted in a location other than the native artery segment being bypassed. These procedures include femorofemoral bypass, cross ilioiliac or iliofemoral bypass, axillofemoral bypass, or thoracofemoral bypass. Extraanatomic bypasses are generally reserved for patients considered high risk for a major open abdominal surgery because of underlying comorbidities or hostile abdominal features such as active infection, adhesions, stomas, or fistulae. The most common procedures will be discussed.

Potential complications seen in both procedures are common to any aortic procedures including intestinal ischemia, graft infection, and graft thrombosis. A review of 5-year outcomes for the different procedures is provided in Table 1.

Aortofemoral Bypass

Aortofemoral (or aortobifemoral) bypass is still considered the gold standard for aortoiliac revascularization. Several important anatomic factors dictate the operative approach and procedure. These factors should be extensively assessed with high-quality cross-sectional imaging (e.g., CTA). Assessment of concomitant renal or visceral artery disease is critically important. The proposed proximal aortic clamp site should be free from large atherosclerotic burden or calcium. The left renal vein typically will serve as the anatomic landmark for the renal arteries and the proximal aortic clamp site. A retro-aortic left renal vein is present in approximately 2% of patients,

TABLE 1 Outcomes of Surgical Revascularization

Procedure	5-Year Patency (%)	Perioperative Morbidity (%)
Aortofemoral bypass	80–90	<5
Aortoiliac endarterectomy	90–92	~2.7
Iliofemoral bypass	72–85	~2.7
Axillofemoral bypass	80–84	<5
Femorofemoral bypass	65–70	<5
Thoracofemoral bypass	60–79	5–6

and a circumaortic left renal vein is present in approximately 8% of patients. These left renal vein variants are very vulnerable to injury, with a rate of 40% of cases. Needless to say, careful assessment of the preoperative CT scan imaging and evaluation of these anatomic variations is crucial in reducing injury during dissection and proximal clamping.

The status of a patient's pelvic circulation may influence the proximal anastomotic configuration (end-to-end vs. end-to-side). Most favor an end-to-end configuration, which allows for direct aortic thromboendarterectomy, more favorable blood flow dynamics, and theoretically less risk of development of an aortoduodenal fistula.

However, the end-to-side configuration should be strongly considered in patients whose pelvic perfusion or inferior mesenteric artery perfusion would be entirely sacrificed with an end-to-end configuration. For example, in patients with severe external iliac artery disease or bilateral external iliac occlusions, an end-to-side proximal anastomosis would confer continued antegrade pelvic flow through the existing patent common iliac and hypogastric arteries (Fig. 6).

Another example is a patient with a large, patent inferior mesenteric artery with concomitant proximal visceral disease (e.g., celiac or superior mesenteric artery stenosis). Bowel perfusion would be maintained with an end-to-side proximal anastomotic configuration in this scenario (Fig. 7). Finally, a patient with a sizeable accessory renal artery arising from the infrarenal aorta that would lose substantial kidney function with a sacrifice of antegrade renal artery flow in an end-to-end configuration would also be best served with an end-to-side anastomosis.

Technique

1. Bilateral femoral artery exposure and control
2. Aortic exposure via abdominal or retroperitoneal approach
3. Creation of a tunnel
4. Heparinization
5. Aortic clamping
6. Anastomoses (proximal then distal)
7. Assessment of patency/perfusion
8. Coverage and closure

The patient is widely prepped and draped from the level of the nipples to the feet bilaterally. The procedure begins with bilateral groin incisions to expose the common femoral, profunda femoral, and superficial femoral vessels. Performing groin incisions before the abdominal incision limits insensible fluid loss. In unique situations in which the external iliac arteries and femoral arteries are spared of disease, an aortoiliac bypass may be performed to the distal external iliac arteries via a transabdominal approach. This technique reduces the risk of infection by avoidance of groin incisions. Assessment of the femoral vessels is important to determine the need for a common femoral or profunda femoris endarterectomy and/or angioplasty. In general, a distal anastomosis incorporating the origin of the profunda femoris artery is critical for achieving durable long-term patency of the graft. With chronic occlusive disease, the inferior epigastric and circumflex iliac arteries can develop into large collateral vessels and should be meticulously protected and maintained. The aorta is exposed through either a midline laparotomy incision or retroperitoneal incision. The retroperitoneal approach may be attractive in patients with previous abdominal operations or a hostile abdomen (the retroperitoneal approach is described in detail in the Unilateral Iliofemoral Bypass section). After entering the peritoneum through a midline laparotomy, the abdominal cavity is inspected for unanticipated concomitant pathology (e.g., malignancy). A nasogastric tube is placed to decompress the stomach and to aid in identifying the esophagus in cases in which supraceliac aortic control is anticipated. The transverse colon is retracted cephalad, and the small bowel is

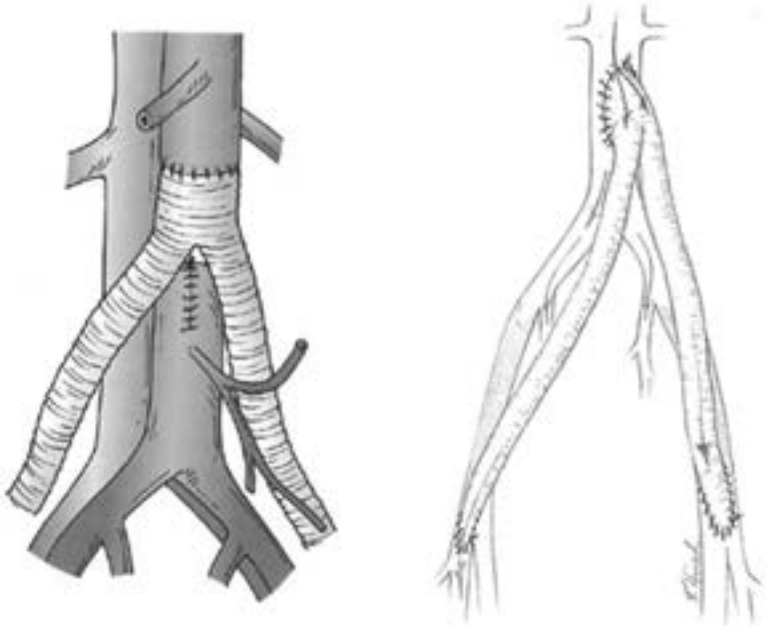


FIG. 6 Proximal anastomosis. End-to-end configuration versus end-to-side configuration. *(Modified from Cronenwett JL, Johnston, KW,* Rutherford's Vascular Surgery. *7th ed. Philadephia: Elsevier; 2010; and Zarins CK, Gewertz BL.* Atlas of Vascular Surgery, *St. Louis: Elsevier; 2005.)*



FIG. 7 Aortoiliac occlusive disease with a large patent inferior mesenteric artery.

retracted to the right upper quadrant. A fixed retractor system (i.e., Omni-Tract) is placed. The retroperitoneal tissue overlying the aorta and the ligament of Treitz is incised to expose the underlying aorta from the renal arteries to the aortic bifurcation. If necessary, the inferior mesenteric vein is ligated to provide better exposure. Care is taken to protect the left renal vein, the inferior mesenteric artery, and the autonomic nerve plexus located near the bifurcation and left common iliac origin. Construction of the tunnels for the bypass graft limbs is done by gentle, blunt dissection simultaneously from the groin posterior to the inguinal ligament and the abdomen over the occluded native iliac arteries. The tunnel must be constructed to run posterior to the ureters to prevent the development of hydronephrosis. Umbilical tape or red rubber catheters are inserted through the tunnel to facilitate passage of the graft limbs.

The patient is systemically anticoagulated with 80 to 100 U/kg of intravenous heparin to achieve an activated clotting time greater than 250 seconds. The aorta is clamped distally and then proximally just inferior to the renal arteries to minimize the chance for embolization. In cases with posterior calcific plaque, clamping the aorta in an anterior-to-posterior fashion may limit the potential for aortic clamp injury and embolization. Other proximal aortic clamp sites include the suprarenal or supraceliac aorta. Percutaneous insertion of an occlusion balloon is another option for proximal control. If suprarenal or supraceliac control is performed, the clamp should be moved caudally to the renal arteries as soon as the proximal anastomosis is performed successfully to limit visceral and renal ischemia time. In cases with severe disease extending to the renal arteries, suprarenal clamping with control of bilateral renal arteries with vessel loops to prevent embolization is mandatory. Quick endarterectomy of the infrarenal aortic neck is performed including the orifice of the renal arteries. A quick bloodletting of the proximal clamp allows release of any residual atheroma followed by aggressive flushing of heparinized saline. The infrarenal clamp is placed followed by the release of the suprarenal clamp and loops on the renal arteries. If an end-to-end configuration is chosen, the aorta at the proximal anastomotic site is transected. The distal stump is oversewn with a permanent monofilament suture (e.g., polypropylene). Pledgeted sutures may be needed for a highly diseased distal aortic stump. An appropriately sized knitted polyester (Dacron) graft is chosen to match the femoral artery diameter. Typically used bifurcated grafts include 18 mm × 9 mm grafts or 16 mm × 8 mm grafts for men and 14 mm × 7 mm grafts or 12 mm × 6 mm grafts for women. The main body of the graft is trimmed 3 to 4 cm from the bifurcation. The proximal anastomosis is performed using a running 3-0 polypropylene suture. If the aortic cuff is thin or fragile, a 3-0 polypropylene interrupted mattress, pledgeted suture technique is advisable. In the end-to-side proximal anastomotic configuration, the aorta is clamped as described earlier. If significant back bleeding is encountered from the collateral lumbar vessels, two overlying side clamps or a large Satinsky clamp can control the bleeding. A longitudinal aortotomy is made, and the edges of the aorta are trimmed to form an ellipse for the anastomosis. The graft is trimmed and beveled to achieve as low a profile as possible. This limits the risk of kinking and limits the amount the graft contacts the duodenum to theoretically limit the risk of aortoduodenal fistula formation. The anastomosis should start near the renal arteries and extend distally to facilitate a low-profile anastomosis. In either proximal anastomotic configuration, after completion of the anastomosis, the proximal clamp is released after clamping the main body of the graft or both iliac limbs to examine the proximal anastomotic integrity and hemostasis. Pledgeted sutures may be used to reinforce the anastomosis. The graft limbs are passed through the preformed tunnels with care to avoid twisting. The limbs should be flushed out after tunneling to confirm great inflow and release any residual debris. The femoral anastomosis is performed in an end-to-side configuration using running 5-0 polypropylene. As stated previously, outflow through the profunda femoris is crucial for long-term graft patency. In cases requiring a profunda femoris artery endarterectomy or profundaplasty, the distal end of the aortofemoral graft can be used as a profunda femoris artery patch angioplasty. Alternatively, an autogenous vein patch or prosthetic patch can be used for the patch angioplasty with the anastomosis subsequently performed to the patch. In cases of chronic superficial femoral artery occlusion, the primary outflow vessel is the profunda femoris artery.

Adequate outflow through the profunda femoris is assessed on the preoperative cross-sectional imaging and/or angiography. In addition, at the time of operation, the profunda femoris can be assessed with a deflated embolectomy balloon catheter to interrogate the length of the profunda femoris artery. A profunda femoris origin that accepts a 4-mm-diameter probe and measures 20 to 25 cm in length is adequate to sustain an aortofemoral graft. Concomitant distal revascularization (e.g., femoropopliteal or femorotibial bypass) is necessary in about 15% to 25% of patients and is indicated in cases of compromised outflow. Before completion of the anastomosis, the distal vessels are allowed to back-bleed, and the graft is flushed of debris. In general, with the chronic occlusive nature of the disease, reestablishment of leg perfusion results in only small hemodynamic changes. Communication with the anesthesia team is paramount, however, before reestablishment of distal perfusion to limit the potential for hemodynamic lability. The distal leg is assessed for perfusion with palpable pedal pulses or audible multiphasic signals. Lack of distal perfusion with adequate inflow (i.e., vigorous flow through the graft) should prompt evaluation of the distal anastomosis for a technical error or raise concern for a distal embolism. Angiography can help delineate the underlying problem. Redo anastomosis is indicated for an anastomotic technical error. Distal embolization is treated with balloon catheter embolectomy. After satisfactory perfusion is assessed through target artery Doppler signals, we reverse the effects of heparin with protamine and ensure adequate hemostasis. Abdominal closure begins with reapproximation of the retroperitoneal tissue to cover the graft, if possible. An alternative coverage option is to mobilize an omental pedicle placed via a transverse colon mesenteric window. The abdomen is closed in the standard fashion. Meticulous groin incision closure in multiple layers is important to limit the risk of infection and wound complications. Wound vacuum dressing has been shown to reduce the risk of groin incision infection in vascular patients who are at high risk because of associated comorbidities such as redo surgery, obesity, and diabetes.

Results

Perioperative mortality is less than 5%. Primary graft patency approximates 100% initially, with 5-year and 10-year primary patency ranging from 80% to 90% and 75% to 85%, respectively. Cumulative secondary graft patency for 2, 5, and 10 years was 97.7%, 95.9%, and 94.4%, respectively. Inferior patency results are documented for patients with ulceration or tissue loss compared with patients with claudication or ischemic rest pain. In addition, age and native aortic diameter have been shown to influence patency after aortofemoral bypass. Patients younger than 50 years of age and those with aortic diameters 18 mm or less have much lower primary patency rates after aortofemoral bypass (50%–65% 5-year primary patency). Infection occurs in 0.3% to 0.7% of cases, and anastomotic pseudoaneurysm formation occurs in 1.4% of cases.

Aortoiliac Endarterectomy

Aortoiliac endarterectomy is an option for patients with localized aortoiliac disease limited to the distal aorta and proximal common iliac arteries who are at high risk of embolization or those with small-caliber vessels, commonly found in young or middle-age women with a history of tobacco use. With the increased use of endovascular interventions and the long-term durability and success of aortofemoral bypass, aortoiliac endarterectomy is uncommonly chosen as a primary procedure. However, it remains a viable option as a secondary procedure in the setting of the infected bypass graft.

Technique

1. Aorto-iliac exposure
2. Systemic heparinization
3. Aortic and iliac clamping
4. Arteriotomy
5. Enterectomy in subintimal plane
6. Patch angioplasty or primary closure
7. Wound closure

Operative exposure is done through a standard midline laparotomy, similar to the abdominal portion of an aortofemoral bypass procedure. Complete mobilization of the distal aorta, inferior mesenteric artery, aortic bifurcation, and proximal bilateral common iliac arteries is achieved with care to protect the autonomic nerve plexus (nervi erigentes) and to avoid injuries to the iliac veins located behind the arteries. A longitudinal aortic incision is made and may be carried onto one of the common iliac arteries. A counter-incision in the contralateral common iliac artery can be made in the case of bilateral common iliac disease. Endarterectomy is performed in the subintimal plane with care to taper or feather the distal end of the endarterectomy. Tacking mattress sutures at the distal edge of the endarterectomy can be used to prevent dissection. The proximal plaque is transected to a smooth edge. The aorta and iliac arteries are flushed of debris, and assessment of the proximal and distal ends of the endarterectomy are performed before closure. The arteriotomies are closed either primarily with 4-0 or 5-0 polypropylene sutures or with a patch (Fig. 8).

Results

Perioperative mortality rates are similar to aortofemoral bypass grafting (2.7% perioperative mortality). Patency rates appear similar to aortofemoral bypass and are 90% to 92% for 5-year patency and 89% for 10-year patency. Complications include limb ischemia secondary to embolization or dissection and aneurysmal dilation in the long term.

Unilateral Iliofemoral Bypass

Unilateral iliofemoral bypass is indicated in cases with limited distal aortic disease and limited ipsilateral proximal common iliac disease. Otherwise, aortofemoral bypass is preferred. High-risk patients for open abdominal surgery (e.g., severe cardiopulmonary dysfunction) may also be candidates for this procedure as this is typically performed through limited retroperitoneal exposure.

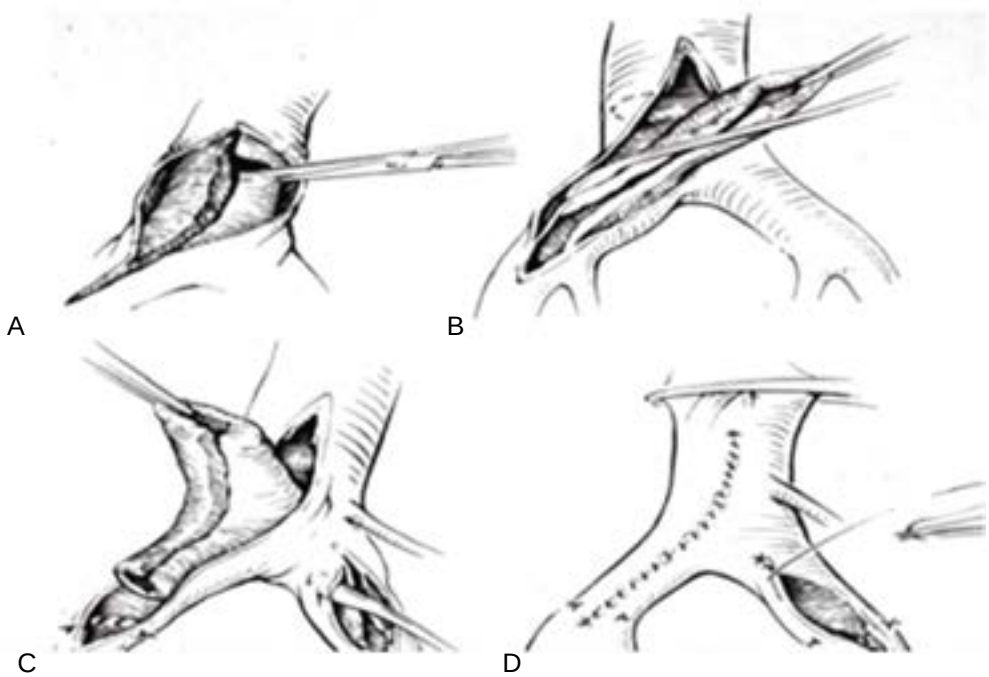


FIG. 8 Aortoiliac endarterectomy. **(A)** The initial incision starts above the occlusive disease and extends to the bifurcation of the right iliacs. **(B)** Endarterectomy begins with a dissecting spatula. **(C)** A counter-incision in the left common iliac permits bifurcation disease to be removed beneath the artery bridge. Endarterctomy is taken into the internal iliac orifice. **(D)** The incision is closed with running suture. *(From Connolly JE, Price T. Aortoiliac endarterectomy: A lost art?* Ann Vasc Surg. *2006;20[1]:56–62.)*

Technique

The patient is positioned supine. Retroperitoneal exposure is facilitated by a "bump" placed under the ipsilateral flank and/or flexing the table to expand the space between the ribs and the anterior-superior iliac spine. A retroperitoneal curvilinear incision is extended from the anterior axillary line to the midline inferior to the umbilicus along the line of the 10th rib. The anterior rectus sheath is incised, and the rectus abdominis muscle is spared and retracted medially. The posterior rectus sheath is incised. The internal and external oblique muscles are incised with electrocautery to expose the transversus abdominis muscle. Beginning laterally, the transversus abdominis muscle and the underlying transversalis fascia are opened to enter the retroperitoneal space. The peritoneum is stripped from the lateral pelvic wall and retracted medially with the intraabdominal contents to expose the underlying psoas muscle. The ureter is identified, protected, and retracted medially. The external iliac artery is readily identified in the distal aspect of the wound and can be followed proximally to the common iliac artery and aortic bifurcation. The proximal clamping site may be found at the proximal ipsilateral common iliac artery or the distal aorta and contralateral proximal common iliac artery. Standard exposure of the common femoral artery, similar to that described earlier for an aortofemoral bypass, is performed. A tunnel is created anterior to the external iliac artery and posterior to the inguinal ligament.

The patient is systemically heparinized. An 8-mm polyester graft is the typical conduit of choice. Proximal anastomosis is performed to the ipsilateral common iliac artery using 4-0 or 5-0 polypropylene sutures. The graft is tunneled distally under the inguinal ligament or in some cases through the obturator foramen, and a distal anastomosis is fashioned similar to an aortofemoral bypass described earlier. The graft is placed deep within the pelvis, where it is less vulnerable to external compression or kinking. After satisfactory reperfusion and hemostasis, the retroperitoneal incision and groin incision are closed in the standard fashion.

Results

Perioperative mortality mirrors aortoiliac endarterectomy at 2.7%. Review of literature shows primary patency rates of 92% at 1 year and 72% to 85% at 5 years. Primary assisted patency at 1 year and 5 years is 91% and 81%, respectively. Secondary patency is 97.5% at 1 year and 93.3% at 5 years. Limb salvage at 5 years is 94%.

Axillofemoral Bypass

In severely high-risk or elderly patients with critical limb ischemia, an axillofemoral (or axillobifemoral) bypass is an alternative to direct aortoiliac revascularization. In addition, it is a reasonable alternative for patients with a "hostile" abdomen, previous radiation therapy, intestinal stomas, infected prosthetic arterial grafts, or aortoenteric fistulae. The axillary artery serves as the inflow for both lower extremities. The axillary artery with higher systolic blood pressure is chosen; however, if both sides are hemodynamically competent, the side ipsilateral to the ischemic leg is given preference.

Technique

1. Determine the best axillary artery for inflow
2. Infraclavicular exposure and control of the axillary artery
3. Bilateral femoral artery exposure and control
4. Tunnel creation
5. Heparinization
6. Axillary then femoral then fem-fem anastomoses created
7. Coverage and closure

Blood pressures are obtained in both arms to determine the optimal side for inflow. Although previous studies have shown improved patency of axillobifemoral bypasses over axillounifemoral bypasses, more recent studies show no significant difference. The patient is positioned supine with the donor arm abducted to 90 degrees. A rolled towel may be used to lift the torso on the donor side to improve axillary artery exposure. The patient is prepped from the neck and chest down to the knees or bilateral feet. A transverse infraclavicular incision is made along the midportion of the clavicle. The underlying pectoralis major is split along its fibers to expose to underlying clavipectoral fascia. The clavipectoral fascia is incised to expose the underlying neurovascular bundle and axillary sheath with its contents. The axillary anastomosis is generally performed in the first part of the axillary artery because of its relationship with the brachial plexus. At this site, the brachial plexus runs posterior to the axillary artery conferring less risk for injury. In the lateral wound, the pectoralis minor is identified and retracted laterally or transected. The lateral pectoral nerve runs just posterior to the medial border of the pectoralis minor and should be protected. The axillary sheath is incised. The axillary vein is anterior in the sheath and is encircled and retracted inferiorly to expose the axillary artery. Proximal and distal control and control of branches are obtained with silastic vessel loops. The bilateral femoral arteries are exposed, as previously described. An externally supported 8-mm-diameter prosthetic graft is chosen. Tunneling is performed with a blunt tunneler routed parallel and anterior to the axillary artery, posterior (under) the pectoralis minor muscle, and down the anterior axillary line in the subcutaneous space anterior to the iliac crest down to the ipsilateral groin. A subcutaneous tunnel is created between each groin in an inverted-*U* configuration. The graft(s) are passed through the tunnels. The patient is systemically heparinized. The proximal anastomosis is created by running a 5-0 or 6-0 polypropylene suture and is oriented parallel to the axillary artery. Placement of the axillary anastomosis in the first portion of the axillary artery and tunneling parallel to the artery in the midaxillary line and posterior to the pectoralis minor allows some redundancy in the graft to prevent anastomotic disruption with arm abduction. The ipsilateral end-to-side femoral anastomosis is created with 5-0 polypropylene sutures. The femorofemoral component is created onto the hood of the axillofemoral bypass graft using 5-0 polypropylene suture. The contralateral femoral anastomosis is created in a standard fashion, as described earlier. Prefabricated externally supported expanded polytetrafluoroethylene (ePTFE) axillobifemoral grafts are also available. This prefabricated graft saves one anastomosis but requires a specific tunneling sequence by pulling the long limb from the ipsilateral groin back to the axilla first and then the short limb from the ipsilateral to contralateral groin incisions. Skip incision might be needed for a tall patient, which makes the tunneling more challenging. It is critical to demonstrate sufficient blood flow in the donor arm beyond the axillary anastomosis by verifying a good radial pulse or appropriate oxygen saturation (as measured by pulse oximetry).

Results

Historically, the patency rates for axillofemoral bypasses varied widely (30%–85%). Perioperative mortality remains less than 5%; however, published long-term survival rates are reported to be approximately 50%, confirming the high-risk status of these patients. More contemporary studies have shown improved primary 1-year and 5-year patency rates of 75% to 96% and 80% to 84%, respectively, which are comparable to aortofemoral bypass. No significant difference in patency is evident between unifemoral or bifemoral distal configurations.

Femorofemoral Bypass

Femorofemoral bypass is used as an alternative revascularization strategy to aortofemoral or iliofemoral bypass in high-risk patients with unilateral common or external iliac artery occlusive disease or in patients with a hostile abdomen. It is dependent on the capacity of one iliac arterial system to deliver enough blood flow to sustain both legs. Thus the status of the donor artery must be assessed. The presence of a pressure gradient greater than 5 to 10 mm Hg down the proposed donor iliac artery necessitates intervention to prevent the arterial steal phenomenon.

Technique

The patient is positioned supine. This procedure can be done with locoregional or spinal anesthesia in patients who are at high risk for general anesthesia. The bilateral femoral arteries are exposed, as previously described. A subcutaneous tunnel between incisions is made to achieve an inverted-*U* configuration. This configuration reduces the acute angle of the anastomosis and reduces the risk of kinking. Tunneling is done in the subcutaneous space. The subcutaneous tunnel prevents bladder or bowel injury and may be necessary for patients with hostile abdominal conditions. Typically, prosthetic grafts are used as a primary conduit (8 mm externally supported ePTFE) as there is no current evidence to suggest superiority of one prosthetic conduit choice over another. Standard end-to-side anastomoses to the femoral arteries and layered groin closure complete the operation. After the anastomoses are completed and all clamps are released, it is critical to demonstrate augmentation of flow in the recipient vasculature and sustained flow in the outflow vessels beyond the donor-side anastomosis, typically using continuous-wave Doppler.

Results

Perioperative mortality is less than 5%. The primary patency rates at 5 years and 10 years are 71.8% and 55.6%, respectively, in a contemporary study. Primary assisted patency rates at 5 years and 10 years are 84.3% and 74.8%, respectively. Secondary patency rates at 5 years and 10 years are 89.8% and 82.9%, respectively.

Thoracofemoral Bypass

This technique utilizes descending thoracic aorta as an inflow source for revascularization in patients with a hostile abdomen, multiple failed anatomic abdominal aortic operations (e.g., failed aortofemoral bypasses), multiple failed extraanatomic revascularization attempts because of compromised inflow, or aortic graft infection.

Technique

The patient is positioned in a modified right lateral decubitus position with a double-lumen endotracheal tube to allow deflation of the left lung; however, some find single-lung ventilation unnecessary. The thorax is elevated 30 to 45 degrees, and the pelvis is maintained as flat as possible to allow access to the right groin. A left thoracotomy incision is made, typically as high as the sixth intercostal space or as low as the ninth intercostal space. The exact location of the thoracotomy is dictated by the proposed site for proximal anastomosis that is free from disease. Bilateral groin incisions are made, as previously described. A 10-mm externally supported prosthetic graft is the usual conduit. A retroperitoneal counter-incision is made in the left flank to facilitate tunneling from the posterior diaphragmatic recess to the left groin. A standard femorofemoral tunnel is created. After systemic anticoagulation, an end-to-side proximal anastomosis is created using 3-0 polypropylene sutures. Proximal control for the anastomosis is obtained using partial occlusion Satinsky clamps or standard proximal and distal clamps. Distal anastomoses are fashioned to preexisting grafts or the femoral arteries, as previously outlined. Chest tube drainage and closure of the incisions complete the procedure.

Results

Perioperative mortality remains around 5% to 6%. The primary patency rate at 1 year is 89%, and at 3 years 80% in different reports, with secondary patency rates of about 83%% at 5 years of follow-up.

Hybrid Revascularization Procedures

In unilateral or bilateral aortoiliac disease extending into the common femoral arteries, a hybrid open surgical technique is an alternative to aortofemoral or iliofemoral bypass grafting. This approach treats the common femoral arteries with endarterectomy and vein patch angioplasty combined with a retrograde approach through the new patch for endovascular angioplasty and stenting to treat the iliac or inflow vessels. Treating one iliac artery with angioplasty and stenting to ensure adequate inflow for femorofemoral bypass has been well described and shown acceptable mid- and long-term durability. Perioperative mortality is around 2% to 15%, reflecting the overall patient health undergoing these procedures. Initial technical success with this approach is reported to be 99% to 100%, with 2-year primary patency rates of 80% to 100% and secondary patency rates of 90% to 100%.

Follow-up

It is important to follow all patients with PAOD who received open or endovascular intervention. It is our practice to see our patients at 1, 6, 12, 18, and 24 months and yearly to ensure patency and maximize medical management. In addition to the physical examination, DUS and ABI are obtained at each visit. If severe stenosis is identified, we intervene proactively with minimally invasive angioplasty to prevent complete occlusion. This dramatically improves the patency of these grafts. Aggressive management of medical comorbidities with smoking cessation, statin therapy, and antiplatelet therapy is crucial in improving long-term survival in PAOD patients.

SUMMARY

Aortoiliac occlusive disease can be a debilitating disease. A structured approach to diagnosis and treatment is crucial for successful results. Management is dictated by the severity of the disease and the health of the patient. With continued advancement in revascularization options, the surgeon should tailor the approach on a case-by-case basis.

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Femoropopliteal Occlusive Disease

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INTRODUCTION

Peripheral artery disease (PAD) is a global epidemic that affected more than 200 million patients worldwide in 2010. Most of these patients are asymptomatic; however, patients with intermittent claudication usually experience a limb loss rate of <5% over 5 years, while patients with critical limb ischemia (CLI) have a 1-year major amputation rate of 25% and death rates of 25%.

Femoropopliteal disease has been treated traditionally with open surgery (femoropopliteal bypass; FPBP) with a favorable 5-year patency rate when saphenous vein (ASV) grafts are used. Several meta-analyses have shown that CLI did not occur for up to 5 years in 50% to 70% of patients who underwent ASV grafting to tibial or pedal targets, with perioperative mortality and limb salvage rates of 3% and 80%, respectively.

A recent study of 467 bypass grafts compared outcomes for ASV and polytetrafluoroethylene (PTFE) grafts and showed the patency rate with ASV was better than PTFE grafts at 5 years (82% vs. 26%, $P < .05$); however, good quality vein may not be available (20%–30%). Bypass with PTFE should therefore be limited to select patients.

Open surgical bypass has certain limitations, for example, postoperative morbidity/wound complication rate of 10% to 20%, prolonged hospital stay/outpatient care, and patient discomfort. De novo stenosis in vein grafts may also occur in 30% to 40% of patients in the first 2 years, which may necessitate graft surveillance or reintervention. Other systemic complications may occur (e.g., cardiac, pulmonary, and renal).

Recently, endovascular therapy has been advocated as an alternative to open bypass. Several studies analyzing outcomes of patients with CLI treated with endovascular therapy have largely been retrospective single-center with significant heterogeneity. The OLIVE registry, a multicenter prospective study, analyzed the outcomes of endovascular therapy for infrainguinal disease in 314 patients with CLI, which showed a 12-month amputation-free survival of 74%, whereas 34% of patients required reinterventions (endovascular, 31.7%, and bypass surgery, 2.6%). These results were satisfactory in these high-risk patients (71% diabetics and 52% on hemodialysis)

and with severe anatomic disease (42% below the knee lesions and >50% TASC types C and D).

OUR CLINICAL EVALUATION/IMAGING

A thorough history and physical examination is important. Cardiovascular risk factor identification is critical, which includes cigarette smoking, hypertension, diabetes, dyslipidemia, etc. In general, the patient's clinical symptoms and a thorough pulse examination should facilitate in diagnosing PAD. Femoropopliteal occlusive disease can be asymptomatic or present with intermittent claudication or limb-threatening ischemia (rest pain and/or trophic changes, e.g., ulceration or gangrene). Claudication (from the Latin word *claudicare*, which means "limping") generally manifests as crampy achy pain in the calf precipitated by walking that occurs at a reproducible distance, relieved with rest, and the location of pain is almost one joint distal to the occlusion. Once the clinical diagnosis is made, noninvasive vascular laboratory can be helpful in confirming the diagnosis and localizing the disease. The most common testing is obtaining the ankle-brachial index (ABI), which can be combined with color duplex scanning of the lower extremity. The ABI is generally calculated as the ratio of the higher systolic pressure in the arm divided by the highest systolic pressure at the ankle, whether the dorsalis pedis or the posterior tibial artery. A normal ABI is generally around 1 ± 10%; an ABI of <0.9 is diagnostic of PAD. It is generally believed that ABI between 0.4 and 0.9 is present in patients with claudications, while an ABI below 0.4 is compatible with rest pain or tissue loss. An ABI >1.2 may be indicative of arterial calcification, which is seen in diabetics and end stage kidney disease (CKD). Some believe that, in these patients, an ABI can be >1.3 to 1.4. Patients with vasculogenic claudication will also show an ABI drop when the patients walk to the point of calf claudications using treadmill testing. If ABI is >1.2 to 1.3, particularly in diabetics or in patients with CKD, obtaining Doppler toe pressures and/or pulse volume recordings might be helpful. A toe-brachial index (TBI) of <0.7 is indicative of significant disease. Color duplex ultrasound is also available in many of the vascular laboratories, where B-Mode imaging and color flow Doppler sampling will determine the location and severity of the disease, including occlusion, which will facilitate proper treatment (i.e., open or endovascular therapy). For patients who need invasive therapy, further imaging is obtained to show both inflow and outflow arteries (e.g., contrast CTA or MRA if CTA is contraindicated). However, if endovascular therapy is anticipated, contrast arteriography might be all that is needed to minimize cost.

TREATMENT

Conservative/Medical Therapy

It is offered to patients with nondisabling claudications or even as an initial step for patients with disabling symptoms. It includes risk factor modifications (e.g., smoking cessation, dietary and pharmacologic therapy) to include statin to lower density lipoprotein cholesterol and triglyceride for treatment of hypertension and diabetes. They should also be given aspirin to reduce the risk of cardiovascular morbidity and mortality. Cilostazol (a phosphodiesterase inhibitor) may provide symptomatic improvement in certain patients with claudication. Exercise programs have been advised to improve walking distance. Supervised exercise programs are more effective than unsupervised. However, if an unsupervised program is initiated, it should be performed at least three times a week for a duration of 30 to 45 minutes, and patients should be encouraged to do it to a point where the claudication symptoms appear. Medical treatment is not the first line of therapy for patients with CLI.

Open Surgical versus Endovascular Therapy

The decision to perform open surgical therapy versus endovascular therapy should be based on several factors including patient's age, severity of ischemia, long-term prognosis, and anatomic complexity. To many, open surgical therapy is still considered the gold standard for patients with ischemic rest pain or tissue loss. However, for many others, endovascular therapy has been advocated as initial therapy. The classification of arterial lesions established by the Trans-Atlantic Inter-Society Consensus for the Management of PAD (TASC II) may be helpful in choosing the appropriate therapy (Fig. 1). It is agreed upon that endovascular therapy is preferable for Type A, B, and C lesions; however, Type D lesions are treated mostly by an open

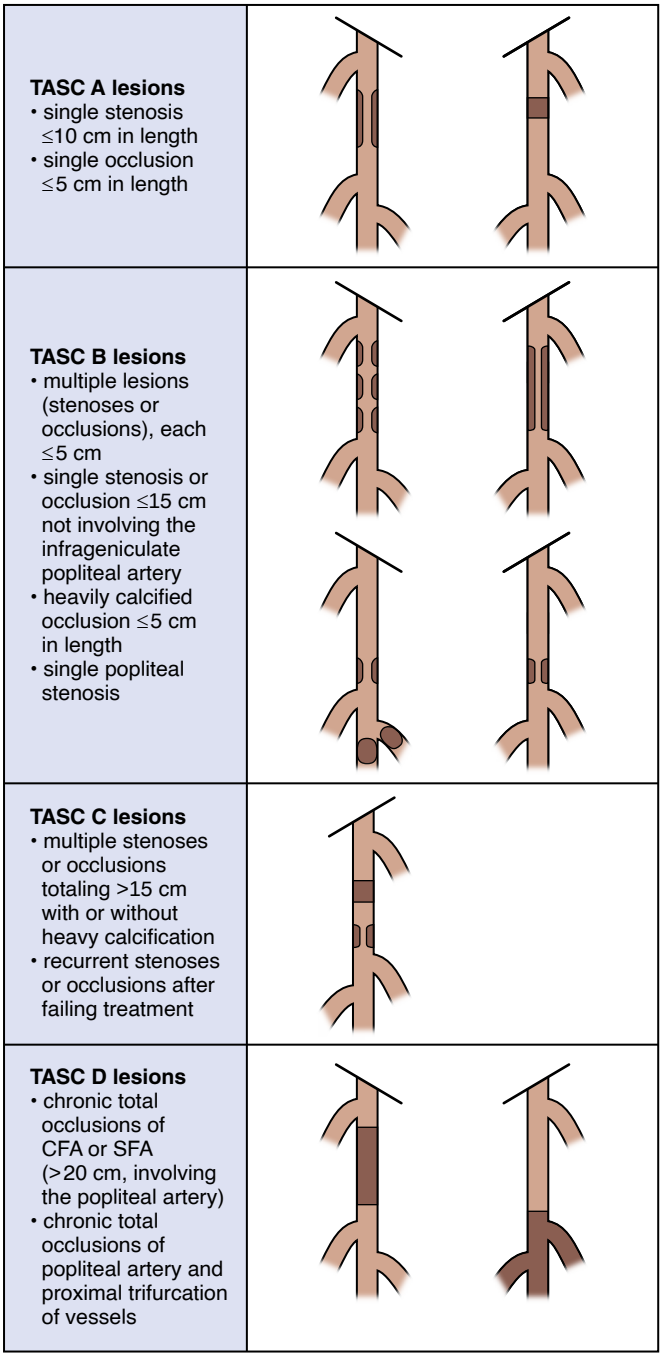


FIG. 1 Treatment of choice for femoropopliteal disease: endovascular vs. open (according to TASC classification). *(From Norgren L, Hiatt WR, Nehler MR, et al., on behalf of the TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease [TASC II].* Eur J Vasc Endovasc Surg. *2007;33:S1–S75.)*

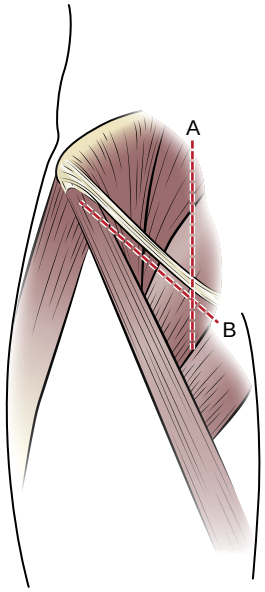


FIG. 2 Groin incision can be done either as vertical *(A)* or oblique *(B)* just above the crease.

surgical bypass. However, some authorities recommend endovascular therapy even for Type D lesions as initial therapy with open bypass if it fails.

Open Surgical Therapy

FPBP is the procedure of choice, which involves a bypass of the occlusive disease with or without endarterectomy of the common femoral artery (CFA), if needed. For successful bypass, adequate inflow site (aortoiliac), outflow vessels, and conduit are needed. The proximal target should be the CFA; however, the superficial femoral artery (SFA) or the proximal profunda can be used with caution. The distal target site can be an above- or below-knee popliteal segment or the tibial vessels. The groin incision can be done either as vertical or oblique just above the crease (Fig. 2). Vertical incision is preferable if common femoral endarterectomy or profundoplasty is needed. A good outflow vessel should be the least diseased with continuous flow to the foot. Every effort should be made to revascularize the target artery that supplies the area if ulceration is present (Fig. 3) based on the angiosome concept.

Exposure of Above- and Below-Knee Popliteal Artery

The above-knee popliteal artery is exposed with a longitudinal incision placed along the anterior border of the sartorius muscle in the distal thigh (Fig. 4). Incision is deepened through subcutaneous tissue in the muscular fascia between the vastus medialis anteriorly and sartorius posteriorly. The adductor hiatus is identified to expose the popliteal artery emerging from the distal SFA. The artery lies medial to its accompanying vein upon entering the vascular sheath. Small branches of the popliteal artery should be handled carefully and not divided to minimize compromising leg circulation if the graft fails. To expose below-knee popliteal artery, the incision is positioned below the knee along the medial aspect (Fig. 4). If this was anticipated before vein harvest, the same below-knee incision for vein harvest can be used. This incision is generally placed one fingerbreadth posterior to the tibia and carried through the fascia. The gastrocnemius muscle is identified and retracted posteriorly to expose the popliteal space. Further, proximal exposure of the popliteal artery/space may be obtained by dividing the tendinous attachment of the sartorius, gracilis, and semitendinosus muscles. For distal grafting to individual tibial vessels, the dissection should continue by detaching some of the soleus muscle fibers, which will expose the tibioperoneal trunk, posterior tibial, and peroneal artery. The anterior tibial artery is generally identified once this process is done.

The Conduit of Choice

Autogenous vein has been the first choice for all infrainguinal bypasses. The great saphenous vein is the preferred choice and should be evaluated with preoperative duplex vein mapping. If this vein is inadequate, a mapping of alternative veins including a lesser saphenous, contralateral greater saphenous vein, and upper arm veins (basilic and cephalic arm) is done. The vein should be nondiseased and at least 3 mm in diameter. Vein bypasses can be placed in a reversed, nonreversed, or in situ configuration. Both reversed and nonreversed vein bypasses have similar patency, particularly for above-knee positions. The in situ is reserved for the distal popliteal artery or tibial vessels because of better matching between the arteries and the vein. Other conduits have been used (e.g., PTFE or Dacron), with or without heparin bonding, with no clear superiority of one over the other. Cryopreserved and human umbilical veins might be used with a similar patency as a prosthetic graft; however, they are expensive and used only in exceptional cases.

Vein Harvest/Bypass Technique

Vein harvest is generally done with several long anterior incisions with skip incisions, which we prefer, versus a continuous long incision. Endoscopic vein harvest can also be done; however, comparative result with open vein harvest has been unsatisfactory. The incision is extended distally along the path, which is marked at the time of preoperative vein mapping or using a bedside ultrasound machine. Vein harvest must be meticulous to minimize damage to the vein. A vessel loop can be used to retract the vein from side to side and help identify all side branches, which should be tied 1 to 2 mm away from the vein to minimize kinking or narrowing of the vein. Once the vein is removed, gentle dilatation with heparinized saline solution is done. Every effort should be made to minimize the time of the harvested vein from not being perfused with the patient's blood. We generally prepare the vein just after exposing both proximal and distal inflow and outflow arteries, so once the vein is harvested, it is ready to be used. For in situ use, the vein is spatulated, and if nonreverse or in situ, the most proximal valve is excised with direct vision. The end-to-side anastomosis is created with 5-0 or 6-0 polypropylene suture. Flow is then restored into the bypass. Valvulotome (LeMaitre) is then used and inserted from the distal end where the remaining valves are gently cut. If the bypass is done in reverse fashion, a tunneler is used, which is inserted just deep to the sartorius muscle and superficial to the SFA; for below-knee popliteal artery bypass, the graft is inserted from above- to below-knee with the index finger creating a tunnel between the heads of the gastrocnemius muscle to prevent compression.

Once the tunnels and conduit are prepared, the patient should be heparinized with 80 to 100 U/kg intravenously. A few minutes later, the procedure starts by occluding the CFA, profunda femoral and SFA, and any other branches. A longitudinal incision is made in the CFA with a #11 blade and extended using angled Potts scissors. Using double-armed 5-0 or 6-0 polypropylene sutures, the proximal anastomosis is done bidirectionally. The vein is allowed to distend with blood after loosening the vascular loops. It is then marked along one side to maintain orientation and prevent vein twisting. Once the vein is tunneled distally, the distal anastomosis is performed in a similar fashion using 6-0 polypropylene sutures (Fig. 5).

It is generally recommended to have completion duplex imaging to assess both proximal and distal suture line, including the conduit. However, completion contrast angiography can be used if there is any

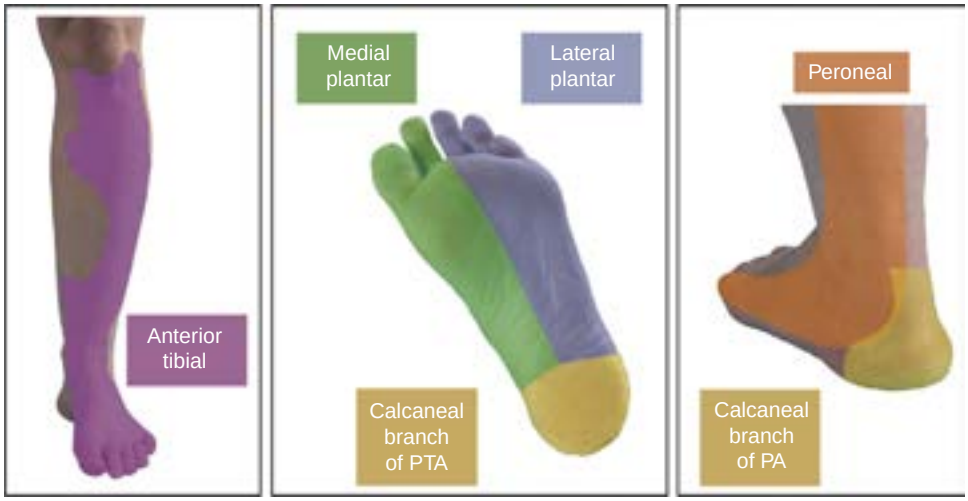


FIG. 3 Angiosome concept. Six angiosomes of the foot and ankle are supplied by three main arteries. *Left,* The anterior tibial artery (ATA) becomes the dorsalis pedis artery that supplies the dorsum of the foot and dorsum side of the toes. *Middle,* Three main branches of the posterior tibial artery (PTA) supply distinct portions of the sole: the calcaneal branch to the heel, the medial plantar artery to the medial foot, and the lateral plantar artery to the lateral midfoot and the forefoot. The PTA supplies the plantar side of the toes, the web spaces between the toes, the sole of the foot, and the inside of the heel. *Right,* The peroneal artery (PA) supplies the lateral border of the ankle and the outside of the heel. *(Iida O, Soga Y, Hirano K, Kawasaki D, Suzuki K, Miyashita Y, Terashi H, Uematsu M. Long-term results of direct and indirect endovascular revascularization based on the angiosome concept in patients with critical limb ischemia presenting with isolated below-the-knee lesions.* J Vasc Surg. *2012;55:363–370.e5.)*

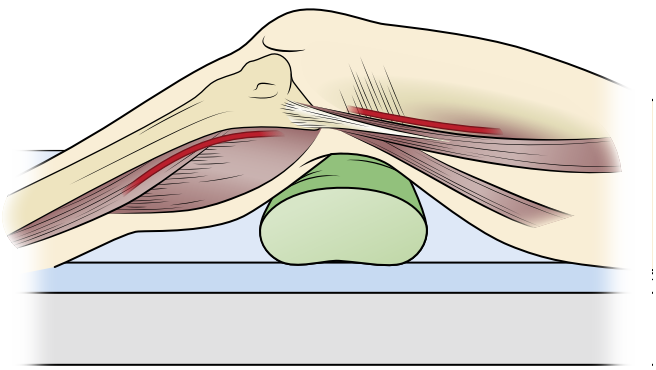


FIG. 4 Exposure of above- and below-knee popliteal artery.

question concerning the technical results. It is critical to evaluate the distal pulses by palpation and the use of continuous wave Doppler. The groin is then closed with multiple layers of absorbable sutures. The skin is closed as usual.

Perioperative Management

Medications are started, including statin and β-blockers. All patients are given one aspirin daily, which continues indefinitely. A soft cast or compression garment is applied on postoperative day 1 and is applied from the knee down. Physical therapy is generally started to help patient's ambulation, and discharge is usually done within a few days postoperatively.

Postoperative Graft Surveillance

There is strong evidence that vein graft surveillance is effective in maintaining graft patency. We generally obtain a first follow-up duplex scan before discharge or, if not feasible, on the first visit to the vascular clinic. If a bypass is normal, then the patient is checked every 4 to 6 months for 24 months and then yearly thereafter. It is believed that nearly one-third of vein grafts will develop lesions, which may threaten patency. Loss of graft patency within the first 30 days implies to a technical factor. Graft failure or impending failure within the first 2 years is secondary to myointimal hyperplasia and after 2 years is due to progressive atherosclerosis. The following noninvasive findings may indicate impending or failing graft: (1) a focal elevated peak systolic velocity >300 cm/s; (2) a peak systolic velocity ratio of ≥3 to 4 in comparison to an adjacent normal segment; (3) a low-flow velocity of <40 cm/s; and (4) a drop of ABI of ≥0.15 from the previous one. Intervention on these failing grafts can be done by open revision or endovascular means.

Femoropopliteal Bypass Using Prosthetic Conduit

Both PTFE or Dacron with heparin bonding has been utilized in this location, particularly when above-knee. The technical aspect is similar to what was described earlier without the need for vein harvesting. Conduit diameter used is generally between 6 to 8 mm; however, we prefer 8 mm conduit for an above-knee location. FPBP below-knee using prosthetic grafts is generally not recommended because of poor patency and is only utilized as a last option.

We previously conducted a prospective controlled study of PTFE grafts versus saphenous veins in disabling claudicant patients with bilateral AK-FPBP in 43 patients (86 limbs) who had SFA occlusion and above-knee reconstitution with 2 to 3 vessel runoffs. Patients were treated on one side with PTFE and on the other side with SVG. They were sequentially assigned to PTFE-SVG alternating with SVG-PTFE. All patients were followed using duplex ultrasound and ankle/brachial indexes at 1 month and every 6 months thereafter. The perioperative complication rates were 5% for PTFE and 12% for SVG. There was no operative death or perioperative amputation for either procedure. The Kaplan-Meier estimate of primary, assisted primary, and secondary patency rates at 72 months were 68%, 68%, and 77% for PTFE and 76%, 83%, and 85% for SVG, respectively.

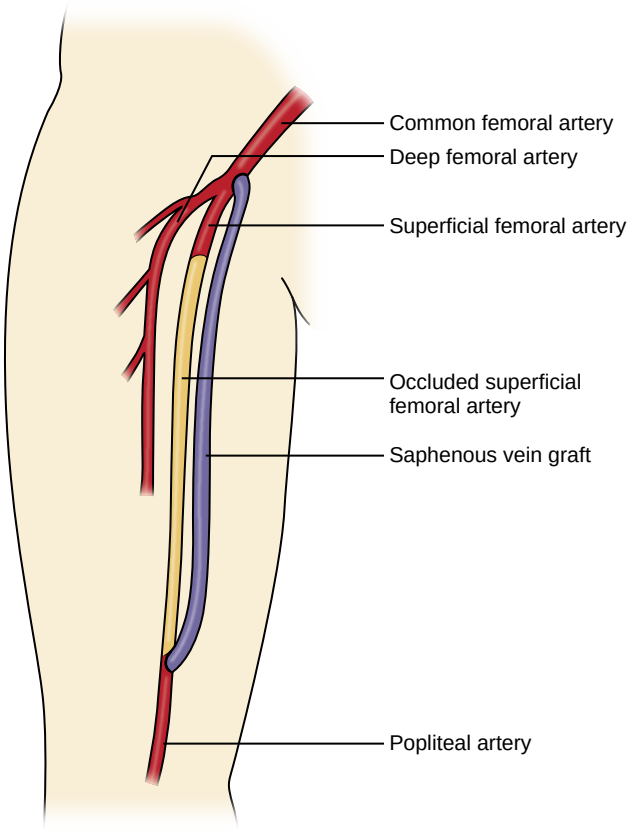


FIG. 5 Bypass done in reverse fashion.

There were no statistically significant differences between primary and secondary patency rates for both grafts; however, the assisted primary patency rates were higher for SVG (P <.05). The crude limb salvage rate at 72 months was 98% for PTFE and 98% for SVG. We concluded that PTFE and SVG for above-knee bypasses have comparable patency and limb salvage rates in claudicant patients with bilateral SFA occlusion and 2 to 3 vessel runoffs. This may justify the use of PTFE for above-knee locations in these selected patients.

Result of Open Surgical Bypass

Several studies compared the result of autogenous vein versus prosthetic FPBP in both above- and below-knee locations. A recent meta-analysis showed that SVG were superior to prosthetic bypasses in both above- and below-knee locations. However, as indicated earlier by our experience, some authorities believe patients who are claudicant and needed only above-knee FPBP who had good runoff (2–3 vessels) might be better off served by the use of PTFE or a prosthesis with the understanding the vein can be saved for future use for below-knee or distal vessels. If autogenous veins were not available for below-knee locations, a PTFE graft with distal anastomotic vein cuff has been suggested to be superior to prosthetic distal anastomosis alone (Table 1).

ENDOVASCULAR THERAPY FOR FEMOROPOPLITEAL DISEASE

Current endovascular therapy includes percutaneous transluminal angioplasty (PTA) stenting, cutting PTA, atherectomy, covered stents, drug-coated balloons/stents, and cryoplasty. The following is a review of the commonly used modalities.

TABLE 1 Graft Patency, Aggregate of Multiple Studies

	Supragenicular Femoropopliteal Bypass			Infragenicular Femoropopliteal Bypass			Femorotibial Bypass		
Type of bypass	**1 y**	**3 y**	**5 y**	**1 y**	**3 y**	**5 y**	**1 y**	**3 y**	**5 y**
SAPHENOUS VEIN									
Primary patency	86%	79%	75%	86%	83%	71%	82%	72%	69%
Secondary patency	89%	83%	80%	82%	87%	83%	88%	79%	79%
Limb salvage	82%	80%	81%				94%	87%	89%
Survival	86%	81%	70%		68%	74%	85%	69%	60%
PTFE									
Primary patency	80%	58%	53%	74%	53%	44%	60%	40%	24%
Secondary patency	87%	65%	70%	69%	48%	46%	65%	47%	28%
Limb salvage	86%	79%	72%	74%	71%	63%	75%	69%	57%
Survival	86%	81%	70%			42%	74%	55%	40%
DACRON									
Primary patency	79%	67%	62%	74%	46%	51%			
Secondary patency	88%	75%	75%						
Limb salvage		94%							
Survival	87%	77%	77%	86%		60%			

PTFE, Polytetrafluoroethylene.

From Ziegler KR, Muto A, Eghbalieh SD, et al. Basic data underlying clinical decision-making in endovascular therapy. *Ann Vasc Surg.* 2011;25:413–422.

Angioplasty/Stenting

The principle of angioplasty is balloon dilation of the reference lesion by inflating the balloon (to several atmospheric pressures) and cracking the plaque. PTA is considered by many to be a controlled dissection. PTA has a favorable outcome in larger caliber arteries, stenosis rather than occlusion, short, and focal rather than multiple with good runoff. PTA has a better result when the indication is claudication rather than CLI.

Technical Consideration

It starts by obtaining arterial access, then identifying the lesion with diagnostic arteriography, followed by crossing the lesion with a guidewire, balloon angioplasty, with or without stenting, and completion angiography to evaluate the result. The contralateral CFA is preferable arterial access; however, in certain thin patients, the ipsilateral CFA may be used for antegrade access. The brachial artery may be used occasionally, particularly in patients with previous aortobifemoral artery bypass graft. The access is either obtained by conventional standard 18-gauge puncture needle or a micropuncture small catheter access needle. Once an access is obtained, a 0.035-inch guidewire can be advanced into the iliac system and then the aorta using a contralateral catheter, and access is obtained to the ipsilateral iliac, CFA, then the SFA/popliteal artery through the lesion. To facilitate the intervention exchanging the access (5Fr 10-cm sheath) for a longer 45 to 55 cm (5Fr or 6Fr sheath), which is positioned at the level of the external iliac or CFA on the side of the intervention, which facilitates wire and catheter support. Spot angiography is used to delineate the lesion. The size and length of the balloon is tailored to the size and length of the artery. Every effort should be made to avoid ballooning a healthy native artery. After completion of angiography, if more than 30% residual stenosis exists or if angioplasty has created a dissection (with significant impairment of the flow), then a self-expanded stent should be placed across the lesion. We prefer giving 3000 to 5000 units of Heparin, which is administered intravenously at the start of the procedure once access is achieved. All patients should already be on aspirin regimen for intervention, which is continued afterward, in addition to clopidogrel (Plavix), which is prescribed for 6 weeks after PTA. PTA after stent placement is usually necessary for complete expansion of the stent.

Crossing an occlusion can be accomplished with several techniques. An angle support catheter in combination with a straight, stiff hydrophilic wire is generally used initially to traverse total occlusion. A combination of the support catheter and hydrophilic guidewire allows crossing many of these total occlusions. However, if that is not successful, other maneuvers might be utilized including subintimal traversal if necessary. This can be achieved by passing a hydrophilic angle guidewire into the subintimal plane with a loop orientation. Using catheter support, the loop is shortened to provide a smaller profile to reenter the luminal space. If that is not successful, reentry into the lumen may be done using a reentry catheter (e.g., the Pioneer or the Outback).

It is generally not recommended to stent the popliteal artery since it is highly mobile and because of its location across the joint, which may lead to stent fracture and higher restenosis rate. Therefore, stenting in this location should be done in select patients. Use of Supera stent by Abbott has been associated with favorable results in this location.

Once the procedure is done, the arterial access site can be closed using a variety of closure devices based on the size of the access sheath and the state of the access vessel (particularly calcification). Manual pressure may be appropriate for smaller access sheath and certain calcific lesions.

PTA for CLI can achieve a 5-year limb salvage rate of 89%, similar to earlier reported values with surgical revascularization, which ranged from 70% to 80%. Although the primary patency after PTA for CLI may be low, the limb salvage rate is quite high. SCVIR Transluminal Angioplasty and Revascularization (STAR) registry analyzed 205 patients (79% with stenosis and 11% with occlusions were treated) with mean lesion length of 3.8 cm for stenotic lesions and 4.7 cm for occlusions. The technical success rate was 95%. The primary patency rates were 87%, 80%, and 69% at 1, 2, and 3 years, respectively. Diabetes and poor runoff scores were associated with decreased patency rates.

The use of stents was initially advanced to improve long-term patency rates from PTA, especially in longer-segment disease. Stenting may reduce elastic recoil and provide a scaffold in the setting of dissection. Initial study results were disappointing, with several randomized trials failing to show any benefit of stent placement over PTA alone. These findings led to the recommendation for stenting only in the setting of a suboptimal technical result following PTA. However, these studies were done using balloon-expandable stainless steel stents, and more recent studies using self-expanding nitinol stents have shown significantly better results. Three major randomized trials comparing primary nitinol stent placement with stent-assisted angioplasty have been reported and show differing results.

The Femoral Artery Stenting Trial (FAST) analyzed outcomes with stand-alone PTA versus primary stenting with a single self-expanding nitinol stent. Only single short-segment lesions of <10 cm were included, with a mean lesion of 45 mm for both groups; 123 patients were assigned to primary stenting and 121 were randomized to PTA alone. Technical success was achieved in 79% of the PTA group versus 95% of the stenting group. Restenosis rates at 1 year, as determined by ultrasound, were not significant (39% in PTA, 32% in stent). Maximal walking distance was slightly improved in the stenting group, but there was no difference in resting ABI or change in Rutherford class. Stent fractures were found in 12% of patients, with no significant increase in restenosis with the presence of fractures.

The RESILIENT Trial is a prospective multicenter trial of 234 patients that compared bare nitinol stents (LifeStent, C. R. Bard) in patients with a mean lesion length of 7.1 cm to PTA patients with a mean lesion length of 6.4 cm. Forty percent of patients with PTA had bailout stent for >30% residual stenosis or dissection. This study suggested a statistical advantage of improved patency with stent over PTA alone. The technical success rate was better with stenting (96% vs. 84%). Freedom from target lesion revascularization was better in the stent group than the PTA group at 6 and 12 months: 94% and 81% versus 47% and 37%, respectively. The stent fracture rate was 3% at 12 months and was not associated with any adverse clinical sequelae. The study showed continued advantages of bare metal stents versus PTA at 3-year follow-up. The authors concluded that, for moderate length lesions, primary stent placement is superior to PTA alone.

The ABSOLUTE Trial (Balloon Angioplasty versus Stenting with Nitinol Stents in the SFA) included 104 patients with severe intermittent claudication and/or tissue loss (Rutherford classes 3–5) with lesions longer than 30 mm. Patients were randomized to PTA plus optional stenting or primary stenting. Mean target lesion length was 112 mm for the stent group and 93 mm for the PTA group. Restenosis rates were significantly lower in the primary stenting group at 2 years (46% vs. 69%). There was no difference between the two groups with respect to Rutherford class upon follow-up, but there was a trend toward improved walking capacity and resting ABI in the stent group. Overall, reintervention rates were lower in the primary stent group.

Challenges in Stenting SFA/Popliteal Lesions

The SFA and popliteal arteries, unlike other arteries, are subject to triplanar intermittent mechanical stresses, including contraction, extension, torsion, flexion, and compression. The efficacy of stents in this location is limited by the fact that they can only deform to a limited extent to stresses exerted on the artery. This lack of flexibility and resistance to stress may induce stent fractures and promote poorer patency.

Cutting Balloon Angioplasty

Cutting ballon angioplasty uses low-pressure balloon catheters mounted with microsurgical blades or microtomes that cut into luminal vessel during inflation. The mechanism of action is controlled disruption of the vessel wall, resulting in more controlled dilatation at lower balloon inflation pressures.

A prospective randomized controlled trial of *de novo* SFA lesions of 43 patients (19% had CLI) compared cutting balloon PTA versus conventional PTA and showed a restenosis rate of 32% in PTA and 62% in the cutting balloon PTA group at 6 months ($P = .048$). Therefore, cutting balloon PTA is not routinely used due to higher costs and inferior results but can be used for in-stent restenosis and diseased arteries in flexion points (CFA or popliteal artery–stent fracture risk).

Atherectomy

Atherectomy involves debulking or atherosclerotic plaque removal. Current devices for this modality include rotational, directional, orbital, and laser atherectomy. Atherectomy for PAD patients is currently used as adjunctive/alternative therapy to traditional PTA or stenting. Plaque debulking leads to an immediate increase in lumen size, which should result in reduced stretch injury of the arterial walls. One potential complication is embolization, although the TALON registry reports a very low embolization rate (0.1%).

The DEFINITIVE Ca++ study included 133 patients with calcified femoropopliteal lesions treated with the Silverhawk or Turbohawk (Covidien) and distal embolic protection. They reported a 93% freedom from major adverse events, which included clinically significant embolization. However, the definitive clinical benefit of atherectomy over PTA was not clear. Larger prospective multicenter trials are needed to highlight the role of atherectomy in femoral popliteal arterial disease.

Covered Stents

Stent-grafts using endovascular techniques attempt to duplicate open prosthetic FPBP. The Viabahn stent-graft (W.L. Gore & Associates, Inc.) consists of a self-expanding nitinol stent bonded to a graft made of expanded PTFE. They perform well in long segment occlusions and SFA restenosis; however, appropriate sizing and adequate runoff are required for optimal outcome and also dual antiplatelet therapy for at least 6 months.

The VIASTAR Trial (Viabahn Endoprosthesis) with Propaten Bioactive Surface versus Bare Nitinol Stent in the Treatment of Long Lesions in SFA Occlusion studied 141 patients randomized to Viabahn or bare metal stents. The 1-year patency rate was higher with long lesions (>20 cm) with covered stents versus bare metal stents (71% vs. 37%, $P = .01$). The Viabahn stent was then modified, and heparin was bonded to the stent. This was examined in the VIPER trial for the treatment of SFA occlusion where the primary and secondary patency rates were improved to 73% and 92%. Lammer et al. reported that PAD patients with long femoral popliteal lesions had significantly improved primary patency rates with covered versus bare metal stents at 24 months; however, there was no significant impact on clinical outcomes and target lesion revascularizations.

Drug Eluting Balloons and Stents

Drug-coated angioplasty balloons (DCB) and drug-eluting stents (DES) are designed to limit the proliferative, reactionary process of neointimal hyperplasia. DCBs were developed to improve the durability of PTA, without the potential drawbacks of stents. It has been hypothesized that stents may actually increase neointimal hyperplasia by causing repetitive trauma and an increased inflammatory reaction. DCBs are designed to curb neointimal hyperplasia by delivering large doses of anticell proliferation agents directly to the site of vessel injury.

Paclitaxel is a proven antiproliferative drug that stops cell division and induces apoptosis. The IN.PACT Admiral DCB coating consists of paclitaxel and urea, a carrier molecule. When exposed to blood during inflation, the urea hydrates and releases paclitaxel. Subsequently, the drug transfers into the wall of the artery and migrates through the vessel wall into the media. The IN.PACT Admiral DCB delivers paclitaxel in solid-phase, thus establishing reservoirs of drug within the vessel wall. These reservoirs permit sustained drug availability (up to 6 months) and release with subsequent long-term antiproliferative effect.

There are several ongoing studies of paclitaxel DCBs in *de novo* and restenotic femoral popliteal lesions. Using DCBs to treat in-stent restenosis is preferred over placing additional stents because additional overlapping stents are associated with a higher rate of stent fracture and restenosis. Currently, there are two DCBs approved for use in the United States, Lutonix 035 (Bard) and IN.PACT Admiral (Medtronic). The majority of clinical trial data on DCBs has predominantly included patients with claudication and lower Rutherford classifications, as opposed to CLI patients. Late lumen loss, target lesion revascularization, and angiographic restenosis significantly favored DCBs in these trials.

FDA approval of the Ranger balloon was based on a Ranger SFA trial that was a randomized controlled trial of 105 patients with 3:1 ratio of DCB vs. plain balloon angioplasty over a 12-month period for patients with Rutherford class 2–4. Mean lesion length was 82.5 mm for the Ranger DCB group and 79.9 mm for the control group. DCB group had a patency rate of 86.4% versus 56.5%, and the estimated freedom from target lesion revascularization was 91% in the DCB group versus 69.9% in the control group with a significantly longer time to reintervention.

In our group, we analyzed 228 patients with femoral and popliteal disease treated with DCB angioplasty. Forty percent of patients had claudication (Rutherford Stage 2–3) and 60% were classified as CLI (Rutherford Stage 4–5). Mean follow-up was 12 months. Primary patency rates were 82% and 71% for 1 and 2 years in patients with TASC A-C lesions vs. 29% and 14% for TASC D lesions. Symptom improvement was 76% for claudication vs. 49% for CLI. Limb salvage rates at 1 and 2 years were 100% for claudicants vs. 85% and 74% for CLI.

The LEVANT Trial (Lutonix Paclitaxel CB [Bard] for Prevention of Femoral Popliteal Restenosis) randomized 101 patients to Lutonix DCBs or uncoated balloons. There was a significant increase in primary patency at 12 months with the Lutonix 035 DCB versus plain balloon angioplasty (74% vs. 57%, $P < .001$). At 24 months, the major adverse events (death, amputation, target lesion thrombosis/reintervention) were 39% for DCB and 46% for uncoated balloon patients ($P = .45$). It should be noted that the results of DCBs have not been encouraging for below-knee vessels. The IN.PACT DEEP study identified a potential safety signal with a trend toward an increased rate of major amputations in the DCB study arm.

Medtronic's IN.PACT SFA trial is a prospective, multicenter, randomized trial in which 331 patients with intermittent claudication and CLI, secondary to femoral popliteal PAD, were randomly assigned in a 2:1 ratio to treat with DCB (Paclitaxel) or PTA. Over 90% of lesions were *de novo*, with a mean lesion length of ≥8 cm in both groups. A higher primary patency at 12 months in the IN.PACT Admiral DCB group was noted, compared with the PTA group (82% vs. 52%, $P < .001$). The rate of clinically driven target lesion revascularization was 2.4% in the DCB group versus 20.6% in the PTA group ($P < .001$). There was no device/procedure related death or major amputation.

The THUNDER trial followed 154 patients who were treated with DCBs, angioplasty with paclitaxel in contrast medium, or no paclitaxel (control group) for 5 years. The target lesion revascularization was significantly lower in the DCB versus the control group (21% vs. 56%, $P = .0005$). DCBs also had lower binary restenosis (17% vs. 54%, $P = .04$). DCBs had reduced target lesion revascularization over 5 years.

Limitations of DCB

The use of cytotoxic agents, such as paclitaxel, may have an adverse impact on wound healing. Furthermore, patients with PAD,

especially those with CLI, often present with calcified plaque, which is difficult to treat and is often associated with poor procedural and long-term success. Preparing the vessel with atherectomy before using DCBs is a strategy that may hold some promise in improving the therapeutic effect of DCBs in calcified lesions.

Concern for increased risk of cardiac death from paclitaxel led to a multicenter, randomized, open registry-based clinical trial of 2289 patients published in the *New England Journal of Medicine* that randomly assigned patients to drug-coated device vs. an uncoated device. Patients had peripheral vascular disease ranging from claudication to chronic limb ischemia. Endpoint was all-cause mortality.

Patients with chronic limb ischemia during the entire follow-up showed incidence of death of 33% in the drug-coated group versus 33% in the uncoated drug group. Among claudicants, rates were 10% versus 9% subsequently.

During follow-up of 1 to 4 years, there was no difference in all-cause mortality of drug-coated versus uncoated device.

Drug-Coated Stents (DCS)

SIROCCO I and II Trials: Sirolimus-eluting stents (Cordis Smart nitinol self-expanding stent) were compared with bare metal stents. There was no difference of in-stent restenosis at 6 months and 2 years. However, the Zilver PTX (paclitaxel) stents (Cook Medical) proved to be safe, efficient, and superior to PTA with provisional stent placement. In a study by Dake et al. with the Zilver PTX stent, 474 patients were randomized to primary DES or PTA with provisional stents with subsequent secondary randomization to bare metal stents or DES for patients requiring provisional stents. The event-free survival at 1 year was 90% for primary DES versus 83% for the control arm ($P = .004$). The primary patency rate at 1 year was 83% for DES versus 33% for PTA alone.

Later studies with Zilver PTX stents reported a primary patency rate of 83% for DES and 65% for PTA, excluding acute PTA failure ($P < .001$). The data still supported safety and efficacy of DCS at 5 years. In a larger prospective registry of 787 patients, the 2-year freedom from target lesion revascularization with primary DES placement was 80.5% in the single-arm study. The Zilver PTX stent was also examined for the treatment of in-stent restenosis. In patients with a mean lesion length of 13 cm (31% total occlusions), procedural success was 98%, primary patency rate at 1 year was 79%, and freedom from target lesion revascularization at 2 years was 61%. Dual antiplatelet therapy is recommended for 6 months with the use of the Zilver PTX. Later 5-year data showed that DCS (paclitaxel) had better patency rates than standard PTA (66.4% for lesions 65 ± 40 mm in length) and better freedom from target lesion revascularization (85%).

More recently, the results of the Imperial Study, which was a randomized trial of comparison in patients with femoral popliteal disease comparing Eluvia paclitaxel stent (Boston Scientific) and the Zilver PTX paclitaxel stent (Crook), were reported. The trial was conducted at 65 centers randomizing 465 patients with femoral and popliteal disease in a 2:1 ratio of Eluvia versus Zilver PTX in Rutherford class 2–4. Mean lesion length was 83 cm. One-year primary patency rate was superior with Eluvia at 86.8% vs. 81.5% with Zilver PTX, a difference for noninferiority (primary endpoint) and superiority. Primary safety endpoint of major adverse events (including MALE and MACE) Eluvia was shown to be noninferior to Zilver PTX (4.9% vs. 9%).

At 24 months, target lesion revascularization was less for patients with Eluvia vs. Zilver PTX (12.7% vs. 20.1%). Primary patency rate at 24 months was 83% for Eluvia and 77% for Zilver PTX.

DCB versus DES for SFA Interventions

Lesion length, type of recanalization (subintimal vs. intraluminal), degree of calcification, and lesion site (ostial, popliteal) should all be considered when choosing a primary strategy. As a general rule, one must avoid stenting when unnecessary due to the possibility of a worse behavior of stent restenosis. It is generally recommended to use a DCB for a TASC B, C, or D lesion upon first presentation and also for restenotic lesions, as well as for in-stent restenosis in the femoropopliteal area. If significant flow-limiting dissection remains, use of a DES as a kind of bailout stent is appropriate.

Primary Amputation

Some authorities feel primary amputation may be appropriate in select patients (e.g., those with significant tissue loss who are not likely to return to ambulation and with long-standing functional impairment). Patients who are also paralyzed with contractures or have short life expectancy, severe sepsis, end-stage renal disease, or other systemic disease would be better served with primary amputation.

CONCLUSION

Based on a nearly universal procedure success rate, low morbidity and mortality, and improving patency rates with new devices, endovascular therapy is the recommended treatment of choice for TASC A–C lesions, although open surgical bypass with ASV grafts is a durable choice in low-risk patients. Two new studies, BASIL-2 and -3 and BEST-CLI, are enrolling patients to further compare open versus endovascular therapy for selected patients with CLI. Until more well-designed randomized trials are completed, physicians should rely on their best clinical judgment.

Suggested Readings

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Tibioperoneal Arterial Occlusive Disease

Natalia O. Glebova, MD, PhD

Approximately 8 to 12 million people suffer from peripheral arterial disease (PAD) in the United States, which rivals the prevalence of coronary artery disease. In 2001, US Medicare spent more than $4.3 billion on PAD treatment, and an estimated $21 billion was spent in the United States on vascular-related treatment, with the majority being treatment for PAD. PAD is a systemic inflammatory process that affects the entire arterial tree; however, the anatomic patterns of distribution are associated with specific patient demographics, medical risk factors, and symptoms. The symptoms of PAD are caused by inadequate blood flow to a skeletal muscle bed due to a more proximal flow-limiting arterial stenosis or occlusion. Claudication (from the Latin *claudico*, meaning "to limp") is defined as pain in the thigh or calf muscles with exercise that is relieved at rest. Typically, patients with claudication symptoms alone are not at a greatly increased risk of limb loss. Critical limb ischemia (CLI) occurs when there is such limited blood flow to the leg that, even at rest, the metabolic demands of the tissue are not met. CLI is characterized by pain at rest and/or tissue loss (ulceration or gangrene). Patients with CLI are at risk for limb loss if expeditious intervention to restore arterial perfusion is not performed. Patients with a predominant distribution of atheroocclusive disease in the tibial and peroneal arteries are more likely to initially present with signs and symptoms of CLI than patients with proximal femoropopliteal disease secondary to the absence of collateral vessel flow to the foot. Revascularization in these patients is often challenging due to anatomic factors, disease severity, and patient comorbidities. Patients with tibioperoneal occlusive disease (TPOD) are typically diabetic with a high prevalence of renal insufficiency compared with patients with PAD in more proximal arterial distribution. These patients are also at significant risk for vascular disease of the coronary, cerebral, and renal arteries; thus, when an intervention is planned, the surgeon must consider the patient's comorbidities to weigh the risks and benefits of the planned intervention.

PATIENT ASSESSMENT

In the assessment of a patient with TPOD, a complete history and physical examination are critical for planning treatment. This evaluation should include an assessment of the patient's functional status with regard to current ability to ambulate, the patient's expectations of therapy, risk stratification for major adverse cardiac events (MACE), as well as the patient's social and home support. The 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines outline the recommended perioperative cardiovascular evaluation. For patients who have less than a 1% chance of MACE based on combined surgical and patient characteristics, no further cardiac workup is required. Several risk calculators are available online for convenient determination of a patient's cardiac risk, including one developed by the American College of Surgeons. Unfortunately, the majority of vascular patients and vascular procedures fall under the "elevated risk" category where there is a 1% or greater risk of MACE. If a patient has moderate or greater functional capacity defined as four or more metabolic equivalents (classically described as being able to "walk up a flight of stairs"), then no further workup is typically required. In patients with CLI, such symptomatic evaluation is often limited as patients are often unable to walk for any significant distance secondary to leg pain from critically low blood flow, and this may preclude the identification of significant cardiac disease that would become symptomatically apparent if the patient was able to walk. If a patient has poor or unknown functional capacity and the results of further testing would influence decision making or perioperative care, then pharmacologic stress testing is warranted with subsequent coronary revascularization if an abnormality is found.

A thorough examination of the leg and foot helps determine the likelihood of functional salvage. The examiner should note the patient's ability to walk, evidence of flexion contractures, or other neuromuscular disabilities that may affect ambulation. The presence of local infection, soft tissue edema, venous disease, and prior surgical incisions may influence the choice of intervention. Physical examination should also focus on the arterial perfusion of the symptomatic limb. The ankle-brachial index (ABI) is one noninvasive test used to diagnose PAD. An ABI of 0.9 or less signifies a hemodynamically significant stenosis. The ABI can be falsely elevated with calcified vessels, and if the ABI is found to be 1.4 or greater, it is likely unreliable. In this case, the toe-brachial index (TBI) may be a more accurate tool to determine the presence of PAD (a TBI of 0.7 or less is indicative of a significant arterial stenosis). CLI in general occurs at ABI <0.4 or TBI <0.5, but this is patient-dependent. The examiner should note the presence and quality of the femoral, popliteal, posterior tibial, and dorsalis pedis pulses. The quality of femoral pulses is a crucial aspect of the examination because diminished femoral pulses reveal concomitant suprainguinal occlusive arterial disease, for which an inflow revascularization procedure would be indicated. Inflow disease involving the common and external iliac arteries should be addressed before or during distal revascularization. Likewise, an atherosclerotic common femoral artery can be reconstructed with endarterectomy at the time of bypass. A palpable pulse in the popliteal artery usually indicates absence of flow-limiting proximal stenosis or occlusion in the femoral artery. This is a common finding in young diabetic patients who have disease predominantly in

the tibial and peroneal arteries. Dorsalis pedis and posterior tibial pulses are often not palpable in patients with TPOD, and Doppler assessment with a handheld probe is most helpful. Triphasic signals indicate normal arterial wall transduction of systolic and diastolic pressures; transduction signals become attenuated to a biphasic pattern with mild to moderate disease and become monophasic with severe disease. Absence of hair and presence of a shiny tone of the skin on the lower leg reflect chronic arterial insufficiency, and evidence of ulceration is a sign of severe ischemia and high risk for limb loss. Along with a thorough physical examination, preoperative laboratory tests are conducted, with particular attention to renal function, in anticipation of imaging studies with contrast materials that may be nephrotoxic.

The vascular laboratory is a crucial adjunct to the preoperative evaluation. Not only can the vascular laboratory provide ABIs and TBIs, but arterial perfusion can also be estimated from segmental blood pressures measured at the upper thigh, mid-thigh, calf, and ankle. A pressure change greater than 20 mm Hg between each segment indicates an intervening flow-limiting stenosis and is helpful to determine the level of disease. If a venous conduit is to be considered for surgical bypass, a duplex ultrasound of bilateral lower extremities should be performed to ensure that the proposed vein is adequate, with a diameter of at least 3 mm throughout its length.

Once a patient is determined to have CLI, it is imperative to plan an expeditious revascularization procedure with endovascular techniques or surgical bypass because the risk of limb loss within 1 year of diagnosis is 40%. One may assume that primary amputation is a less morbid procedure in the patient with CLI who is at high operative risk; current data reveal that the 30-day mortality rates for endovascular intervention (2%–8%) and surgical bypass (2%–6%) in CLI are similar, whereas the rate is generally higher for primary amputation (6%–12%). High-resolution imaging is essential for planning revascularization, regardless of whether a surgical or endovascular approach is being considered. While computed tomographic angiography (CTA) is excellent in evaluation for proximal arterial disease of the aorta, iliacs, and femoral arteries, it is limited in assessment of tibial disease due to the small caliber of vessels and frequent presence of arterial calcifications interfering with one's ability to distinguish between contrast and calcification. Digital subtraction angiography (DSA) with iodinated contrast material delivered via an intraarterial catheter is considered the gold standard for evaluation of TPOD. DSA image quality is not compromised by calcification of the arterial wall, and selective catheter placement in the femoral artery or distally can provide high-quality images of the tibial vessels, which can be difficult to evaluate with other modes of imaging. If a tibial bypass is planned, we recommend a diagnostic angiogram, which can be done either before the day of surgery or concomitantly with the planned bypass to verify the suitability of the bypass target. In diabetic patients and patients with renal insufficiency, nephrotoxicity of iodinated contrast material can be minimized with preprocedure and postprocedure hydration with normal saline, administration of acetylcysteine, and selection of a nonionic contrast agent. Carbon dioxide (CO_2) gas can be used as a contrast agent during angiography; imaging with CO_2 is often quite good for endovascular intervention or visualization of a potential bypass target. CO_2 can also be used as an adjunct to allow selection of the most distal artery in the treatment leg, which allows minimization of contrast injection if contrast is indeed required for adequate visualization of a tibial bypass target. Multiple-slice spiral CTA is a noninvasive technique for imaging the entire arterial tree from the abdominal aorta to the level of the foot; it provides superb spatial and temporal resolution with a single-bolus infusion of contrast agent. The accuracy of CTA in visualizing lumen patency is restricted by calcification in the vessel wall, a frequent occurrence in the tibial arteries of diabetic patients. Magnetic resonance angiography (MRA) has poorer resolution compared with CTA but is not affected by calcification. Use of gadolinium-based contrast helps increase image quality but is limited in patients with renal failure (glomerular filtration rate of 60 mL/min/1.73 m^2 or less) because of the risk of nephrogenic systemic fibrosis. Time-of-flight MR imaging can be used without contrast and can yield high quality imaging.

In the initial planning for intervention for the patient with TPOD, noninvasive testing should be performed first, which includes ABIs, segmental pressures with toe pressures, and, if abnormal, followed with arterial duplex ultrasound of the symptomatic extremity. If on physical exam the patient has symmetric femoral pulses and there is no evidence of inflow disease on noninvasive vascular studies, the next step in imaging should be diagnostic angiography for possible endovascular intervention or to obtain high-resolution images of a potential bypass target. If there is evidence of inflow disease, then a CTA or MRA of the abdomen/pelvis with lower extremity runoff should be performed. In the planning of a surgical bypass, the target artery chosen for the distal anastomosis should have continuous unimpeded flow to the plantar arches of the foot, especially in patients with tissue loss. In many diabetic patients, the peroneal artery is the only remaining patent artery below the knee; however, either the anterior branch to the dorsalis pedal artery or the posterior branch to the posterior tibial artery (ideally both) must be intact to provide perfusion to the foot as the peroneal artery terminates above the ankle. In patients with occlusion of the tibial and peroneal arteries throughout the lower leg, the plantar and tarsal arteries should be examined as possible sites for a distal anastomosis for limb salvage. In the angiosome model of revascularization, if multiple tibial vessels are available for bypass, then the artery providing the majority of flow to the wound should be revascularized. Typically, the anterior tibial artery supplies the anterior ankle and dorsum of the foot, the posterior tibial artery supplies the plantar aspect of the foot, and the peroneal artery supplies the anterolateral ankle.

SELECTION OF INTERVENTION

Patients who present only with claudication should initially be managed nonoperatively, as fewer than 5% of such patients progress to CLI and limb loss. Furthermore, arterial interventions in claudicants are associated with a three- to fourfold increased risk of limb loss as compared with medical management in a 2021 Veterans Health Administration study and should be avoided with preference given to medical treatment of claudication. Treatment should focus on cardiac risk factor modification. Patients should stop using all tobacco products, be placed on aspirin and statin if not contraindicated, and have medication adjustments for optimal blood pressure and glycemic control. A supervised exercise program of 30 to 60 minutes of exercise, such as walking three times a week, should be instituted; treatment with Cilostazol may be considered to improve exercise tolerance in claudicants.

Patients with rest pain or tissue loss should be offered prompt intervention to prevent limb loss. The primary objectives in treating patients with TPOD are to relieve pain, promote healing of ulcers, preserve a functional limb, and restore or maintain the ability to ambulate. These objectives must be tempered by the patient's general medical condition, current ambulatory status, and previous operations. In general, the success of surgical bypass depends on the availability of a single segment of autogenous vein of suitable diameter, whereas success of endovascular treatment is determined by extent of atherosclerotic disease, as quantified by the Trans-Atlantic Inter-Society Consensus (TASC) II Working Group. Infrapopliteal lesions are categorized in severity from classes A to D (Fig. 1). The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial is the only randomized trial (452 patients) in which outcomes of surgical bypass and percutaneous transluminal angioplasty (PTA) were compared for treatment of severe infrainguinal PAD and provides level 1 evidence in the field. At 1 year, the amputation-free survival (AFS) rates were equivalent; however, at 2 years, AFS rates were better among the patients undergoing bypass. The BASIL authors concluded that bypass with autogenous vein is the best treatment for patients with severe limb ischemia expected

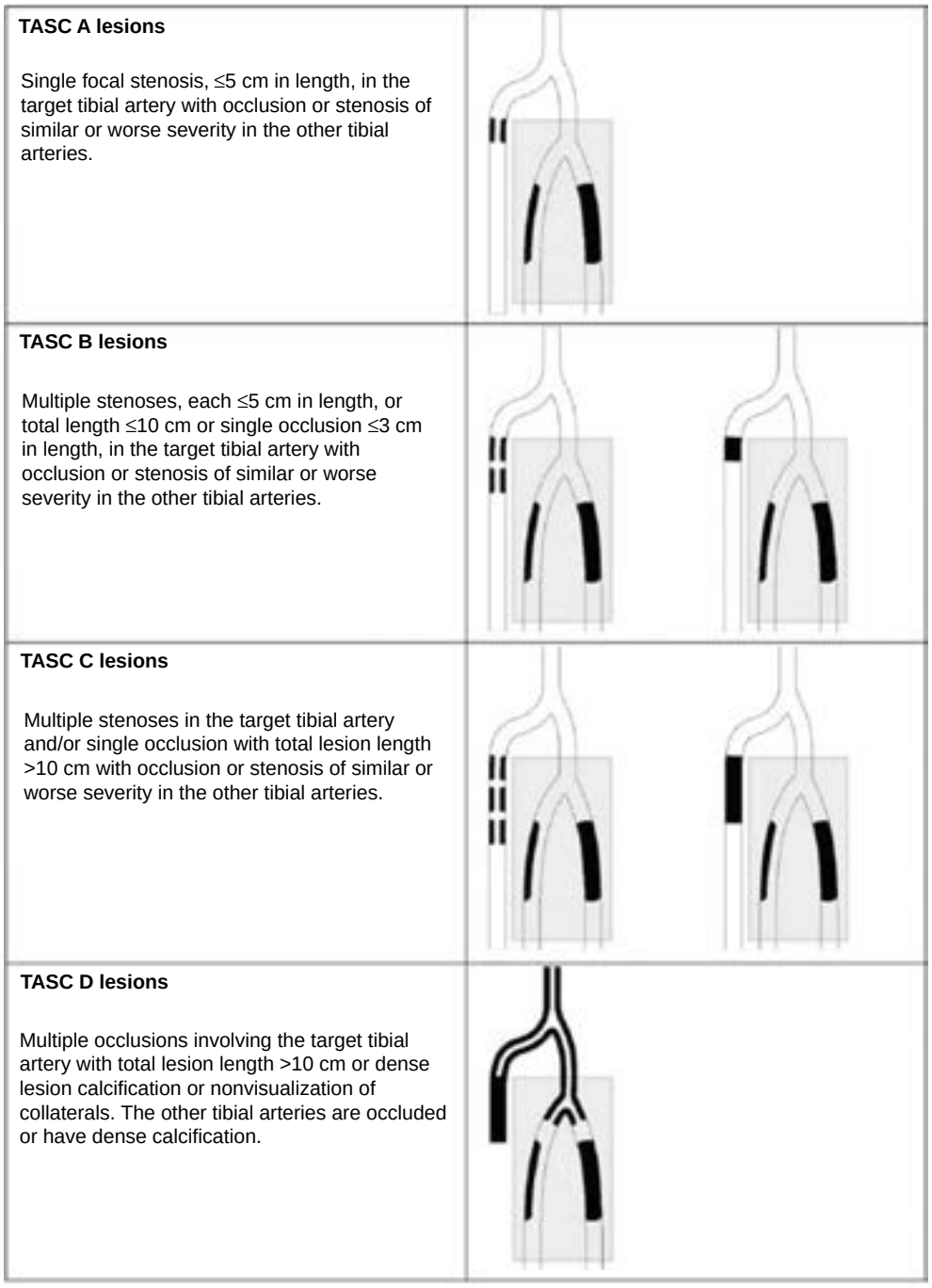


FIG. 1 Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) classification of infrapopliteal lesions. The unshaded area represents the target lesion; area inside the shaded rectangle represents typical background disease. *(Reprinted from Jaff MR, White CJ, Hiatt WR, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).* Vasc Med. *2015;20[5]:465–478.)*

to survive more than 2 years, and bypasses with prosthetic grafts in patients without sufficient autogenous vein are associated with poor results. Endovascular interventions are the preferred option for TASC classes A, B, and single-level C lesions, whereas surgical bypass has been recommended for multilevel TASC classes C and D lesions in a patient with average surgical risk. Bypass historically has been the first choice with significant tissue loss (ulcer larger than 1 cm or gangrene involving the foot; Fig. 2). However, some patients with TASC D lesions with severe comorbidities precluding significant anesthetic administration or renal insufficiency may be better served with endovascular intervention which may have limited long-term patency but may be adequate to heal current tissue loss while minimizing short term perioperative morbidity and mortality. In fact, some studies show that endovascular-first approach is associated with improved AFS in patients with CLI, especially those with dialysis dependence, as compared with surgical bypass treatment. Much-anticipated results of the BASIL-2 and the Best Endovascular versus best Surgical Therapy in patients with Critical Limb Ischemia (BEST-CLI) may change the currently accepted choice of initial intervention in patients with CLI.

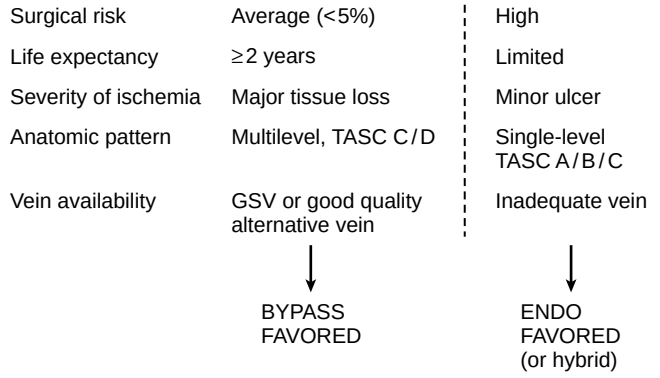


FIG. 2 Schema for bypass or endovascular treatment (ENDO). *GSV,* Greater saphenous vein; *TASC,* Trans-Atlantic Inter-Society Consensus (class). *(From Conte MS. Critical appraisal of surgical revascularization for critical limb ischemia.* J Vasc Surg. *2013;57:2.)*

SURGICAL BYPASS

All patients are maintained on aspirin before the surgical procedure. Clopidogrel therapy can be continued as well if the patient is on this medication preoperatively. Unless it is contraindicated, warfarin (Coumadin) as well as the direct oral anticoagulants (DOACs), need to be stopped several days before elective open operations. If limb ischemia is acute, however, patients are admitted and undergo systemic anticoagulation with intravenous heparin, which can be stopped en route to the operating room.

Anesthesia and Positioning

Options for anesthesia include local, epidural, regional block, and general anesthesia. We prefer general anesthesia for patient comfort, as most surgical bypasses to the tibial arteries require 4 to 6 hours, but the choice of anesthesia should be tailored to the patient and their associated risks. Regional anesthesia with epidural is another excellent choice for a higher perioperative risk patient. The patient is placed supine on the operating fluoroscopy table, and any open wounds are covered with an Ioban drape. Hair is clipped over the anticipated incision sites. We mark the course of the greater saphenous vein (GSV) on the skin using duplex ultrasonography guidance before the start of the operation to help prevent the creation of skin flaps. The skin of the lower abdomen, both groins, the operative leg(s), and feet are painted with ChloraPrep. Two Bovie electrocautery devices are used to enable simultaneous arterial exposure and vein harvest.

Operative Exposures

Inflow Vessels

The CFA is the artery most commonly used for the proximal anastomosis and is easily exposed with either a transverse incision in the groin crease or a longitudinal incision centered over the femoral pulse. We prefer to use the transverse incision as it heals better in our experience. Even when an endarterectomy of the inflow artery is necessary, we find that with appropriate retraction, exposure may be attained via a transverse groin incision such that endarterectomy from the external iliac to the common femoral artery bifurcation and even the profunda femoris (PFA) is possible. Subcutaneous dissection is performed with the help of Bovie electrocautery, and obvious lymph nodes and lymphatics are controlled with ties. The proximal CFA, PFA, and superficial femoral arteries (SFA) are circumferentially controlled with vessel loops. If conduit length is limited and there are no flow-limiting lesions in the CFA or SFA, alternative inflow sites for the proximal anastomosis include the PFA, middle and distal SFA, and the popliteal artery above and below the knee. A lateral approach to the profunda is a useful approach for inflow when the patient has a normal CFA to avoid a redo groin operation or to stay away from an infected field. Diabetic patients frequently have no significant arterial occlusive disease above the knee, and a popliteal-tibial bypass is a reasonable choice in such situations when available conduit length is limited.

Outflow Vessels

When a tibial bypass is necessary, the anterior or posterior tibial arteries are the first choice for the distal outflow anastomosis because they are more accessible and in direct continuity with the arterial arches of the foot. The peroneal artery is selected if the anterior tibial and posterior tibial arteries are diffusely diseased. The target for the distal anastomosis must be free of calcified plaque as this may lead to dissection of the intima and compromise graft patency. Preoperative imaging with DSA is utilized to help determine the most suitable distal target.

Proximal Posterior Tibial and Peroneal Arteries

To expose the tibioperoneal trunk and the proximal segments of the posterior tibial and peroneal arteries, an incision is made approximately 2 cm posterior to the medial edge of the tibia, starting just below the knee joint and extending distally for 10 to 15 cm. If the ipsilateral GSV is being used as a conduit, one can make the incision directly over the course of the vein, which is marked on the skin preoperatively. The fascia of the gastrocnemius muscle is incised, and the medial head is retracted posteriorly with a Weitlaner retractor with dull prongs. The popliteal fossa is entered, and the popliteal vein is encountered medial and anterior to the artery and usually has several large tributary branches at the level of the tibioperoneal trunk that should be ligated and divided. The popliteal vein is then mobilized with sharp dissection and retracted posteriorly with a vessel loop, which exposes the distal popliteal artery. The soleus muscle is detached as close as possible to the tibia, and a second Weitlaner retractor is placed. Meticulous dissection with Metzenbaum scissors exposes the distal popliteal artery and is continued distally to expose the tibioperoneal trunk, which then bifurcates to the posterior tibial and peroneal arteries usually approximately 2.5 cm from the origin of the anterior artery. Care must be taken because there are multiple vein branches that tear easily; thus these should be ligated and divided when encountered to avoid bleeding, as the transected vein will retract into the muscle if inadvertently torn. The two concomitant veins that usually run parallel to each artery are equally friable and send branches that cross the arteries at frequent points; these branches should be ligated.

The middle segment of the posterior tibial artery is exposed with a longitudinal incision approximately 2 cm posterior to the medial edge of the tibia (Fig. 3A) and extended for 10 cm. The fascia is incised longitudinally, and soleus is divided off the tibia. Once the soleus is retraced posteriorly, the posterior tibial artery can be found in the plane between the flexor digitorum longus and soleus muscles. The artery is dissected sharply on the anterior surface with Metzenbaum scissors, again with care to ligate and divide venous branches that cross the artery anteriorly (Fig. 3B). When isolating tibial arteries, we avoid circumferential dissection and only clear the artery on the most anterior surface facing the surgeon. This avoids inadvertent damage to the artery from sharp dissection. Circumferential dissection of tibial arteries is unnecessary as we use tourniquet control for the distal anastomosis (described later) and never clamp the tibial arteries to avoid damaging these fragile vessels.

The distal posterior tibial artery can be exposed at the medial ankle with an incision 1 cm posterior to the distal tibia; this may be extended posterior to the medial malleolus. The flexor retinaculum is divided, and the artery is found between the tendons of the flexor

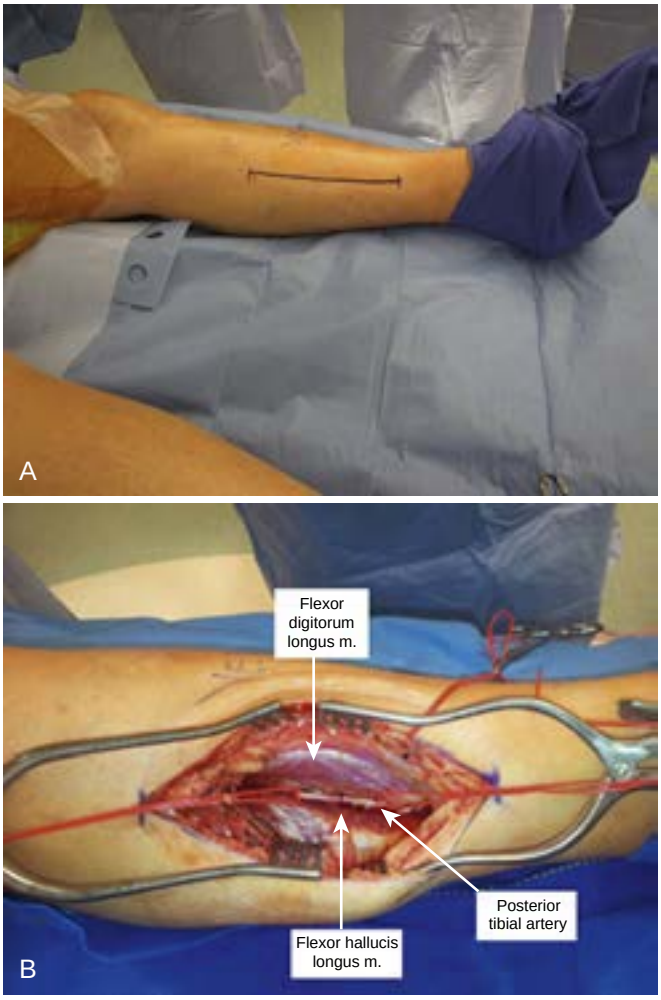


FIG. 3 Exposure of the posterior tibial artery. **(A)** An incision is made on the middle third of the medial portion of the leg. **(B)** The posterior tibial artery lies between the flexor digitorum longus and flexor hallucis longus muscles, which are separated with sharp and blunt dissection.

digitorum longus and flexor hallucis longus muscles. The bifurcation of the posterior tibial artery into the medial and lateral plantar branches can be found by creating a curvilinear incision from behind the medial malleolus to the instep of the foot for 5 cm. Division of the abductor hallucis muscle is usually necessary to facilitate exposure. The lateral plantar artery takes a slightly more inferior course to the medial plantar artery and is often larger. Usually a segment suitable for bypass can be exposed before it courses laterally across the sole of the foot.

The middle segment of the peroneal artery can be exposed through the same incision used to expose the posterior tibial artery (2 cm posterior to the tibia). Once the fascia is incised, the soleus is divided off the tibia and retracted posteriorly, taking the posterior tibial neurovascular bundle with it. The fascia over the flexor digitorum longus muscle is divided, and the plane of dissection is carried deeper, where the peroneal artery can be found. The distal peroneal artery can be exposed via a lateral incision and partial fibulectomy. The skin incision is placed laterally over the fibula, and the bone is cleared of all muscular and tendinous attachments (Fig. 4A and B). The bone is then gently resected for a distance of at least 8 cm, and the peroneal artery is found medially on the flexor hallucis longus muscle (Fig. 4C and D).

Anterior Tibial Artery and Dorsalis Pedis Artery

The anterior tibial artery is exposed through a longitudinal incision placed between the tibia and fibula (Fig. 5A). The fascia overlying the tibialis anterior and the extensor digitorum longus muscles is opened, and the groove between these two muscles is separated (Fig. 5B), which exposes the anterior tibial artery, its concomitant veins, and the deep peroneal nerve (Fig. 5C). The dorsalis pedal artery is the continuation of the anterior tibial artery onto the dorsum of the foot and is exposed by an incision made between the first and second metatarsal bones. The incision is made off to the side of the artery, not directly over it; this allows for the creation of a skin flap to provide tissue coverage for the bypass graft. After the deep fascia is incised, one separates the extensor hallucis longus and brevis muscles to expose the artery.

Conduit

For patients with TPOD, bypass grafting with single-segment GSV remains the best conduit option for long-term patency; 1-year and 5-year limb salvage rates exceed 90% and 80%, respectively. If the ipsilateral portion of the GSV is inadequate or was previously used for bypass, then the GSV from the contralateral leg should be used. If no GSV is available and endovascular attempts for revascularization are unsuccessful, then the lesser saphenous vein or the basilic and cephalic veins from the arms are other options, if they are of adequate diameter. The basilic and cephalic veins, if not damaged by repeated venipuncture, can be harvested as a single continuous graft of significant length. Splicing of multiple vein segments is sometimes required to obtain the required conduit length. We splice vein segments over a pediatric feeding tube to facilitate the creation of the conduit with two 7-0 polypropylene sutures to prevent purse stringing of the venovenous anastomosis that can occur with a single running stich. A distal origin bypass from the profunda or distal SFA/popliteal artery can be considered if no proximal stenosis is identified to minimize the conduit length needed. Bypass to the tibial vessels should be with autogenous conduit. If no leg or arm vein is available, then bypasses with heparin-bonded expanded polytetrafluoroethylene (ePTFE) with a distal vein patch, or cryopreserved vein may be considered, although the use of prosthetic conduits or cryopreserved vein in infrapopliteal revascularization is suboptimal as 2-year patency with such conduits is as low as 20%, with even lower limb salvage rates when compared with native vein conduits.

The GSV can be procured with either open or endoscopic techniques (Fig. 6). For open vein harvests, a long continuous incision can be used or multiple skip incisions of 10 cm in length separated by a 3- to 5-cm skin bridge may be made. It is crucial that the GSV be exposed and extracted with meticulous technique because injury and repair may compromise patency. The vein side branches should be ligated approximately 1 to 2 mm distal to their origin from the GSV to prevent crimping and luminal narrowing of the GSV. The final harvesting of the conduit should be done after exposure of the proximal and distal arterial targets, which allow estimation of the length of conduit necessary and helps minimize ischemia of the vein. The GSV can be used in a reversed, nonreversed, or in situ manner. For bypass to the tibial arteries, the best lumen size match is typically found with a nonreversed GSV, which requires valvulotomy. To help facilitate valvulotomy, we recommend completing the proximal anastomosis, which will allow distension of the vein with blood and using a Mills valvulotome to lyse the valves that can be visualized through the dilated vein. If size mismatch is not significant, the GSV may be used in a reversed fashion. In situ GSV bypasses are limited by proximity of the GSV to the inflow and outflow vessels and are used typically for femoral to proximal tibial bypasses in patients who are at low risk for wound infection that could expose the nontunneled GSV (and thus usually not used in diabetics and smokers, who are at high risk for wound infection in general).

Inflow Anastomosis

The distal external iliac artery, CFA, PFA, and SFA are exposed as previously described. Tunnels for the bypass graft are created

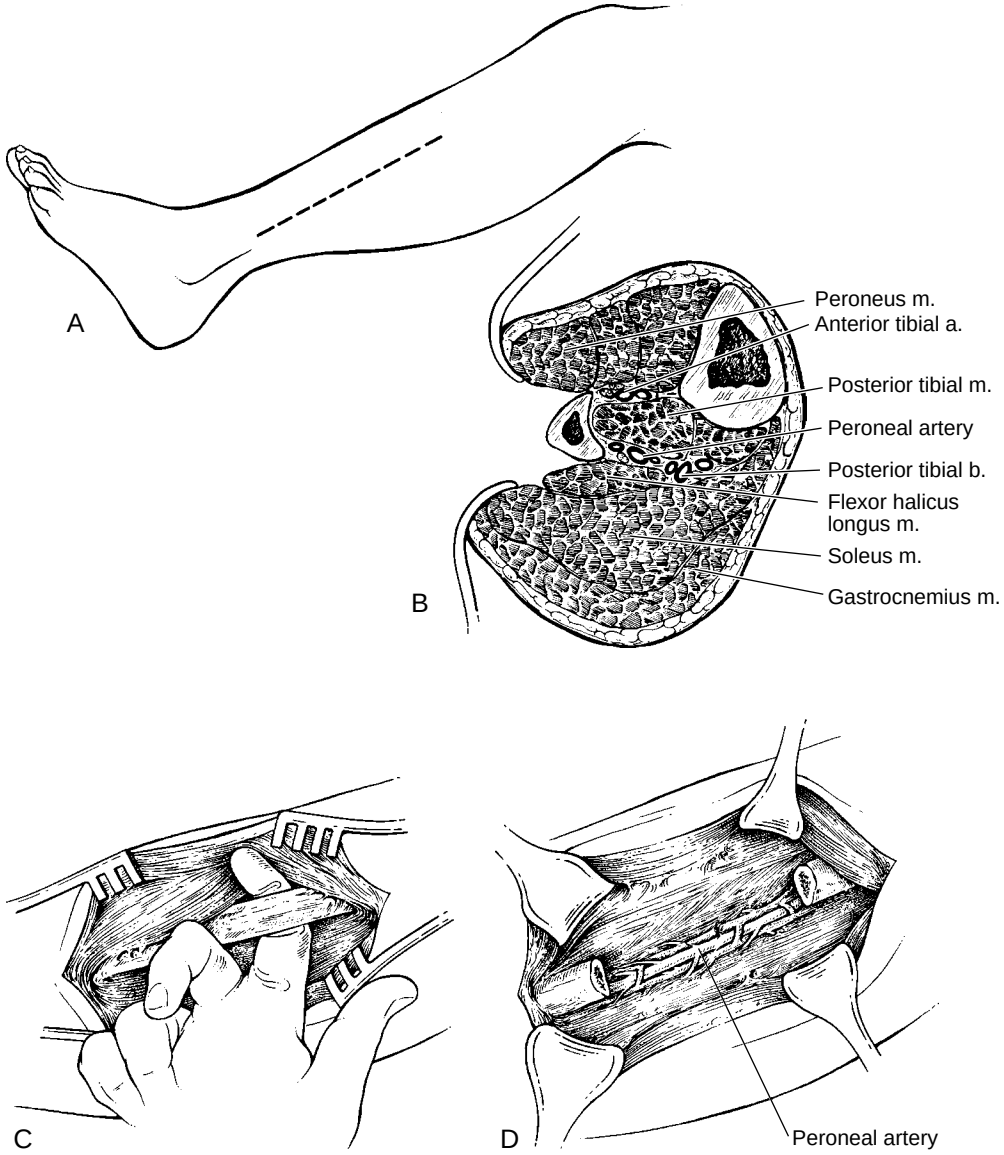


FIG. 4 Lateral exposure of the peroneal artery. **(A)** The incision is made longitudinally over the fibula. **(B)** Cross-section view of the lower leg, illustrating the lateral approach with fibula resection. **(C)** The muscle and fascia are stripped from the fibula, and an 8-cm section is removed. **(D)** The peroneal artery is exposed and seen to lie on the surface of the hallucis longus muscle. *(Copyright Herbert Dardik, 2001).*

(described later), and the patient undergoes systemic anticoagulation with heparin at an initial dose of 100 units/kg, followed by periodic boluses to maintain an activated clotting time of greater than 250. The CFA is palpated to determine the site that is most free of atherosclerosis. Atraumatic clamps are placed on the SFA, PFA, and proximal portion of the CFA, and an arteriotomy is created with a No. 11 scalpel blade. The arteriotomy is extended with Potts scissors to 25 to 35 mm, depending on the diameter of the GSV. The proximal portion of the GSV is beveled to accommodate the arteriotomy and the anastomosis is created with 5-0 or 6-0 polypropylene suture in a continuous manner. In patients without proximal flow-limiting lesions, more distal sites can be used for the proximal anastomosis including the profunda and popliteal arteries.

Tunnels for Bypass Grafts

Before the patient receives heparin for the proximal anastomosis, a tunnel for the bypass graft is created by advancing a tunneling device or a large aortic clamp in either an anatomic or subcutaneous fashion. We prefer an anatomic tunnel because it requires less conduit length, the vein graft has less of an acute angle as it turns to the distal anastomosis, and it is protected by the soft tissues of the leg and distanced from the skin and wounds in patients with TPOD who are usually poor healers due to diabetes and tobacco abuse. To reach the proximal third of the posterior tibial and peroneal arteries, the graft is tunneled from the adductor hiatus thorough the popliteal fossa to maintain a straight path. One must ensure that the vein passes between the heads of the gastrocnemius muscle at the popliteal fossa to avoid compression of the vein. The main advantage of the subcutaneous tunnel is that the graft is close enough to the skin to allow for percutaneous access for future endovascular procedures if needed, as well as easier access to the graft for open revisions. If the ipsilateral vein is harvested, subcutaneous tunneling is still possible, but one must stay away from the harvest site to avoid possible exposure of the bypass graft to a wound infection involving the vein harvest site. Once the proximal anastomosis is completed, the vein graft is clamped distally and inflated with blood. The vein is marked

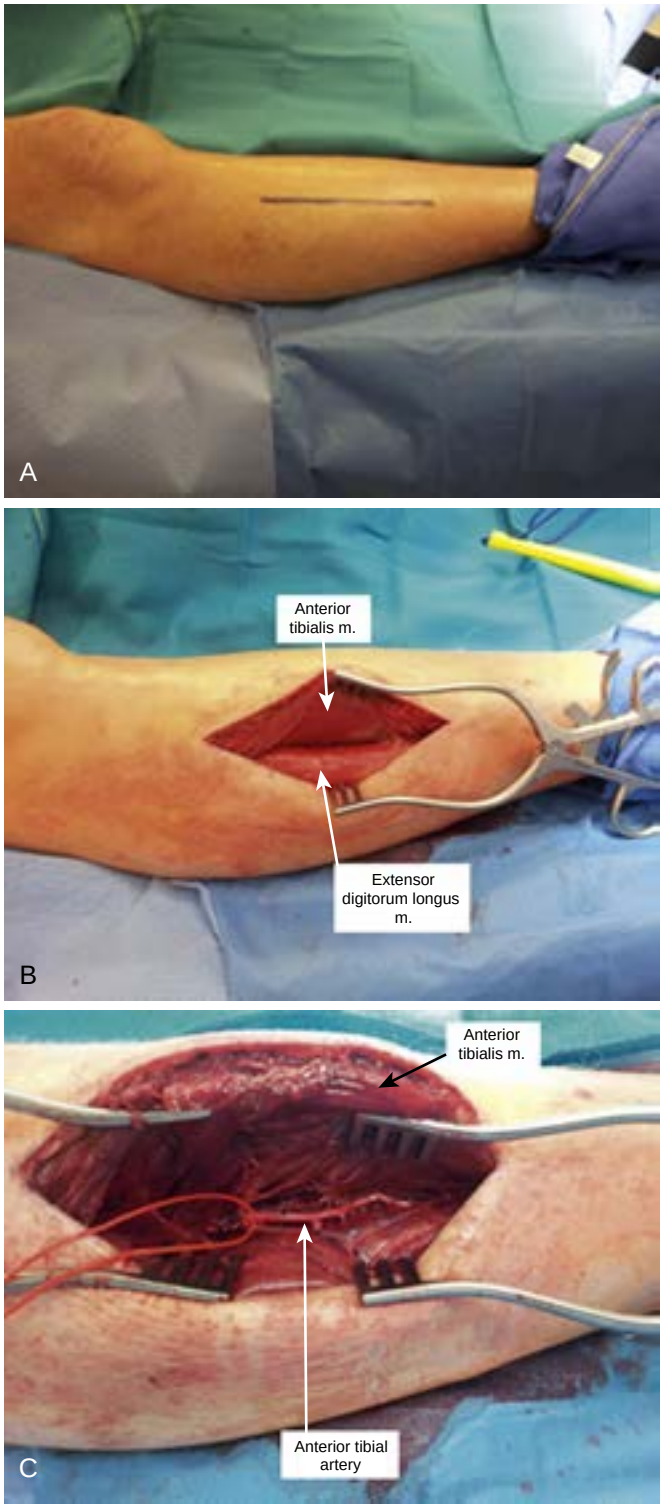


FIG. 5 Exposure of the anterior tibial artery. **(A)** A longitudinal incision is placed lateral to the anterior border of the tibia. **(B)** The groove between the tibialis anterior and the extensor digitorum longus muscles is separated. **(C)** The anterior tibial artery is exposed.

longitudinally on its anterior surface to prevent twisting and passed through the tunnel. Vein flow is then checked; any twisting in the tunnel will result in a reduced blood flow after tunneling as compared with the strength of the blood flow before tunneling of the vein. We prefer to use the Oregon tunneler as it allows the creation of the tunnel from either the distal or the proximal aspect of the wound.



FIG. 6 The greater saphenous vein is exposed with a series of incisions along its course on the medial aspect of the leg. Skin bridges are left in place to minimize tension on the incision closure and prevent wound dehiscence. Alternatively, a continuous incision may be made along the entire length of the greater saphenous vein.

Outflow Anastomosis

Creation of the outflow anastomosis requires adherence to meticulous technique and gentle manipulation of arteries, many of which are calcified. Loupe magnification is essential. We do not control tibial vessels with vessel loops or clamps, and we do not dissect tibial vessels circumferentially. Instead, we use a pneumatic tourniquet placed on the thigh and inflated after the leg is exsanguinated with an Esmark. An arteriotomy is initiated with a Beaver blade, with care not to lacerate the posterior wall of the artery. In general, the arteriotomy should be approximately 1.5 times the diameter of the vein graft because longer anastomoses tend to flatten the hood of the vein and create a sharp angle at the heel, which lead to flow turbulence and consequently a nidus for intimal hyperplasia. A 7-0 polypropylene suture is used to create the distal anastomosis. The tibial artery is handled minimally; it is touched with fine pickups only when necessary and very gently.

ENDOVASCULAR REVASCULARIZATION

Indications for Intervention

With lower rates of perioperative morbidity and mortality, high rates of technical success, and equivalent rates of limb salvage, PTA of the tibial and peroneal arteries is a critical skill of the vascular surgeon. Evidence of long-term efficacy was provided by the Beth Israel Deaconess Medical Center, which demonstrates that PTA of the tibial and peroneal arteries results in 1- and 5-year primary patency rates of 57% and 38% and limb salvage rates of 84% and 81%, respectively. According to the TASC II classification for infrapopliteal lesions, PTA is recommended for TASC classes A, B, and single-level C lesions in the tibial or peroneal arteries. In general, lesions that are more amenable to successful endovascular interventions are stenoses shorter than 4 cm or segments of occlusion shorter than 2 cm. Extensive disease that involves the trifurcation, numerous stenoses, a diffusely diseased tibioperoneal artery, or long occlusions are best treated with surgical bypass. In these situations, endovascular therapies may be employed as an adjunct to open surgical bypass to improve inflow or outflow during bypass procedures or for patients

who are poor candidates for open surgical bypass because of either a lack of conduit or significant medical comorbid conditions.

Vascular Access and Imaging

Preprocedure imaging with CTA is most helpful in planning the point of arterial access and locations of critical stenoses and occlusions. For tibioperoneal interventions, the contralateral CFA is the preferred access site. If this is not a suitable option, either because of extensive atherosclerosis or because of the presence of an aorto-bifemoral graft, then the left brachial artery or ipsilateral CFA can be accessed with an antegrade approach. The contralateral CFA is accessed with a 21-gauge needle with ultrasound guidance and a microwire is advanced under fluoroscopic guidance. A 5Fr transitional dilator is then placed. Over a stiff wire, a 5F or 6F sheath is placed in the artery. A diagnostic catheter is advanced into the abdominal aorta and exchanged for a catheter designed to go over the bifurcation. As with open surgical bypass, inflow and outflow must be considered in maintaining perfusion throughout the infrapopliteal system. The advantage of contralateral retrograde access is that it allows for access to the aortoiliac and femoropopliteal regions; stenoses in these areas can be addressed at the same time as the infrapopliteal intervention in many cases. Once the aortic bifurcation is crossed, the short sheath is then exchanged for a longer and stiffer sheath that is placed in the ipsilateral femoral or distal external iliac artery for diagnostic imaging. The sheath can then be advanced into the SFA for stable access to support the various devices and catheters used in infrapopliteal interventions. A crossing catheter is used to provide adequate support to cross-tibial arterial occlusions. We tend to use 0.014- or 0.018-inch wires with added weight at the tip, which provide pushability to cross the infrapopliteal lesions. If this route is unsuccessful, pedal arteries can be cannulated under ultrasound guidance, and a wire can be advanced in a retrograde direction. A snare device can then be employed to grasp the proximal wire and navigate it through the tibial arteries (Fig. 7A–D). Careful consideration must be had if one decides on retrograde tibial access as one does not want to damage the distal outflow and eliminate a possible bypass target.

Precise mapping of infrapopliteal anatomy is crucial for proper intervention. Imaging of the trifurcation is usually performed with a zero-degree anterior-posterior view. A 30-degree ipsilateral oblique or 90-degree true lateral view may be needed to properly detail the anterior and posterior tibial arteries. While tibial vessels are imaged, the catheter should ideally be positioned in the distal popliteal artery.

Balloon Angioplasty and Stent Placement

The mainstay of endovascular treatment of the tibioperoneal vessels has been PTA. Balloons suitable for these interventions range from 1.5 to 4 mm in diameter and are up to 22 cm in length. Currently available tibial arterial balloons are delivered in shaft lengths of up to 170 cm. It is better to use a balloon length that will cross the entire lesion in a single pass. These balloons are noncompliant and low profile, and a long inflation time of 1 to 3 minutes reduces the risk of dissection of the artery. If disease is still present, then the balloon can be inflated for 3 to 4 minutes.

The use of stents has previously been a bailout technique after PTA if there was greater than 30% stenosis or flow limiting dissection after balloon inflation. The stents used in these situations were classically bare metal, and the restenosis rate was approximately 50% at 6 months. There had been a growing trend toward placement of drug eluding stents (DES) in hopes of improving patency rates similar to those observed with the use of DES in coronary revascularization. Because of the comparable caliber of coronary and tibioperoneal arteries, researchers in several studies have employed coronary DES in the infrapopliteal arteries. There are now four randomized trials with four meta-analyses to show that DES have better patency, reduced reinterventions, reduced amputation rates, and improved event-free survival over PTA alone or with bare metal stent placement. Drug eluting balloons (DEB) have also been used in infrapopliteal lesions but are currently somewhat controversial due to unresolved issues involving possible increase in mortality and questionable long-term benefits. Once the decision has been made to perform an intervention, the patient should be systemically heparinized with an initial dose of 100 units/kg followed by periotic boluses to maintain an activated clotting time above 250 seconds. All lesions should be treated if possible, and completion angiography should be performed to evaluate distal runoff. At the end of the procedure, several arterial closure devices are available. Protamine can be administered at the physician's discretion to reverse the anticoagulation. Closure devices have a similar complication rate as compared with manual pressure but decrease the time needed to hold pressure and shorten the time to patient ambulation.

OTHER TECHNOLOGIES

Mechanical atherectomy devices, both rotational and directional, can be used to remove a portion of the atheromatous plaque from the luminal surface. The advantage of this method is a decrease in the plaque burden in comparison with PTA and stent placement; however, there is concern for distal embolization of plaque when using these devices, and the use of a distal embolic protection device is encouraged. Furthermore, high quality data are currently lacking to show efficacy or advantage of using atherectomy in addition to PTA or stenting for infrapopliteal lesions. For occluded lesions, several crossing devices are available, if a wire and support sheath are not adequate to cross a lesion.

POSTINTERVENTION MANAGEMENT AND SURVEILLANCE

After intervention, patients are placed in a monitored setting in which pulses are routinely checked every 1 to 2 hours. Patients who received an endovascular intervention with percutaneous access to the groin are kept on strict bedrest with the hip in a neutral position for 6 hours if manual pressure was held for hemostasis and no closure device was used. After a period of observation of 6 hours and if no hematoma is present at the access site, discharge may be considered for patients who underwent percutaneous endovascular intervention. Those who undergo an open surgical bypass are kept in a monitored setting overnight or longer to assess for hemodynamic stability and fluid shifts. After this period of time, the focus can then shift to physical therapy and mobility. The leg after a bypass typically becomes swollen; this may increase patient discomfort, as well as result in problems with wound healing. We routinely use a multilayer compressive dressing of cast padding and Coban self-adherent wrap (3M) (unless contraindicated by subcutaneous bypass tunnel). Limitation of intravenous fluids as well as diuresis once hemodynamically stable are also important for postoperative care. All patients should be maintained on aspirin after intervention. Dual antiplatelet therapy of aspirin and clopidogrel is prescribed to endovascular therapy recipients. Statin therapy has been shown to improve the patency rate in bypass recipients, and this is routinely started or continued.

Patients who have undergone bypass grafting should have stringent outpatient follow up. Particular attention should be paid to symptoms (return of claudication, development of new wounds, or reopening of prior wounds) and physical exam. Bypass surveillance should be performed. Noninvasive vascular imaging is performed with measurement of the ABI and arterial bypass duplex ultrasound before discharge after the operation and then again at 1 month, 3 months, and then every 6 months for up to 2 years followed by yearly evaluation in the clinic. Increasing focal velocities within the bypass or at the anastomoses or a decrease in the ABI of more than 0.15 should prompt further investigation with angiography and angioplasty of any hemodynamically significant stenoses to prevent

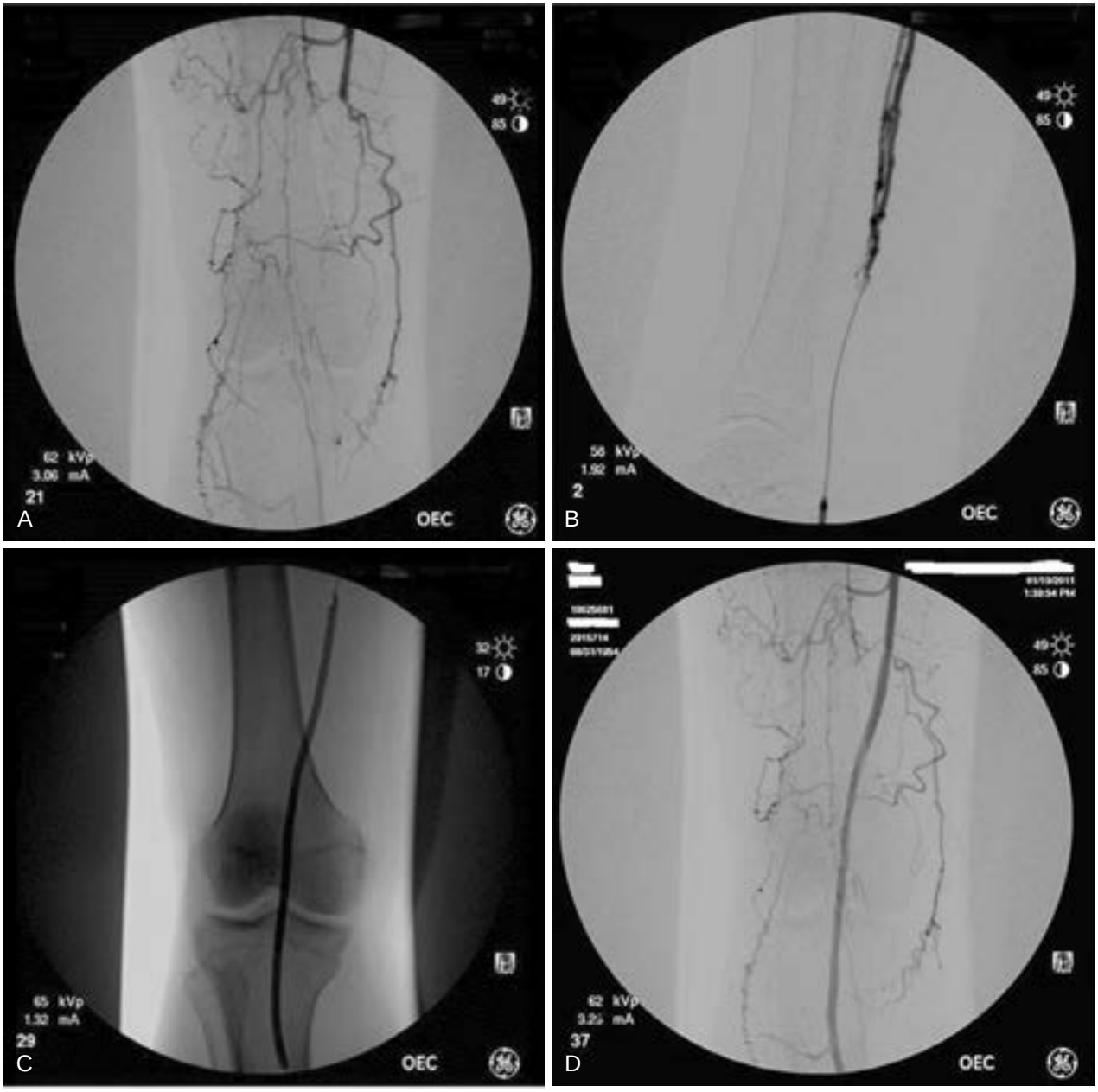


FIG. 7 Retrograde access of the posterior tibial artery in a patient with critical limb ischemia and previously harvested great saphenous vein. **(A)** Chronic total occlusion that could not be traversed with subintimal dissection with a guide wire. **(B)** Retrograde access of the posterior tibial artery with a 0.014-inch guidewire and Quick-Cross catheter that is snared from the ipsilateral common femoral artery (CFA) access. **(C)** Inflation of 3 mm × 20 cm balloon placed in an antegrade manner after wire exchange. **(D)** Completion arteriogram, demonstrating unrestricted flow to the ankle. *(Courtesy George A. Akingba, MD, PhD).*

graft failure. Patients with endovascular interventions are monitored at similar intervals.

COMPLICATIONS

Immediate complications include hemorrhage or graft thrombosis and necessitate reoperation. Hemorrhage manifests as an expanding hematoma in the groin or leg and possibly hemodynamic instability. Affected patients should be taken back to the operating room for exploration and evacuation of the hematoma to prevent shock, infection, or formation of a pseudoaneurysm. Early graft thrombosis is usually the result of a technical error, but can arise from compression of the graft, twisting of the graft, undiagnosed inflow disease, or an unknown hypercoagulable state. Affected patients should undergo thrombectomy and arteriography to evaluate for technical problems related to anastomoses, twisting of the graft, an intimal flap, or inadequate outflow. Late complications include infection, pseudoaneurysm formation, and graft thrombosis. Graft thromboses up to 24 months after the initial operation probably result from neointimal hyperplasia at the distal anastomosis, whereas those that occur after this period are typically caused by recurrent atherosclerotic disease. For endovascular treatment, the most common complication is access related complicating up to 4% of all catheter-based treatment. A high puncture is associated with a retroperitoneal hematoma that

may require arterial repair in the operating room, and low punctures are associated with arteriovenous fistula development or thigh hematoma and pseudoaneurysm formation.

FUTURE TREATMENT: CELL-BASED THERAPIES

Although revascularization with either surgical bypass or endovascular techniques can result in exceptional improvements in patients to TPOD with acceptably low rates of morbidity and mortality, approximately 20% to 40% of patients with CLI are not candidates for these interventions because of lack of conduits or because of extensive disease within the outflow tibial vessels. For these patients with unreconstructable small vessel arterial disease, medical management with cardiovascular risk factor optimization and use of pentoxifylline and ArtAssist intermittent compression treatment device may help in avoiding amputation. In addition, stem cell therapies are emerging as a potential option, with some prospective study data showing improvement in wound healing and freedom from amputation in patients with severe limb threatening PAD without revascularization options injected with bone marrow mononuclear cells harvested from the iliac crest. Upcoming prospective randomized clinical trials such as the NOMA (No More Amputations) trial will further evaluate the potential for cell-based therapies for CLI.

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Popliteal and Femoral Artery Aneurysm

Rae S. Rokosh, MD, Daniel J. Wong, MD, MHS, and Elliot L. Chaikof, MD, PhD

FEMORAL ANEURYSM

True aneurysms and pseudoaneurysms of the femoral artery are the most common type of peripheral aneurysms encountered. Femoral artery aneurysms can be further classified into degenerative true aneurysms; pseudoaneurysms, including iatrogenic, traumatic, or para-anastomotic; and infected or mycotic aneurysms. Treatment options vary significantly depending on the etiology, presence of infection, and location of the aneurysm, and thus the diagnosis, management, and procedural concerns for each subtype will be discussed separately.

Degenerative Femoral Artery Aneurysm

True degenerative aneurysms of the femoral artery are rare. The common femoral artery (CFA) is the most likely location, while isolated aneurysms in the distal superficial femoral artery (SFA) or profunda femoris artery (PFA) are less frequent. Population-based studies in the 1990s estimated a prevalence of femoral aneurysm of 5 per 100,000 in the United States with a heavy male predominance. An important consideration in the patient with a femoral aneurysm is the synchronous presence of a contralateral femoral aneurysm (26%–50%), abdominal aortic aneurysm (AAA; 48%–90%), or popliteal aneurysm (27%–48%). An aortic aneurysm that meets the threshold for repair should be addressed before, or in conjunction with, an asymptomatic peripheral aneurysm. Approximately half of patients are asymptomatic at the time of peripheral aneurysm diagnosis, with symptomatic patients presenting with a pulsatile mass, pain, or distal ischemia. Ultrasound and cross-sectional imaging such as CT or MRI can be used to characterize the size of the aneurysm and simultaneously screen for the presence of other aneurysms.

Indication for Repair

Patients presenting with symptoms from local compression or distal ischemia should undergo repair. In the presence of an asymptomatic aneurysm, the goal is to prevent distal ischemia due to thrombosis, embolization, or, rarely, rupture. Historical series suggested that a femoral aneurysm >2.5 cm should be repaired, but more contemporary literature suggests that a femoral aneurysm <3.5 cm with absent or chronic intraluminal thrombus is unlikely to present with rupture or embolism. While perioperative mortality for open femoral aneurysm repair is ≤1%, morbidity may be observed in 10% to 20% of patients.

Approach

Surgical repair, rather than an endovascular-first approach, is the treatment of choice for CFA aneurysms. The routine use of stent grafts to exclude degenerative femoral aneurysms is not the preferred approach due to the risk of stent fracture in the setting of dynamic hip flexion and the preference to avoid PFA orifice occlusion. In the setting of distal embolization, thromboembolectomy or pharmacomechanical thrombolysis may be used initially to restore distal perfusion.

Open surgical repair of a femoral artery aneurysm requires reconstruction with an interposition vascular graft (Fig. 1). A longitudinal incision is made over the femoral artery with dissection to the nonaneurysmal proximal common femoral or distal external iliac artery. Exposure of the distal external iliac artery will require division of the inguinal ligament or a retroperitoneal approach via an oblique incision two to three fingerbreadths above the inguinal ligament. Exposure of the SFAs and PFAs should also be obtained. If dissection of the PFA proves difficult due to the size or location of the aneurysm, control of the profunda femoris can be obtained by balloon occlusion using a 3Fr Fogarty catheter positioned 1 cm distal to the orifice after the aneurysm is opened (Fig. 2).

Once proximal and distal control has been obtained, the patient is heparinized, vessels are occluded, the sac is opened, and the thrombus is removed. If the aneurysm is confined to the CFA without

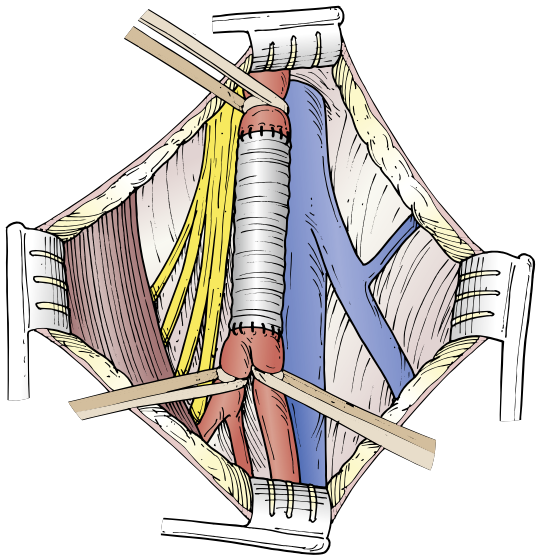


FIG. 1 Interposition graft repair of a femoral artery anastomotic pseudoaneurysm. *(From Cronenwett JL, Johnston KW. Rutherford's Vascular Surgery. Philadelphia: Elsevier; 2014.)*

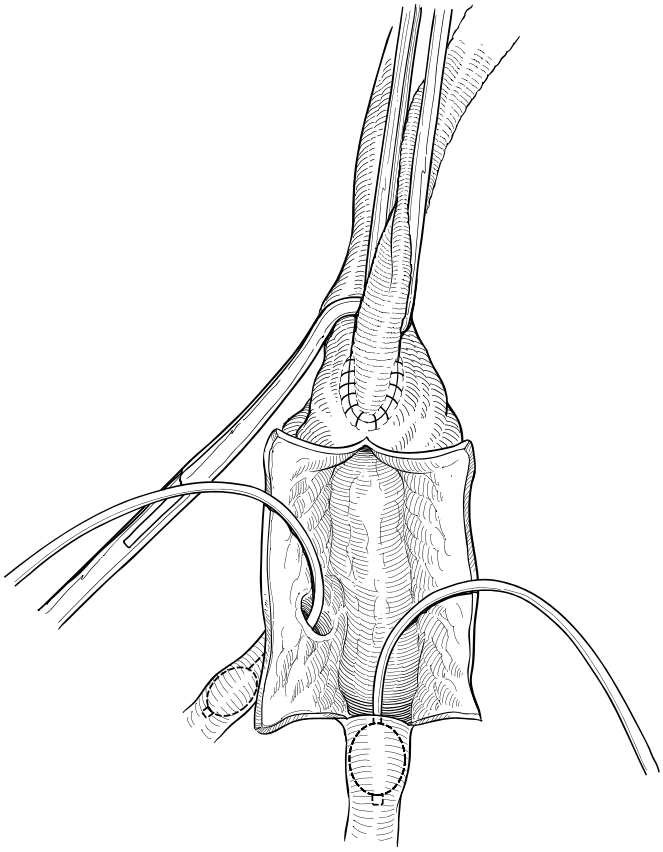


FIG. 2 Distal control of the profunda and superficial femoral arteries can be achieved from within the aneurysm using occlusive balloon catheters after the aneurysm is opened. *(From Chaikof EL, Cambria R. Atlas of Vascular Surgery and Endovascular Therapy: Anatomy and Technique. Philadelphia: Elsevier; 2014.)*

involvement of the SFA or PFA, the vessel can be reconstructed using an 8- or 10-mm interposition polytetrafluoroethylene (PTFE) or Dacron graft. If the aneurysm is more extensive and involves the SFA or PFA, interposition grafting should be performed with either reimplantation or use of a jump graft to the PFA. If the PFA cannot be revascularized, distal perfusion should be ensured. In the setting of concomitant occlusive disease, femoral-popliteal or femoral-tibial bypass may be required.

Iatrogenic Femoral Artery Pseudoaneurysm

The incidence of femoral artery pseudoaneurysm following diagnostic or therapeutic catheterization varies from 0.05% to 4%. Risk factors include large sheath size, anticoagulation, obesity, and a high arterial puncture site. Prevention of a pseudoaneurysm is best achieved by routine use of ultrasound-guided vascular access. A femoral pseudoaneurysm may present as a pulsatile mass, although physical exam can be limited by body habitus or hematoma. Duplex ultrasound is the primary means of diagnosis, which allows evaluation of pseudoaneurysm size, neck dimension, and evaluation for the presence of a concomitant arteriovenous fistula.

Indication for Intervention

In the absence of compressive symptoms, including pain, skin blisters, or symptoms of femoral nerve entrapment, small pseudoaneurysms (<1 cm) will often thrombose spontaneously or with ultrasound-guided compression if the patient is not systemically anticoagulated. Follow-up ultrasound should be conducted within 2 weeks to confirm thrombosis. A pseudoaneurysm that is >2 cm, symptomatic, or persistent should be treated.

Approach

For iatrogenic asymptomatic pseudoaneurysms >2 cm, ultrasound-guided thrombin injection into the pseudoaneurysm sac has become the preferred method of treatment, provided there is a narrow, long neck between the pseudoaneurysm and the femoral artery to minimize the risk of thrombin injection reflux into the artery. Ultrasound-guided compression alone, in the absence of thrombin injection, remains an option but is often less well tolerated due to the pain of sustained compression, typically three successive 20-minute compressions, and has a lower success rate for pseudoaneurysms >1 or 2 cm. For thrombin injections, a two-syringe method can be used with one syringe containing 3 mL of saline and the other containing a thrombin solution connected using a three-way stopcock (Fig. 3). Originally thrombin concentrations as high as 1000 IU/mL were used, but with increased experience, concentrations as low as 20 to 100 IU/mL have been reported in the literature to be effective. Visualization of the tip of the 22- to 25-gauge needle can be assisted using an echogenic needle. The pseudoaneurysm is punctured and a test injection with saline is visualized on ultrasound. This serves a dual purpose to both confirm needle placement within the pseudoaneurysm, as well as to minimize the risk of accidental injection of thrombin into the native artery, which can result in thrombosis or distal emboli. Small amounts of thrombin (0.1–0.2 mL) are then injected until cessation of flow within the sac is confirmed. For multilobulated pseudoaneurysms, the lobe most proximal to the native vessel is targeted to promote subsequent thrombosis of the more distal lobes. Preserved flow in the femoral artery and vein is confirmed via ultrasound at the end of the procedure. If there is a wide neck and the patient is a prohibitive risk for open repair, an intraarterial balloon may be inserted from the contralateral femoral artery and inflated to exclude the pseudoaneurysm during thrombin injection. A follow-up ultrasound is performed 24 hours after injection to confirm thrombosis.

Open surgical repair is indicated for an iatrogenic pseudoaneurysm that is expanding, fails nonoperative treatment, displays unsuitable anatomy for thrombin injection, or is associated with a painful hematoma, skin breakdown, or symptoms suggestive of femoral nerve entrapment. A longitudinal groin incision over the aneurysm

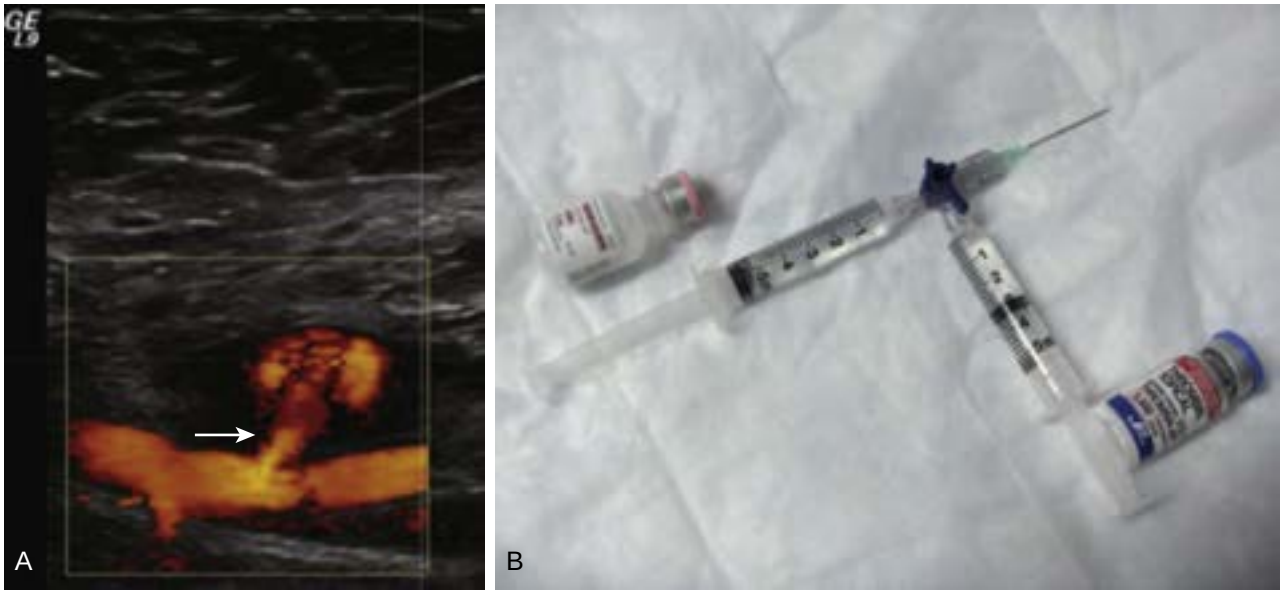


FIG. 3 **(A)** Duplex ultrasound demonstrating femoral pseudoaneurysm with neck (*arrow*). **(B)** Two syringes with saline and thrombin connected with 3-way stopcock used for injection of pseudoaneurysm. (***A*** *from From Cronenwett JL, Johnston KW.* Rutherford's Vascular Surgery. *Philadelphia: Elsevier; 2014;* ***B*** *from Webber GW, Jang J, Gustavson S, Olin JW. Contemporary management of postcatheterization pseudoaneurysms.* Circulation. *2007;115:2666–2674.)*

is performed and proximal and distal control achieved. If the sac is inadvertently entered, bleeding is controlled by digital pressure until proximal control is gained and the puncture site primarily repaired with a 5-0 Prolene suture. The hematoma is evacuated and a 7-mm Jackson-Pratt drain placed in the wound.

Paraanastomotic Femoral Artery Aneurysm

The femoral artery is the most common location of an anastomotic aneurysm associated with an aortofemoral bypass graft, commonly presenting years after the initial operation as a pulsatile groin mass. An anastomotic pseudoaneurysm may occur due to suture line disruption, infection, or arterial wall degeneration.

Indication for Repair

Operative repair of an anastomotic femoral pseudoaneurysm is recommended if greater than 2.0 cm in diameter or if infection is suspected by the presence of a draining sinus, erythema, or perigraft fluid. CT imaging can assess for the presence of synchronous anastomotic pseudoaneurysms at the aortic anastomosis or in the contralateral groin.

Approach

Noninfected Anastomotic Pseudoaneurysm

In the absence of infection, exposure of the graft limb, common femoral, superficial femoral, and profunda femoris arteries should be performed. As needed, proximal control of the graft limb can be achieved by dividing the inguinal ligament or retroperitoneally via an oblique suprainguinal incision. In a heavily scarred operative field, control of the SFAs and PFAs can be achieved using Fogarty balloon catheters from within the aneurysm (see Fig. 2). Following heparinization, the aneurysm sac is opened, thrombus removed, distal graft resected, and reconstruction performed using a 6- to 8-mm interposition PTFE graft or patch angioplasty, with revascularization of the SFAs and PFAs as indicated.

Infected Femoral Anastomotic Pseudoaneurysm

If infection is suspected, blood cultures should be sent and empiric antibiotics initiated. Graft infection should be suspected if exploration reveals a poorly incorporated graft or perigraft fluid. This scenario requires removal of the infected graft with restoration of distal perfusion via extraanatomic reconstruction or the use of an autologous vein or a cryopreserved allograft. CT imaging can help to determine whether infection is limited to the groin or involves the proximal graft or contralateral limb. If infection is confined to the distal limb, the clean portion of the procedure is conducted initially. Proximal control of the uninfected portion of the limb is achieved through a retroperitoneal approach via an oblique incision, extending lateral to the rectus, 3 cm above the inguinal ligament, to a point halfway between the costal margin and iliac crest in the midaxillary line. The proximal uninfected graft limb is exposed, avoiding injury to the ureter, and divided with a small margin sent for culture. The distal end of the graft is oversewn, mobilized from surrounding tissues, and displaced distally. Extraanatomic options for revascularization include an obturator bypass, an axillofemoral bypass to the SFA, or an axillopopliteal bypass. An obturator bypass requires creating a tunnel through the medial aspect of the obturator foramen avoiding injury to the obturator artery and nerve, to the SFA in the midthigh. An end-to-end anastomosis is created using an externally supported PTFE interposition graft between the end of the uninfected graft limb and an end-to-side anastomosis to the SFA. Incisions are closed, an occlusive dressing placed, and the contaminated portion of the procedure performed. A groin incision is made, vascular control obtained, the infected graft removed, and intraoperative cultures sent. Infected tissues should be debrided, robustly irrigated, and the femoral artery defect closed with a vein patch to preserve flow to the PFA. A sartorius muscle flap should be mobilized to cover the femoral vessel. In patients with prohibitive surgical risks and limited lifespan, or for those presenting with rupture, several case series report the feasibility of endovascular stenting as a temporizing measure followed by either lifelong antibiotic therapy and secondary surgical debridement or definitive management.

Primary Infected Femoral Artery Aneurysm

A primary infection of the femoral artery most often occurs due to a contaminated percutaneous closure system or intravenous drug use. Patients may present with an enlarging pulsatile mass, sepsis, distal emboli or hemorrhage. Blood cultures are obtained and

empiric antibiotics initiated. Goals of the operation include removal of infected tissue, repair of the femoral artery, and restoration of distal perfusion. Options for repair depend upon the extent of local arterial destruction. If limited damage, a vein patch angioplasty may be feasible, but more extensive arterial destruction may require reconstruction with autologous femoral vein, cryopreserved vein, or an extra-anatomic bypass. An obturator bypass may be preferable when the aneurysm is secondary to intravenous drug injection to minimize the likelihood of future needle sticks. Cultures should be obtained and antibiotics continued at least 6 weeks postoperatively. A sartorius muscle flap should be used to provide direct coverage of the arterial repair.

POPLITEAL ANEURYSM

The popliteal artery is generally considered aneurysmal when >1.5 cm in diameter. Risk factors for popliteal artery aneurysm (PAA) growth include initial aneurysm size at presentation and presence of intramural thrombus. As the incidence of PAA is relatively rare, less than 3% in the general population, there have been few modern natural history studies of PAAs. Approximately 50% patients have contralateral popliteal aneurysms and 30% to 40% have synchronous AAA, which occur in a higher proportion of patients if bilateral popliteal aneurysms are present. The majority of PAAs are true degenerative aneurysms. Rupture is rare, whereas distal ischemia from thromboembolization is the most common cause of morbidity. Duplex ultrasound, CT, and MRI are effective methods for diagnosis and establishing size. In contrast to a femoral aneurysm, endovascular treatment of a popliteal aneurysm with a self-expanding covered stent graft may be feasible in many patients. Important considerations to determine whether an endovascular or surgical approach is most appropriate include the patient's operative risk, size of the aneurysm, presence of intraluminal thrombus, compressive symptoms, adequate landing zones, number of patent runoff vessels, and presence of distal ischemia.

Indication for Repair

Asymptomatic aneurysms that are ≥2 cm in size should be repaired in the healthy adult. For high-risk asymptomatic patients, the most recent guidelines suggest repair can be deferred until the PAA is ≥3 cm, particularly in the absence of intraluminal thrombus. All symptomatic PAAs should be repaired.

Open Surgical or Endovascular Repair

Historically, surgical bypass has been the gold standard for PAA repair, with excellent long-term patency and limb salvage rates. However, as endovascular techniques and endoprostheses have improved, endovascular repair of PAA has become increasingly more common. To date, there are no trials directly comparing the two repair modalities, but there is growing evidence to support the use of endovascular repair in the appropriate clinical context. For those asymptomatic patients with ≥5 year life expectancy, current guidelines recommend open surgical repair over an endovascular approach. Open repair consists of revascularization from the distal superficial femoral or proximal above knee popliteal artery to the below knee popliteal or tibioperoneal trunk using a saphenous vein or synthetic bypass graft via a medial or posterior approach. An autologous vein graft is preferred in the presence of an adequate great saphenous vein >3 mm in diameter. For those patients with more proximal popliteal or distal SFA aneurysms that do not cross the knee, or those of advanced age with significant medical comorbidities who are anatomically suitable, endovascular repair is a viable alternative. Anatomic criteria to achieve good outcomes with endovascular repair include proximal and distal landing zones of at least 15 mm in length within normal healthy vessel to achieve an adequate seal for the stent graft, minimal aneurysmal kinking or tortuosity, and good tibiopedal runoff (≥2 vessels). Recent evidence has demonstrated that endovascular repair in the appropriate clinical context is associated with decreased length of stay and reduced wound complications, as well as similar reintervention rates and primary patency at 1 and 3 years when compared with open surgical repair.

Approach: Repair in the Absence of Acute Thrombosis

Preoperative vein mapping, baseline ankle-brachial index (ABI), and a lower extremity CTA, MRA, or conventional arteriogram are conducted in preparation for repair to evaluate aneurysmal morphology as well as the identification of either appropriate inflow and outflow targets for surgical bypass or adequate landing zones and endoprosthesis sizing for endovascular repair.

Two anatomic approaches are commonly used for surgical repair, a medial or posterior approach. The medial approach is preferred for those aneurysms extending beyond the popliteal fossa. The knee is bent and the leg externally rotated. The saphenous vein is harvested, and proximal and distal control obtained. A tunnel is created from the above to below knee popliteal fossa. After heparinization, the aneurysm is opened, any arterial backbleeding branches ligated from within the aneurysm sac, and a standard bypass performed with either saphenous vein or a prosthetic graft. If patent at the time of repair, the PAA must also be ligated both proximally and distally as close as possible to the sac itself. Care should be taken to avoid division of the medial musculotendinous attachments of the knee if possible, as this maneuver is associated with marked pain postoperatively.

The posterior approach is advantageous for a large aneurysm confined to the popliteal space or to decompress an enlarging aneurysmal sac after previous bypass and ligation. The patient is positioned prone, and a "lazy S" incision is performed with the lateral portion across the posterior flexion crease (Fig. 4) to minimize risk of wound contracture or dehiscence. Access to the artery is direct and the popliteal vein can be retracted laterally. Proximal and distal control is established with care to preserve the tibial and peroneal nerves, which usually course lateral to the aneurysm and can be retracted laterally with the popliteal vein for appropriate arterial exposure. Following heparinization the sac is opened, thrombus removed, collateral vessels suture ligated, and an interposition graft performed. In the event that there is a large size mismatch between conduit and popliteal artery, a bypass can be performed as well via this posterior approach.

Endovascular repair of a popliteal aneurysm is performed with a flexible nitinol self-expanding covered stent, such as the Viabahn endoprosthesis (W.L. Gore & Associates, Inc., Flagstaff, AZ). Characteristically, ipsilateral antegrade femoral artery access is obtained. Angiographic views with the knee in a flexed position are helpful to confirm appropriate stent sizing and to avoid stent termination or overlapping stents in the region of maximum flexure. Stent grafts should be oversized by 10% to 15% and, if multiple stents are required, 2 cm of overlap is recommended (Fig. 5). Appropriate stent apposition between healthy vessel and any additional regions of stent overlap can be achieved with noncompliant balloon conformation. Angiography with and without knee flexion at case completion should be performed to confirm baseline distal runoff as well as assess for any stent occlusion, kinking, or migration with dynamic knee mobility.

Irrespective the route of repair, routine postoperative surveillance includes clinical evaluation, ABI, as well as duplex ultrasound at 3, 6, and 12 months during the first year and, if stable, annual duplex imaging thereafter. There is a paucity of high-level data regarding the best antithrombotic approach after lower extremity revascularization, and the vast majority of available evidence is derived from peripheral occlusive arterial disease rather than PAAs. Therefore, postoperatively patients should be maintained on a minimum of

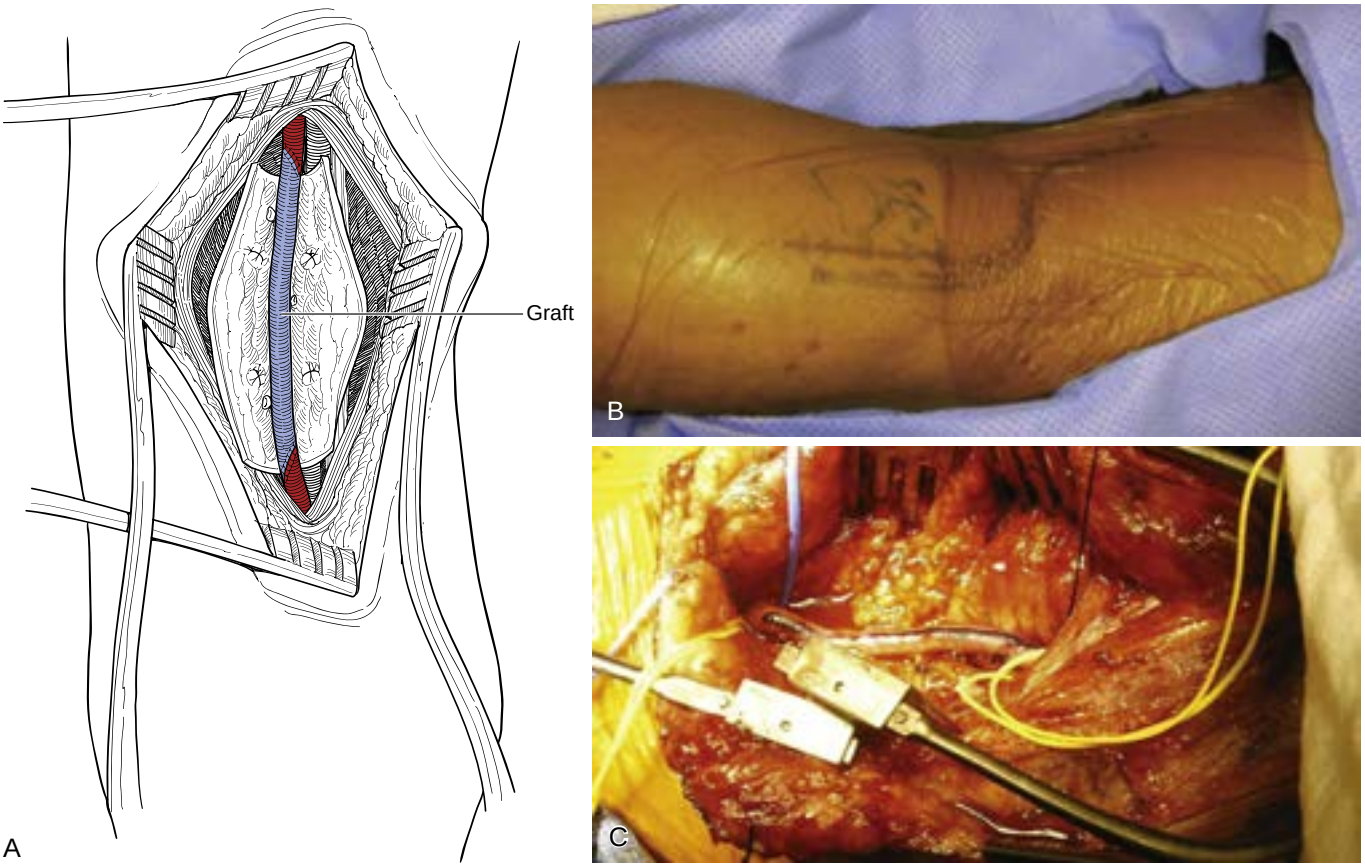


FIG. 4 Posterior approach to popliteal aneurysm repair. **(A)** Illustration of saphenous vein interposition graft. **(B)** Lazy S incision is used with superior portion beginning medially and extending laterally over flexion crease. **(C)** Completed saphenous bypass interposition graft. *(From Chaikof EL, Cambria R.* Atlas of Vascular Surgery and Endovascular Therapy: Anatomy and Technique. *Philadelphia: Elsevier; 2014.)*

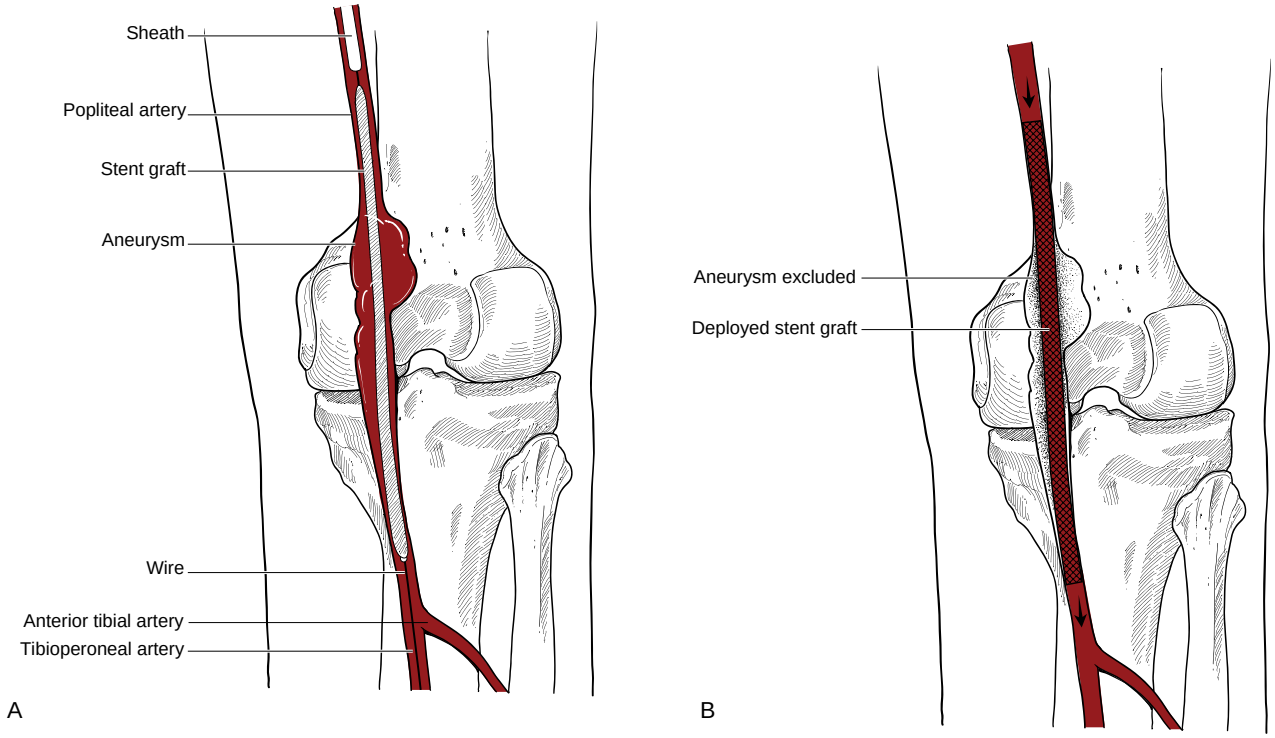


FIG. 5 Covered stent placement excluding popliteal aneurysm. Adequate proximal and distal seal zones are achieved without compromising runoff. *(From Chaikof EL, Cambria R.* Atlas of Vascular Surgery and Endovascular Therapy: Anatomy and Technique. *Philadelphia: Elsevier; 2014.)*

aspirin 81 mg indefinitely. The decision to use dual-antiplatelet or anticoagulation therapy should be individualized with careful evaluation of the risk-benefit profile.

Approach: Repair in the Presence of Acute Thrombosis

Patients presenting with a popliteal aneurysm and acute limb ischemia, as evident by diminished or absent pedal signals accompanied by pain, motor, or sensory findings, have a significantly increased risk for major amputation. Anticoagulation is initiated and a CTA or conventional angiography performed to determine if the aneurysm is occluded, evaluate the presence and extent of distal embolization, and assess the patency of the tibiopedal runoff arteries. If motor and sensory function is intact or symptoms are mild, catheter-directed thrombolysis can be performed to reestablish patent runoff followed by definitive endovascular or surgical repair. Should there be evidence of profound limb threatening ischemia, the patient should proceed directly to an operating room with imaging capability. Thromboembolectomy of the popliteal artery and distal tibial vessels can be conducted with the aid of adjuncts such as pharmacomechanical thrombolysis; the aneurysm excluded; and a bypass performed. Concern for or evidence of compartment syndrome necessitates a four-compartment fasciotomy. Limbs that are not candidates for salvage at presentation should undergo primary amputation rather than risk the complications associated with the revascularization of a nonviable limb.

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Treatment of Claudication

Qingwen Kawaji, MD, and Margaret W. Arnold, MD

It is estimated that peripheral arterial disease (PAD) affects 8 to 12 million Americans and over 200 million citizens globally. The prevalence of PAD is on the rise, both domestically and internationally. Recent analysis showed a relative increase of 23.5% during the first decade of the new millennium; this trend was present in low-income, middle-income, and high-income countries. Women of low-income and middle-income countries were diagnosed with PAD more often than men even at a younger age. Although only 1% to 3% of patients diagnosed with PAD will develop critical limb ischemia, PAD is associated with coronary heart disease and cerebrovascular disease. The 1-year incidence of myocardial infarction and stroke was higher in patients diagnosed with PAD than coronary arterial disease. Not only is PAD associated with higher morbidity and mortality, but it is also costly. In the United States, the Reduction of Atherothrombosis for Continued Health (REACH) registry estimated that $21 billion was spent in 2004 for vascular-related hospitalizations, and the US Medicare program estimated that more than $4.3 billion was spent on PAD–related treatments in 2001. The cost of PAD is unlikely to decrease given the increasing prevalence as well as use of invasive treatments in the United States.

Globally, the strongest risk factors for PAD include age, diabetes, and smoking. Other risk factors for PAD are similar to those of other atherosclerotic vascular diseases, such as elevated C-reactive protein, hyperhomocysteinemia, hyperlipidemia, hypertension, and chronic kidney disease. Men and postmenopausal women have a similar prevalence of PAD. However, women are most likely to be misdiagnosed as a result of atypical symptoms. African Americans have a lower ankle-brachial index (ABI) than Caucasians after risk factor adjustments; this may not be clinically relevant as it is present among healthy patients. The treatment of PAD and appropriateness of such treatments have been debated rigorously in the past few years. Race, socioeconomic status, and rurality have been reported to influence treatments of PAD.

ASSESSMENT

Screening

Despite PAD's association with other comorbid diseases, the US Preventive Services Task Force does not recommend routine screening of PAD with ABI because of insufficient evidence. A systematic review published in 2015 by Alahdab et al. and commissioned by the Society of Vascular Surgery examined data on benefits, harms, and cost-effectiveness of 43 studies and found that current quality of evidence supporting routine screening was low. It is important to note that patients with PAD have increased risk factors for atherosclerosis in other arterial beds such as coronary, carotid, and renal arteries. Furthermore, PAD is also a recognized risk factor for abdominal aortic aneurysm (AAA). Currently there are no data on AAA screening in patients with asymptomatic PAD; the American Heart Association and American College of Cardiology (AHA/ACC) recommend a screening duplex ultrasound examination for AAA in patients with symptomatic PAD. There is no sufficient evidence to support routine screening in all patients with PAD for asymptomatic atherosclerosis in other arterial beds.

Clinical Presentation and Evaluation

Claudication, defined as fatigue, discomfort, pain, and cramping caused by imbalance of blood perfusion and muscle metabolic demand, is the most common symptom of lower extremity PAD. Typical claudication symptoms are induced by exercise and relieved with resting. They can affect the buttock, hip, or leg and may

cause muscular weakness and instability. However, it is important to remember that only 10% of individuals with PAD have classic symptoms of intermittent claudication (IC); the majority of others experience other symptoms or are completely asymptomatic. Therefore, a detailed history and physical examination is the cornerstone of diagnosis.

When taking a history, it is important to spend time on the details of the symptoms patients are experiencing, such as distance walked before onset of symptoms, time elapsed before resolution of symptoms, specific movements/exercises/positions that worsen/alleviate discomfort, functional status, and any other associated symptoms. Other differential diagnoses may present similarly as claudication, and it is important to differentiate them from one another (Table 1). Furthermore, risk factors associated with PAD should also be documented: age, diabetes (how well it is controlled), kidney disease, smoking status, hyperlipidemia, hypertension, other inflammatory disease, other known atherosclerotic disease (coronary, carotid, subclavian, renal, mesenteric artery, AAA), and family history of PAD. Physical examination should include a full vascular assessment of cardiac, coronary, abdominal, and peripheral systems. Pulse palpation

TABLE 1 Differential Diagnosis of Intermittent Claudication

Condition	Location	Characteristic	Effect of Exercise	Effect of Rest	Effect of Position	Other Characteristics
Calf IC	Calf muscles	Cramping, aching discomfort	Reproducible onset	Quickly relieved	None	May have atypical limb symptoms on exercise
Thigh and buttock IC	Buttocks, hip, thigh	Cramping, aching discomfort		Quickly relieved	None	Impotence; may have normal pedal pulses with isolated iliac artery disease
Foot IC	Foot arch	Severe pain on exercise	Reproducible onset	Quickly relieved	None	Also may present as numbness
Chronic compartment syndrome	Calf muscles	Tight, bursting pain	After much exercise	Subsides slowly	Relief with elevation	Typically heavy muscled athletes
Venous claudication	Entire leg, worse in calf	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep vein thrombosis, signs of venous congestion, edema
Nerve root compression	Radiates down leg	Sharp lancinating pain	Induced by sitting, standing, or walking	Often present at rest	Improvement by change in position	History of back problems, worse with sitting, relief when supine or sitting
Symptomatic Baker's cyst	Behind knee, down calf	Swelling, tenderness	With exercise	Present at rest	None	Not intermittent
Hip arthritis	Lateral hip, thigh	Aching discomfort	After variable degree of exercise	Not quickly relieved	Improvement when not weight bearing	History of degenerative arthritis
Spinal stenosis	Often bilateral buttocks, posterior legs	Pain and weakness	May mimic IC	Variable relief, but can take a long time to recover	Relief by lumbar spine flexion	Worse with standing and extending spine
Foot/ankle arthritis	Ankle, foot, arch	Aching pain	After variable degree of exercise	Not quickly relieved	Possible relief by not bearing weight	Variable, may relate to activity level and present at rest

IC, Intermittent claudication.
Modified from Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).

and auscultation for bruits should be performed for carotid, abdominal, and femoral systems. The lower extremity should be carefully examined for signs of PAD and chronic limb-threatening ischemia (CLTI): dry skin/skin breakdown, wounds, infection, muscle atrophy, discoloration, absent distal hair growth, and weakened/absent distal pulses. Clinical history and examination are used to stage PAD, either with Fontaine's or Rutherford's classification systems (Table 2).

As a component of physical examination, measurement of the ABI is the primary method for establishing a diagnosis of PAD (Figure 1). ABI is performed by measuring the systolic blood pressure from the bilateral brachial arteries, dorsalis pedis, and posterior tibial arteries while the patient is supine. The ratio is calculated by taking the higher pressure of two arteries on each leg divided by the higher of the two brachial pressures. An index of less than 0.9 is diagnostic for PAD. ABI could be falsely elevated due to noncompressibility of the arteries from calcification; when ABI is ≥1.4, a toe-brachial index (TBI) is useful as digital arteries are less calcified. A TBI ≤0.7 is significant for hemodynamic arterial insufficiency. In patients who present with classic symptoms of PAD/claudication and a normal/borderline ABI at rest, an exercise ABI can be helpful in making the diagnosis. Using exercise ABI in diagnosing PAD can be challenging because of the variety of protocols for this test. Overall, the ABI is obtained immediately after completing the exercise. A decrease in ABI to a value ≤0.9 is indicative of hemodynamically significant arterial stenosis. Additional studies such as duplex ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and invasive angiography are reserved generally for highly symptomatic patients who may benefit from revascularization. It is recommended that all patients with IC follow up annually for assessment of lifestyle modifications, medical therapy optimization, and disease progression monitoring with ABIs.

TREATMENT

Management of patients with PAD includes treatment of comorbid disease, functional status improvement, and limb preservation. This can be achieved through lifestyle modification, optimization of treatment of comorbid diseases, and revascularization. IC severely affects quality of life and is associated with reduced survival. Upon initial diagnosis of PAD, patients must be educated on the progression of PAD and the importance of treatment compliance and follow-up regardless of symptoms. Patients with diabetes may develop CLTI without developing claudication first.

Medical Management

Smoking Cessation

The association between smoking and PAD is well recognized and studied. The severity of PAD symptoms correlates to the extent of smoking history. Smoking cessation reduces mortality risk,

TABLE 2 Fontaine's Classification of Peripheral Arterial Disease and Rutherford's Classification of Chronic Limb Ischemia

Fontaine		Rutherford			
Stage	**Clinical Findings**	**Grade**	**Category**	**Clinical Findings**	**Objective Criteria**
I	Asymptomatic	0	0	Asymptomatic	Normal treadmill or reactive hyperemia test
IIa	Claudication symptoms at distances >200 m	I	1	Mild claudication	Completes treadmill exercise; ankle pressure after exercise >50 mm Hg, but at least 20 mm Hg lower than resting value
IIb	Claudication symptoms at distances <200 m		2	Moderate claudication	Between categories 1 and 3
			3	Severe claudication	Cannot complete standard treadmill exercise; ankle pressure after excise <50 mm Hg
III	Ischemic rest pain, mostly in feet	II	4	Ischemic rest pain	Resting ankle pressure <40 mm Hg; ankle or metatarsal pulse volume recording flat or barely pulsatile; toe pressure <30 mm Hg
IV	Necrosis and/or gangrene of the limb	III	5	Minor tissue loss: nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure <60 mm Hg; ankle or metatarsal pulse volume recording flat or barely pulsatile; toe pressure <40 mm Hg
			6	Major tissue loss: extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

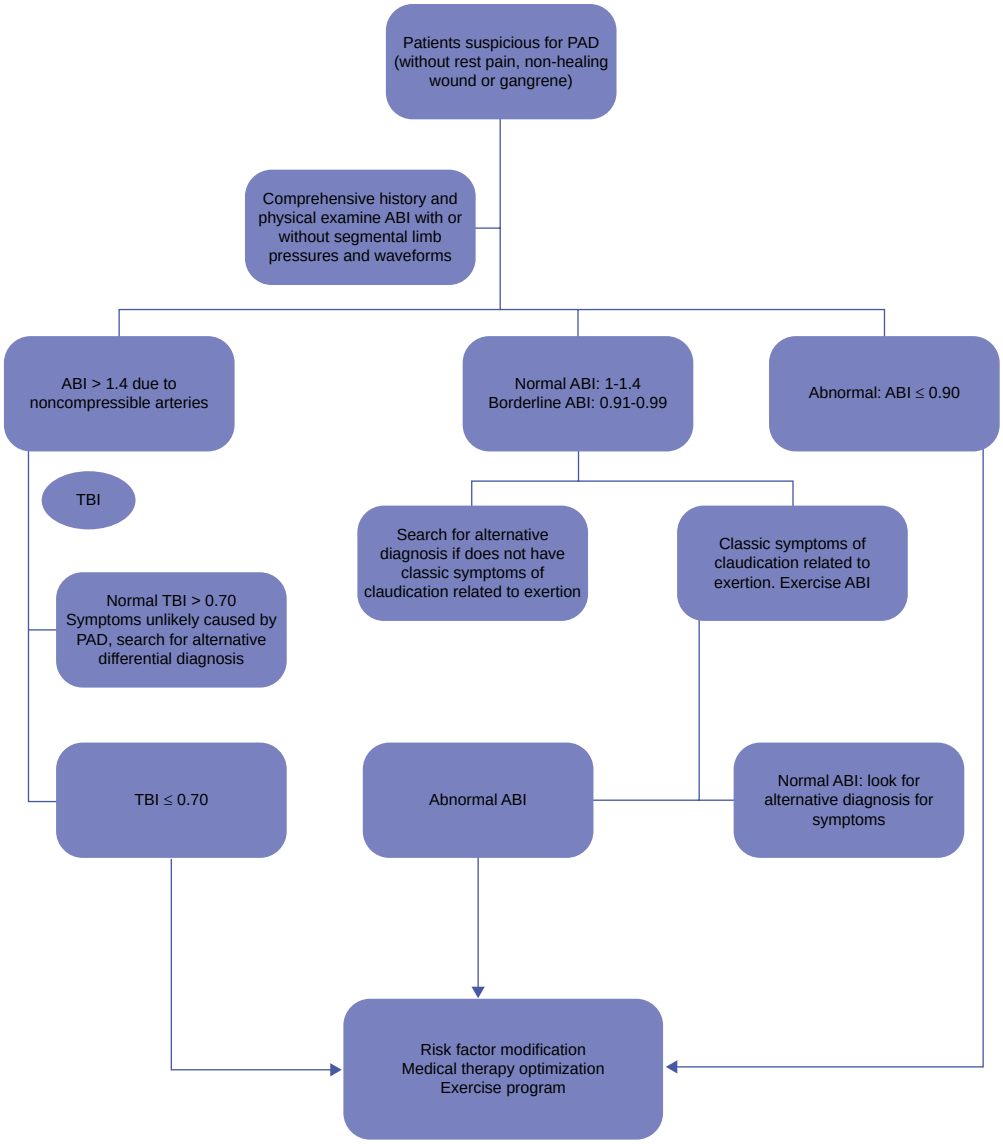


FIG. 1 Algorithm for peripheral arterial disease diagnosis in symptomatic individuals without signs of chronic limb-threatening ischemia.

progression of PAD to CLTI, amputation, heart attack, stroke, and bypass graft failure. Patients should be referred for counseling. The use of bupropion and varenicline have shown improved rates of abstinence.

Diabetes Mellitus

About one-third of patients with diabetes mellitus also have PAD. They are also more likely to develop wounds and progress to CLTI without having claudication symptoms. These patients are 5 to 10 times more likely to undergo amputation than nondiabetic PAD patients. The Society for Vascular Surgery practice guidelines recommend optimizing diabetes control with a hemoglobin A1c goal of <7.0%.

Hypertension

Hypertension is risk factor for cardiovascular disease as well as PAD. Recommendations for hypertension management have been published extensively. Previous concerns regarding worsening claudication as a side effect of beta blockers were proven invalid in a randomized controlled trial published in 1991 by Radack et al. Angiotensin-converting enzyme inhibitors (ACEIs) are shown to reduce mortality and cardiac events in patients with left ventricular dysfunction; use of ramipril showed a 25% cardiac event reduction in patients with PAD.

Hyperlipidemia

Evaluation of statin therapy initiation in patients without an atherosclerotic cardiovascular disease (ASCVD) diagnosis is based on the estimation of 10-year cardiovascular risk rather than specific lipid levels according to the 2018 AHA/ACC guidelines on management of blood cholesterol. Although the risk calculator does not include PAD specifically, it includes major risk factors for PAD such as age, gender, race, blood pressure, diabetes, and smoking status. Patients with clinical ASCVD such as acute coronary syndrome, history of myocardial infarction, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, aortic aneurysm, or PAD are recommended to begin high-intensity statin therapy with an aim of achieving a 50% or greater reduction in low-density lipoprotein

cholesterol (LDL-C) levels. Aside from cardiovascular risk reduction, statin therapy has also been shown to increase walking distance in two studies published in 2003 by Mohler et al. and Mondillo et al.

Antiplatelet and Antithrombotic Therapy

Antiplatelet therapy with aspirin in doses of 75 to 325 mg/day has shown to decrease cardiovascular events and vascular-related deaths in patients with symptomatic PAD. Clopidogrel has shown to be just as effective if not more in risk reduction; it is a comparable alternative for patients who have aspirin intolerance. Currently, there is no evidence to suggest that dual antiplatelet therapy is more effective than a single agent, especially with the elevated bleeding risk. There is a lack of evidence to suggest benefits of warfarin in the PAD population.

Homocysteine-Lowering Therapy

Homocysteine is a known risk factor for PAD. The association of homocysteine with atherosclerosis was initially documented in 1969 by McCully et al. when studying the vascular pathology of children with inherited disorders of homocysteine metabolism. Approximately 1 in 3 patients diagnosed with PAD also have an elevated homocysteine serum level, whereas the prevalence of elevated homocysteine in the general population is 1%. Although clinical trials have shown that folic acid and cobalamin (vitamin B_{12}) can lower homocysteine levels, there is no strong evidence currently to suggest that lowering homocysteine levels correlates with reduction of cardiovascular adverse events in patients with PAD.

Cilostazol and Pentoxifylline

In the United States, cilostazol and pentoxifylline are the only two medications currently approved by the US Food and Drug Administration (FDA) for IC symptom relief. Pentoxifylline was approved in 1984; it works by reducing blood viscosity and platelet aggregation to enhance blood flow. Its effects are modest, but it is generally a well-tolerated and safe drug. Dosing of pentoxifylline starts at 400 mg three times a day, with a maximum dosage of 1800 mg per day. Side effects of pentoxifylline include nausea, headache, drowsiness, anorexia, and exacerbation of hypertension. Cilostazol, a phosphodiesterase III inhibitor, was approved by the FDA for IC in 1999. Cilostazol works by direct vasodilation and platelet aggregation suppression; it can increase maximal walking distance in as short as 4 weeks. Cilostazol is contraindicated in patients with any level of heart failure and can cause headache and diarrhea. Effectiveness of cilostazol and pentoxifylline were studied in a randomized controlled trial by Dawson et al. In this study, cilostazol had a 54% maximal walking distance improvement, while pentoxifylline had a 30% improvement. The Society for Vascular Surgery guideline currently recommends a 3-month trial of cilostazol (100 mg twice a day) in patients without congestive heart failure and pentoxifylline (400 mg three times a day) for patients with contraindications to cilostazol.

Exercise Therapy

The effectiveness of exercise therapy in the management of claudication has been well studied and is the foundation of claudication therapy (Box 1). Benefits of an exercise program include collateral blood vessel enlargement, angiogenesis, nitric oxide–induced vasodilation, enhancement of bioenergetics of skeletal muscle, and hemorheology. Before initiating any exercise program, it is important to address medical therapy for optimization of comorbid disease as well as atherosclerotic risk reduction. Patients should be screened to ensure that their participation in an exercise program is safe. These programs come in a variety of forms: they can be self-directed, supervised, institution based, or home based and of varying intensity and duration. Studies have found that walking is superior to other forms of lower extremity exercise and that the greatest effects were achieved with walking programs that had at least three sessions per week with a duration of more than 30 minutes per session and the usage of near-maximal claudication pain as an endpoint.

BOX 1 Sample Walking Program Handout for Patient Use

Benefits of a Walking Program

Using a walking program to treat claudication has many benefits. It not only enables you to walk farther and faster, but it also helps with weight reduction and improves your outlook on life (as any exercise program will). Walking is the appropriate exercise for people with claudication (pain in calves or thighs with walking) because walking is the activity that is limiting you.

Rules of a Walking Program

1. Walk 6 days a week. Take the same day off each week. For example, if you take Sunday off the first week, it is the day you will take off each week.
2. Walk at about the same time each day. This enables your walking program to become part of your daily routine. After 1 or 2 weeks, your spouse, family, and friends will know that you will not be available at that time of day unless they want to walk with you.
3. Start by walking a 30 minutes a day. The time you take to rest (to let the pain subside) counts as part of your 30 minutes of exercise. Eventually you will be walking nonstop for the entire 30 minutes. After 2 months, increase your time to 45 minutes, and only increase it further if desired.
4. A slow, steady walk is best if you want to walk a maximum distance. Shorter, faster walks with more frequent rests will increase your endurance quicker; our recommendation is to start out with slow, steady walks for the first 1 or 2 months. After that, try faster, shorter walks several times each week with slower walks on the other days.
5. Remember that the pain that you feel in your legs is not an indication of any damage. It may be annoying and make you stop, but you are not damaging your muscles. If you can walk with the pain for a while, it will help increase your endurance.

Good luck! You will enjoy your walks. Caution: smoking is not permitted while walking.

Published in 2012, the CLEVER trial randomized 111 patients with IC caused by aortoiliac occlusive disease to optimal medical care, medical care with supervised exercise therapy, or medical care with stent revascularization. The study found that at 6 months, exercise therapy with optimal medical care provided the greatest improvement in peak walking time, and the stent revascularization group had the greatest improvement in quality-of-life parameters. There was no statistically significant difference found in peak walking time between the supervised exercise group and stent revascularization group. Currently, there is no strong evidence to prefer endovascular interventions over exercise therapy for the treatment of claudication when the patient is eligible for both. However, it is important to note that exercise therapy is not only a primary treatment for claudication, but it can also be an adjunct treatment to patients who underwent surgical intervention for claudication.

Current recommendations state that a supervised exercise program consisting of walking at least three times a week for a duration of 30 to 60 minutes for at least 12 weeks is the first-line therapy. When supervised programs are unavailable, home-based exercises with a minimum of 30 minutes of walking three to five times a week are desirable. Patients who have undergone revascularization for IC should participate in either a supervised or home-based exercise program.

Revascularization

When treated with optimized medical therapy, less than 5% of patients with claudication will progress to CLTI such as rest pain and

tissue loss or require amputation. Although IC is relatively benign, its effect on loss of ambulatory function, activities of daily living, occupation, and quality of life should not be minimized. Between 20% and 30% of patients with IC will eventually require intervention as a result of worsened disability despite lifestyle modifications and optimized medical therapy. Prophylactic intervention in patients with IC that is well tolerated is not indicated. ABIs or anatomic findings do not dictate the need for intervention in IC either. The decision to perform revascularization for IC is highly individualized; it should be based on the patient's functional impairment, quality-of-life changes, evidence of significant disease, and assessment of benefit versus risk.

It is important to remember that claudication may not be the only source of decreased functional status. Other factors such as arthritis, spinal stenosis, or myositis should be investigated and considered when discussing treatment options and potential outcomes after intervention. Patients with significant cardiovascular disease, chronic obstructive pulmonary disease, morbid obesity, or stroke may not benefit from intervention for IC as their comorbid diseases have a greater impact on their functional status and quality of life. Some studies have shown that although surgical and endovascular therapy are superior to medical therapy alone for improvement in walking performance, they are not superior to supervised exercise programs. Therefore, patients with IC should be managed with a 6-month trial of smoking cessation, medical therapy, and an exercise program with or without cilostazol before surgical or endovascular intervention.

Numerous studies have been published regarding the appropriateness and outcome of peripheral vascular intervention (PVI) for claudication. Using Medicare data between 2015 to 2017, Hicks et al. found that 3.2% of patients underwent PVI within 6 months of initial claudication diagnosis, and 320 physicians had an early PVI rate of ≥14%. Another study published in 2020 by Bath et al. discovered that of the 16,152 patients who underwent intervention for IC, only 32% were free from IC occurrence according to life table analysis, which did not meet the Society for Vascular Surgery guidelines for long-term freedom from recurrent symptoms of >50% at 2 years. This study also found that before undergoing intervention, medical management for many patients was not optimized. The personalized nature of PVI for IC and variety of methods/devices available for revascularization prompt future studies to further investigate the optimal intervention of choice and standardization of treatment.

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Pseudoaneurysms and Arteriovenous Fistulas

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A pseudoaneurysm (PSA), or false aneurysm, is a focal outpouching of an artery that does not include all layers of the arterial wall. This outpouching may be contained by the adventitia or may consist only of a rim of fibrous tissue containing thrombus and arterial flow in continuity with a defect in an artery. In other words, it is a contained bleed from a focal site of the arterial wall. PSAs most commonly result from iatrogenic injury to the arterial wall but can be attributed to other etiologies as well (Box 1). Injury to the arterial wall results in pulsatile flow into the perivascular space, dissection into surrounding tissues, and hematoma formation. A persistent passage from the injury site results in a flow channel, or *neck,* leading into a false lumen, or *sac,* with to-and-fro arterial flow between the artery and the sac (Fig. 1). PSAs, unlike true aneurysms, lack all three normal elements of the arterial wall and are therefore at increased risk of rupture with potentially catastrophic bleeding. Postcatheterization femoral artery PSAs are the focus of this chapter.

RISK FACTORS

PSAs are most frequently seen as a complication related to percutaneous arterial access. The common femoral artery (CFA) is the most common access site for catheter-based interventions for cardiologists, interventional radiologists, and vascular surgeons alike. Techniques for accessing the CFA vary and include direct palpation of the pulse, fluoroscopic guidance, and ultrasound-guided access. The latter has become more prevalent because it results in fewer access-related complications and is considered the standard of care. Nonetheless, the incidence of femoral artery PSAs is increased when the puncture site is not in the CFA, but rather in the external iliac artery, superficial femoral artery (SFA), or profunda femoral arteries (PFA).

Risk factors for the development of iatrogenic PSAs associated with arterial access procedures are listed in Box 2. These can be divided into procedure-related and patient-related factors. Increased complexity of intraarterial interventions has been shown to increase the risk of vascular complications. Therapeutic interventions such as arterial angioplasty and stenting, atherectomy, and thrombolytic therapy have a higher rate of PSA formation (2%–8%) than diagnostic procedures (0.05%–2%). Related to both the therapeutic nature and complexity of interventions, larger diameter catheter or sheath use is also correlated with higher rates of PSA formation. Other procedural-related risk factors include simultaneous arterial and venous puncture, urgent versus elective procedures, the use of arterial closure devices, and insufficient duration of puncture site compression after the sheath is removed. PSA formation is less common when ultrasound guidance or fluoroscopic localization of the middle one-third of the femoral head is used for common femoral artery puncture. Patient-related risk factors contributing to PSA formation include advanced age, female gender, obesity, preprocedural thrombocytopenia, and postprocedural antiplatelet or anticoagulation use.

Diagnosis

PSAs may be asymptomatic or may present with mild tenderness to palpation or swelling in the groin after catheterization. Although

BOX 1 Etiologies of Pseudoaneurysm Formation

Acquired

Trauma

Penetrating
- Gunshot wound
- Stab wound

Blunt or stretch
- Proximity injury

Infection

Drug abuse
Contamination
Bacterial seeding

Iatrogenic

Anastomotic

Patch
Bypass graft
Vascular access

Spontaneous

Vasculitis

Behcet's disease
Polyarteritis nodosa

BOX 2 Risk Factors for Pseudoaneurysm Formation

Procedural Factors

Therapeutic vs Diagnostic Procedure

Complex procedures
Larger sheath size (>8Fr)
Prolonged procedure
Simultaneous artery and vein cannulation
Use of closure device

Poor Technique

Low (SFA or PFA) or high (EIA) puncture sites
Inadequate compression of puncture site

Patient Factors

Advanced age
Female gender
Obesity
Hypertension
Hemodialysis-dependent end-stage renal disease
Concurrent anticoagulation
Calcified vessels
Steroid use

EIA, External iliac artery; *PFA*, profunda femoral artery; *SFA*, superficial femoral artery.

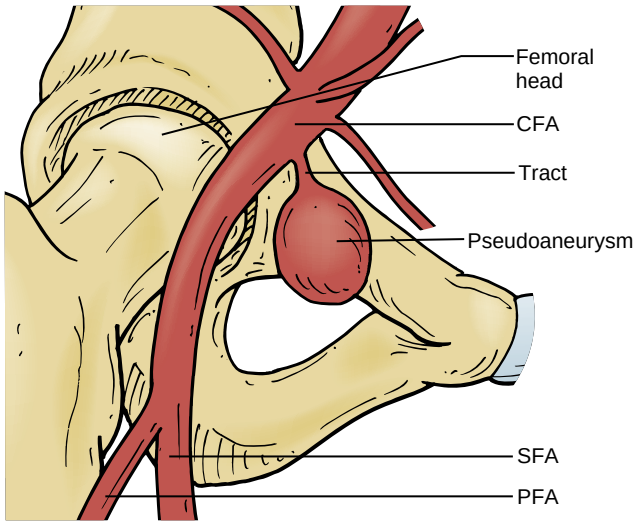


FIG. 1 Common femoral artery *(CFA)* pseudoaneurysm and tract (neck). *PFA*, Profunda femoral artery; *SFA*, superficial femoral artery.



FIG. 2 Mass effect of a pseudoaneurysm causing pressure necrosis of the overlying skin.

this is the most common presentation of a PSA, more severe symptoms can be seen related to the mass effect of a PSA and associated hematoma. Large PSAs with associated hematoma may result in skin necrosis (Fig. 2) and/or compression of nerves and vessels in the groin. Lower extremity swelling, deep venous thrombosis, and/or ischemia secondary to vessel compression are rare but serious findings. Ruptured PSAs may present with hemodynamic collapse and significant groin or thigh swelling.

Any patient who experiences pain disproportionate to that expected after a percutaneous procedure should undergo evaluation to exclude PSA. Examination should include a thorough peripheral pulse examination, documentation of the ankle-brachial index, and limited ultrasonography of the vasculature in the affected groin. Laboratory assessments such as decreased platelet count (<200,000/L) or elevated D-dimer values have been shown to correlate with diagnosis of a PSA on duplex.

The diagnostic examination of choice is duplex ultrasound (DUS, 5- to 7-MHz linear transducer). Because B-mode imaging alone is unable to differentiate a PSA from a hematoma, color Doppler should be used to enhance the diagnostic accuracy of ultrasound (sensitivity, 94%; specificity, 97%) as it allows for identification of pulsatile flow within the sac. The typical appearance of a PSA on DUS is demonstrated in Figures 3 and 4. Active flow within the PSA sac is often referred to as *to-and-fro flow* or a *yin-yang pattern*. The PSA sac size (maximal diameter) and the length and width of the

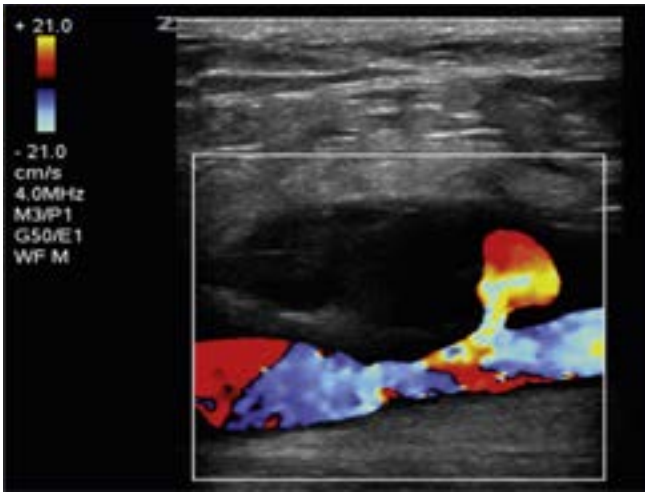


FIG. 3 Duplex ultrasound findings of a pseudoaneurysm include a fluid collection adjacent to the femoral artery, a high-velocity jet through the arterial wall, and a neck or communication with the artery.

neck should be measured with DUS because they are important for guiding treatment options. If an arterial duplex examination cannot be performed or if the results are equivocal, computed tomography imaging (with intravenous contrast) can be used to make the diagnosis of PSA (Fig. 5) or to obtain more detailed anatomic information to plan a surgical repair. In addition to assessing the PSA, DUS or computed tomography angiography should assess for secondary injuries, including posterior intimal arterial injury and presence of an arteriovenous fistula (AVF).

Treatment

Several treatment options for iatrogenic femoral PSAs exist. The therapeutic choice depends on the PSA size, neck characteristics, and the patient's symptoms. Treatment options include observation, ultrasound-guided compression (USGC), percutaneous ultrasound-guided thrombin injection (UGTI), and open surgical repair. More recently, creative therapeutic approaches have been described, including more advanced endovascular occlusion of the PSA neck, saline or glue injection, or hybrid endovascular/open and endovascular/injection techniques.

Observation

Studies have shown that most small PSAs (<2–3 cm) thrombose spontaneously within 4 weeks for patients not on anticoagulants. Conservative management, or a watch-and-wait policy, has been advocated for small and asymptomatic PSAs. Spontaneous resolution can be unpredictable; therefore, patients with small PSAs require periodic surveillance with DUS. The disadvantage of this watch-and-wait policy is that patients undergoing surveillance may have activity restrictions, discomfort with serial DUS, and prolonged hospital stays. PSAs that do not thrombose risk enlargement and additional complications; thus, adhering to a scheduled follow-up is critical. Patients considered at risk for being lost to follow-up should undergo definitive treatment initially.

USGC

USGC therapy has been shown to be a safe and noninvasive method for treatment of PSAs with success rates ranging between 73% and

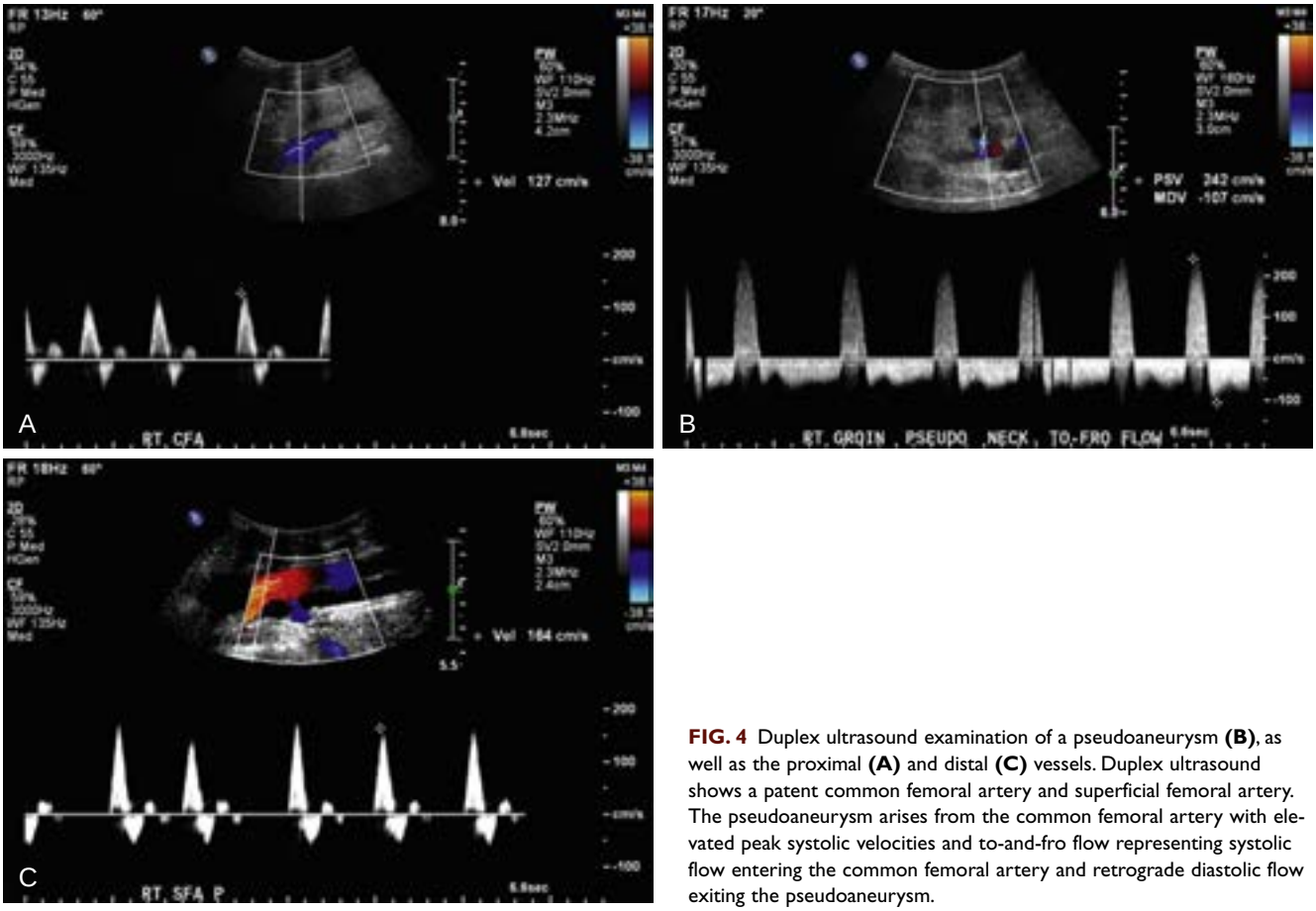


FIG. 4 Duplex ultrasound examination of a pseudoaneurysm **(B)**, as well as the proximal **(A)** and distal **(C)** vessels. Duplex ultrasound shows a patent common femoral artery and superficial femoral artery. The pseudoaneurysm arises from the common femoral artery with elevated peak systolic velocities and to-and-fro flow representing systolic flow entering the common femoral artery and retrograde diastolic flow exiting the pseudoaneurysm.

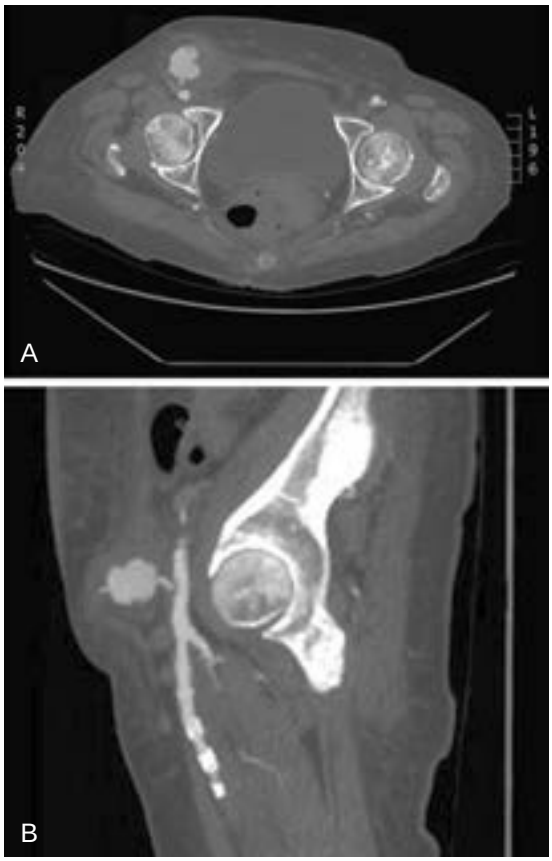


FIG. 5 Axial **(A)** and sagittal **(B)** CT angiographic images of a right femoral pseudoaneurysm and neck.

93%. Ultrasound is used to identify the PSA sac and neck. The ultrasound transducer is positioned over the PSA neck, and pressure is applied until there is obstruction of flow within the neck and sac. During compression of the PSA, cessation of flow within the PSA is verified with continual duplex imaging, whereas flow in the native artery is preserved. Blind manual compression has also been described but lacks continual monitoring to ensure complete occlusion of flow into the PSA and therefore risks inadequate treatment, especially when even small position changes by the patient can require the operator to make similar adjustments to maintain complete occlusion. Compression is usually held for increments of 10 to 15 minutes. This is repeated until successful PSA sac thrombosis is achieved, or until a discretionary failure time is met. Compression times average 33 minutes for acute PSAs and 51 minutes for more chronic PSAs (>14 days).

Limitations of USGC include both patient-specific and operator-dependent factors. Patient-specific concerns include the location of the PSA, body habitus, and ability to be compliant with or tolerate compression. Suprainguinal PSA compression is generally not recommended because it may result in PSA rupture and inability to quickly control bleeding. Brachial artery PSAs usually require operative decompression because of symptomatic nerve compression. It is more technically challenging to both achieve and maintain compression in an obese patient without operator fatigue. Compression is also time consuming and may not be well tolerated by patients. Conscious sedation can be administered with improved tolerance but requires increased resources (such as advanced nursing care and appropriate bed/unit placement during the procedure and recovery) and may increase overall risk to the patient. Operator-dependent factors include variable or inadequate compression, fatigue, and the time-dependent nature of the task.

Predictors of poor outcome with USGC include concomitant anticoagulation, large PSA size (>4 cm), and patient obesity. Patients with these negative predictors generally have lower technical success rates (25%–35%), higher recurrence rates (20%), and greater complication rates (3.6%) than patients without these factors. Complications and contraindications to USGC are listed in Box 3.

UGTI

UGTI has become the treatment of choice for medium-sized postcatheterization PSAs (2–5 cm). Thrombin is injected into the PSA sac for immediate thrombosis of the PSA (Fig. 6 and Box 4). This is an off-label use of thrombin; it is US Food and Drug Administration–approved for topical use only. UGTI is contraindicated in the setting of lower extremity ischemia, infection, AVF, and pregnancy.

UGTI has several advantages compared with USGC for the treatment of PSAs. The procedural time is shorter, the procedure is better tolerated by patients, and the technical success rate is greater (>96%). In addition, UGTI can be used effectively in the setting of concomitant anticoagulation or for suprainguinal PSAs. The ability to perform this procedure in the outpatient setting or at the bedside also reduces the relative cost. Complications of UGTI include arterial thrombosis (<2%), PSA rupture, treatment failure, or allergic response to bovine thrombin. Arterial thrombosis has been associated with the treatment of small PSAs (<2.5 cm). Complications related to neck length are more variably reported; arterial thrombosis has been shown not to be related to short neck length (<5 mm) although necks shorter than 2 mm have demonstrated increased risks of embolic complications. Exposure to bovine factor V may cause some patients to form antibodies that cross-react with human factor V and induce coagulopathy. Patients who undergo UGTI should have a follow-up duplex in 24 to 48 hours to ensure continued thrombosis of the PSA.

Endovascular Repair

Covered stents have been widely used in the treatment of aneurysms, but their use in femoral PSAs is limited. Current barriers include high cost, lower patency rates, the need for larger delivery systems, and the lack of long-term data. Endovascular repair is not recommended if treatment of the PSA requires placing a stent across the groin crease or across the origin of the PFA. Covered stent use can be considered for treatment of suprainguinal PSAs where the distal endpoint of the stent does not cross beneath the inguinal ligament. Complications unique to covered stents include infection, migration, and thrombosis. Long-term duplex surveillance is required postprocedure to monitor for in-stent restenosis and stent patency.

The use of covered stents for treatment of infected PSAs is not recommended. In the setting of advanced cancer, definitive treatment

BOX 3 Complications and Contraindications of Ultrasound-Guided Pseudoaneurysm Compression

Complications

Rapid enlargement of the PSA sac
Skin necrosis
Distal embolization
Venous thrombosis
Rupture

Contraindications

Peripheral ischemia
Cutaneous ischemia
Infection
Surgical graft
Suprainguinal PSA

PSA, Pseudoaneurysm.



FIG. 6 Ultrasound-guided thrombin injection. A 1-mL syringe containing bovine thrombin (1000 units/mL) and a 5-mL syringe with sterile normal saline flush are connected to a three-way stopcock fitted with a 22-gauge needle (40 mm or 70 mm). If the pseudoaneurysm (PSA) is deeper than 3.75 cm, then a 21-gauge × 9 cm Echotip needle (Cook Medical) can be used. The PSA sac is visualized in transverse and longitudinal views on duplex ultrasound. The thrombin port is placed in the "off" position and the saline port is placed in the "on" position. The needle and transducer are kept parallel as the needle is advanced under ultrasound guidance. Puncture into the sac is kept superficial and far from the PSA tract. Proper needle placement is confirmed by aspiration of blood, and a small injection of saline will produce a flash of color on duplex ultrasound. The thrombin port is placed in the "on" position and the saline port is placed in the "off" position. Thrombin is then injected into the PSA sac in 0.2-mL aliquots until there is cessation of blood flow in the PSA sac and tract. This can usually be achieved in seconds. The tract should never be directly injected because of the risk of thrombosis of the native artery. An average of 300 units (0.3 mL) of thrombin (range, 50–1000 units) is required to thrombose the PSA sac. An arterial duplex is repeated 24 hours postprocedure to check for recurrence (0%–9%) and to rule out postprocedure complications.

of a PSA via covered stent placement with or without coiling and covering of the PFA may have a role. Covered stent use has also been described in intravenous drug abusers who present with ruptured PSAs or acute sepsis associated with an infected PSA. In these settings, the stent provides a bridge to arterial reconstruction by obtaining hemostasis or allowing for surgical debridement of the infected tissue before reconstruction. When definitive arterial reconstruction is anticipated, preservation of the profunda is recommended.

Some authors have described using endovascular balloon occlusion of the origin of the PSA at the time of thrombin injection to reduce the risk of intraarterial thrombosis, especially if there are concerns for a wide or short neck. This risks access site complications at the contralateral femoral access site but has been performed successfully. Case reports have also described the use of various arterial closure devices (e.g., Angio-Seal and Star-Close, Perclose ProGlide, Amplatzer plug) to treat iatrogenic PSAs.

Open Surgical Repair

Noninfected Pseudoaneurysms

Patients with contraindications to compression therapy or thrombin injection should be considered for open surgical repair. These include peripheral or cutaneous ischemia, infection, presence of a surgical graft, large suprainguinal PSAs, or those who present with complicated PSAs (i.e., rapid enlargement, distal embolization, rupture) (Fig. 7). Repair of suprainguinal PSAs requires retroperitoneal access to achieve proximal control of the iliac vessels. Hybrid open and endovascular techniques, in which endovascular balloon occlusion is used to provide proximal and/or distal control through either the PSA itself or via contralateral femoral access, have been described.

Once proximal and distal control are obtained, the PSA can be opened and the defect repaired. Often, the actual arterial injury is small and can be repaired with a simple, interrupted polypropylene suture. The back wall of the artery should be inspected to ensure no posterior arterial injury. Patch angioplasty may be required if the arterial wall is significantly damaged or if there is luminal narrowing of the artery with primary repair. Any hematoma should be evacuated, and in the setting of a large tissue defect or hematoma, drain placement may be necessary. Complications associated with open surgical repair include wound infection, bleeding, lymphocele, radiculopathy, perioperative myocardial infarction, and death.

BOX 4 Three-Way Stopcock Technique of Ultrasound-Guided Thrombin Injection

- The patient's groin is prepped and draped in the usual sterile fashion.
- The distances from the skin to the most superficial portion of the PSA sac and the distance to the PSA tract are measured.
- The skin and subcutaneous tissue are infiltrated with 1%–2% lidocaine.
- A three-way stopcock is prepared as described in Figure 6.
- The needle is advanced under DUS guidance to the depth measured in step 2 and the PSA sac is entered superficially. Entry into the PSA sac is confirmed by aspiration of blood and proper placement of the needle tip is confirmed by saline injection on DUS. The needle must be in the PSA sac and *not* in the tract, artery, or vein.
- The thrombin port is turned on and the saline port is turned off. Thrombin is injected gently in 0.2-mL aliquots until the PSA sac and tract are thrombosed or until 1.0 mL (1000 units) of thrombin is used.
- If there are ≥2 PSA sacs, then the most superficial sac is injected first.
- If the tract persists, do *not* inject directly into the tract. Follow the patient as the tract normally thromboses within 24 hours.
- A DUS is repeated 24 hours postprocedure to check for recurrence (0%–9%) and rule out postprocedure complications such as arterial or venous thrombosis.
- This procedure may be performed on an outpatient basis with the patient discharged immediately after injection.
- A PSA that recanalizes after thrombin injection may be reinjected on follow-up visit.

DUS, Duplex ultrasound; *PSA*, pseudoaneurysm.

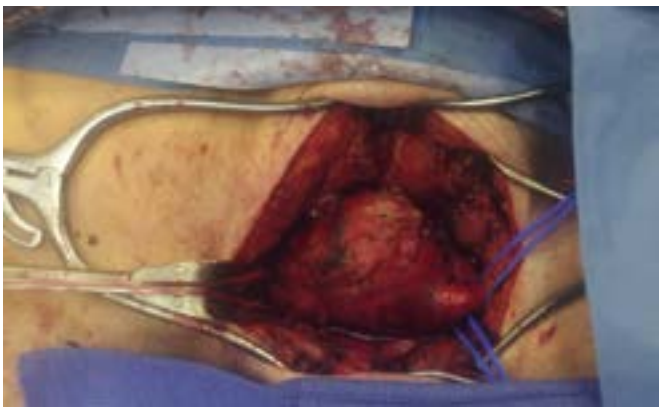


FIG. 7 Noninfected femoral pseudoaneurysm requiring open surgical repair because of its large size and overlying skin necrosis.

Infected Pseudoaneurysms

Compression or injection of infected PSAs is contraindicated, and they must be treated promptly and operatively. Management includes appropriate antibiotic coverage, debridement of infected tissue, and arterial repair or replacement with autogenous vein graft. Arterial ligation without revascularization is reserved for aggressive bacterial infection and may be associated with intermittent claudication or limb loss. Muscle flap coverage of the tissue defect may be required to further protect the repair. Except for rare circumstances, such as providing immediate hemostasis of an acute rupture with planned definitive management including stent removal once the patient is stabilized, endovascular occlusion with covered stents should be avoided.

Alternate Percutaneous Methods

Paraaneurysmal saline injection has been described as an alternate method to either USGC or UGTI for PSAs. This technique uses ultrasound guidance to position a needle outside of the artery along the PSA neck, and injects normal saline (30–80 mL) into the extravascular tissue to cause external compression of the PSA neck and obliteration of flow within the PSA. A second injection on the opposite side of the PSA neck is sometimes required, and the injection is followed with five minutes of manual compression.

Cyanoacrylate glue has also been used for percutaneous treatment of PSAs. Various reports describe intrasac injection, much like thrombin, or injection into the collapsed PSA walls. This second method uses USGC of the PSA before injection, with subsequent injection of small aliquots of the glue directly into the apposed walls of the PSA. Compression is continued for 5 minutes, and injection and compression are repeated if signs of reperfusion are seen with gradual release of compression. Administration of cyanoacrylate glue has also been described using contralateral arterial access to provide balloon occlusion across the PSA neck during injection.

Although studies have demonstrated initial success with each of these techniques, further investigation is warranted.

Anastomotic Pseudoaneurysms

Anastomotic PSAs are an infrequent but important late complication of prosthetic arterial reconstruction (Fig. 8). The femoral arterial anastomosis is the most common site for an anastomotic PSA (13.6%). The presence of an anastomotic PSA should raise suspicion of a graft infection, and treatment should be planned with this in mind. An anastomotic PSA is typically composed of a fibrous pseudocapsule surrounding an occult graft infection or arterial degeneration in a previously endarterectomized artery. Because anastomotic PSAs are unpredictable and are associated with a high incidence of rupture, they should be treated early and aggressively.

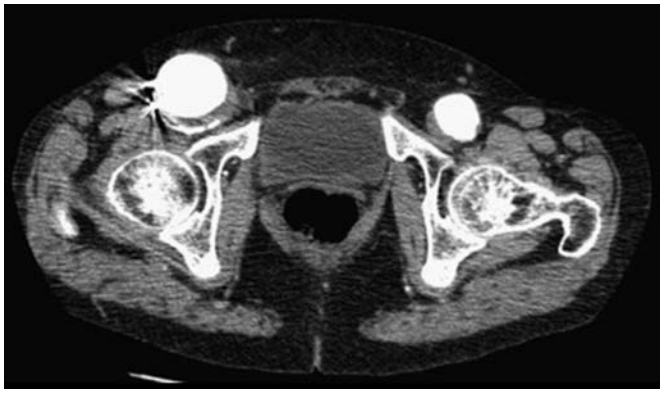


FIG. 8 Bilateral femoral anastomotic pseudoaneurysms. This patient underwent bilateral common femoral endarterectomies and an aortobifemoral bypass for aortoiliac occlusive disease 15 years before presentation. There are no fluid collections or edematous streaks within the tissue surrounding the pseudoaneurysms, which suggests no evidence of infection. On physical examination and laboratory testing, no clinical evidence of infection was found.

Observation can only be recommended for patients with very small PSAs, prohibitive operative risk, or short life expectancy. Operative repair is generally recommended for all groin anastomotic PSAs greater than 3 to 4 cm in diameter. If there is no evidence of infection and a well-incorporated graft, interposition graft replacement of the degenerative aneurysmal portion of the existing graft can be performed safely. If the graft is infected, removal and replacement of all infected graft and tissue is necessary. Revascularization may require extraanatomic bypass grafting through a noninfected field or replacement of the infected conduit with autogenous femoral vein. Grossly infected arterial beds may require coverage with sartorius or rectus femoris muscle flaps. Endovascular repair of femoral artery anastomotic PSAs has been reported; however, it is generally not recommended in the setting of infection or when stenting would result in occlusion of the PFA origin.

ARTERIOVENOUS FISTULA

An AVF is an abnormal communication between an artery and vein. Although AFVs can be congenital, they are more frequently iatrogenic or traumatic. Femoral AVFs almost always develop secondary to penetrating injuries or percutaneous vascular interventions. The incidence of postcatheterization femoral AVF is 0.2% to 2%. Patient-related risk factors include female gender, hypertension, and ongoing anticoagulation. Age and morbid obesity have not been identified as risk factors. Procedural-related risk factors include left-sided groin punctures and high levels of anticoagulation (>12,500 units of periprocedural heparin). Postcatheterization femoral AVFs will be the focus of this section.

Diagnosis

The diagnosis of an AVF in the extremities can be made with history and physical examination. Physical examination may reveal a loud bruit on auscultation and a thrill on palpation. A to-and-fro holosystolic/diastolic bruit at the puncture site is pathognomonic for an AVF, and the intensity of the sound on auscultation typically correlates with the size of the fistula. Large AVFs may also present with unilateral limb swelling, mild to severe limb ischemia (claudication or tissue loss), or heart failure. If physical examination findings are not diagnostic but an AVF is suspected, DUS can be a useful diagnostic tool. AVFs are characterized by high arterial peak systolic velocities proximal to the fistula resulting from low resistance at the fistula site. Reduced arterial flow distal to the fistula is secondary to shunting, and bidirectional or turbulent flow is seen at the fistula site. The venous side of the AVF demonstrates pulsatile flow with elevated peak systolic velocities that result from mixing of arterial and venous flows.

Treatment

Iatrogenic AVFs, unlike traumatic AVFs, may close spontaneously. Studies have shown that 38% to 56% of iatrogenic postcatheterization femoral AVFs resolve spontaneously. Iatrogenic AVFs are more likely to persist in patients with chronic renal insufficiency or concomitant steroid use. Patients with small or low-flow AVFs may never develop symptoms and can be safely managed conservatively. Repair is indicated for all symptomatic patients.

Open Surgical Repair

Surgical repair is the traditional method for treating femoral AVFs and is associated with morbidity and mortality rates of 25% and 8%, respectively. The principle of surgical repair is obliteration of the connection between the artery and vein with restoration of vessel

patency. Proximal and distal control of both the artery and vein is required. Because AVFs can result in significant enlargement of venous structures, operative repair can be associated with significant blood loss. Preoperative placement of arterial or venous balloons for intraoperative occlusion may help decrease blood loss during the repair, and cell-saver and rapid-infusion devices can be used when large volumes of blood loss are anticipated. Repair can be achieved with primary closure of the fistula tract, vein patch angioplasty, or interposition bypass graft.

Endovascular Repair

Endovascular treatment of iatrogenic or traumatic femoral AVFs is becoming more commonplace. Catheter-based interventions are indicated for high-risk surgical patients, or those who present with "hostile" anatomy such as morbid obesity, previous femoral interventions, or prior groin surgery, and those with obvious massive enlargement of venous collaterals. The most common endovascular method of treating AVFs is placement of a covered stent in the arterial system to occlude the connection between artery and vein. Contraindications to endovascular repair include patients in whom endovascular stenting will obliterate the PFA or cross the groin crease. The placement of CFA stents also precludes use of that site for future endovascular access. Venous stents are usually reserved for iliac vein or inferior vena cava AVF occlusion after unsuccessful intraarterial stent placement. SFA stent grafts for iatrogenic femoral AVFs have a reported 1- and 4-year primary patency of 76% and 55%, respectively, and a 4-year secondary patency rate of 80%.

Alternative endovascular methods for treatment of AVFs include embolization with coils, cyanoacrylate glue, collagen or gelatin, and others. During embolization, percutaneous venous access with balloon inflation may be required to occlude the venous outflow if there is a short tract connecting the artery and vein. Using detachable coils and packing smaller coils after larger coils can reduce inaccurate placement. Amplatzer plug occlusion of a femoral PSA with concomitant AVF has also been described.

Suggested Readings

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Management of Peripheral Arterial Thromboembolism

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BACKGROUND/OVERVIEW

Embolus, derived from the Greek word *embolus* or *plug,* refers to intravascular material that originates in one location and travels to a remote site. When an embolus lodges in a distal artery or arteriole, it causes interruption of blood flow to downstream tissue. In the case of the peripheral arteries, this often leads to acute limb ischemia (ALI). A vascular emergency occurring in approximately 1.5 in 10,000 patients per year, ALI can result in severe morbidity and mortality if not diagnosed and managed expeditiously. Acute limb ischemia presents a challenge for the surgeon because of the consequences of potential tissue injury and the associated medical comorbidities inherent to this patient population. Diagnosis of ALI secondary to embolism can often be made by a comprehensive history and physical examination along with selective use of diagnostic imaging studies. The goals of management of peripheral arterial embolism include immediate anticoagulation and expeditious restoration of arterial circulation using open or endovascular techniques as well as identification and appropriate treatment of the embolic source.

CLASSIFICATION, SITE, AND SOURCE OF EMBOLISM

Peripheral arterial embolism can be classified according to the size of the embolus (macro or micro), the site of embolism (extremity, visceral, or cerebral), and the source of embolism (cardiac and noncardiac) (Table 1).

Macroemboli are usually composed of organized thrombus, with the heart being the most common source. Anatomically, arterial emboli to the extremities typically lodge at bifurcations, obstructing flow and resulting in distal ischemia with the lower extremities more often affected than the upper extremities. In the lower extremity, the most common site is the bifurcation of the common femoral artery (CFA), followed by the aortoiliac arterial segment and the popliteal artery. In the upper extremity, the most common location is the brachial artery at the bifurcation of the radial and ulnar arteries, followed by the axillary artery at the origin of the deep brachial artery. Embolism is the most common cause of upper extremity ALI. In the lower extremity, because of the high prevalence of arterial occlusive disease, ALI is most commonly a result of in-situ thrombosis.

Cardiac causes of peripheral embolism account for approximately 80% of all cases. This includes emboli originating in the left atrium of patients with atrial arrhythmias, left ventricular thrombus in the setting of a recent myocardial infarction (MI), prosthetic heart valves, valvular heart disease caused by rheumatic fever or endocarditis, and atrial myxomas. Approximately 0.5% of patients with atrial fibrillation (AF) will experience clinically significant non-cerebrovascular systemic embolic events translating into an incidence of 0.24 per 100 patient-years. Two-thirds of these events affect the extremities, and one-third affect the visceral-mesenteric circulation. Patients with permanent rather than paroxysmal AF and those with AF of longer duration (>2 years) are at highest risk. The use of anticoagulation in this patient population has been associated with a lower incidence of systemic embolic events, with direct oral anticoagulants (DOACs) shown to be at least as effective as vitamin K antagonists. The 30-day mortality after experiencing a systemic embolic event in this patient population is 15% to 25% and has remained relatively unchanged over the past three decades. Additionally, 18% of these patients experience major adverse cardiac events within 1 year of a

TABLE 1 Classification and Frequency of Extremity Arterial Embolism

Classification	Approximate Frequency (%)
SITE OF EMBOLI	
Lower Extremity	**84**
Aortoiliac	25.7
Common femoral	34
Superficial femoral	4.5
Popliteal	14.2
Tibial	5.6
Upper Extremity	**16**
Brachial	9.1
Axillary	4.5
Radial and ulnar	2.4
ORIGIN OF EMBOLI	
Cardiac Source	**80**
Atrial fibrillation	
Mural thrombus	
Ventricular aneurysm	
Rheumatic heart disease	
Valvular prosthesis	
Infectious endocarditis	
Atrial myxoma	
Noncardiac Source	**15**
Iatrogenic	
Ulcerative plaque	
"Shaggy aorta"	
Aortic aneurysm	
Aortic mural thrombus	
Peripheral arterial aneurysm	
Paradoxical embolus	
Foreign body	
Unknown	**5**

lower extremity thromboembolic event. The thromboembolic risk for prosthetic heart valves ranges from 0.6% to 2.3% per patient year, with similar rates among patients with mechanical valves on therapeutic anticoagulation and patients with bioprosthetic valves. Mitral prosthetic valves have a two to three times greater risk compared with prosthetic aortic valves because of differences in flow hemodynamics.

Noncardiac etiologies of peripheral arterial emboli account for 15% to 20% of peripheral arterial emboli. Sources of emboli include arterial aneurysms, most commonly involving the aorta or popliteal artery, atherosclerotic plaques, trauma, thrombosed native arteries or bypass grafts, and paradoxical emboli from a deep venous thrombosis that embolizes into the arterial circulation through an intracardiac septal defect.

In contrast with macroemboli, microemboli are typically composed of platelet aggregates or cholesterol crystals originating from atherosclerotic plaque. They can occur spontaneously as a result of plaque rupture or secondary to plaque disruption caused by arterial instrumentation during a percutaneous endovascular procedure. Embolization of this debris into small arterioles induces an inflammatory response leading to luminal occlusion and focal ischemia without major tissue loss. However, the degree of injury correlates with the aggregate volume of embolus and can be extensive in some cases.

CLINICAL PRESENTATION

Acute ischemia is often characterized by the "six *P*s": pain, pulselessness, poikilothermia, paresthesia, pallor, and paralysis. The clinical presentation may vary depending on location of embolus, duration of occlusion, extent of collateral circulation caused by existing arterial occlusive disease, and underlying etiology.

History and physical examination help differentiate an acute embolic event from a thrombotic occlusion or chronic peripheral arterial disease (PAD). Pertinent history includes prior embolic episodes, recent MI, arrhythmias, valvular heart disease, aneurysmal disease, dissection, prior vascular interventions, and hypercoagulable states. Overall cardiovascular risk factors including hypertension, hyperlipidemia, diabetes, and smoking should be assessed. A critical detail to note is the duration of symptoms, as irreversible muscle and nerve injury starts after 6 to 8 hours of severe acute ischemia.

Acute onset of ischemic pain in a patient without preexisting symptoms of PAD and a normal vascular examination of the nonischemic limb suggests an embolic event. Such patients are often able to pinpoint the exact onset of symptoms, and the degree of limb ischemia is usually severe. A history of AF, prior MI, or valvular disease may be present. In contrast, older patients with a history of claudication, rest pain, or nonhealing ulcers are likely to have preexisting PAD, and symptoms usually reflect in-situ thrombosis of a diseased vessel. In patients with an acute-on-chronic process, the established collateral circulation may limit the magnitude of ischemia. However, it can be difficult to reliably distinguish between embolic and thrombotic causes, especially in older adult patients with risk factors for PAD. Differential diagnosis of ALI also includes acute aortic dissection, aneurysmal disease, iatrogenic trauma, or a hypercoagulable state.

Physical examination is used to determine the severity of acute limb ischemia and level of occlusion, and it aids in determining the most appropriate management. Acute limb ischemia is graded using Rutherford's classification based on the neurologic and vascular examination of the affected limb (Table 2). The affected extremity is visually evaluated for color, livedo reticularis, and cyanotic mottling and felt for changes in temperature while comparing such findings to the contralateral limb. Motor and sensory examination aims to localize areas of decreased or abnormal sensation and muscle weakness or paralysis. In the lower extremity, the deep peroneal nerve in the anterior compartment is most susceptible to ischemia and can manifest with diminished sensation at the first web space and weakness of dorsiflexion. This is often an early sign of severe ischemia. Asymmetric loss of palpable distal pulses and Doppler signals with an accompanying "water-hammer" pulse proximal to level of occlusion, as well as delayed or absent capillary refill may be noted.

Peripheral microembolism typically presents with localized toe or finger pain and is more commonly observed in the lower extremities. Patients with lower extremity microembolization or "blue toe syndrome" develop painful and discolored toes. Depending on the degree of embolization, patients may have palpable pedal pulses. Involvement of the toes on both feet suggest that the culprit lesion is proximal to the aortic bifurcation. Other potential skin manifestations include petechiae, purpura, and splinter hemorrhages. Palpation of the abdomen, popliteal fossa, and groin is important as it may reveal culprit aortic, popliteal, or femoral aneurysms.

DIAGNOSTIC EXAMINATION

Imaging can help elucidate the etiology to identify the responsible ulcerative plaque; exclude dissection, a thrombosed aneurysm, or acute thrombosis of an atherosclerotic vessel; and aid in operative planning. However, imaging should not delay the need for emergent

TABLE 2 Clinical Categories of Acute Limb Ischemia

		Findings		Doppler Signals	
Category	**Description/Prognosis**	**Sensory Loss**	**Muscle Weakness**	**Arterial**	**Venous**
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent neurologic damage	Profound, anesthetic	Profound, paralysis (rigors)	Inaudible	Inaudible

Modified from Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;2(3):517–538.

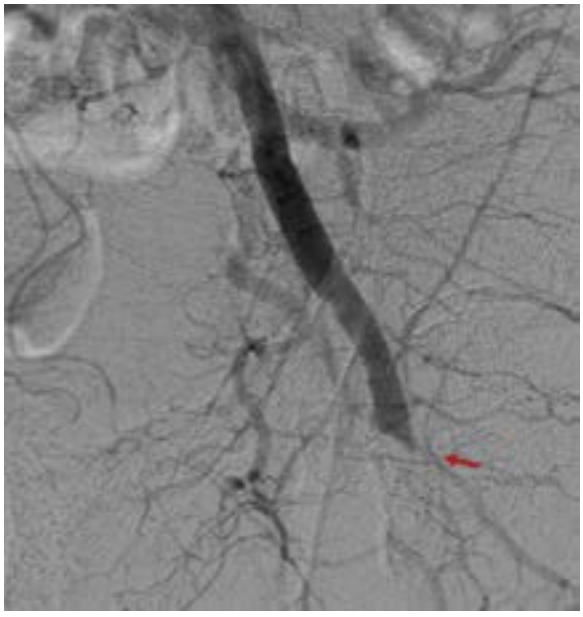


FIG. 1 Angiogram showing an abrupt cutoff of the left common femoral artery consistent with the appearance of an embolus *(arrow)*.

revascularization in patients with profound ischemia given the risk of irreversible muscle and peripheral nerve damage.

Current imaging modalities include duplex ultrasonography (DUS), magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and digital subtraction angiography (DSA). CTA of the chest, abdomen, and pelvis with lower extremity runoffs is preferred as it can be performed expeditiously at most centers. CTA requires a large volume of iodinated contrast, which should be considered in patients presenting with renal insufficiency. In such cases, direct intraoperative assessment with DSA using a limited volume of contrast dye or carbon dioxide may be preferred. The typical angiographic appearance of an acute embolus is that of an abrupt vessel occlusion with a "meniscus" sign and minimal contrast filling distal to the occlusion (Fig. 1).

MANAGEMENT

Initial Medical Management

When peripheral artery embolism is suspected, initial management includes intravenous fluid resuscitation and anticoagulation. Fluids should be isotonic and avoid added potassium until baseline renal function is assessed. In the absence of contraindications to therapeutic anticoagulation, a loading bolus of 80 to 100 U/kg of intravenous heparin should be administered to prevent propagation of the thrombus and maintain patency of collateral vessels. This is followed by a 15–18 U/kg per hour infusion to achieve an activated partial thromboplastin time (aPTT) goal of 60 to 100 seconds. Direct thrombin inhibitors, lepirudin (cleared renally) or argatroban (metabolized by the liver) may be used in patients with intolerance to heparin with a similar aPTT goal. A 12-lead ECG should be obtained to evaluate for arrythmia. Laboratory studies, including a complete blood count, basic metabolic panel, coagulation studies, creatinine phosphokinase (CPK), lactate, and blood bank sample for type and screen should be ordered.

Selection of Approach

The two primary approaches for treatment of ALI caused by peripheral artery thromboembolism are open surgical thromboembolectomy and percutaneous endovascular therapy consisting of catheter-directed thrombolysis (CDT), pharmacomechanical thrombectomy (PMT), or aspiration mechanical thrombectomy (AMT).

A Cochrane meta-analysis of five prospective randomized controlled trials compared catheter-directed thrombolysis using recombinant tissue plasminogen activator (rtPA) or urokinase with surgical embolectomy in patients with ALI. The 1-year death and amputation rates were similar; however, significantly higher rates of stroke (1.3% vs. 0%), major bleeding (8.8% vs. 3.3%), and distal embolization (12.3% vs. 0%) were observed in patients who underwent thrombolysis. Unfortunately, these trials did not include more contemporary methods of PMT. A more recent meta-analysis including 25 studies examining endovascular and surgical revascularization techniques in ALI also concluded that catheter-driven thrombolysis techniques had comparable limb salvage rates to open surgery albeit with a higher risk of hemorrhagic complications. However, conclusions regarding the use of a hybrid approach or comparisons between various endovascular techniques could not be made.

Several factors including severity of ischemia, time to reperfusion, chance of recovery, etiology, location of embolus, procedural risks, comorbid conditions, and cost should be considered when selecting the approach to revascularization in any given patient.

An endovascular approach should be contemplated in patients with a marginally threatened limb (Rutherford I and IIa), those at medically high-risk for open surgery, and in the setting of a thrombotic occlusion. Patients with distal emboli, as observed in patients with a normal femoral pulse but absent distal pulses, may benefit from an initial angiogram and CDT/mechanical thrombectomy. This strategy may be more effective in establishing reperfusion of

smaller distal vessels as well as elucidating concomitant atherosclerotic lesions that may be treated endovascularly. In the case of thromboembolism associated with a popliteal artery aneurysm, establishment of distal peripheral circulation using thrombolysis is the recommended strategy in the absence of immediate limb threat. The disadvantage of CDT is the relatively longer period required to achieve tissue reperfusion and the risk of potential bleeding complications. Percutaneous mechanical thrombectomy techniques were introduced to address these shortcomings, decreasing the need for prolonged infusion times and reducing the need for multiple procedures required for successful thrombolysis. Absolute contraindications to pharmacologic thrombolysis include active bleeding, stroke or neurosurgical procedure within 3 months, malignant intracranial neoplasm, history of hemorrhagic stroke, or recent gastrointestinal bleed. Relative contraindications include severe hypertension, central nervous system tumors or known intracranial pathology, trauma, and major surgery within 3 weeks.

Open embolectomy is preferred in patients with an immediately threatened limb (Rutherford IIb) because of the ease and speed of establishing reperfusion and in patients with a contraindication to fibrinolytic therapy. Ideally these cases are performed in a hybrid operating room that allows for use of adjunctive endovascular techniques and completion angiography. An open femoral embolectomy is indicated in patients with an absent or water hammer ipsilateral femoral pulse and normal contralateral femoral pulse, while the absence of both femoral pulses suggests an aortic thrombus requiring bilateral femoral embolectomies. Upper extremity emboli are most often managed with an open approach because of small vessel size, ease and speed to reperfusion, and few complications.

In patients with irreversible ischemia (Rutherford III) with complete loss of motor and sensory function, inaudible arterial and venous Doppler signals, and the presence of livedo reticularis, revascularization may cause life-threatening physiologic changes with little chance of functional limb salvage. A primary amputation in this setting is preferable to avoid multiple organ failure and death.

Open Surgical Technique

The balloon embolectomy catheter, introduced by Thomas J. Fogarty and colleagues in 1963, remains the primary open surgical technique in the treatment of acute peripheral arterial embolism. The Fogarty embolectomy catheter allows for thromboembolic material to be extracted distal and proximal to the arteriotomy site.

The choice of arteriotomy depends on several factors, including anticipated location of emboli, convenience of vascular exposure, and the ease of arteriotomy closure. For iliac, femoral, and popliteal emboli, the CFA is the access of choice because of ease of exposure and relatively large diameter. Bilateral CFA access is required for embolectomy of an embolus at the aortic bifurcation. A popliteal or tibial thrombus can be approached using the below-knee popliteal artery. The distal brachial artery, at its bifurcation, is usually accessed during upper extremity embolectomy. Smaller arteries, at the ankle or wrist, can also be accessed in selected cases.

Open surgical exposure is performed with proximal and distal control obtained using vessel loops. Systemic heparin is administered. An arteriotomy is created at the arterial bifurcation to allow intraluminal access to branch vessels. The decision to perform a transverse or longitudinal arteriotomy depends on the quality of the artery, extent of arterial occlusive disease, and possible need to use the arteriotomy for inflow of a distal bypass graft. A transverse arteriotomy is used when the artery is relatively normal, whereas a longitudinal arteriotomy is preferred if the artery is diseased and further access to the artery is needed for endarterectomy or bypass.

The balloon-tipped catheter is introduced through the arteriotomy and advanced beyond the embolus. Inflation of the balloon is performed during slow withdrawal of the catheter and leads to concomitant clearance of the occlusive material (Fig. 2). Care must be taken with this technique as there is potential for inducing further arterial trauma. Although saline is used to fill the balloon by some, we believe that use of air allows for better sense of the appropriate amount of tension between the inflated balloon and the intimal surface of the artery. Inflation of the balloon should only occur as the catheter is moved to gain a sense of when enough air fills the balloon to result in some resistance between the balloon and the arterial wall. The presence of atherosclerotic disease may result in increased resistance to withdrawal, in which case the balloon should be partially deflated to prevent injury to the diseased vessel. Overdistention of the balloon or passage into a branch vessel may result in arterial dissection or rupture. The embolectomy catheter is used to clear the vessel proximal and distal to the arteriotomy until at least two passes result in no further withdrawal of embolic material. Adequate proximal inflow and distal back bleeding suggest a successful result but do not confirm complete thrombus retrieval. Pathologic analysis of the embolus should be considered in cases of unclear etiology to evaluate for tumor thrombus, myxoma, or an infectious source.

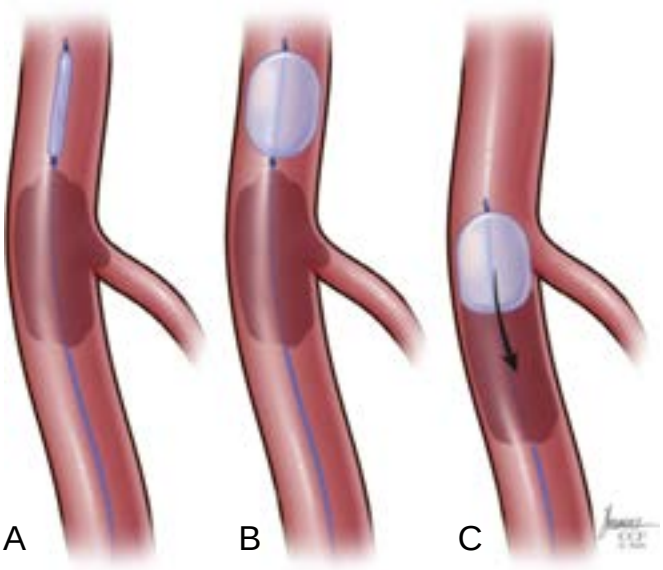


FIG. 2 Balloon thromboembolectomy technique. **(A)** The balloon-tipped catheter is introduced via arteriotomy and passed through the embolus beyond the occlusion. **(B)** The balloon is inflated while slowly withdrawing the catheter to prevent damage to the arterial wall. **(C)** The inflated balloon catheter is withdrawn to clear the thromboembolic material.
(From Seegmiller CJ, Cogbill TH. Management of peripheral arterial thromboembolism. In Cameron JL, Cameron AM, eds. Current Surgical Therapy. *13th ed. Philadelphia: Elsevier: 2020:1016.)*

The arteriotomy is closed and the affected limb examined for evidence of restored perfusion. A transverse arteriotomy is closed primarily, while a longitudinal arteriotomy usually requires closure using a patch to avoid creation of a stenosis. Intraoperative angiography should be performed if the limb remains inadequately perfused and there is need to delineate arterial anatomy to locate residual thrombus or identify a potential bypass target. Residual thrombus may be treated with 2 to 4 mg of recombinant rtPA flushed into the distal arterial bed. In the event of vasospasm of the distal arteries, intra-arterial vasodilators such as papaverine or nitroglycerin can be administered. If revascularization is inadequate and a suitable distal target vessel is present, open surgical bypass may be indicated. In the absence of a distal bypass target, anticoagulation should be continued and the extremity observed to determine the level of amputation required.

Arterial thromboembolectomy is associated with high morbidity and has an operative mortality approaching 30%. This underscores the critically ill nature of patients with acute limb ischemia and the

importance of an experienced anesthesia provider. Consideration should be given to performing brachial and femoral embolectomies under local anesthesia; however, more difficult technical approaches and those requiring correction of underlying atherosclerotic disease will likely require general anesthesia.

Aortic and Lower Extremity Embolectomy

An embolus at the aortic bifurcation should be approached with bilateral femoral artery exposures. The common, superficial, and deep femoral arteries should be identified and controlled. After systemic heparinization, arteriotomies are created in the distal CFA and a 5Fr or 6Fr embolectomy catheter is passed cranially, approximately 25 cm into the infrarenal aorta. The contralateral femoral artery should be occluded during each passage of the embolectomy catheter to minimize inadvertent embolization from the aorta down the opposite limb. After inflow is established, distal embolectomy of the superficial femoral and popliteal arteries is performed with a 3Fr or 4Fr catheter, and embolectomy of the deep femoral artery (DFA) is performed with a 3Fr catheter. Care must be taken not to advance the embolectomy catheter farther than 20 mm into the DFA to prevent injury to its smaller branches. An embolus to the CFA is approached in a similar fashion.

Emboli to the tibial vessels can be challenging to treat**.** When the embolectomy catheter is inserted through the superficial femoral artery, it usually takes a straight path into the peroneal artery. Insertion of the catheter into other tibial vessels can be facilitated by bending the catheter tip. If blind insertion is unsuccessful, over-the-wire Fogarty catheters are a modification to the original device and allow selective passage into target vessels under fluoroscopic guidance. If unsuccessful reestablishing distal flow, an open exposure of the below-knee popliteal artery is performed through a medial lower-leg incision. Control of the popliteal artery proximally and the anterior tibial, posterior tibial, and peroneal arteries distally is obtained. Because of the smaller vessel size, a longitudinal arteriotomy is created over the origin of the anterior tibial artery with plan for patch closure. A 2Fr embolectomy catheter is then advanced distally. Retrograde embolectomy via cutdown on the dorsalis pedis or posterior tibial arteries at the ankle is performed when other maneuvers do not allow adequate thrombectomy of the distal tibial arteries.

Brachial Embolectomy

The distal brachial artery is exposed through a longitudinal incision proximal to the elbow and may be extended across the antecubital fossa in an S-shaped incision to expose the proximal radial and ulnar arteries. After proximal and distal control is obtained, a transverse arteriotomy is created over the brachial bifurcation and a 3Fr or 4Fr embolectomy catheter is passed proximally into the subclavian artery. Inadvertent embolization to the cerebral circulation may occur if the catheter is passed into the aortic arch. Measuring the catheter externally against the patient's chest and arm can help estimate distance and prevent passage proximal to the subclavian artery origin. Distally, a 2Fr embolectomy catheter is passed into radial and ulnar arteries. Forearm artery exposure at the wrist may be required.

Percutaneous Endovascular Techniques

Catheter Directed Thrombolysis

Ultrasound guidance to the contralateral femoral artery is obtained, and a diagnostic angiogram is performed to guide further therapy. In addition to providing a more complete evaluation of the arterial inflow, obtaining access remote from the embolus decreases the risk of bleeding complications because of the proximity of the puncture site to the delivery of the thrombolytic agent. After the occlusion is identified on arteriography, a sheath of appropriate length is inserted and a hydrophilic coated angled guidewire is passed through the occlusion. If the guidewire is unable to cross the thromboembolus, this may represent acute thrombosis of a preexisting atherosclerotic plaque. Once the occlusion is crossed, a multi sidehole catheter is advanced over the wire and positioned across the clot. A bolus of thrombolytic, most commonly 10 mg of rtPA is delivered, followed by initiation of a continuous infusion through the catheter at 0.5–1 mg/hour. The sheath is secured in place, and a continuous heparin infusion at a constant rate of 500 U/hour is administered through the side port to prevent catheter-associated thrombosis. The patient is admitted to the intensive care unit for close neurovascular monitoring as well as monitoring of the access site. Laboratory tests, including aPTT and fibrinogen, should be checked every 4 to 8 hours to monitor for systemic thrombolysis. The tPA infusion is held if the fibrinogen level drops below 100 mg/dL or more than 50% from baseline. Reimaging is performed in 12 to 24 hours after initiation of lysis to assess for resolution.

Pharmacomechanical Thrombectomy

Under ideal circumstances, percutaneous mechanical thrombectomy expeditiously reduces overall clot burden and increases the surface area of exposed clot to enable more effective pharmacologic lysis. Various devices have been designed to use suction, rotational infusion, ultrasound, or a high-velocity rheolytic jet to achieve mechanical thrombectomy. Pharmacomechanical thrombolysis uses the percutaneous device to first lace the thrombus with a bolus of thrombolytic, typically 10 mg of rtPA. After a dwell time of 20 minutes, mechanical thrombectomy is performed. The AngioJet Thrombectomy System (Boston Scientific, Marlborough, MA) is a rheolytic device that works on the premise of Bernoulli's principle. Circumferentially oriented pressurized saline jets fragment the thrombus with creation of a low-pressure zone, which facilitates the removal of the resultant thrombotic debris through catheter side holes. In a large multicenter registry, successful outcome, defined as completion of the procedure without need for revascularization, bypass, or amputation and absence of substantial or complete occlusion in any vessel, was achieved in 83% of patients. More than one-half of the patients (52%) did not require adjunctive catheter-directed thrombolysis.

Aspiration Mechanical Thrombectomy

Another option for removal of fresh thromboembolic material without the need for use of fibrinolytics is the Indigo continuous AMT system (Penumbra Inc, Alameda, CA). This technology, available in the United States since 2008 for cerebral revascularization in acute ischemic stroke, utilizes a catheter delivered over a wire to the site of occlusion, through which continuous vacuum suction is applied to extract the thrombus.

Compartment Syndrome

Despite successful revascularization, limb loss may occur from development of acute compartment syndrome as previously ischemic tissue swells within the confined fascial space of the calf or forearm (Fig. 3). The more severe the ischemia, the more likely a reperfusion compartment syndrome is to develop. In patients with a history of prolonged ischemia (>6 hours) and those with limb edema observed after reperfusion, prophylactic fasciotomies are recommended. Four compartment fasciotomies of the lower leg are performed through medial and lateral incisions (Fig. 4). Upper extremity ischemia is often less severe because of collateral circulation; however, fasciotomies to release the volar and dorsal forearm compartments may be required (Fig. 5). If tissue swelling extends to the hand, consultation with a hand surgeon is recommended for additional carpal tunnel release and hand fasciotomies. Fasciotomy wounds are left open, and a vacuum-assisted closure device is applied in the postoperative period to decrease muscle edema. Incomplete skin release and attempts at early closure must be avoided as they may lead to muscle necrosis.

Patients who have not undergone fasciotomy are followed closely with serial examinations, and compartment syndrome is suspected in those who develop a tense swollen extremity with pain on passive

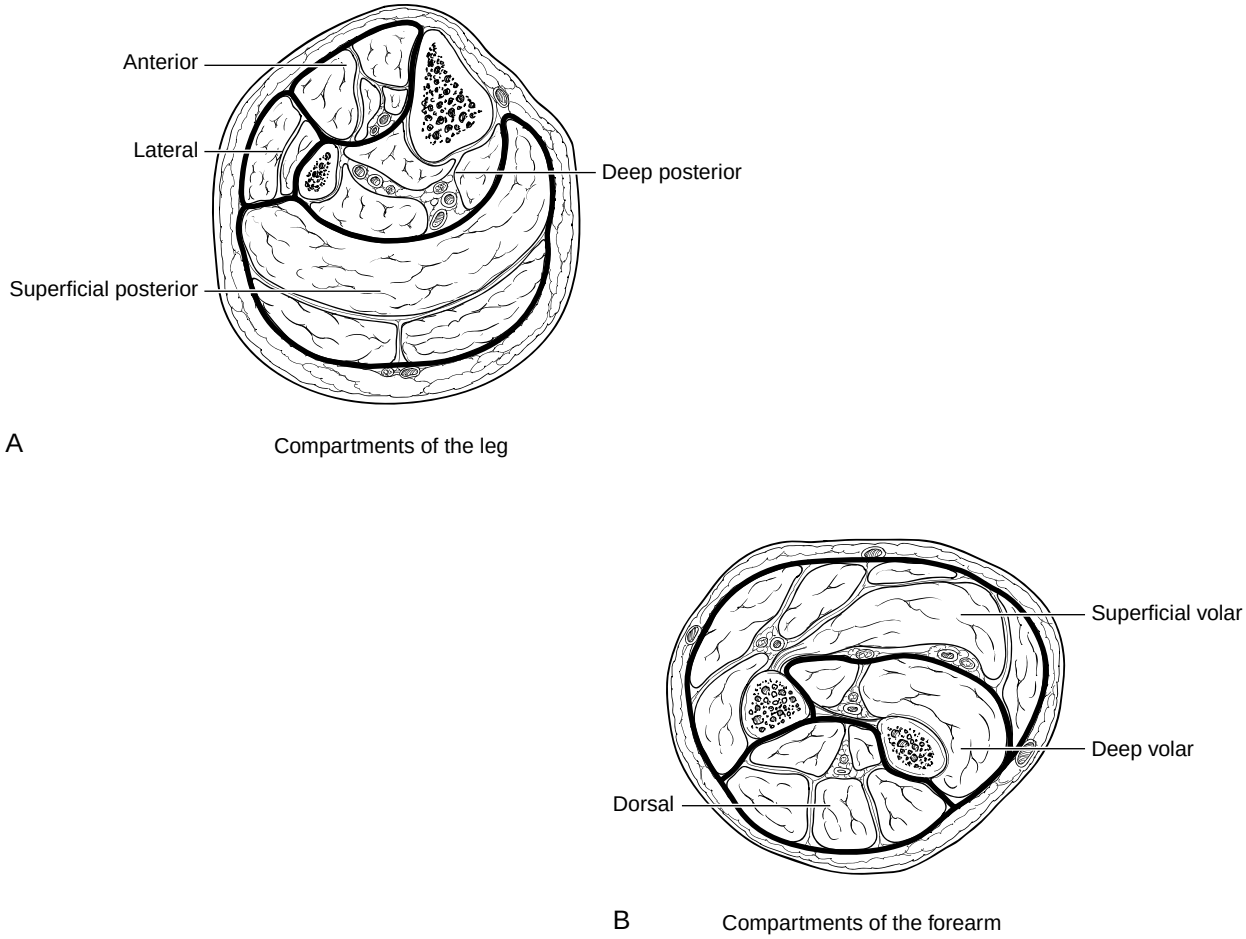


FIG. 3 Compartments of the calf **(A)** and forearm **(B)**. *(From Rasmussen TE, White JM. Upper and lower extremity fasciotomy. In: Chaikof EL, Cambria RP.* Atlas of Vascular Surgery and Endovascular Therapy. *Philadelphia: Elsevier: 2014:619–623.)*

motion; weakness; or decreased sensation. In sedated, neurologically impaired or uncooperative patients who cannot be followed with serial examinations, direct compartment pressures can be measured. Fasciotomy should be performed if compartment pressures are elevated (>30 mm Hg), the difference between the diastolic pressure and compartment pressure is <10 mm Hg, or if there is high clinical suspicion despite normal compartment pressures. Delay in diagnosis and management of compartment syndrome has devastating consequences and can lead to both limb loss and mortality. Elevated CPK levels and myoglobinuria are late markers of tissue destruction and should not be used to establish the diagnosis of compartment syndrome.

Postoperative Management

Hemodynamic monitoring, routine laboratory analysis with correction of acidosis and electrolyte imbalance resulting from intracellular potassium leak and hydrogen ion release, and serial neurovascular examinations are necessary. Urine output should be trended as a systemic effect of muscle ischemia is rhabdomyolysis, which may cause acute tubular necrosis and renal failure. Aggressive resuscitation with intravenous fluids is the main treatment modality, titrating to urine output >100 cc/hour until the CPK is <5000 U/L. Urine alkalinization with bicarbonate may also be required in patients with significant tissue damage and increasing CPK.

After successful thromboembolectomy, patients should be anticoagulated with heparin and converted to Coumadin or a DOAC as the risk of recurrent peripheral arterial embolism approaches 30%. Patients are maintained on lifelong anticoagulation in the setting of cardiogenic embolism and if the source of embolism is not surgically correctable or cannot be identified.

Patients with microembolism caused by atherosclerotic plaque rupture benefit from antiplatelet agents and statin therapy, which are purported to "stabilize" ulcerative plaque**.** Additionally, there is evidence that nonsteroidal antiinflammatory drugs reduce the local inflammation associated with microemboli.

Once the acute ischemic episode and its sequelae have been managed, the underlying embolic etiology should be investigated. Electrocardiography is performed to identify cardiac dysrhythmias, ischemia, or prior MI. Echocardiography is used to evaluate the heart when a cardiogenic embolism is suspected. Transthoracic echocardiography (TTE) is noninvasive and is performed first. An enlarged atrium, wall motion abnormality, intracardiac thrombus, vegetation, or tumors may be identified. Transesophageal echocardiography (TEE) is more sensitive and should be ordered if the TTE is negative yet suspicion for a cardiac source is high. A TEE with bubble study can identify a patent foramen ovale and lead to the diagnosis of paradoxical embolism. CTA including the chest, abdomen, and pelvis is performed to evaluate for aortic atheroma or aneurysm. Lower extremity runoff is included if the source is thought to arise from a more distal vessel. Bilateral lower extremity DUS for deep vein thrombosis should be performed if a paradoxical embolus is suspected. A hypercoagulable workup may be indicated in patients suspected of having a hypercoagulable state.

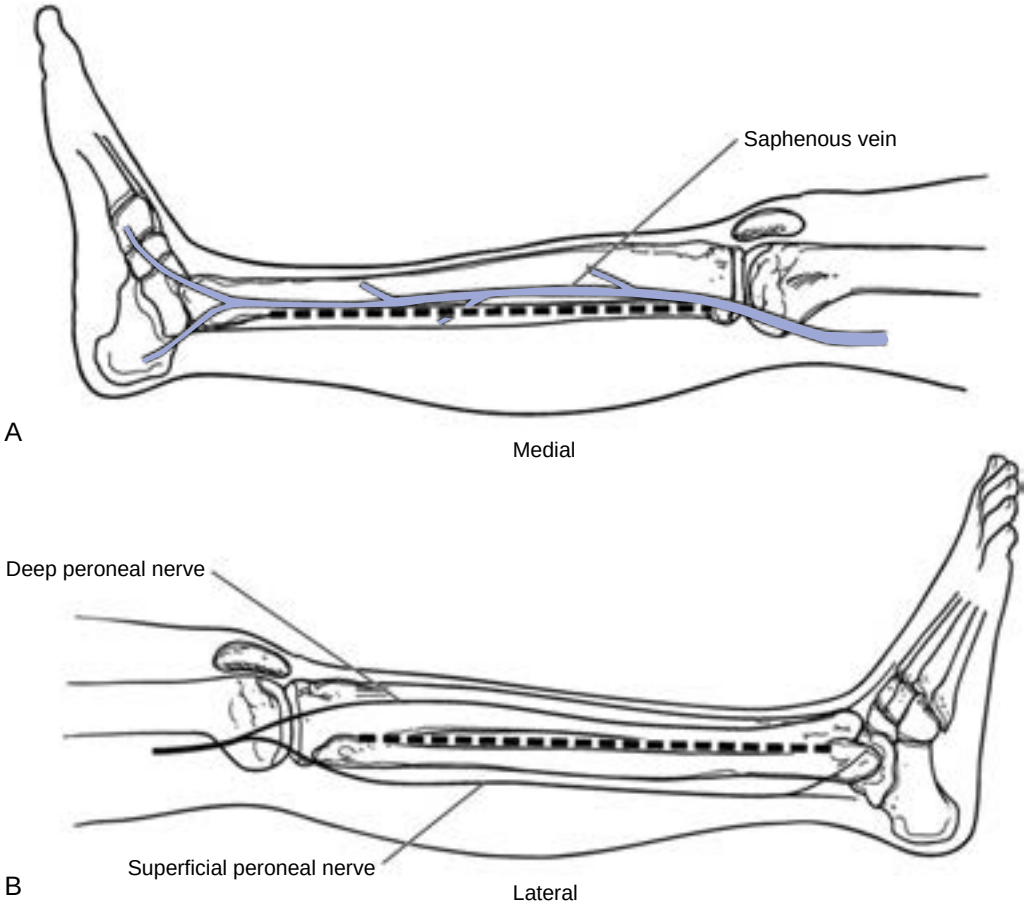


FIG. 4 Lower extremity fasciotomy. **(A)** Both posterior compartments are released through a medial incision 2 to 3 cm posterior to the medial border of the tibia. The fascia of the superficial posterior compartment is incised, and the soleus muscle attachments to the tibia and interosseous membrane are divided to release the deep posterior compartment. **(B)** The anterior and lateral compartments are exposed through a longitudinal skin positioned between the anterior crest of the tibia and the fibula. Parallel incisions are used to release the fascia of the anterior and lateral compartments, which are separated by the intermuscular septum. Care is taken to avoid injury to the superficial peroneal nerve. *(Modified from Rasmussen TE, White JM. Upper and lower extremity fasciotomy. In Chaikof EL, Cambria RP.* Atlas of Vascular Surgery and Endovascular Therapy. *Philadelphia: Elsevier: 2014:619–623.)*

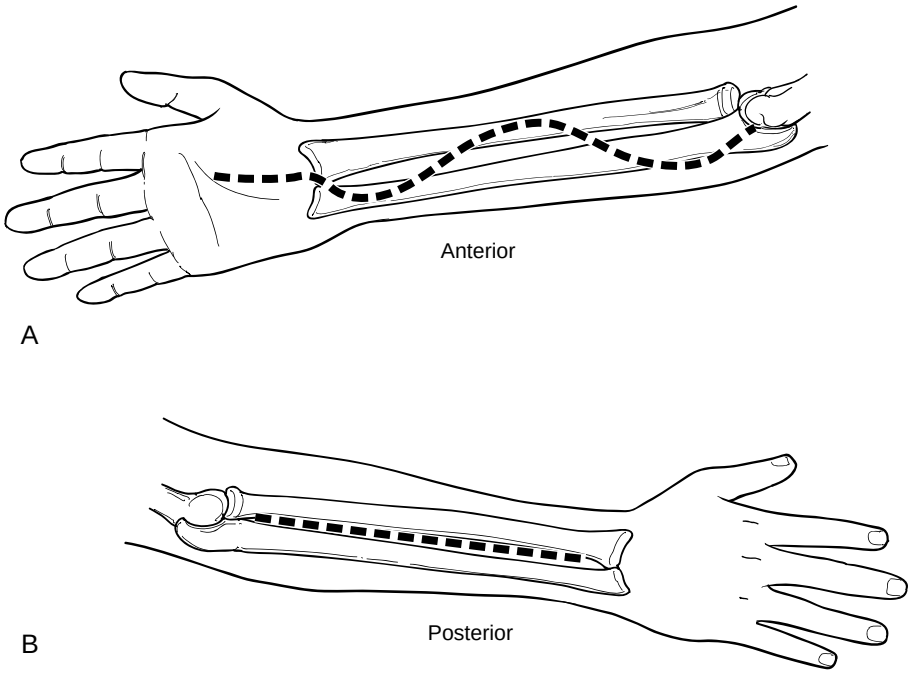


FIG. 5 Forearm fasciotomy. **(A)** Fasciotomy of the upper extremity begins medially in the arm and becomes sinusoidal from medial to lateral at the antecubital fossa, incorporating the bicipital aponeurosis. The incision must extend sufficiently lateral to open the fascia over the mobile wad. The fascia of the deep compartment is incised between the flexor carpi ulnaris and flexor digitorum superficialis, retracting the ulnar nerve and artery laterally. **(B)** The extensor compartment is released through a longitudinal incision from the lateral epicondyle extending to the distal one-third of the posterior forearm. *(Modified from Rasmussen TE, White JM. Upper and lower extremity fasciotomy. In Chaikof EL, Cambria RP.* Atlas of Vascular Surgery and Endovascular Therapy. *Philadelphia: Elsevier: 2014:619–623.)*

If a discrete noncardiogenic source is identified, it is treated if the risk of the procedure is acceptable. Stent-grafts can be used in the thoracic and abdominal aorta to address both aneurysms and ulcerative plaque responsible for embolization. Aortobifemoral bypass and infra-inguinal bypass can also be utilized. Atherosclerotic lesions in the aortic arch are difficult to treat and therefore tend to be managed conservatively.

CONCLUSION

Patients with acute peripheral arterial thromboembolism are usually elderly with multiple associated medical comorbidities. Expeditious diagnosis and treatment are of utmost importance in reducing severe morbidity and mortality. Management of these patients is challenging, and operative mortality with open embolectomy is reported to be between 20% and 30%. Limb salvage for survivors, however, is excellent, with rates approaching 80%. In patients with in-situ thrombosis, limb salvage rates tend to be significantly lower. Depending on the source, recurrent emboli can occur in up to 20% to 30% of patients despite appropriate anticoagulation.

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Acute Peripheral Arterial and Bypass Graft Occlusion: Thrombolysis and Thrombectomy

Gray R. Lyons, MD, and Robert P. Liddell, MD

BACKGROUND

Acute limb ischemia (ALI) is a vascular emergency caused by sudden occlusion of native arteries or bypass grafts. Timely management of ALI requires expedited clinical evaluation, diagnostic workup, and initiation of appropriate treatment. In addition to open surgical options, endovascular therapies include catheter-directed thrombolysis (CDT) and mechanical thrombectomy. Patients with severe ALI require immediate revascularization, whether by surgical or endovascular thrombectomy. Patients with less severe disease and no contraindication to thrombolytic infusion may be candidates for CDT. The relative risks and merits of each approach should be considered in the clinical context based on patient presentation and available resources. This chapter describes how to select the appropriate therapy for ALI, with an emphasis on the role of endovascular techniques.

INDICATIONS

Clinical Assessment

The clinical assessment of a patient with ALI should begin with a thorough history, focusing on the patient's presenting symptoms and current overall health. A history of rest pain, claudication, myocardial infarction, stroke, hypertension, diabetes mellitus, atrial fibrillation, aneurysmal disease, smoking, high cholesterol, vasculitis, and prior vascular or endovascular surgery is important to obtain. The initial physical examination should assess for the dominant clinical signs and symptoms of ALI, which traditionally include the "six "*Ps*": pain, pulselessness, poikilothermia, paresthesia, pallor, and paralysis. The presence of one or more of these findings and the abruptness of their onset may also aid in determining the underlying etiology. New or asymmetric neurologic deficits suggest an advanced state of ischemia, with sensory deficits preceding motor deficits. Fixed mottling of the skin with muscle necrosis and induration implies irreversible limb ischemia.

A formal stratification system, developed by Rutherford, helps guide the evaluation and management of ALI while defining prognosis (Table 1). Acutely ischemic limbs are described as *viable, threatened,* or *irreversibly ischemic*. Viable limbs are not immediately threatened and do not exhibit loss of sensory or motor function. Threatened limbs demonstrate mild to moderate sensory deficits, sometimes with associated motor deficits, and are salvageable with appropriate, timely intervention. Irreversibly ischemic limbs with profound neuromuscular deficits cannot be salvaged with revascularization and ultimately require amputation. Therefore, the minimum necessary components of the physical examination include assessment of limb sensory and motor function to triage the patient to the appropriate treatment category.

The presentation of ischemia is determined by a number of factors, including the etiology of the obstruction, level of obstruction, adequacy of collateral circulation, extent of thrombus propagation, underlying peripheral vascular disease, and cardiac output. Although variable based on the network of existing collaterals, a period of 6 hours is generally accepted as the window in which revascularization is absolutely necessary for ALI. However in practice, the degree of ischemia is more important than the absolute duration of ischemia; therefore patients must be assessed on an individual basis and in a timely fashion.

IMAGING ASSESSMENT

Imaging is done to evaluate the extent of blood flow compromise, localize culprit flow-limiting lesions, and identify other sequelae of peripheral vascular disease (dissection, aneurysmal disease, thrombus, vasculitis). An acutely ischemic limb may be imaged with Doppler ultrasound (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA) before treatment. When choosing an imaging modality for native vessel disease, clinicians should take into account whether the patient has underlying renal insufficiency, diabetes, or implanted metal devices. For patients who have normal renal function and are not diabetic, initial evaluation with either CTA or MRA is reasonable based on their similar excellent diagnostic capabilities. DUS imaging is more operator dependent than cross-sectional imaging but has the advantages of a noncontrast technique, dynamic

TABLE 1 Clinical Categories of Acute Limb Ischemia

		Findings		Doppler Signals	
Category	**Description/Prognosis**	**Sensory Loss**	**Muscle Weakness**	**Arterial**	**Venous**
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent neurologic damage	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Modified from Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;2:517–538.

assessment, and radiation-free imaging. DUS can be augmented with concurrent noninvasive physiologic testing, including segmental blood pressure and pulse volume recordings.

DSA provides the most anatomically detailed imaging of the vascular system. The chief benefit of DSA is that endovascular therapies may be initiated in the same setting as diagnostic angiography, as arterial access is already achieved. Although DSA is a more invasive technique when compared with MRA and CTA, the risks associated with arterial access are minimal.

SELECTION OF THERAPY

Once the diagnosis of ALI is made, treatment should be initiated as soon as possible with the goal of reperfusion of the ischemic limb. Regardless of the etiology, all patients without contraindications receive IV fluids, supplemental oxygen, an 81-mg dose of aspirin, and a 100 U/kg bolus of IV heparin followed by a continuous infusion titrated to a partial thromboplastin time of 2.0 to 2.5 times control. Patients with viable, nonthreatened limbs (Rutherford class I) are treated with heparin and observation, followed by more definite therapy once comorbidities, functional status, and activity level are determined. Patients with threatened limbs can benefit from revascularization, and the immediacy of treatment is dictated by the degree of threat: marginal (class IIa) or immediate (class IIb). The selection of therapy type is based on provider experience and resources as well as patient clinical and anatomic factors. Limbs that are revascularized late in the progression of disease may require fasciotomy of affected compartments to prevent further tissue loss, and these patients risk hyperkalemia, myoglobinemia, acute kidney injury, and sepsis. Revascularization should not be attempted in patients with cadaveric limbs (class III) because of the futility of the treatment and the potential for life-threatening complications.

Recommended Interventions for Disease in Native Arteries

Catheter-directed thrombolysis was first described by Charles Dotter in 1974. When compared with high-dose systemic intravenous thrombolysis, CDT resulted in significantly more favorable outcomes with fewer adverse bleeding events. A number of randomized multicenter trials have been conducted to compare CDT with surgery for ALI. The Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial showed that CDT produces outcomes similar to surgery when used to treat thrombosed native arteries presenting within 2 weeks of the onset of symptoms. In patients presenting greater than 2 weeks from the onset of symptoms, surgery showed more favorable outcomes. The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial showed that CDT may be attempted and then abandoned when unsuccessful in favor of more localized surgery, without increasing mortality or amputation rate. A number of retrospective studies have also demonstrated that performing CDT and angioplasty before attempting surgery can reduce the number of patients who will ultimately require surgical bypass or amputation. Although these studies do not provide definitive answers to a preferred treatment in all cases, they do suggest that CDT may improve outcomes without compromising the efficacy of subsequent surgery. Therefore, if readily available, CDT should be the first-line therapy for acute native artery occlusion, with endovascular or surgical intervention to treat underlying disease once unmasked.

Before initiating CDT, one should assess the extent of disease in the affected limb, not only the thrombosed segment, but also in the vasculature proximal and distal to the occlusion. The assessment of distal runoff is sometimes hindered by the fact that outflow distal to an occlusion is often significantly limited. If prior studies are available, their review is often helpful in identifying possible causative underlying stenoses as well as defining distal runoff. If prior studies are not available, it is important to attempt to cross the occlusion and directly assess distal runoff without causing distal embolization. According to the TransAtlantic Inter-Society Consensus (TASC II) guidelines on management of peripheral vascular disease, focal stenoses are best treated with percutaneous balloon angioplasty (PTA) and/or stenting once the native artery is opened with CDT. In contrast, long-segment stenosis, diffuse disease, or limited runoff from the affected vessel should dissuade one from initiating CDT. In diffusely diseased vessels, thrombolysis serves to only consume time while exposing the patient to potential bleeding complications; therefore these patients often will be triaged directly to surgical bypass.

In patients with native vessel occlusions caused by embolic disease, lack of well-developed collaterals often results in dramatic, poorly tolerated symptoms very early in the course of ischemia. When initial assessments suggest minimal baseline atherosclerotic disease or when history points to an embolic occlusion, these patients should undergo surgical embolectomy. CDT in combination with mechanical embolectomy is also an option. These endovascular techniques are especially efficacious below the knee, where angiographic guidance allows for evaluation and selective interventions in small arteries.

Recommended Interventions for Disease in Bypass Grafts

The STILE trial demonstrated lower amputation rates with CDT compared with surgery for thrombotic occlusions of bypass grafts. In patients with thrombosed bypass grafts, timing of the graft failure determines the appropriate treatment. If the patient presents within

the first 30 days after bypass, graft failure is most often a result of technical problems with the graft. If the bypass is partially open, imaging usually reveals the causative lesion; the most common finding is a distal anastomosis stenosis. Possible etiologies specific to native vessel conduits include an undersized venous conduit or perivascular hematoma resulting from improper vein preparation. Patients with early bypass failure typically undergo surgical revision. An endovascular approach is only recommended in the case of an isolated angiographic lesion that appears amenable to PTA. More often, thrombolysis alone serves only to open the bypass temporarily. The underlying causative lesion quickly reasserts itself, and thrombosis recurs.

If the bypass becomes occluded beyond the 30-day perioperative period, one should first consider the severity of the ischemia and the indications for the original surgery. If the ischemia does not threaten the viability of the limb, as it did in 30% of the patients in the STILE trial, and the original bypass was performed to treat life-threatening ischemia, a watch-and-wait approach may be warranted. It is unlikely that any revision of the graft will provide long-term improvement in limb perfusion, but it is possible that further surgery could make things worse. In these cases, noninvasive imaging and DSA are appropriate to assess whether distal target vessels are available for a secondary bypass and whether endovascular treatments could improve outflow from the poorly functioning bypass.

In cases of life-threatening ischemia occurring beyond the 30-day perioperative window, the most common causative lesion is focal intimal hyperplasia, typically at a valve or anastomosis. CDT is the treatment of choice in these instances as it allows for identification of the treatable lesion. CDT also restores flow through the thrombosed collaterals, thus reperfusing the threatened limb. Thrombolysis should be followed by PTA once the focal lesion is identified. If a causative lesion can be identified and treated, the 1-year patency is more favorable than if there had been no lesion. Grafts maintained exclusively by CDT and PTA have been found to have excellent long-term patency rates, especially if ABIs immediately after treatment are high. There are however two caveats: first, the outcomes of thrombolysis are generally more favorable in venous grafts compared with synthetic grafts; second, the 1-year patency of CDT in diabetic patients is significantly lower compared with nondiabetic patients. In these patients, if imaging reveals a suitable distal target vessel, secondary bypass is a superior treatment choice because of its higher patency rates.

Patients with vein grafts more than 1 year old are excellent candidates for CDT. Failure is usually a result of progressive atherosclerotic disease in the inflow or outflow vessels. CDT will often unmask a normal-appearing graft with poor inflow or outflow vessels, which themselves can be treated via endovascular means to maintain graft function.

Techniques

Catheter-Directed Thrombolysis

The role of CDT is to (1) restore flow, (2) reveal an underlying causative lesion, and (3) improve perfusion of the outflow vessels.

Preoperative Planning

If CDT will be utilized as part of the ischemic limb treatment plan, the preprocedural consent should describe the risk of hemorrhage, limb loss, renal failure, anaphylaxis, stroke, and death. Bleeding is the most frequent significant complication associated with CDT. Intracranial hemorrhage can often be devastating but is fortunately rare, having been reported in 1.2% (STILE) to 2.1% (TOPAS-1) of patients undergoing CDT. Absolute contraindications to CDT include active/life-threatening bleeding, aortic dissection, recent intracranial or intraspinal surgery or trauma, and intracranial arteriovenous malformations or aneurysms. Relative contraindications include surgery within the previous 4 weeks, uncontrolled hypertension, gastric ulcers, recent stroke, pregnancy or recently postpartum, and intracranial neoplasms.

Technique

CDT is initiated in an angiography suite or operating room with fluoroscopic imaging available. Operators should use appropriate radiation safety precautions. Iso- or low-osmolar contrast should be used throughout. A pre-procedure pulse examination should be performed and documented in both limbs. The procedure is typically performed under conscious sedation.

Retrograde contralateral access is obtained with arterial puncture of the common femoral artery over the femoral head. Ultrasound-guided 21-gauge micropuncture access is recommended as a failed puncture is less traumatic to the vessel and less likely to result in pseudoaneurysm than with 18-gauge single-wall access. A 5F vascular sheath is placed, a 5F flush catheter is advanced over the infrarenal aorta, and DSA is performed.

Once the thrombosed vascular segment is identified, the wire-catheter combination should be advanced over the iliac bifurcation to the levels of the contralateral (affected side) external iliac artery. After a wire is placed in the contralateral external iliac artery, the access catheter and vascular sheath are exchanged for a 6F to 7F, 40- to 45-cm sheath such as a Balkin (Cook Medical, Bloomington, IN) or Destination (Terumo, Somerset NJ) into the contralateral external iliac artery.

The thrombosed segment is then traversed with a wire and catheter of operator preference. We prefer a combination of a 4F or 5F Glide catheter (e.g., cobra or angle taper [Terumo, Somerset, NJ]) and a 0.035-inch hydrophilic guidewire (e.g., Glidewire [Terumo] or Roadrunner [Cook Medical]). This combination imparts excellent maneuverability and will cross most occlusions. Often, a firmer "cap" can be felt at the proximal end of an occlusion; once this is traversed, the wire will pass easily through the soft thrombus. Inciting stenotic lesions may be encountered, especially at the distal end of a thrombosed segment. Gentle, controlled wire movements are paramount to prevent dissection and perforation. Although gentle "puffs" of contrast may be injected through the catheter to assess location, forceful injections should never be performed because of the risk of embolization. Rarely, a microwire (<0.018") and microcatheter (<3Fr) may be advanced coaxially to aid in crossing diseased vessels with severe stenosis.

Once the thrombosed segment is crossed, the length of the occlusion should be defined and measured. A multiple side-hole infusion catheter is then advanced over the wire through the occlusion (e.g., Pulse Spray Infusion System [AngioDynamics, Queensbury, NY]). Although there is a large choice of potential infusion catheters, there is no compelling evidence that any catheter leads to superior outcomes. An infusion length is selected such that the most proximal side hole is just above the thrombus, and the distal side hole is just above the distal extent of the thrombus. After the infusion catheter is in position, the guidewire is removed, and the end hole may be plugged with an occlusion or infusion wire, depending on the infusion catheter used. The sheath and catheter are sutured to the skin, and the infusion catheter is secured to the sheath with adhesive tape and suture to prevent catheter displacement. Low-dose heparin, 150 to 300 U/hour, is infused via the arterial sheath to prevent a thrombus from forming in the sheath or in the proximal artery. Full-dose systemic anticoagulation is generally held during the arterial thrombolysis infusion.

Limited data are available to compare the efficacy of fibrinolytic agents for use in CDT. In the United States, streptokinase, anistreplase, alteplase (recombinant tissue plasminogen activator [tPA]), reteplase, and tenecteplase are available. Efficacy and safety are comparable among the various agents for CDT.

There are a number of different thrombolysis techniques described in the literature, including continuous infusion, bolus method, pulse

spray, and graded infusion. The simplest and most often employed technique is continuous infusion, which requires the least procedure time and is an appropriate choice for relatively mild ALI. The bolus method involves delivery of a single concentrated dose of thrombolytic agent throughout the occlusion and then initiation of a continuous infusion. The pulse spray technique refers to repeated forceful injection of small aliquots of thrombolytic agent, thus distributing the agent rapidly throughout the thrombus as well as mechanically disrupting the thrombus. Pulse spray is initiated and continued in the angiography suite until antegrade flow is restored. In the graded infusion technique, the rate of drug infusion is diminished over time. Although there is no evidence of significant differences in amputation-free survival between the methods, studies have shown faster thrombolysis times when bolus or pulse spray methods are combined with continuous infusion. The increased speed of bolus or pulse spray methods must be balanced against the possible increased risk of bleeding complications and distal embolization associated with these techniques in some reports.

Many dosage regimens exist, but results are generally equivalent, and the risk of bleeding complications increases as the dose and duration of therapy increases. A typical CDT infusion rate is 0.5 mg/hour of 10 mg/L tPA (50 mL/hour) for 12 to 24 hours, with or without an initial bolus of 2 to 10 mg tPA diluted in approximately 10 mL. Alternatively, a pulse spray dose may be employed with 1 mg/min tPA administered in short, forceful pulses for 15 minutes, followed by continuous infusion if there is residual thrombus.

Monitoring

Patients undergoing CDT are admitted to a monitored bed where vascular and neurologic checks are performed every 2 hours. Fibrinogen, hematocrit, hemoglobin, platelets, and partial thromboplastin time are assessed every 4 to 6 hours. The tPA infusion rate is reduced by one-half if fibrinogen decreases below 150 mg/dL and discontinued if fibrinogen decreases below 100 mg/dL. Alternatively, cryoprecipitate can be given to increase the fibrinogen level and allow for continued infusion of tPA. However, there is no prospective evidence that monitoring fibrinogen and titrating tPA lowers bleeding risk, and consequently, many practices do not monitor fibrinogen levels during CDT.

Increased pain in the treated limb is expected and indicates successful thrombolysis, with pain occurring as a result of distal microemboli and washout of cytokines. Other clinical variables such as temperature, color, pulse, and capillary refill should all indicate improving perfusion. If ischemic signs worsen, the infusion setup and catheter position should be evaluated; in severe cases, CDT is aborted and alternative revascularization therapy is considered.

If limb ischemia is stable or improving, reevaluation with angiography is indicated every 6 to 24 hours until flow is restored. At the time of angiography, an inciting stenotic lesion may be identified and warrant further treatment, such as angioplasty or stent placement, to prevent re-thrombosis. Once a satisfactory angiographic result is obtained, all wires, catheters, and sheaths are removed from the patient, and hemostasis is achieved with the use of a vascular closure device or manual pressure.

MECHANICAL THROMBECTOMY

Similar to CDT, the goal of mechanical thrombectomy is to restore flow and improve perfusion to the affected limb. Mechanical techniques carry the added benefit of shorter duration of therapy and faster restoration of flow.

Preoperative Planning

Considerations for mechanical thrombectomy are similar to that of CDT, with the exception of reduced bleeding risk if tPA is not used. Patients who might otherwise have a contraindication to CDT, such as those with recent surgery or intracranial hemorrhage, may still safely undergo mechanical thrombectomy without the use of tPA. Additionally, mechanical thrombectomy may be favored in cases of an immediately threatened limb (Rutherford IIb) as immediate revascularization is required for limb salvage.

Technique

Mechanical thrombectomy is performed in an angiography suite or comparable facility. Similar to CDT, arterial access is obtained, a vascular sheath is placed, and angiography is performed to identify the thrombosed segment. Several commercially available devices exist to perform mechanical thrombectomy; two commonly used platforms include the AngioJet (Boston Scientific, Marlborough, MA) and Indigo (Penumbra, Alameda, CA) thrombectomy systems.

AngioJet is a pharmacomechanical peripheral thrombectomy device characterized by an end-hole catheter with two side holes: one expels jets of fluid, and the other concurrently aspirates. The rheolytic action of this catheter disrupts the thrombus and removes it from the vessel. A variety of catheters are available in different lengths and sizes for different indications.

Once the wire has traversed the area of thrombosis, the AngioJet catheter is prepared and advanced over the wire to the treatment area. The device is activated, and once the rheolytic action has commenced, the catheter is slowly advanced and retracted along the wire, turning intermittently to disrupt all clot. An initial pass can be made using "Power Pulse," an infusion of tPA along with the expelled fluid. After a short dwell period, another pass is made in conventional mode. Between passes, the catheter can be injected through a side port to evaluate for residual clot, though the operator should take care to inject gently by hand so as not to dislodge and embolize the thrombus down the leg.

Of note, the AngioJet is known to cause hemolysis in addition to thrombolysis. Hemoglobinuria, hyperkalemia, and acute kidney injury have been described with this device, although these complications are rare when the volume of thrombus is small and the device run time is low. Refer to the instructions for use supplied by the manufacturer for additional details. AngioJet has also been shown to cause microembolization, although the clinical significance of this is unclear. If distal embolization is a concern, consideration may be given to using an embolization protection device, such as the Emboshield NAV6 (Abbott Vascular, Abbott Park, IL) and SpiderFX (Medtronic, Minneapolis, MN).

Indigo is an aspiration thrombectomy device characterized by a flexible "CAT" catheter connected to a continuous vacuum engine. The catheter is directed to the thrombosed segment, and the wire is removed. The bare catheter is gently advanced to engage the thrombus, and the suction is applied by use of a flow switch. After a brief pause to allow the thrombus to enter the catheter, the catheter is retracted until flowing blood is seen in the canister, and the suction is rapidly disengaged with the flow switch to prevent exsanguination. Care must be taken to carefully monitor the canister and blood flow as rapid exsanguination can occur with this device. Newer models include automated systems to prevent rapid aspiration of unclotted blood. Refer to the instructions for use supplied by the manufacturer for additional details.

Aspiration is repeated with the Indigo system for several passes until the thrombus is removed. The catheter may be injected directly to evaluate for residual thrombus. Again, care must be taken to inject gently to prevent pushing the thrombus into distal vessels. Embolic protection devices may be used if necessary.

Many devices exist for mechanical thrombectomy, and the available technology will continue to evolve. Irrespective of which device is used, once a satisfactory angiographic result has been achieved, the catheter is removed from the body. If there is an inciting lesion, such as an area of stenosis caused by atherosclerotic plaque, this may be treated once the acute thrombus has been removed. Closure of the arteriotomy is then performed with the use of a vascular closure

device or manual pressure. If the acute thrombus was not sufficiently evacuated by mechanical thrombectomy, CDT can still be initiated in appropriate patients.

Follow-up

The goal of thrombectomy, whether by catheter-directed thrombolysis or mechanical thrombectomy, is to provide timely, safe, effective, and durable revascularization of the affected limb. After successful revascularization, the patient should be medically optimized, including selection of appropriate antiplatelet and/or anticoagulation therapy. Underlying vascular risk factors should be addressed with antihypertensives, glycemic control, statins, and smoking cessation. Patients with underlying vascular disease may be followed clinically with noninvasive testing; consideration for advanced imaging and possible re-intervention is recommended for patients with changes in physiologic testing or worsening clinical symptoms.

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Management of Infected Grafts

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INTRODUCTION

Graft infection is a dreaded complication following revascularization procedures, particularly with the use of prosthetic conduit materials. Its occurrence results in significant morbidity and high rates of limb loss, and it conveys a significant mortality risk. Infection rates vary by anatomic location, the pathology being treated, and the presence of existing systemic infections or contamination during the initial procedure. Open aortic graft implantations have an infection rate between 0.5% and 3%, which interestingly mirrors the infection rate of endovascular stent-grafts, at 0.2% to 5%, despite the comparatively minimally invasive approach. Lower extremity grafts have similar infection rates, up to 4.7% to 6%, with higher rates associated with those in the groin. As expected, infections in grafts placed for dialysis access occur at higher rates as a result of repeated manipulations, occurring in 9% to 20% of patients. Regardless of the location of the graft or pathology being treated, the key to a successful clinical outcome is early diagnosis and treatment, including the removal of all infected graft material, debridement to healthy tissue margins, and coverage of any exposed vessels.

DIAGNOSIS

The presentation of graft infection is highly variable; it may range from an open wound with exposed graft material in the most obvious cases to much more subtle signs and symptoms (Fig. 1). As such, there must always be a high index of suspicion balanced with a detailed history and physical examination in patients who present with constitutional or vague symptoms as they may be the only indications of a late infection. The timeline of events is of particular interest because although they are less common, early infections (seen up to 4 months after graft placement) are more frequently associated with highly virulent pathogens such as *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa*, and they typically require more aggressive management because of their higher rate of complications. In contrast, late graft infection (onset after 4 months) is predominantly associated with *Staphylococcus epidermidis*.

An examination should be thorough and include evaluation of the surgical site as well as distal pulses. Erythema, fluctuance, or a draining fluid collection are particularly worrisome findings and should prompt urgent investigation. Infection may also result in graft occlusion and result in emergent presentation with an acutely threatened limb. When infection is suspected but not obvious, then laboratory tests and imaging are required for diagnosis. A complete blood count (CBC) and blood cultures should be obtained early, and the patient should be started on broad-spectrum antibiotics. It should be noted that patients who present with late graft infection characteristically have negative culture results, blood or otherwise, because of the low virulence of such related pathogens. Markers of inflammation such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) may also be elevated in patients with graft infection and should be obtained with initial laboratory tests.

Imaging

Computed tomography (CT) is the current gold standard imaging modality in the diagnosis of graft infection (Figs. 2 and 3) and should be the modality of choice in all suspected intracavitary (abdominal or thoracic) graft infections. Key findings include perigraft air or fluid collections, soft-tissue changes such as fat-stranding or loss of tissue planes, or pseudoaneurysm, although such findings may not be seen in the acute stages of infection. Such findings are best appreciated with intravenous contrast. Use of CT is limited in patients in



FIG. 1 An exposed femoral-femoral bypass graft with a mobilized sartorius muscle flap for coverage. *(From Cronenwett JL, Johnston KW, eds. Rutherford's Vascular Surgery. 8th ed. Philadelphia: Elsevier; 2014.)*

whom iodinated contrast is contraindicated or when there is significant artifact from previous metal implants.

Ultrasound is the initial test of choice for suspected extracavitary graft infections. It is readily available, noninvasive, and can be performed at the bedside if necessary. Perigraft fluid may be visualized and can be suggestive of infection. By using color-flow modes, intravascular flow can be easily delineated from extravascular fluid collections. Ultrasound may also show a pseudoaneurysm, hematoma, or soft tissue mass, or it can be used to assess for graft patency. Its utility in intracavitary evaluation is limited commonly by anatomic and physiologic constraints, such as vessel depth or the presence of bowel gas. Quality and reliability of ultrasound imaging, more so than other modalities, is subjective to the skill of the technician.

Magnetic resonance imaging (MRI) has similar utility to CT with the added advantage of distinguishing perigraft fluid from chronic inflammation with the help of T1- or T2-weighted imaging. There is no radiation exposure, and contrast is not required, although gadolinium does help to delineate the vasculature structures from adjacent anatomy. Limitations of MRI include significant cost, length of time for image acquisition, and nephrogenic systemic fibrosis in renal patients who are given the contrast agent, which is of particular concern in patients with a glomerular filtration rate (GFR) less than 30 mL/min.

Nuclear medicine studies, such as a tagged white blood cell scan or positron emission tomography (PET), are also used in the diagnosis of graft infection. Tagged white blood cell scanning aims to show abnormal accumulation of leukocytes in perigraft tissue. This test will not delineate the vasculature but can be used in conjunction with CT or MRI to determine the presumed location of the increased uptake as it correlates to graft location. This is a very sensitive test but is not useful in the early postoperative period because of the normal inflammatory response that occurs as part of the healing process. This test also takes some time to complete, often with multiple trips to the nuclear medicine division. PET scans are a newer diagnostic modality with high sensitivity because of the increased uptake of fluorodeoxyglucose (FDG) by inflammatory cells. Like the tagged white blood cell scan, this test may lead to a false-positive result in the postoperative period because of the increased metabolic activity and normal inflammatory response during healthy recovery.

Finally, endoscopy is occasionally employed for the evaluation of a very specific infection resulting from fistulous or erosive communication between the bowel and graft material. It should be considered in patients with a previous aortic graft placement who present with an upper GI bleed. Ideally the technician will visualize the entire esophagus, stomach, and duodenum to look for any sign of a fistula as well as other causes of the bleeding. Although it has a limited role, it is not a modality to discount in these situations (Fig. 4).

TREATMENT

The basic consideration for graft infection is to eradicate the infection and preserve perfusion. There are many options for accomplishing this, and treatment should be individualized while abiding by basic surgical principles. With this in mind, the best approach to graft infection falls into essentially one of three categories: (1) graft excision with revascularization, (2) graft excision without revascularization, or (3) graft preservation. Within these broad categories are multiple options for repair, and the most appropriate treatment should be tailored to the patient for the ultimate goal of preserving life and limb. In all cases, coverage of the repair with autologous tissue (e.g., muscle flaps, omentum) may be used to decrease rates of future reinfection, and deep cultures should be obtained to allow for speciation of the infectious agent and better selection of antimicrobial therapy.

Graft Excision with Revascularization

Graft excision with revascularization is required if preserved in-line arterial flow is necessary for limb or branch vessel perfusion. This may include infected aortic grafts placed for occlusive or aneurysmal disease or in extracavitary grafts if the initial procedure was performed for chronic limb-threatening ischemia. This type of intervention should include removal of all infected graft material and debridement to healthy tissue margins. Reconstruction is aimed at reducing the rate of re-infection while maintaining adequate flow and may include additional augments, such as local tissue rearrangements or muscle flap coverage.

Extra-Anatomic Bypass

Extra-anatomic bypass with excision of all prosthetic material for infected intracavitary abdominal grafts has traditionally been considered to be the gold standard for repair. This procedure ensures that all infected material is removed and that new conduit is placed through healthy, uninfected tissue planes. The most common procedure performed is an axillofemoral graft with a femoral-femoral bypass or an axillobifemoral bypass using expanded polytetrafluoroethylene (ePTFE) as a conduit (Fig. 5). In the setting of infection in the common femoral region, the outflow anastomosis can be made to any distal unaffected vessel, usually the superficial femoral artery (SFA) or the profunda femoris, depending on vessel patency and infectious burden. If the SFA or profunda is utilized as the outflow vessel, the approach to these vessels should be made laterally to the sartorius muscle to avoid contamination from the femoral triangle.

If there is a need for revascularization of the contralateral limb, a femoral-femoral bypass with a prosthetic may be performed if there is no groin infection. Alternatively, an ilioiliac bypass may be an equally viable option if the iliac vessels are not within a contaminated field. If a groin infection is present and a femoral-femoral bypass is necessary, then the use of a saphenous vein or cryopreserved vein or artery conduit may be considered. Once the lower extremities are revascularized, the infected graft is completely excised, and infected tissue is debrided.

The surgical approach to an infected intracavitary graft is either transperitoneal by laparotomy or by a retroperitoneal approach, which may be useful in avoiding intraabdominal adhesions from previous procedures. Exposure of the supraceliac aorta may be required for proximal control depending on the extent of the infected field

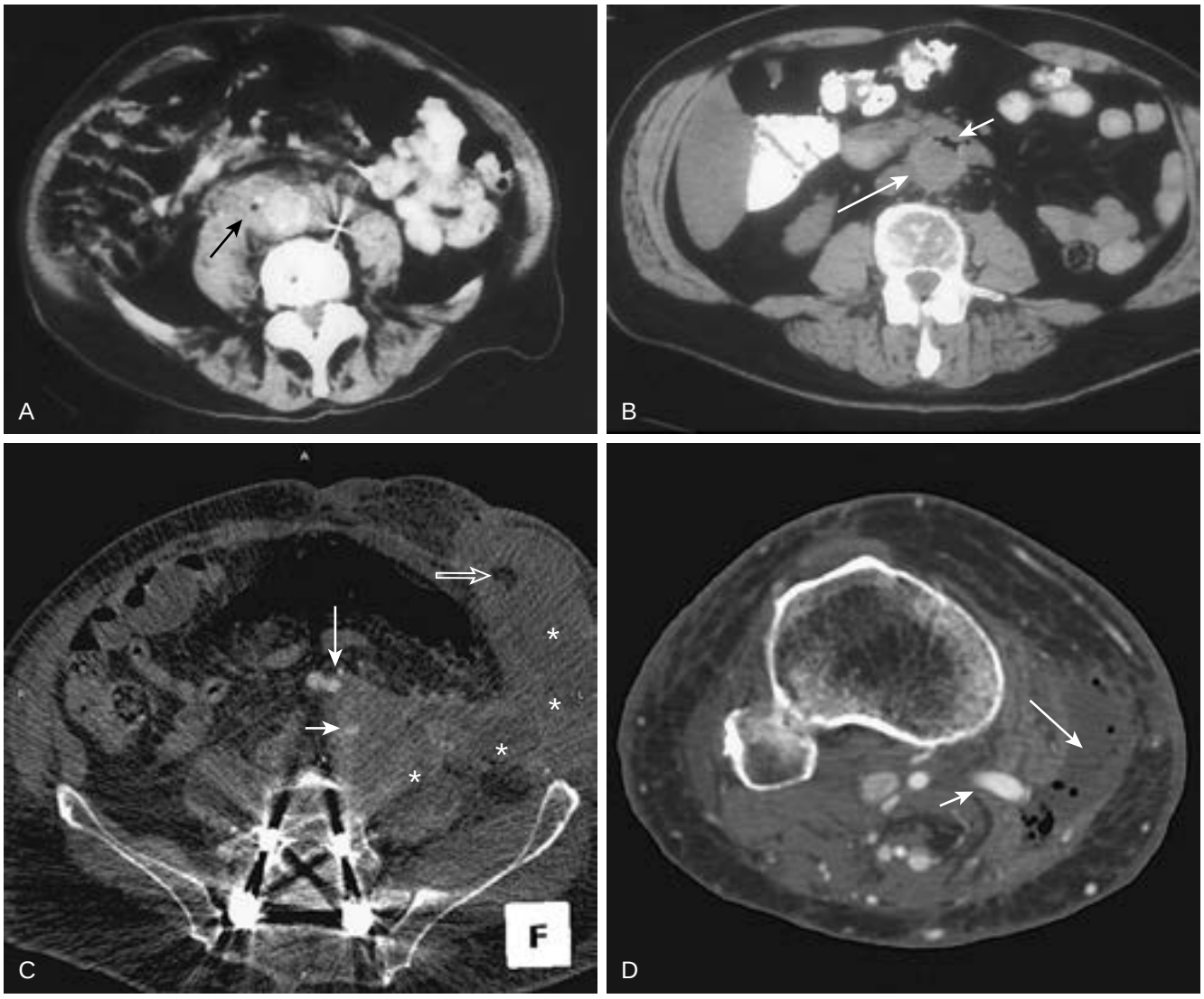


FIG. 2 CT images demonstrating vascular graft infection. **(A)** Perigraft fluid. **(B)** Thickened perigraft tissue and air within the graft and perigraft tissue. **(C)** Pseudoaneurysm of graft limb anastomosis. **(D)** Air and abscess at the infrageniculate level *(long arrow)*, patent graft into abscess. *(From Hallett JW, Mills JL, Earnshaw JJ, et al, eds.* Comprehensive Vascular and Endovascular Surgery. *2nd ed. Philadelphia: Elsevier; 2009.)*

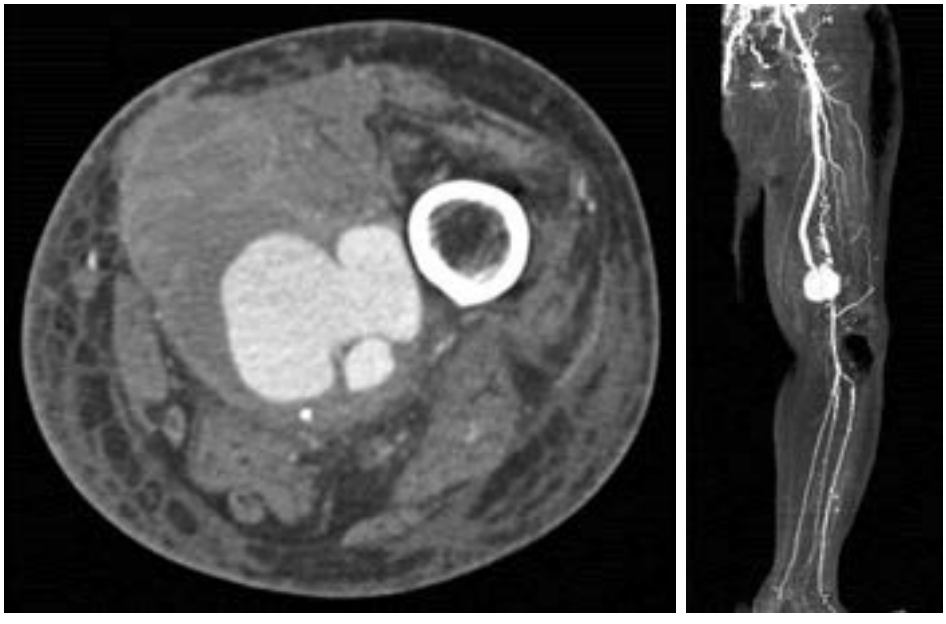


FIG. 3 CT angiogram reveals a pseudoaneurysm arising from distal anastomosis of an infected femoral-to–popliteal artery bypass graft. *(Courtesy Adam Ring, MD.)*

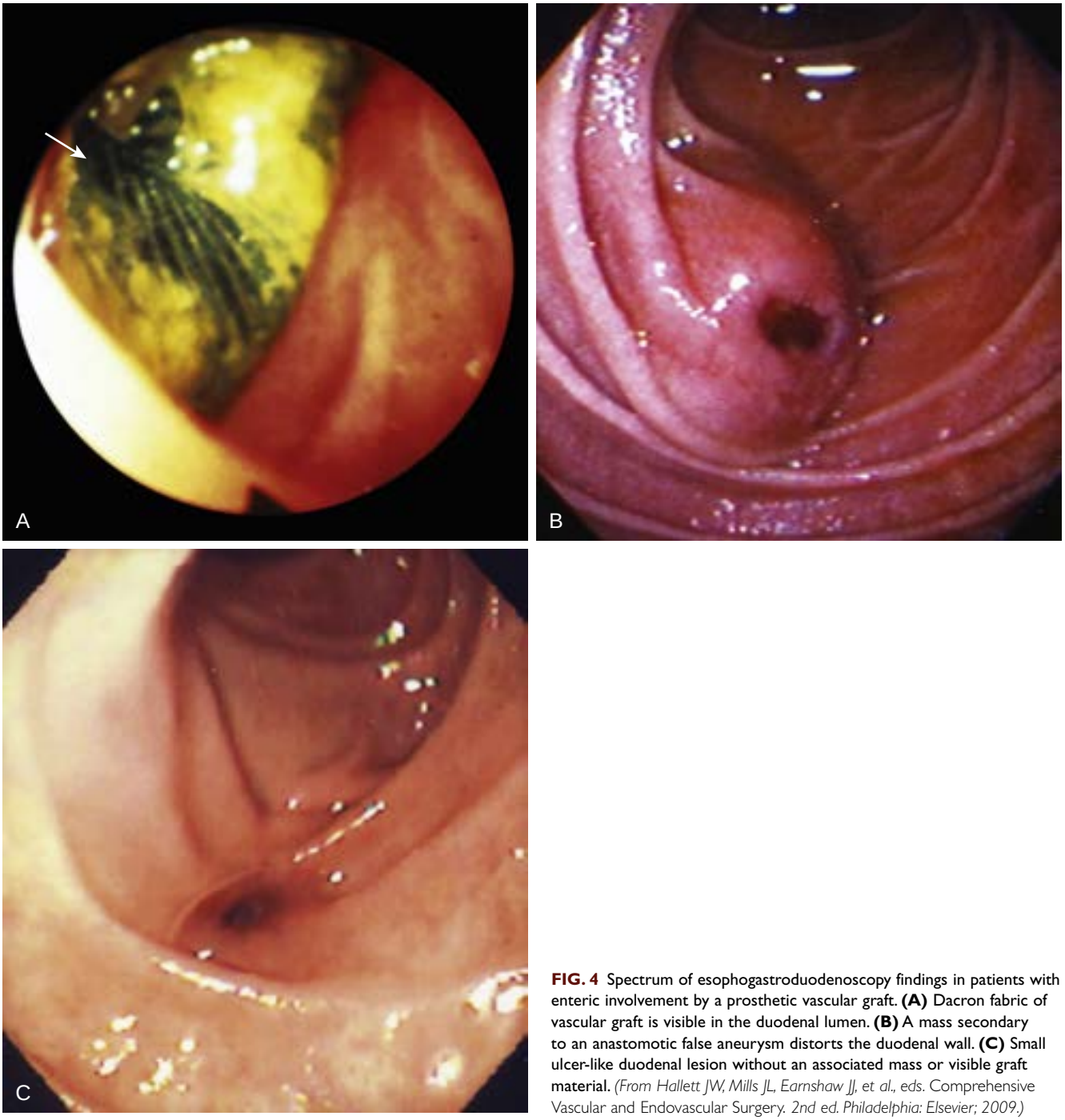


FIG. 4 Spectrum of esophagastroduodenoscopy findings in patients with enteric involvement by a prosthetic vascular graft. **(A)** Dacron fabric of vascular graft is visible in the duodenal lumen. **(B)** A mass secondary to an anastomotic false aneurysm distorts the duodenal wall. **(C)** Small ulcer-like duodenal lesion without an associated mass or visible graft material. *(From Hallett JW, Mills JL, Earnshaw JJ, et al., eds.* Comprehensive Vascular and Endovascular Surgery. *2nd ed. Philadelphia: Elsevier; 2009.)*

and inflammation. Distal control of the bilateral iliac arteries should be obtained, and ureters should be identified and protected. In the preoperative period, ureteral stent placement may be particularly useful in assisting with the operative identification of the ureters given the possibility of grossly altered and inflamed retroperitoneal anatomy. The infrarenal aorta should be debrided to healthy tissue, and the proximal portion should be oversewn in a double-layer fashion with nonabsorbable monofilament suture to reduce the risk of an aortic stump blowout, a complication with near-universal mortality. The same closure technique should be performed for the distal aorta or iliac arteries. The aortic stump should be covered with omentum, and the retroperitoneum should be widely drained.

Complications of extraanatomic bypasses with graft explantation include reinfection (3%–37%), early mortality, limb loss (3%–15%), and aortic stump blowout with life-threatening hemorrhage (3%–24%). Extraanatomic bypass for infected grafts often requires a lengthy operative time, frequently over two procedures. Patency rates of the ultimate revascularization are not as robust as those of anatomic bypasses.

In Situ Antibiotic Impregnated Graft Replacement

In situ prosthetic graft replacement with antibiotic-impregnated or antimicrobial grafts is acceptable for many patients, particularly those with low-virulence pathogens, an aortoenteric fistula, or

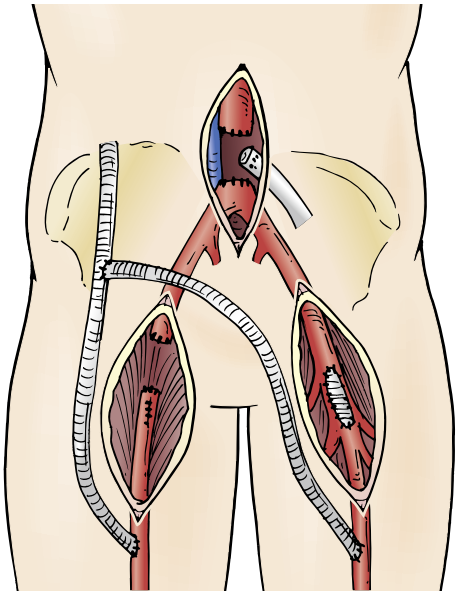


FIG. 5 Axillary artery-to–bilateral superficial femoral access with ligation of aorta and exclusion of infected groins. *(From Sidawy AN, Perler BA, eds. Rutherford's Vascular Surgery. 9th ed. Philadelphia: Elsevier; 2019.)*

erosion with impending hemorrhagic catastrophe. The procedure includes proximal and distal control, excision of all graft material, debridement of infected tissue, irrigation with antibiotic solution, and immediate replacement with a new prosthetic graft. When possible, the graft material should be tunneled through a new route, and all should be covered with omentum or other tissue coverage, including muscle flap coverage with either the sartorius or gracilis muscle in the groin. The prosthetic materials most commonly used are Dacron soaked in rifampin or silver-impregnated prosthetic grafts. The patient will need to be maintained on therapeutic intravenous antibiotics for 6 to 8 weeks and, in some cases, lifelong suppressive oral antibiotics. Benefits of this revascularization technique include short operating times, excellent patency, and durability, with low amputation and mortality rates. It can be employed in emergency settings in which the surgeon does not have adequate time to harvest autologous vein or thaw cryopreserved tissue. Its use in more aggressive microbial infections (drug-resistant pathogens *E. coli, S. aureus, P. aeruginosa*) is called in to question, and there is a potential for developing rifampin-resistant organisms over time.

In Situ Cryopreserved Allograft Replacement

In situ arterial allograft replacement is another alternative that consists of removing all infected graft material, debridement of tissues, antibiotic irrigation, and new conduit placement with cryopreserved aorta. Again, the patient will receive 6 to 8 weeks of antibiotics postoperatively. Similar to the antibiotic-impregnated grafts, the advantage of this technique is a one-stage procedure, but this technique uses autogenous material rather than prosthetic material to decrease reinfection rate. The disadvantage of this method of reconstruction include the lack of availability, the cost, and the time necessary for implantation, which requires thawing the frozen product before use. There is also concern for aneurysmal degeneration over time and the need for continued surveillance of the graft; therefore, its use in aggressive microbial infections remains a controversial topic. Long-term patency rates of this graft are less than those of prosthetic material but greater than those of extraanatomic bypasses. Amputation rates are low (less than 8%), and mortality varies widely (9%–56%).

In Situ Venous Autograft

In situ venous autograft creation, also known as a *neo-aortoiliac system* (NAIS) procedure, consists of reconstructing the aortoiliac system using a femoral-popliteal vein as conduit (Fig. 6). Preoperative venous duplex of the bilateral lower extremities is necessary because of the long length of sizeable vein that is needed to ensure patency of the veins. It is unlikely that the saphenous vein will be of good caliber for use, but in the event that it is (7–8 mm), one of the deep veins may be preserved in each leg. Longitudinal thigh incisions are made laterally to the sartorius muscle for harvest of the deep vein. The adductor hiatus is divided to expose the superficial femoral vein and its branches. These branches are ligated, and the vein is harvested from the level of the profunda femoris as far distally on the popliteal vein as needed for adequate length. Care is taken to preserve the profunda femoris vein, and the superficial femoral vein is taken flush at its origin to reduce the risk of deep venous thrombosis. Once the vein graft is obtained, the incisions are closed, preferably over drains. Multiple authors have described "staging" the NAIS procedure in which the vein is harvested with side branches ligated and left in situ, and the patient returns next day for the aortic portion of the case. This makes the operation much less arduous on the surgeon and has similar patency rates.

After the clean vein harvest is complete, the procedure continues with exposure of the infected graft. This includes gaining proximal and distal control, excision of all graft material, debridement of infected tissue, and irrigation with antibiotic solution. Once this is done, the femoral vein is attached to the proximal aorta in a non-reverse fashion for appropriate size match. If the size mismatch is too great, then other techniques may be necessary; two segments of superficial femoral vein can be anastomosed to each other, making a pantaloon configuration. The composite ends are then sewn in an end-to-end fashion to the aorta (Fig. 7). Alternatively, if the mismatch is too great, then the aortic stump can be oversewn, and the vein graft can be anastomosed to the anterior surface of the aorta in an end-to-side fashion. The vein graft can then be tunneled through the previous tunnels and constructed to the femoral artery in an aortofemoral fashion. The contralateral limb is then revascularized by creating an anastomosis with the second vein segment at the midpoint of the aortofemoral graft and then passing this to the

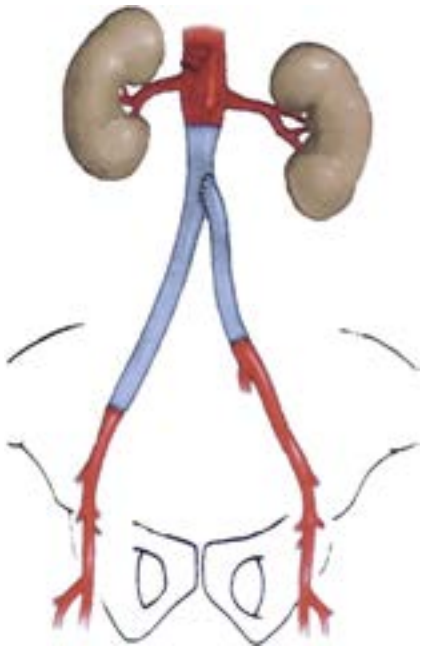


FIG. 6 Depiction of the neo-aortoiliac (NAIS) procedure with replacement of the aorta with femoral-popliteal vein segments. *(From Jackson MR, Joiner DR, Clagett GP. Excision and autogenous revascularization of an infected aortic stent graft resulting from a urinary tract infection. J Vasc Surg. 2002;36:622–624.)*

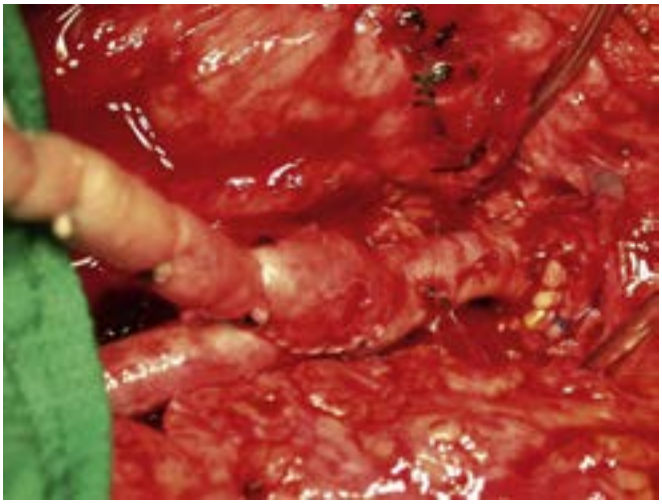


FIG. 7 Neoaortoiliac system replacement of an infected aortic graft with a harvested femoral popliteal vein. (Patient's head at right of photo.) The vein is anastomosed in an end-to end fashion with the aorta *(right)* with an end-to-side anastomosis of vein to vein to create a bifurcation *(center)*. *(Courtesy Ahsan Ali, MD).*

contralateral groin where the distal anastomosis is made. The groins are closed, usually with muscle flap coverage.

The advantages of this procedure include the antimicrobial protection of an autograft, in-line flow, complete removal of the infected endograft, no concern for immunogenicity of the conduit, and likely eradication of the infection. The disadvantages include procedure length and the complications that come with deep vein harvest, notably leg swelling and potential venous compartment syndrome, which may require fasciotomies. Long-term reinfection rates are close to 0%, and mortality rates following the NAIS procedure range from 8% to 33%.

In situ venous allograft replacement is a procedure with similar construction to the NAIS procedure, but it utilizes cryopreserved vein. This procedure avoids the deep vein harvest and the complications that go along with it, but it still allows for full excisional debridement of all infected material. Again, the cryovein is anastomosed to the aorta in an end-to-end fashion, and the graft can then be tunneled to the femoral arteries in an aortobifemoral bypass fashion. As described earlier, the original tunnels can be used for this procedure and muscle flaps to close the groins. Cryovein is more readily available than is the cryoaorta or arterial pieces in many institutions. However, the procedure remains lengthy, and although the conduit is autologous, its use in aggressive microbial infections is still debated.

Graft Excision without Revascularization

Graft excision without revascularization can be considered in cases in which the initial procedure was performed for claudication or in cases in which the graft is thrombosed and the patient does not have critical limb ischemia. Although the goal in most infected graft procedures is the removal of graft material and maintenance of flow, this may not be necessary in all patients depending on anatomic location and indication for initial placement. The optimal operative technique in this case is to preserve as many branches as possible to maintain collateral flow. The arteriotomy remaining after graft removal is repaired, commonly with a vein patch to avoid narrowing the vessel. In some cases, a small cuff of graft is left behind and oversewn. This will not narrow the artery but may pose a future problem with retained graft material in the infected field and should not be performed in the setting of highly virulent pathogens or an immunocompromised patient. Patients are at risk of limb loss, even if their initial procedure was not for critical limb ischemia. Their native vessel may have progressed with calcific disease, and the nature of the graft removal may disrupt any collateral vessels feeding the outflow; therefore, the limb should be closely monitored postoperatively for evidence of ischemia.

Graft Preservation

A final option for graft infection is graft preservation with wide local wound debridement while infected material is left behind. This technique should be reserved for select circumstances. Patent grafts with limited, segmental infections or those with less virulent pathogens can be considered. Infections limited to the perigraft tissue, nonvirulent species, and no systemic sepsis are criteria necessary before preservation is attempted. Appropriate patients should undergo debridement of all infected tissue with thorough washout of the area. This may be required several times to ensure that the infection has been eradicated while only healthy, uninfected tissue remains. Repeat cultures of the area are also necessary to continue to guide treatment, although it is not uncommon for clinically infected spaces to have negative culture results. Once there are negative cultures and only healthy tissue remains, the wound can be closed or covered. If the tissue in the surrounding area is healthy, then muscle flap coverage is a good option. The wound may also benefit from negative-pressure vacuum-assisted closure (VAC) therapy or even require a skin graft. Multiple authors have described antibiotic bead placement in infected fields for such grafts that cannot be explanted or for a period of antibiotic instillation with drainage if drains can be placed near the abscessed graft. Conservative management of intracavitary graft infections in these manners may be successful, but it is exceedingly more difficult to preserve graft material without persistent or recurrent infection. Partial graft preservation may also be possible, particularly in patients with isolated infections of a limb of a prosthetic graft. The infected segment is removed, unhealthy tissue is debrided, and the graft is replaced with autogenous, autologous, or antibiotic-soaked Dacron. This new conduit is often tunneled through clean tissue planes, with some surgeons utilizing the obturator canal to navigate around the infected field. Graft preservation is difficult and may ultimately fail, but the features that increase success are low-virulence organisms, absence of perigraft abscess or sepsis, and early-appearing local tissue infection (Figs. 8 and 9).

INFECTED STENT GRAFTS

Aortic stent graft infection is a rare problem, but it clearly poses a large concern for morbidity and mortality in these patients. Given the increasing extent of endovascular management of vascular diseases, this issue promises to become much more prevalent. Additionally, as surgeons have become more adept and aggressive with repair of large vascular problems using this minimally invasive approach, more patients are now being offered endovascular repairs who would otherwise not be safe candidates for open repairs, largely because of severe systemic illness. Infections in this older and sicker population are therefore challenging. Currently 0.2% to 5% of abdominal or thoracic stent grafts become infected. The source of infection is thought to be systemic bacteremia with hematogenous or direct seeding of the stent graft. This bacteremia may be the result of interval known systemic infections, chronic infections, placement of the stent graft in an infected field, or in patients who have had repeated interventions performed after their initial procedure. Time to diagnosis is usually within 22 months of surgery.

Patients may be asymptomatic but mostly will present with pain, fever/chills, development of an endoleak, fistula, or rupture. Diagnosis is largely made by CT angiogram (CTA) but can also be made via the other modalities discussed earlier (Fig. 10). In patients with presumed infection, blood cultures should be taken, and the patient should be started on broad-spectrum antibiotics.

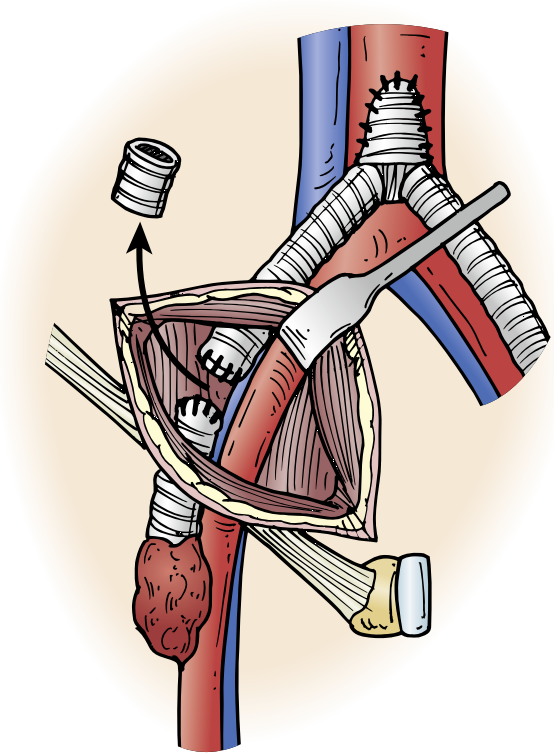


FIG. 8 Retroperitoneal exposure of a noninfected graft limb through clean tissue planes. *(From Cronenwett JL, Johnston KW, eds.* Rutherford's Vascular Surgery. *8th ed. Philadelphia: Elsevier; 2014.)*

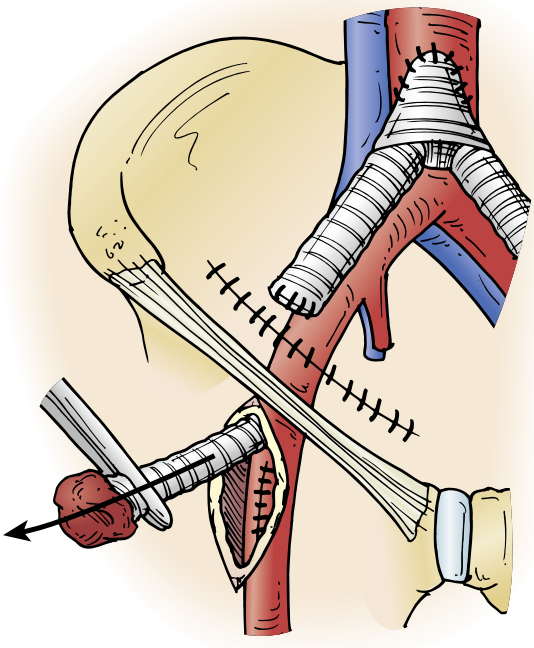


FIG. 9 Removal of an infected graft portion from the groin. Replacement with a vein, cryopreserved artery, or rifampin-soaked Dacron graft is performed for revascularization if needed. *(From Cronenwett JL, Johnston KW, eds.* Rutherford's Vascular Surgery. *8th ed. Philadelphia: Elsevier; 2014.)*

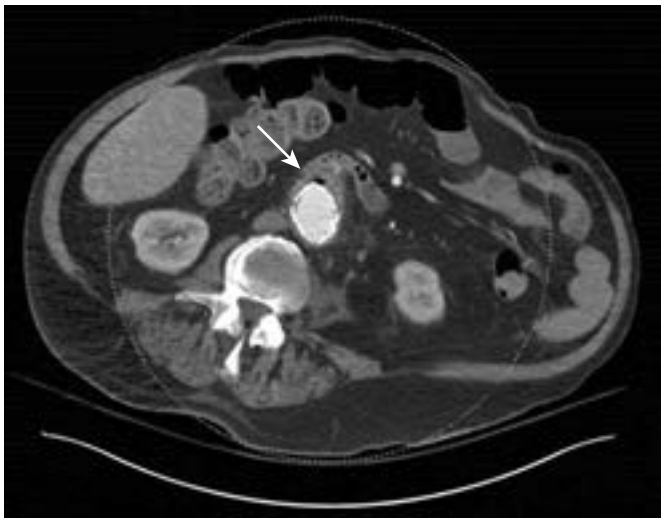


FIG. 10 CT angiogram reveals air and fluid around an abdominal stent-graft. The duodenum is shown looping over the top of the graft with an aortoenteric fistula ***(arrow)***. *(Courtesy Michael Williams, MD.)*

If the patient is able to withstand an open operation, then preparation should be the same as for the intracavitary infected grafts. The options for removal of the infected material and maintaining flow are the same as for the infected aortic grafts. After the abdomen is opened and infected tissue debrided, proximal and distal control is obtained on the aorta. The proximal control may need to be supraceliac or even in the thoracic aorta. The aorta is opened, and the stent graft is removed. This approach can pose a challenge, particularly in grafts with suprarenal fixation. Once the graft is removed, then aortic reconstruction is accomplished by in situ prosthetic graft placement, in situ arterial allograft, in situ venous autograft, or in situ venous allograft. The alternative is an extraanatomic bypass with removal of all infected material and oversewing of the aorta. These patients have fairly high long-term morbidity and mortality, with up to 35% having a perioperative complication and an overall 5-year survival of 50%. Patients with infected thoracic endografts have poorer outcomes than those with infected abdominal endografts, and the use of autologous or autogenous material as a conduit has been demonstrated to be superior.

INFECTED DIALYSIS ACCESS GRAFTS

Prosthetic arteriovenous access is used for a large number of chronic renal disease patients on dialysis. These grafts can essentially be anastomosed to any artery and vein that are in close proximity, including access in the arms, groins, and chest wall. Because this graft is repeatedly punctured for dialysis and located superficially with occasional axillary or inguinal placement, there is a relatively high rate of infection ranging from 9% to 20%.

These graft infections can present like any other graft infection, but with the repeated use there is a high risk of pseudoaneurysm or hemorrhage. Patients often present with malaise, fever, erythema, or purulent drainage from previous access sites. Once graft infection is suspected, blood cultures should be collected, and the patient should be placed on empiric antibiotics. Imaging may not be required in clinically obvious infections. However, some infections may follow a more indolent course, and ultrasound or a tagged white blood cell scan can aid in diagnosis.

As described previously, all infected material should be removed. An incision should be made over the area of the anastomoses, and control should be obtained both proximally and distally on the artery and the vein using standard operative technique. This may

require a counterincision or several depending on how well the graft is incorporated. Once the graft is removed, the veinotomy is closed primarily. A vein patch obtained from either saphenous vein or a nearby vein, if available, should be used to close the artery to prevent narrowing. Skin and subcutaneous tissue or muscle is then used to close the area over the vein and artery. If there is evidence of significant infection, such as purulent drainage, the skin should be left open to heal by secondary intent or a wound VAC should be placed. The patient will need a temporary dialysis line until the infection is cleared, at which time a more permanent access can be entertained.

CONCLUSION

Although prosthetic graft infection is a diagnosis no surgeon wants to make, the key to a favorable outcome is prompt diagnosis and intervention. The patient will need control of sepsis, broad-spectrum and then targeted antibiotics, debridement of the infected tissue, removal of all graft material when able, and revascularization as needed. With careful patient selection and timely repair, salvage of these patients is possible via a number of surgical options.

SUGGESTED READINGS

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Atherosclerotic Renal Artery Stenosis

Douglas Rodgers, MD, and Joseph S. Giglia, MD

Atherosclerosis is the most common cause of renal artery stenosis (RAS), accounting for 90% of cases. Atherosclerotic RAS has been implicated as a significant contributor to systemic hypertension and impaired renal function. It is important to understand that RAS is rarely the sole cause of hypertension or renal dysfunction. Although the incidence of RAS may be as high as 43% in certain high-risk groups, there are no data to justify prophylactic treatment of asymptomatic patients. The majority of patients with symptomatic RAS should be managed medically, with invasive intervention reserved for only a select subset of patients. As in other areas of vascular intervention, the advent of catheter-based endovascular interventions has increased the number of procedures for RAS often without regard for the natural history or the clinical outcomes. Open surgical reconstruction is still indicated in a limited number of situations with very specific indications.

INCIDENCE

The incidence of atherosclerotic RAS is approximately 5.4% in patients with resistant hypertension, and it may affect as many as 6.8% of adults older than 65 years of age. It is even more prevalent in those with vascular disease, with estimates between 22% and 60%. Risk factors associated with atherosclerotic RAS include advanced age, hyperlipidemia, peripheral arterial disease (PAD), cerebrovascular disease (CVD), and coronary artery disease (CAD), with the severity of atherosclerotic RAS often paralleling the severity of CAD.

NATURAL HISTORY

Although RAS often is implicated as a cause of systemic hypertension and worsening renal function, it is more frequently discovered as an incidental finding on diagnostic imaging. In studies using sequential angiography, atherosclerotic RAS lesions progressed in 11% to 44% of subjects. Progression to complete occlusion occurred in only 10% to 16% of patients with more than 60% stenosis. In patients studied by ultrasound, complete occlusion occurred in only 7% of patients with a stenosis greater than 60%. Progression of these lesions may be even less common, as a significant increase in RAS was seen annually in only 0.5% of patients with cardiovascular risk factors. The ultimate endpoint of the disease process is hypertension resistant to medical therapy and progressive renal dysfunction resulting from ischemia, with renal atrophy being documented in 5.5%, 11.7%, and 20.8% of patients with normal renal arteries, renal arteries with less than 60% stenosis, and renal arteries with more than 60% stenosis, respectively. A critical issue is whether the renal parenchyma has already undergone permanent irreversible changes that will not be altered by intervention on a proximal main renal artery.

EVALUATION

Duplex ultrasound is the initial method of choice for RAS screening. The degree of stenosis is best determined by measurement of each renal artery peak systolic velocity (PSV). Normal renal arteries have a PSV of 60 to 100 cm/s. Renal artery PSV greater than 180 cm/s is indicative of RAS greater than 60%. The ratio of renal artery PSV to aortic PSV (RAR) is also useful in identifying significant stenosis with an RAR >3.5 indicating greater than 60% stenosis. However, it is important to note that the RAR is invalid if the aortic PSV is greater than 100 cm/s, suggesting severe aortic disease. The other signs of RAS include intrarenal vascular tardus-parvus waveforms and renal atrophy. Evaluation of renal size also plays a role in management; a kidney length of more than 7 or 8 cm has been advocated as a parameter favoring revascularization in the setting of RAS. A critical portion of the examination is calculation of the resistive index ([peak systolic velocity – end diastolic velocity]/peak systolic velocity) within the kidney. Elevated resistive indices (>.8) indicate permanent irreversible renal parenchymal damage that would not be expected to improve by renal artery intervention. Computed tomography angiography and magnetic resonance angiography are more sensitive and specific modalities for delineating the precise anatomy and degree of RAS. Conventional arteriography remains highly accurate for identification and quantification of RAS but should only be undertaken if therapeutic intervention is planned.

TREATMENT

Although atherosclerotic RAS is associated with increased cardiovascular morbidity and mortality, there is no current evidence to support revascularization of asymptomatic patients or patients with well-controlled hypertension. Several randomized trials have brought into question the utility of renal artery stenting for the treatment of

renal artery stenosis. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), Angioplasty and Stenting for Renal Artery Lesions (ASTRAL), and the Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) trials have all concluded there is no benefit of stenting over medical therapy as there was no improvement in renal function, blood pressure control, or mortality in any of the studies. However, it is important to note that the entry criteria for these studies were significantly flawed. As a result, the studies included mostly patients that one would not expect to benefit from revascularization while omitting those that would likely benefit from intervention. For example, during the CORAL trial, enrollment was broadened to include patients with well-controlled hypertension, and patients with a recent history of congestive heart failure were excluded. In the ASTRAL trial, patients were only included in the study if their physicians could not decide whether their patients might benefit from revascularization, specifically excluding patients believed likely to benefit. ASTRAL and STAR were underpowered to reach statistical significance. Both of them are criticized for including a substantial amount of patients without significant renal impairment. Additionally, of the patients assigned to stenting, 21% of ASTRAL and 29% of STAR patients allocated to revascularization could not have possibly benefited because they did not receive a stent for various reasons. However, these patients were still analyzed in the stented group by intention to treat. In STAR, this included 12 of the 64 patients assigned to receive a stent but were found to have less than 50% RAS. Instead of concluding that there is no benefit of stenting in the treatment of RAS, these three studies should be interpreted as offering further support for medical management in patients without clinically and hemodynamically significant RAS, emphasizing the importance of patient selection for revascularization. There is, however, a substantial amount of retrospective evidence to support revascularizing patients with clinically and hemodynamically significant RAS. Thus, revascularization of patients with atherosclerotic RAS is currently reserved for high-grade RAS in the clinical setting of either ischemic nephropathy with severe hypertension or renovascular hypertension refractory to maximal medical therapy. Young patients in whom flash pulmonary edema or other acute clinical sequalae caused by atherosclerotic RAS also may benefit from revascularization.

MEDICAL THERAPY

All patients with atherosclerotic RAS are at increased risk for cardiovascular morbidity and mortality; therefore, hypertension and factors known to be associated with progression of atherosclerosis should be controlled aggressively.Hypertension control should start with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). Calcium-channel blockers, β-blockers, chlorothiazide, or hydralazine may be added for better control. There is good evidence that ACE inhibitors and ARBs are helpful in patients with underlying cardiac disease and nephropathy. Most patients are able to tolerate ACE inhibitor or ARB therapy. However, ACE inhibitors can decrease glomerular filtration rate (GFR) by blocking efferent arteriolar constriction, and therapy must be monitored closely to ensure that the decrease in GFR is minimal.Additionally, patients should be started on a statin and antiplatelet therapy (either low-dose aspirin or clopidogrel). For patients with diabetes, good glycemic control (hemoglobin A1c <7.0%) should be targeted. As in all patients with atherosclerosis, smoking cessation is essential and should be emphasized.

RENAL ARTERY STENOSIS SURVEILLANCE AND FOLLOW-UP

Although there are no quality data on RAS surveillance, the authors recommend duplex ultrasound initially every 6 to 12 months for patients with RAS greater than 60% to assess for progression of stenosis and renal atrophy. Blood pressure must be monitored carefully along with measurement of serum creatinine or estimated GFR. An abrupt change in control of hypertension or renal function may prompt earlier reimaging of the renal arteries.

REVASCULARIZATION

Revascularization can be accomplished by endovascular procedures or by open surgery. Endovascular approaches are preferred in most cases because of their minimally invasive nature, excellent early results, and lower periprocedural morbidity and mortality when compared with open surgery. Open renal artery surgery is reserved for renal artery revascularization in combination with elective aortic reconstructions that require an open approach, urgent salvage of endovascular technical failures resulting in hemorrhage or renal ischemia, or revascularization of renal artery branches that are not amenable to endovascular repairs. Open renal artery revascularization may also be required in select patients with aortic aneurysms or dissections treated with endovascular techniques.

ENDOVASCULAR THERAPY

While primary angioplasty is the standard endovascular treatment for renal artery fibromuscular dysplasia, primary stenting for atherosclerotic RAS is associated with improved success rates and less recurrent stenosis relative to angioplasty alone. Thus, percutaneous balloon angioplasty with primary endoluminal stenting is the current standard for endovascular treatment of RAS while primary angioplasty is mainly reserved for the treatment of recurrent stenosis. Rarely, atherosclerotic stenosis spares the ostium and is localized to the mid or distal main renal artery. In this situation, perform primary angioplasty and reserve stenting for unsuccessful treatment with residual stenosis or flow-limiting dissection.

The endovascular approach typically begins with standard percutaneous femoral artery access using the Seldinger technique. After access is obtained, a diagnostic catheter is inserted into the aorta at the level of the first lumbar vertebral body and an aortogram is obtained in the anteroposterior (AP) position (Fig. 1). Alternatively, the brachial artery can be used for access if there is significant aortoiliac occlusive disease, the renal arteries have significant inferior angulation, after unsuccessful cannulation via a femoral approach, or there is unfavorable aortoiliac anatomy (Fig. 2). Since the renal arteries often arise from the aorta in anterolateral or posterolateral positions, ostial lesions may neither be appreciated nor appear to be significant from the AP position. In this situation, an oblique projection may be necessary to better identify the lesion. A weight-based dose of unfractionated heparin is administered intravenously after the appropriate size sheath is in place. The targeted renal artery is cannulated by introducing a wire into the artery using an end hole selective catheter (Fig. 3). A steerable sheath may also be considered for additional wire and catheter support, especially if the renal arteries have significant angulation off the aorta. After the artery is cannulated, an angiogram is obtained to confirm intraluminal position. An appropriately sized balloon expandable stent is selected. The shortest possible stent that allows for adequate coverage of the lesion with ~2 mm extension into the aorta should be chosen. The diameter is selected so that it is equal to the distal normal-appearing artery, being careful not to mistake any poststenotic dilatation as normal distal artery. Proper positioning of the stent may be possible by advancing the stent bareback over the wire. However, in the setting of critical stenosis, it may be preferred to protect the stent with the sheath during positioning. This is achieved by first advancing the sheath and its dilator through the stenosis over the wire. After the dilator is removed, the stent is advanced into proper position inside the tip of the sheath. Before deployment, the sheath is withdrawn into the aorta to uncover the stent. Alternatively, if the stent is unable to be advanced through a critical stenosis, predilatation angioplasty may be performed with a short, 2- to 3-mm diameter balloon. Once in optimal position, percutaneous balloon angioplasty



FIG. 1 Aortogram illustrating a proximal left renal stenosis.

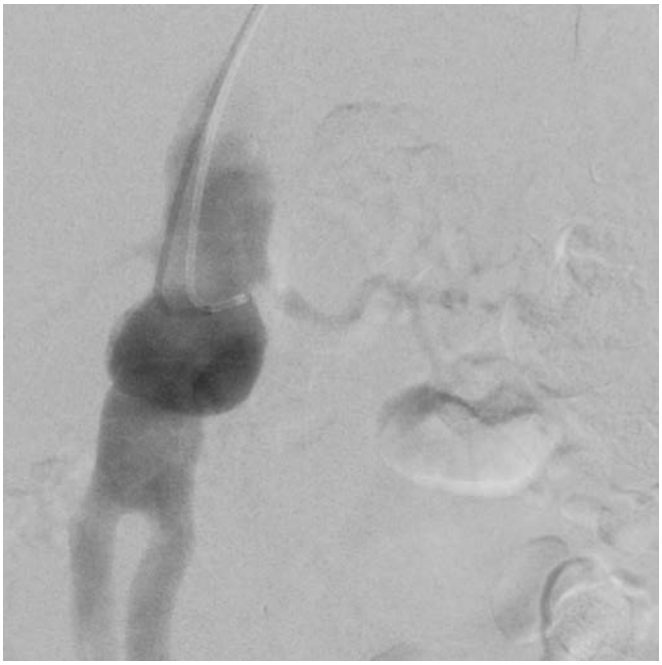


FIG. 2 A left brachial or radial approach is used if there is unfavorable aortoiliac artery anatomy.

is performed to deploy the balloon expandable stent by fully inflating the balloon (Fig. 4). It is critical that the stent is placed extending 1 to 3 mm into the aortic lumen, as the renal disease is often contiguous with aortic wall plaque (Fig. 5). The proximal end of the stent is then flared with a slightly larger balloon. Repeat selective renal

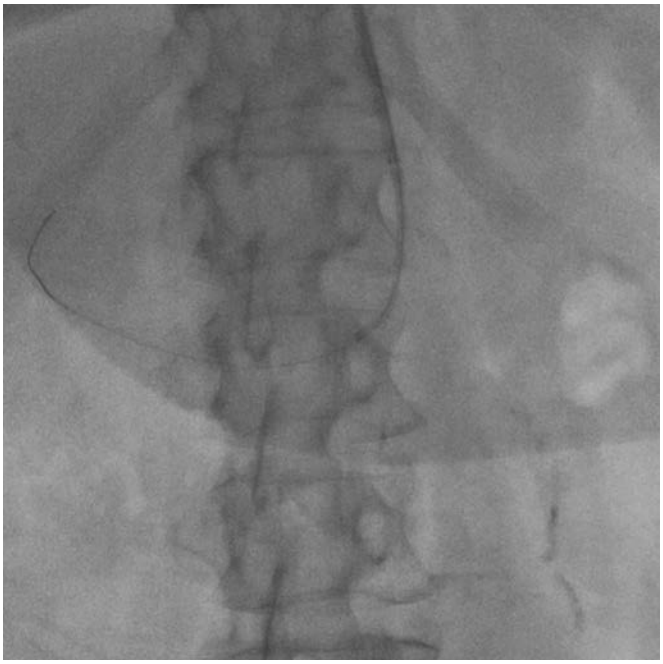


FIG. 3 Right renal artery has been cannulated and a wire advanced distally.

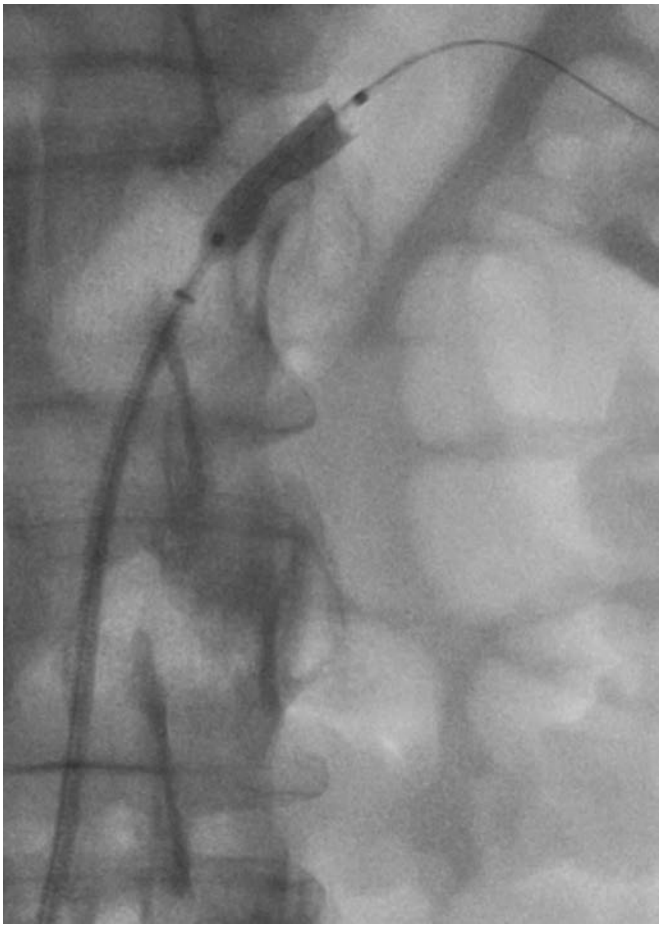


FIG. 4 Left renal artery stenosis treated with an appropriately sized balloon-expandable stent from a femoral artery approach.



FIG. 5 Proximal end of the stent is positioned into the aortic lumen because the renal artery plaque is often continuous with aortic disease.

angiography is performed before removing the guidewire to confirm patency. Residual narrowing within the stent should be treated with repeat balloon angioplasty. An adequate result is defined by less than <30% residual stenosis on angiography. Completion angiography is then performed after the wire is removed over an end-hole catheter. Control of the access sites may be accomplished with a closure device or simple removal of the sheath followed by manual pressure after the activated clotting time has decreased below 180 seconds. Open brachial artery repair may be selected in patients with small arteries or if there was increased risk for hemorrhage or thrombosis. Clopidogrel is prescribed for at least 30 days after stenting, and low-dose aspirin therapy is continued indefinitely. The patient should be seen 2 weeks postoperatively to assess the access site, renal function, and blood pressure.

COMPLICATIONS

Complications include rapid postintervention decline in renal function, which can result from atheromatous embolization or contrast-induced nephropathy. Contrast-induced nephropathy is seldom an issue because the procedure can be performed with minimal dilute dye or carbon dioxide. Pre- and postprocedure hydration is routinely performed for patients not at risk for congestive heart failure.

Renal artery rupture is a rare but serious complication during percutaneous balloon dilation and stent deployment, so it is critical to maintain wire access of the vessel until satisfied with postintervention anatomy. In the event of rupture of the renal artery, a covered stent may be deployed to control the site of perforation. Endovascular access to a ruptured vessel may be exceedingly difficult or impossible if wire selection is lost before repair. An urgent open salvage operation may be required but is rarely successful secondary to the duration of warm ischemia.

Renal capsule perforation with hemorrhage can occur if a wire extends distally through the kidney. It is critical to maintain control of a hydrophilic wire while it is in the renal artery and to maintain visualization of the tip with fluoroscopy at all times. It may be necessary to use an angled hydrophilic wire to cross a severely stenotic lesion, but it should be exchanged for a braided J-tip (3 mm) wire before proceeding with the intervention.

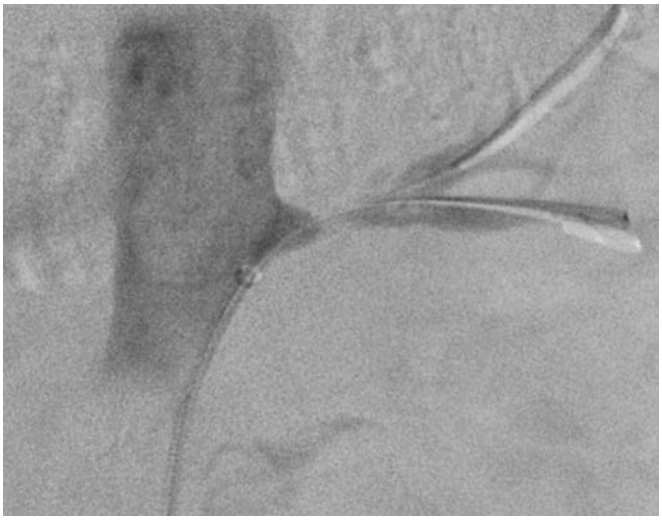


FIG. 6 Dual-wire technique is used to maintain access to both renal artery branches in this situation with a proximal left renal artery stenosis and an early bifurcation.

Renal artery dissection can occur when traversing tight calcified lesions. In addition, branch vessels may be compromised with treatment of a proximal lesion. Occasionally, a dual wire configuration is needed to maintain access to both branches (Fig. 6).

Access site complications including femoral pseudoaneurysm, hematoma with potentially significant blood loss, lymphatic leak, and femoral artery dissection are possible. It is mandatory to use ultrasound guidance to locate an appropriate access site in the common femoral artery to minimize access site complications. In addition, fluoroscopy should be used to localize the femoral head to enhance the ability to control hemorrhage with manual compression following femoral sheath removal.

OUTCOMES

Control of hypertension, measured by number of antihypertensive medications, has been demonstrated to improve in up to 80% of RAS patients treated by angioplasty and stenting. Renal dysfunction, measured by serum creatinine or estimated GFR, has been shown to stabilize or improve in 60% of RAS patients.

SURVEILLANCE AND FOLLOW-UP

Although there are no quality data on RAS surveillance after angioplasty and stenting, the authors recommend a duplex ultrasound within 1 month after the procedure to document the postprocedural change in renal artery PSV and in the RAR. Additional duplex ultrasounds are then performed every 6 to 12 months to assess for recurrent stenosis and renal atrophy. Blood pressure must be monitored carefully along with measurement of serum creatinine or estimated GFR. An abrupt change in control of hypertension or renal function may prompt earlier reimaging of the renal vasculature.

ENDOVASCULAR MANAGEMENT OF RESTENOSIS

Restenosis rates are as high as 50% at 12 months and 60% at 18 months. A renal artery PSV >180 cm/s suggests recurrent stenosis.

For asymptomatic patients with recurrent stenosis, increased surveillance should be considered with reintervention reserved for worsening renal function or blood pressure control. In-stent restenosis (ISR) is the most common pattern of disease recurrence encountered. ISR secondary to intimal hyperplasia is especially challenging to treat endovascularly as balloon angioplasty alone often has minimal impact. Thus, alternative strategies such as performing initial dilatation with a cutting balloon or using a balloon-expandable covered stent should be considered.

OPEN SURGICAL REPAIRS

In contemporary management, open renal artery surgery is mainly reserved for patients with symptomatic atherosclerotic RAS who are undergoing elective open surgery for aortic disease or rarely when urgent salvage of endovascular technical failure is indicated. Additionally, open surgery can be considered for patients that cannot be treated endovascularly due to either renal artery anatomy or revascularization of renal artery branches.

For elective open renal artery revascularization, careful preoperative risk assessment is essential. RAS is a marker for generalized atherosclerosis, and these patients must be screened for CAD, PAD, and CVD. Preoperative cardiac and pulmonary assessments are paramount to assess perioperative risk and initiate therapy to mitigate risk.

Open surgical techniques for treating RAS can be broadly classified as either direct surgical repair or indirect repair with an extraanatomic renal artery bypass. Aortorenal bypass and thromboendarterectomy are the most common direct surgical repairs. Aortorenal bypass is the more versatile option. However, transaortic thromboendarterectomy may be preferred for bilateral ostial atherosclerotic disease. Hepatorenal and splenorenal bypasses are the two most common extraanatomic renal artery bypasses. Alternatively, the left and right renal arteries also may be revascularized with prosthetic or vein bypass grafts originating from the iliac arteries. Direct aortorenal reconstructions are preferred to indirect methods because half of patients will require bilateral surgery, and 40% of patient will have concomitant occlusive disease involving the celiac axis. However, when the aorta is heavily diseased with calcific atherosclerotic plaque, the required aortic clamping for direct repair may not be feasible, and an extraanatomic bypass may be considered. Additionally, an extraanatomic bypass may be required in select patients with aortic pathologies being treated with aortic endografts. During direct repair, perfusion with cold preservation solution should be considered if the renal ischemia time is expected to be more than 40 to 60 minutes. Mannitol may also help to prevent the development of acute renal failure by renal vasodilation, flushing of renal tubules, and scavenging free radicals. For open revascularization, 12.5 mg of Mannitol should be administered intravenously during aortic and renal dissection.

AORTORENAL ARTERY BYPASS

The patient should be positioned with the umbilicus at the level of the bed break with the table angled at 15 degrees. The most versatile approach for open repair is the midline incision from xiphoid to pubis in the event that other procedures are indicated. Alternatively, a transverse supraumbilical incision may be made, providing better exposure of the pararenal aorta and proximal renal arteries. Traditionally, the small bowel is retracted to the right side of the abdomen and the posterior retroperitoneum is incised longitudinally overlying the aorta at the base of the mesentery. The duodenum is mobilized at the ligament of Treitz and reflected to the patient's right to expose the left renal vein. To completely expose the left renal vein and renal hilum, the incision of the posterior peritoneum can be extended along the inferior border of the pancreas to the left. The inferior mesenteric vein can be ligated without consequence as needed. The left renal artery lies posterior to the vein. Alternatively, full mobilization of the left colon and splenic flexure provides the best exposure of the pararenal aorta and proximal renal arteries. It is easily performed and may be associated with decreased postoperative ileus (Fig. 7). The pancreas is retracted cranially and left renal vein is mobilized. The gonadal and adrenal veins must be ligated and divided to allow for adequate mobilization. Special attention must be given to the lumbar vein that often exits the posterior renal vein as it can easily be avulsed during mobilization of the renal vein. For full mobilization of the left renal vein, the lumbar vein should also be ligated and divided. Once mobilized, the left renal vein can be retracted cephalad or caudal to expose the underlying aorta and left renal artery. It is important to note that the surgeon must determine whether division of the left renal vein will be necessary for additional exposure before ligating and dividing these important renal vein collaterals. Proximal division of the left renal vein can safely be performed only if these branches are preserved. The proximal right renal artery can be exposed by retracting the left renal vein cephalad and the inferior vena cava to the patient's right, which may require ligating additional lumbar veins. To expose the distal right renal artery and renal hilum, the right colon and duodenum must be mobilized medially. On the right, inferior polar renal arteries frequently course anterior to the IVC, and all such vessels should be presumed to be renal branches. Dissection and distal exposure of the renal arteries should be extended beyond the diseased artery. A healthy segment of artery can be identified by inspection and gently palpating the vessel over a right angle.

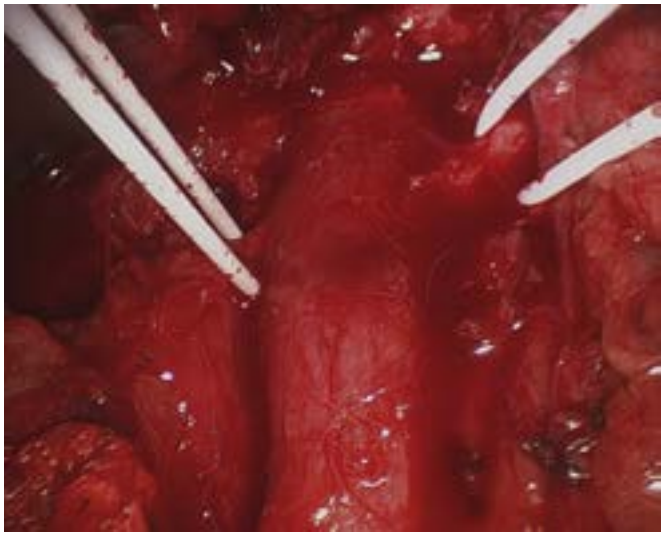


FIG. 7 Retrocolic exposure instead of the standard inframesocolic approach provides excellent access to the juxtarenal aorta and both renal arteries as seen in this intraoperative image.

The preferred inflow source is the infrarenal aorta. Autologous saphenous vein is often the preferred conduit if it is adequate caliber (>4 mm). Alternatively, a 6-mm prosthetic graft or autologous hypogastric artery can be used. The patient is systemically heparinized before obtaining control of the arteries. An elliptical arteriotomy of the anterolateral aorta is created with a No. 11 blade or an aortic punch. The conduit is spatulated and an end-to-side anastomosis is then fashioned using running 5-0 polypropylene sutures. The graft is distended with arterial pressure before being cut to length. Appropriate graft length is important to avoid undue tension or redundancy, which can be a cause of early graft thrombosis. The distal end of the graft and the distal end of the renal artery are spatulated and an end-to-end anastomosis is then fashioned using 6-0 polypropylene sutures. Before completing the anastomosis, the conduit is flushed of debris and air and back bleeding from the native renal artery is performed. The stump of the proximal end of the renal artery is oversewn with running 4-0 polypropylene sutures. After completion

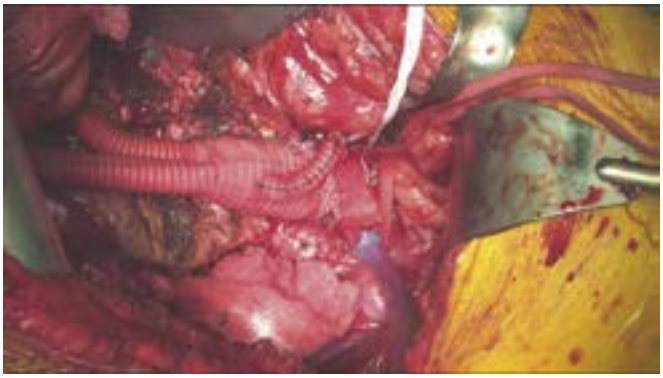


FIG. 8 The left renal limb is constructed from the aortobiiliac bypass graft for repair of an infrarenal aorta abdominal aneurysm.

of the anastomosis, flow within the distal renal artery is evaluated with handheld continuous wave Doppler ultrasound and/or an ultrasonic flow probe.

When performing concurrent aortic and renal artery construction, the authors prefer to perform the proximal anastomosis of the renal limb on the back table before insertion to minimize ischemic time to the kidney. Cautery is used to create a graftotomy on the anterolateral aspect of the aortic component of the graft. The proximal anastomosis is then performed using 5-0 polypropylene sutures. After the proximal aortic anastomosis is performed, the vascular clamp is repositioned onto the graft cranial to the renal limb. The distal end of the renal limb is then prepared and sutured to the renal artery as previously described. After completing the renal artery reconstruction, reperfusion to the kidney is obtained by repositioning the proximal vascular clamp caudal to the renal limb before completing the distal aortoiliac reconstruction in standard fashion (Fig. 8).

AORTORENAL ENDARTERECTOMY

The exposure of the pararenal aorta and renal arteries through the base of mesentery is the same as for an aortorenal bypass as explained earlier. The left and right renal arteries are dissected from their ostia to a point beyond the distal extent of the plaque, and vascular loops are placed around each of the renal arteries. The aorta is circumferentially dissected free above and below the renal artery origins. Intravenous unfractionated heparin is administered. Vascular loops are used to control the renal arteries. The suprarenal and infrarenal aorta are controlled with atraumatic vascular clamps. Transaortic endarterectomy is performed via a transverse aortotomy extending onto the renal arteries. Atheromatous plaque is removed carefully with a vascular freer elevator to achieve tapered endpoints. Occasionally, a small distal shelf will require placement of a 7-0 polypropylene tacking sutures. The aortotomy is closed with a patch aortoplasty.

EXTRAANATOMIC RECONSTRUCTION

For a splenorenal bypass, a flank or transverse supraumbilical incision is often performed. The descending colon is mobilized from the sigmoid colon to the splenic flexure along the white line of Toldt and a left to right medial visceral rotation is performed. The avascular plane between the mesocolon, posterior surface of the pancreas and Gerota's fascia overlying the anterior surface of the kidney is developed, which allows the pancreas to be elevated from the retroperitoneum. The splenic artery is identified as it courses along the superior border of the pancreas and the proximal splenic artery is carefully mobilized from the pancreas. The left renal vein is exposed and mobilized to expose the underlying left renal artery. The adrenal, gonadal and lumbar branches are ligated and divided to permit adequate exposure. The left renal artery should be mobilized from its origin for 2 to 3 cm distally. Intravenous unfractionated heparin is administered, and the splenic artery is controlled with an atraumatic vascular clamp and is ligated and divided distally to maximize available length for the bypass. The distal splenic artery stump is oversewn with 4-0 polypropylene sutures. After the left renal artery is controlled proximally and distally, it is transected as close as possible to its aortic origin. The proximal stump is oversewn with 4-0 polypropylene sutures. The transected end of the splenic artery and the transected end of left renal artery are spatulated and an end-to-end anastomosis is created using 6-0 polypropylene sutures (Fig. 9). An eversion endarterectomy of the proximal left renal artery or an interposition vein graft can be performed if additional length of the vessel is required for a tension-free anastomosis. When the splenic artery is significantly calcified and tortuous, a better option may be to use a saphenous vein graft to create a splenorenal bypass. The spleen is left in situ if collateral circulation is intact and there is no evidence of a capsular tear. Splenectomy should be performed if there is any indication of capsular injury secondary to the risk of postoperative hemorrhage.

The right renal artery may be revascularized using the common hepatic artery as the inflow source. A right subcostal incision is preferred. The white line of Toldt is incised from the cecum to the hepatic flexure and the colon and mesentery are mobilized medially. A Kocher-like maneuver is then performed, and the duodenum and pancreas are reflected to the left. The right renal vein is mobilized and retracted either cephalad or caudal to expose the underlying right renal artery as it courses dorsal to the inferior vena cava. The common hepatic artery is exposed after incising the lesser sac and



FIG. 9 Completed splenorenal bypass. Note the left renal artery is rotated cephalad and anastomosed to the transected splenic artery. The left renal vein is being retracted with a Penrose drain to expose the aorta.

it is identified as it courses to the left of the common bile duct. Dissection is continued until the common hepatic artery, proximal gastroduodenal artery (GDA) and proximal proper hepatic arteries are exposed. The common hepatic artery is left intact, and a reversed saphenous vein interposition graft is anastomosed at the origin of the transected GDA in a spatulated fashion (Fig. 10). This technique requires that the proximal superior mesenteric artery is free of significant stenosis and not dependent on the GDA for significant collateral blood flow. The distal GDA is oversewn. The vein graft is then anastomosed to the right renal artery either in an end-to-side or an end-to-end configuration. An end-to-side configuration may be used for a proximal stenosis without evidence of distal embolization and an end-to-end configuration is necessary if the proximal renal artery requires ligation (Fig. 11).

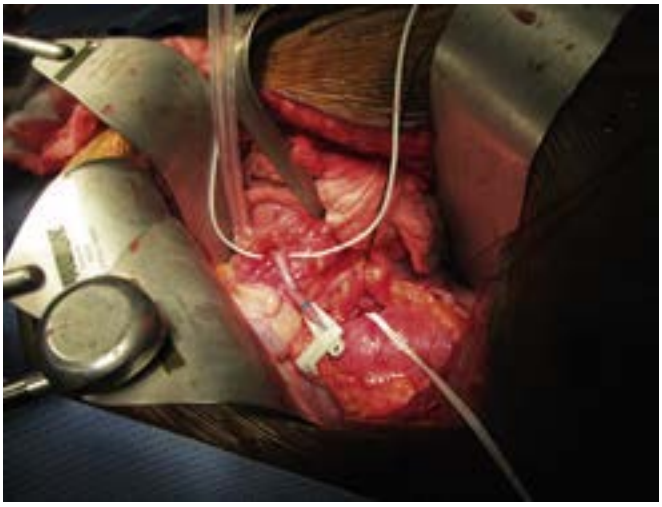


FIG. 10 Proximal anastomosis of a right hepatorenal bypass with vein. The saphenous vein graft is sewn to the common hepatic artery at the site of origin of the gastroduodenal artery. Methylene blue is used to mark the vein to assist with proper orientation.

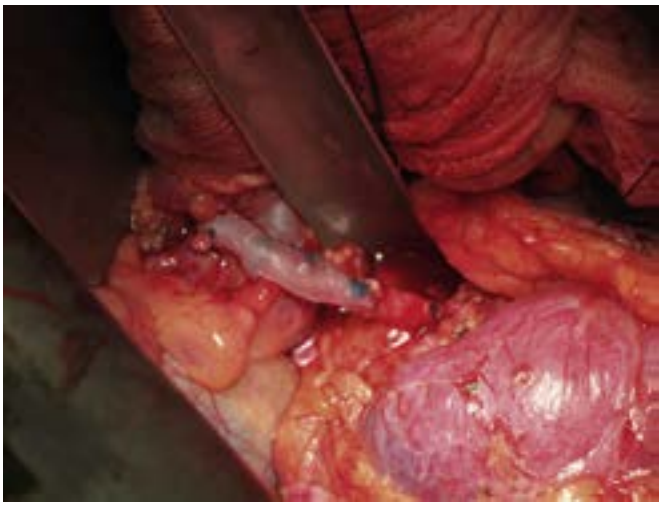


FIG. 11 Distal anastomosis of a right hepatorenal bypass with a saphenous vein graft. In this case, it was performed in an end-to-end configuration to prevent retrograde flow into the false lumen of an aortic dissection.

COMPLICATIONS

Cardiovascular and pulmonary complications are common after open renal artery revascularization. Dialysis-dependent renal failure occurs in only 1% of patients. The perioperative mortality rate is between 2% and 6%. Thirty-day mortality has been associated with increasing age, chronic renal failure, and history of congestive heart failure.

RESULTS

Approximately 85% of patients experience blood pressure improvement or cure postoperatively. Renal function improves or stabilizes in approximately 60% of patients who undergo open repair. As many as 70% of selected patients who recently started dialysis may no longer require dialysis after open renal artery revascularization. Early postoperative stenosis occurs in only 1% to 2% of patients.

SURVEILLANCE AND FOLLOW-UP

Although there are no quality data on RAS surveillance after bypass or endarterectomy, the authors recommend a duplex ultrasound 30 days after the procedure to interrogate the graft and flow in the renal arteries. Duplex ultrasounds are performed every 6 to 12 months to assess for recurrent stenosis and renal atrophy. Blood pressure must be monitored carefully along with measurement of serum creatinine or estimated GFR. An abrupt change in control of hypertension or renal function may prompt earlier reimaging of the renal vasculature.

SUMMARY

Atherosclerotic RAS may cause systemic hypertension or impaired renal function. The vast majority of patients with symptomatic RAS are managed successfully by careful control of hypertension and risk factors associated with the progression of arteriosclerosis. Revascularization is recommended for RAS patients with renovascular hypertension that is not responsive to maximal medical therapy, ischemic nephropathy, and young individuals in whom flash pulmonary edema is caused by RAS. Revascularization by renal artery angioplasty and stenting has largely supplanted open renal artery surgery because of its minimally invasive nature, excellent early renal artery patency, and decreased periprocedural morbidity and mortality. Open renal artery bypass and endarterectomy currently are reserved for urgent salvage after technical endovascular failures and procedures in combination with elective aortic reconstructions that require an open approach. Open extraanatomic renal artery bypass operations may be helpful when treating patients with aortic aneurysms or dissections when using aortic endografts.

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Raynaud's Phenomenon

David S. Strosberg, MD, and Alan Dardik, MD, PhD

First described by Maurice Raynaud in 1862, Raynaud's phenomenon (RP) has been characterized by pathologic, paroxysmal, reversible vasoconstriction of acral arteries and arterioles in response to sympathomimetic stimuli. These stimuli may be cold, provocative emotional, or pharmacologic. The classic tricolor presentation involves progression from a period of pallor secondary to intense vasospasm, to cyanosis related to pooling of deoxygenated blood, and finally to rebound hyperemia due to gradual vasorelaxation. This leads to the typical pattern of white, then blue, and finally red digits during an episodic event following a stimulus. The overall prevalence in the general population has been estimated to be 3% to 5%, although the prevalence varies in accordance to sex, local climate, and occupational exposures. The nomenclature used to describe this condition—including Raynaud's syndrome, Raynaud's disease, RP, primary Raynaud's, and secondary Raynaud's—has been confusing, misleading, and often erroneously applied. Coined by Hutchinson, RP was a term designed to suggest the variable etiologic mechanisms underlying this condition.

In 1992, LeRoy and Medsger addressed the issue and proposed the following solution: primary RP refers to the characteristic findings without evidence of an underlying medical or surgical condition, or idiopathic in nature. Secondary RP, however, describes the characteristic findings related to an underlying medical or surgical condition.

PRIMARY RAYNAUD'S PHENOMENON

Primary RP is seen worldwide, with higher incidence in colder climates. The median age at onset of primary RP is 14 years, and only 27% of cases begin at the age of 40 or later. Symmetric events involving both hands or both feet are common. Tissue loss or gangrene is not associated with primary RP. Given the idiopathic nature of this subtype, diagnostic tests aimed at identifying underlying contributory causes—such as nail fold capillaroscopy, erythrocyte sedimentation rate (ESR), and serologic markers—are, by definition, normal (Fig. 1; Table 1). A positive family history in first-degree relatives is not uncommon, suggesting a yet to be identified genetic correlation of unknown penetrance.

SECONDARY RAYNAUD'S PHENOMENON

Secondary RP is more commonly is seen after the age of 30. Unlike primary RP, secondary RP is associated with severe attacks that may be isolated to one extremity. Gangrene and ischemic ulceration are possible. Common systemic diseases associated with secondary RP include certain connective tissue, rheumatologic, autoimmune, endocrine, and hematologic disorders. Scleroderma is most commonly associated with secondary RP. Given the asymmetrical patterns of distribution, a thorough workup evaluating for thromboembolic, atherosclerotic, degenerative, and/or compressive arterial etiologies is advisable (Box 1).



FIG. 1 Raynaud's phenomenon in a patient with Ehlers Danlos syndrome to illustrate the color changes associated with stressful stimuli. **(A)** Normal-appearing hand. **(B)** After cold stimuli, the pallor from vasoconstriction can be seen. **(C)** After 30 seconds, the hyperemic red appears in fingers with blood reperfusion. **(D)** Hand after 3 minutes exposed to stimuli.

TABLE 1 Characteristics of Primary and Secondary Raynaud's Phenomenon

	Primary	Secondary
Age	**Younger (<30 years)**	**Older (>30 years)**
Gender preference	Female	Male (depending on secondary cause)
Incidence	Most common	Less common
Familial predisposition	Yes	Yes
Combination with other disease	No, idiopathic	Associated with systemic disease
Vascular defect	Functional dysregulation of autonomic nervous system	Structural changes in connective tissue or vessels
Associated signs	None	Arthritis, sclerodactyly, cardiopulmonary abnormality, rash
Frequency	Precipitated by stimuli	Periodic and stimuli trigger
Severity of symptoms	Long history of mild attacks	Severe and disabling pain
Distribution	Symmetric	Asymmetric
Duration	Self-limited	Need for additional treatment (pharmacologic, surgery)
Critical complications	None	Ischemia and ulcers
Capillaroscopy	Normal (symmetric, thin, and uniform)	Abnormal (dilated, irregular, elongated, and tortuous vessel)
Vascular examination	Normal pulses	Abnormal pulses
Erythrocyte sedimentation rate	Normal	Elevated
Serologic studies	Negative	Antinuclear antibody, autoantibodies
C-reactive protein	Normal	Elevated

BOX 1 Secondary Causes of Raynaud's Phenomenon

Rheumatologic
- Systemic sclerosis (CREST syndrome)
- Sjögren's syndrome
- Systemic lupus erythematosus
- Ehlers Danlos syndrome
- Rheumatoid arthritis
- Dermatomyositis
- Polymyositis
- Mixed connective tissue disease

Autoimmune
- Reiter's syndrome
- Vasculitis (polyarteritis nodosa, Henoch-Schönlein purpura)
- Antiphospholipid syndrome
- Primary pulmonary hypertension

Endocrine
- Hypothyroidism
- Pheochromocytoma
- Carcinoid

Infectious
- Hepatitis B and C infection
- Mycoplasma pneumonia

Medications
- Cyclosporine
- Ergotamine
- Beta-blockers
- Cytotoxic (bleomycin, cisplatin, vinblastine)
- Bromocriptine
- Nicotine
- Cocaine
- Sulfasalazine
- Interferon-alpha and interferon-beta
- Clonidine
- Sympathomimetics
- Estrogen in oral contraceptives
- Caffeine

Occlusive Vascular
- Arteriosclerosis
- Vascular trauma (hypothenar hammer syndrome)
- Buerger's disease
- Thoracic outlet syndrome
- Thromboembolism

Hematologic Proliferative
- Leukemia
- Lymphoma
- Polycythemia vera
- Multiple myeloma
- Disseminated intravascular coagulation
- Cryoglobulinemia
- Cold agglutinin disease

Neurologic
- Migraines
- Carpal tunnel syndrome
- Polyneuropathy

Environmental
- Emotional stress
- Frostbite
- Repetitive trauma or injuries to hand

Malignancy
- Lung, stomach, small bowel
- Paraneoplastic syndrome
- Neurofibromatosis

PATHOGENESIS

The pathogenesis of RP involves a highly localized process with unimpeded, augmented sympathomimetic tone and subsequent vasoconstrictive mechanisms affecting acral arteries, arterioles, and thermoregulatory arteriovenous connections. This has been attributed to overexpression or hyperactivity of postsynaptic alpha-2 receptors, decreased endothelial nitric oxide and prostacyclin production, and altered metabolism of endothelin-1 and angiotensin II. Disrupted capillary flow caused by endothelial dysfunction occurs in severe cases of secondary RP leading to tissue loss and/or gangrene. A chronic inflammatory state from recurring episodes can lead to vascular structural changes such as intimal fibrosis. In addition, imbalances between coagulation and fibrinolysis have been observed in both primary and secondary RP.

DIAGNOSIS

The diagnosis of RP remains primarily clinical. It is critical to differentiate between primary and secondary RP to correctly manage and treat patients as management is considerably different for the two conditions. A detailed clinical history with special emphasis on the location, severity, and frequency of symptoms is required. Seasonal variation and association with stressful situations are important to elicit. A detailed social history focusing on past or present tobacco and/or illicit drug use, as well as a thorough review of active medications and supplements, is critical. The physical examination should include a thorough pulse examination.

A screening diagnostic test is usually a noninvasive arterial study to rule out obstructive pathology (Fig. 2). The study should include evaluation of bilateral extremities with segmental pressures, Doppler waveforms, and wrist/ankle-brachial indices. Plain radiographs are of limited utility, but they may demonstrate heterotopic calcification or cervical ribs suggesting upstream etiologies for secondary RP. Digital plethysmography can be performed. Obstructive lesions will demonstrate blunted, dampened waveforms on pulse contour analysis, whereas vasoconstrictive processes have a pathognomonic peaked dome at the apex of the waveform. Cold immersion testing is a highly sensitive but nonspecific adjunctive diagnostic maneuver. Computed tomography angiography (CTA) or magnetic resonance angiography (MRA) is helpful to screen for upstream or thromboembolic arterial disease. Selective, catheter-directed, digital subtraction angiography is reserved for those cases where noninvasive testing has been inconclusive or has suggested the presence of disease amenable to endovascular therapy.

Serologic tests are appropriate when secondary RP is suspected. This is especially true when systemic symptoms such as myalgias, arthralgias, fever, weakness, and rash are present. A complete blood count, routine blood chemistry panel, antinuclear antibodies test, rheumatoid factor, and complement levels should be drawn (see Box 1).

MANAGEMENT

Nonpharmacologic

Conservative, nonoperative, nonpharmacologic measurements aimed at avoidance of triggers are the cornerstone of therapy for most patients with RP. Cold exposure should be minimized and hand/foot warming measures, such as mittens, applied as often as necessary. Caffeine, cigarette smoking, and other culprit agents should be avoided. The severity and frequency of symptoms determines how drastic a lifestyle modification is required.

Temperature biofeedback has been investigated with varying results. Patients may be taught skin temperature feedback to allow for voluntary control of peripheral vasospastic episodes. Temperature biofeedback has been studied in the randomized setting with variable results, with a recent meta-analysis demonstrating that this technique is not superior to placebo.

Pharmacologic

Patients whose symptoms remain refractory to conservative measures are considered for vasodilatory pharmacotherapy. These medications, while off-label, are prescribed at the lowest possible dose that allows a satisfactory decrease in the frequency and severity of the vasospastic episodes.

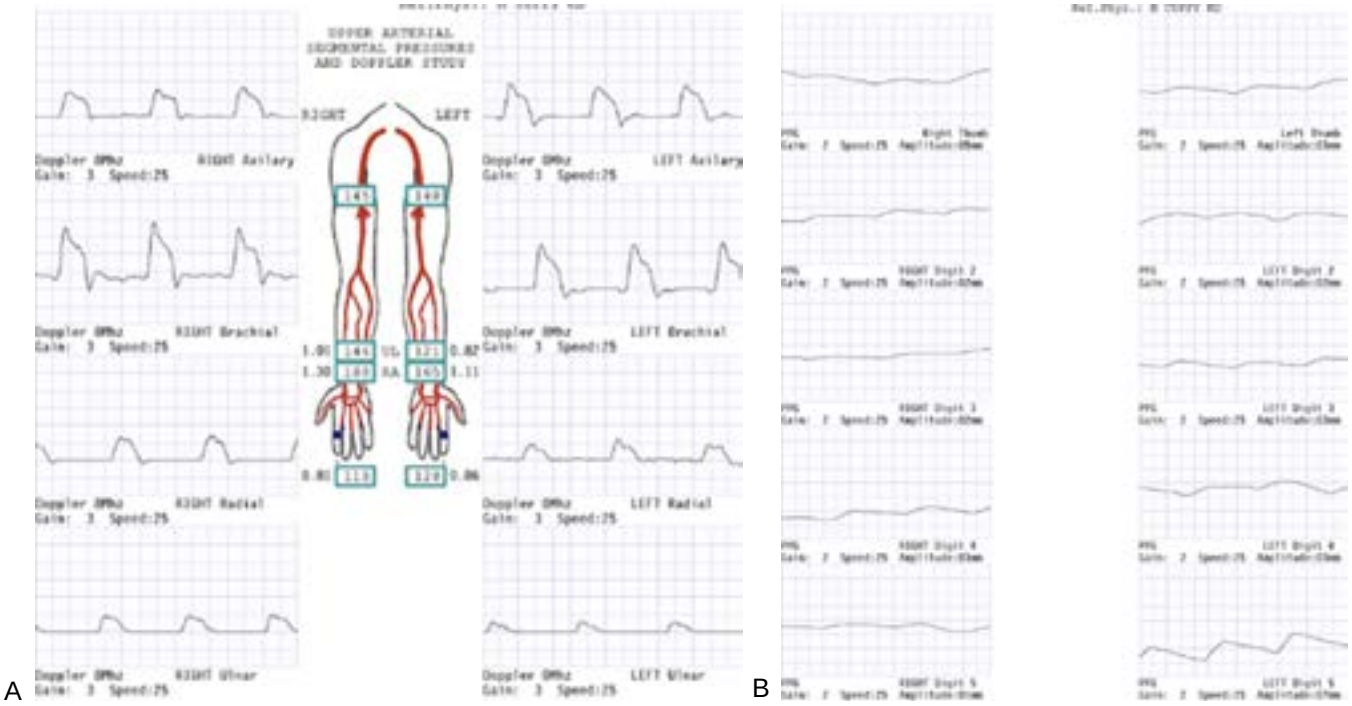


FIG. 2 **(A** and **B)** An example of an abnormal upper extremity noninvasive arterial study. Note the blunted waveforms proximally and the flat digital tracings.

The typical first-line pharmacologic agent for RP is a dihydropyridine-class, long-acting calcium-channel blocker such as nifedipine, nicardipine, or amlodipine. Sustained-release nifedipine, for example, is initiated at a dose of 10 to 30 mg daily to three-times daily. Side effects include hypotension, headaches, weight gain, dizziness, or lightheadedness. Other classes and types of calcium-channel blockers are available and have been used with variable success rates. Phosphodiesterase inhibitors (e.g., sildenafil, tadalafil) may be tried if calcium-channel blockers are ineffective. There are multiple second-line agents for the treatment of RP, including prazosin, losartan, and prostaglandins. These drugs are reserved for recalcitrant cases and usually are utilized by subspecialists in the field. Topical nitroglycerin at 0.5 mg in gel up to four times a day can be used alone or in combination with oral agents. Close monitoring of side effects and vital signs is important in cases of polypharmacy.

Surgical Treatment

Surgical treatment for secondary RP is indicated to treat any identified underlying obstructive pathology (see Box 1). Local wound care is initiated with serial debridement of necrotic tissue and dressing changes. Limited digital amputation may be required with the treatment goal of alleviating pain and preserving function.

Sympathectomy may provide temporary relief of pain and ulcer healing; however, long-term results are variable. Coveliers described a 30-year review of 728 sympathectomies performed on 580 patients with upper extremity digital ischemia, including 13 retrospective studies and 5 prospective studies. In patients with primary RP, 92% of patients reported a positive initial effect, with 58% of patients reporting a long-term beneficial effect. For those with secondary RP, 89% of patients had a long-term beneficial effect. Ulcer healing or improvement was achieved in 95% of patients. A thoracoscopic approach has mostly replaced open cervical exposure. A single thoracoscopic port is placed, and with single lung ventilation, the sympathetic chain is visualized posteriorly overlying chest wall pleura. The pleura are incised, and hook cautery is used to divide the sympathetic chain at each desired level. Horner's syndrome may be recognized after the procedure; compensatory hyperhidrosis has also been described.

Adventitial stripping of the digital arteries of the hand is often a last resort in the treatment of refractory RP. First described by Flatt in 1980, the technique commences with a palmar incision centered at the distal palmar arch. After the palmar fat has been retracted, each digital artery is cleared around its circumference. Under microscopy, the adventitia of each digital artery is circumferentially stripped for 4 mm with care not to perforate the artery. The dissection is carried out distal to the junction of the distal perforating artery with the common digital artery. Electron microscopy of the specimens has confirmed the presence of sympathetic fibers. Alternatively, adventitial stripping of the radial and ulnar arteries at the wrist, with resection of the nerve of Henle, has also been described. Although several case series have demonstrated promising outcomes, these results should be interpreted cautiously given the variations in patient selection, reported measure, and surgical technique.

Extended periarterial sympathectomy involves adventitial stripping of the proper and common digital arteries, the superficial arch and ulnar artery extending into the mid-forearm, and the dorsal radial artery. In the setting of ulnar or radial occlusion, a vein bypass is performed from the proximal wrist artery to the superficial palmar arch. In a series by Merritt of 48 patients who underwent 58 extended periarterial sympathectomies, sustained improvement of ischemic pain was reported in 94.8% of cases, and 78% of patients with ulcers completely healed. Sensory evaluation, measured by Semmes-Weinstein monofilament testing, improved from 4.15 to 3.29 postoperatively.

Botulinum toxin-A (BoNT-A) may also be utilized for distal sympathectomy. BoNT-A is injected into the interstitial space around the digital neurovascular bundles. Approximately 10 units (2 mL) of reconstituted onabotulinum toxin A is injected into each neurovascular bundle at the palm just proximal to the first annular pulley. In a study of 33 patients, 28 had reduction of pain at rest. All patients with chronic ulcers healed within 60 days. There were seven patients who required repeat injection for return of symptoms. Complications of BoNT-A injection include transient intrinsic muscle weakness lasting 2 to 4 months and rarely systemic side effects such as nausea, generalized muscle weakness, or flulike symptoms.

Alternative methods have been proposed in selected cases with varying results. Transcutaneous nerve stimulation may be used to induce vasodilation. Using low frequency stimulation, a small group of four patients with RP exhibited a rise in skin temperature with temporary relief of ischemic pain. Spinal cord stimulators may also reduce pain and promote ulcer healing.

Laser therapy has been investigated as an alternative treatment modality in RP. A small, randomized controlled trial investigated 48 patients, randomized into either 685-nm wavelength diode laser versus sham therapy. All patients were treated 5 days a week for 3 weeks. The patients in the low-level laser therapy had a reduction in frequency and intensity of vasospastic attacks compared with sham therapy. A similar study trialing multiwave locked system laser therapy, which emits two wavelengths of continuous 808-nm and pulsed 905-nm laser, demonstrated a similar reduction in frequency and intensity of vasospastic attacks. Ulcer resolution and recurrence has yet to be evaluated with laser therapy.

SUMMARY

RP encompasses two broad categories of disease depending on the etiology, location, and severity of symptoms. Primary RP is a more benign, idiopathic condition with a more symmetric distribution affecting the bilateral hands and/or feet. Its diagnosis is mainly clinical with adjunctive noninvasive studies that can help rule out upstream pathology and/or rule in provoked vasospasm. Lifestyle modifications and avoidance of provocative stimuli remain the cornerstone of therapy. Refractory cases can be treated with a variety of off-label pharmacologic agents, most commonly long-acting calcium channel blockers. Secondary RP is a more severe form of disease most commonly associated with scleroderma. Other contributing causes include upstream obstructive pathologies, compression-related syndromes, thromboembolic phenomena, and systemic inflammatory conditions. Treatment is aimed at addressing the underlying cause and minimizing symptoms. Less responsive to pharmacotherapy, secondary RP has also been treated with a variety of adjunctive surgical/interventional maneuvers that have yielded equivocal short to midterm outcomes. Further research into the behavioral and alternative therapeutic modalities is ongoing.

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Thoracic Outlet Syndrome

Timothy K. Williams, MD, Zachary German, BSPH, and Julie A. Freischlag, MD

INTRODUCTION

Thoracic outlet syndrome (TOS) represents several disease states, with a constellation of signs and symptoms depending on the structures involved. The underlying pathophysiology is compression of the neurovascular structures of the upper extremity where they emerge from the chest, the region known as the thoracic outlet. Estimates of incidence range from 3 to 80 per 1000 in the population. In general, there are three forms of TOS described, namely neurogenic, venous, and arterial. Neurogenic TOS (nTOS) is by far the most common form, accounting for 95% of all cases. This occurs due to compression of the brachial plexus within the interscalene triangle, which is bordered by the first rib, the anterior scalene muscle, and the middle scalene muscle (Fig. 1). The second most common is venous TOS (vTOS), which accounts for approximately 4%. vTOS arises from compression of the axillosubclavian vein within the costoclavicular space, which is bound by the first rib, clavicle, and anterior scalene muscle. The subclavius muscle and tendon, which connects the first rib and the clavicle, frequently compresses the vein in this region (see Fig. 1). Finally, arterial TOS (aTOS) occurs in about 1% of all cases and develops due to compression of the axillosubclavian artery within the interscalene triangle. This disorder commonly occurs in association with a cervical rib. Aside from being rare, aTOS is frequently insidious in its evolution, making it a challenge to diagnose. It frequently manifests with evidence of limb ischemia due to distal embolization from aneurysmal degeneration or from vessel occlusion. Although these three disorders are all defined as TOS, the presentation, diagnosis, and management vary significantly.

DIAGNOSIS AND TREATMENT

Neurogenic Thoracic Outlet Syndrome

Thoracic outlet syndrome is largely a clinical diagnosis, established based on a careful history and physical examination. Unfortunately, no gold standard diagnostic modality exists to either confirm or exclude the diagnosis; however, select tests can be employed that influence the strength of the diagnosis. TOS can develop due to acquired factors (trauma or repetitive overhead activity) or congenital anatomic predispositions (cervical rib or anomalous tissue bands). Common presenting symptoms include upper extremity paresthesias, pain within the C8-T1 dermatome, and/or arm weakness. These symptoms are typically exacerbated by arm abduction and alleviated by adduction. nTOS occurs most commonly in women, with a ratio of nearly 10:1. Additional symptoms include anterior neck, back, and shoulder pain of varying degrees, making this disorder difficult to distinguish from other pathologic conditions.

Several physical exam maneuvers can be employed to support the diagnosis. Many patients will experience tenderness to palpation over the anterior scalene muscle in the low anterior neck. Classically, Adson's maneuver has been used to assess for TOS, with ablation of pulses at the wrist representing a positive test; however, this and other similar arm abduction tests can be positive in upwards of 20% of healthy, asymptomatic individuals and should therefore not be used to support the diagnosis. The clinical test that has proven most beneficial is the elevated arm stress test (EAST), where the arms positioned in the "hold up" position (90 degrees of shoulder abduction, external rotation, and elbow flexion) (Fig. 2). The patient is instructed to continuously open and close their hands for 3 minutes, with reproduction of the patient's symptoms defined as a positive test. A chest radiograph should be performed to assess for the evidence of a cervical rib (Fig. 3A) or rudimentary first rib (Fig. 3B), as well as other bony abnormalities including previous clavicular fractures. Duplex ultrasonography is commonly performed to assess for arterial and venous compression, which can serve as indirect evidence of compression within the thoracic outlet. Computed tomography (CT) can measure the costoclavicular and interscalene spaces, and the finding of a costoclavicular space smaller than the length or width of the interscalene space can be suggestive in the diagnosis of TOS. Other diagnostic modalities such as such as magnetic resonance imaging (MRI) and electromyography (EMG) are costly and add little to the diagnosis of nTOS, and therefore should not be routinely performed. Additionally, MRI has been shown to have low sensitivity for detecting TOS, is time intensive, and can exacerbate symptoms when provocative maneuvers are applied. In select patient populations with atypical symptoms or suspicion for alternate pathologies, these tests may play an important role.

When the diagnosis remains equivocal, an anterior scalene muscle block can be performed, which is widely accepted as a useful

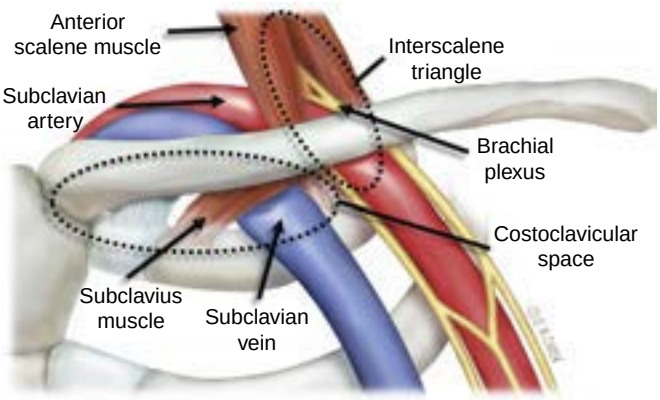


FIG. 1 Anatomy of the thoracic outlet. Key structures within the thoracic outlet: subclavius muscle, subclavian vein, anterior scalene muscle, subclavian artery, and brachial plexus. Two key anatomic apertures depicted include the costoclavicular space and interscalene triangle. *(Courtesy S.A. Chen.)*



FIG. 2 The elevated arm stress test. The arms are held at 90 degrees of abduction and external rotation with the elbows at 90 degrees of the flexion to narrow the interscalene triangle. Hands are rapidly opened and closed to elicit the patient's symptoms, which is suggestive of nTOS. *(Courtesy Mayo Foundation for Medical Education and Research.)*

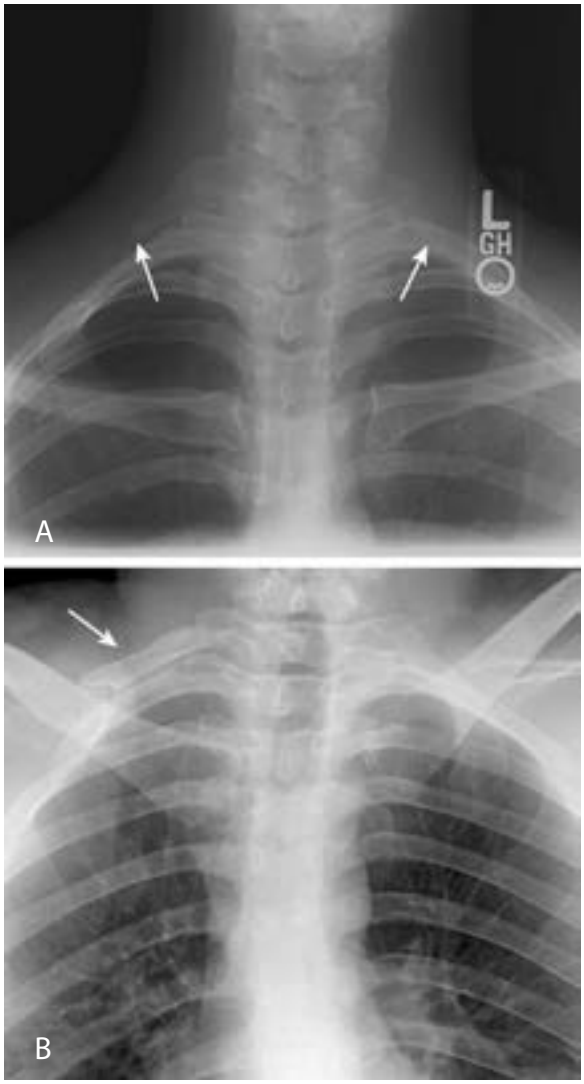


FIG. 3 Bony abnormalities in thoracic outlet syndrome. **(A)** Chest radiograph demonstrating bilateral cervical ribs. **(B)** Chest radiograph demonstrating a rudimentary first rib. Both bony abnormalities can predispose individuals to neurogenic and arterial TOS. *(A modified from Kirkwood ML, Valentine RJ. Thoracic outlet syndrome. In: Cronenwett JL, Johnston KW, eds. Rutherford's Vascular Surgery, 8th ed. Philadelphia: Elsevier; 2014:1969–1976.e1.)*

diagnostic adjunct for suspected nTOS. This involves the injection of a short-acting local anesthetic directly into the anterior scalene muscle utilizing ultrasound or CT guidance. The block is meant to induce muscle relaxation, thereby simulating decompression of the thoracic outlet. A positive block is one that effectively reduces the patient's symptoms and has been shown to correlate with symptomatic improvement following surgery. Beyond serving as a diagnostic modality, anterior scalene muscle block will frequently provide short-term symptom relief. When botulinum toxin (Botox) is utilized, longer-term symptom relief can be achieved, with reported duration of up to 3 months. This can be utilized as a bridge to surgical decompression but should not be utilized as primary therapy, as repeated injections can increase the risk of scar formation, thereby complicating future surgery.

Although the presentation of nTOS may vary across patients, a consensus-based diagnostic criteria have been developed by experts in the field (Consortium for Outcomes Research and Education on Thoracic Outlet Syndrome) in an effort to standardize the approach to this challenging patient population. This report states that, for the diagnosis of nTOS, three out of four criteria must be met: signs and symptoms of pathology occurring at the thoracic outlet, signs and symptoms of nerve compression, absence of other pathology potentially explaining the symptoms, and a positive response to a properly performed scalene muscle test injection.

Preoperative management centers around physical and/or occupational therapy, activity modifications/restrictions, and pharmacotherapy. In general, a minimum of 2 to 3 months of physical therapy upfront should be performed, as many patients with nTOS will experience significant improvements and may not require surgery when activity modifications or postural changes have proven beneficial. Muscle relaxants, nonsteroidal antiinflammatory drugs, and analgesic agents are commonly utilized as adjuncts in management.

For those patients with history, physical exam, and diagnostic findings to support the diagnosis of nTOS, along with a suboptimal improvement following a reasonable trial of physical therapy, surgical intervention should be strongly considered. In general, a lower threshold for surgical intervention should be considered in those patients with a compelling diagnosis combined with a fixed bony abnormality such as a cervical or rudimentary first rib.

Venous Thoracic Outlet Syndrome

Venous TOS represents the second most common form of TOS and involves compression of the subclavian vein within the costoclavicular space. Most commonly, this stems from acquired anatomic changes such as hypertrophy of the anterior scalene and subclavius muscles or from trauma to the anterior chest, particularly in the context of a clavicular fracture. It is frequently seen in young, otherwise healthy adults or adolescents, in athletes, and those who are exposed to occupational conditions that demand repetitive overhead use of the arms. Over time, this repetitive mechanical injury to the vein leads to progressive scarring, inflammation, narrowing and ultimately thrombosis (Paget-Schroetter syndrome). Common presenting signs and symptoms include arm swelling, pressure, fatigue, cyanosis, and a sensation of heaviness. In contrast to nTOS, patients do not typically experience debilitating pain but may experience discomfort from tense edema. In those with a subacute or late presentation, evidence of venous collaterals along the chest wall may be apparent. Patients with venous compression in the absence of true thrombosis or occlusion may experience similar symptoms, but these tend to be more mild and relieved by arm rest (McCleery syndrome).

The diagnosis can be suspected based on history and physical exam findings; however, it is definitively established with duplex ultrasound, CT venography, or conventional venogram. Typically, duplex ultrasound is the standard initial diagnostic modality. Findings supporting the diagnosis of vTOS include loss of flow on color Doppler in the distal subclavian vein and a continuous venous waveform (lack of phasicity) within the axillary vein. Other studies include conventional chest radiographs, which should be routinely performed to assess for bony abnormalities. In the absence of complete occlusion, venous compression can be elicited with the arm in varying degrees of abduction, resulting in an ablation of flow. Less commonly, intravascular ultrasound has been used to diagnose vTOS, particularly when it is suspected but not confirmed by other modalities. This approach can readily identify venous compression, partial thrombosis, or chronic sequela of prior thrombotic events within the costoclavicular space.

Preoperative management is centered around anticoagulation. For patients with a severe, acute presentation (onset less than 14 days), catheter-directed thrombolysis can be considered, although this remains controversial. Venography characteristically demonstrates abundant collateral vessels and stenosis/occlusion of the axillosubclavian vein at the costoclavicular junction (Fig. 4). In general, angioplasty should be avoided before surgical decompression, as this seldom rectifies the underlying extrinsic compression of the vessel and result in further injury. For subacute or chronic presentations, thrombolysis plays no role in management.

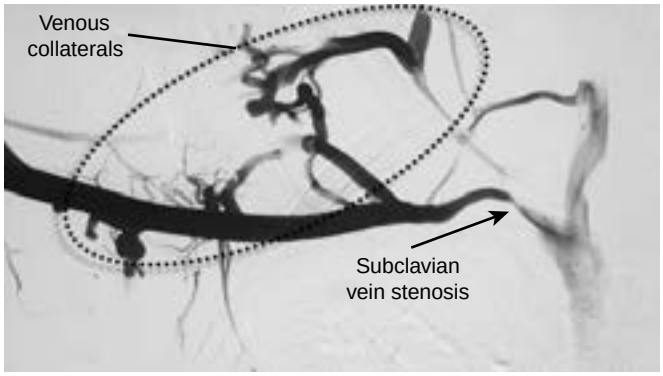


FIG. 4 Venogram in a patient with vTOS. Venogram after transaxillary first rib resection and scalenectomy shows venous stenosis within the costoclavicular space, which resulted in abundant collateral vessels providing venous drainage of the arm.

In patients without secondary causes for venous thrombosis of the axillosubclavian vein (i.e., central venous catheters, documented hypercoagulable state), surgery is typically indicated. The timing of surgery remains an area of controversy, with some advocating for early surgical decompression and others promoting an upfront period of anticoagulation (weeks to months) before surgery. It is the author's stance to perform early decompression (within 1 week) for acute presentations to minimize the inflammatory cascade produced by acute thrombosis, with a more protracted approach for patients with a chronic presentation (2–4 weeks).

Arterial Thoracic Outlet Syndrome

Arterial TOS (aTOS) is the rarest form of TOS, representing approximately 0.5% of patients overall. As with vTOS, it tends to occur in younger patients and most commonly occurs in patients with bony anomalies such as a cervical or rudimentary first rib. The underlying pathology of this disorder is repetitive trauma to the subclavian artery, which leads to progressive vessel stenosis, occlusion, or aneurysmal degeneration with distal embolization. Presenting symptoms commonly include arm or hand claudication. Patients may also experience typical signs or symptoms of acute limb ischemia, including paresthesias, poikilothermia, paralysis, pallor, and pulselessness. Because distal embolization may cause variable degrees of ischemia, patients may experience an insidious progression of the disease and present late, with abrupt episodes of exacerbation punctuated by intervals of improvement. In advanced disease, patients may experience tissue loss or even digit gangrene.

Initial assessment should include duplex ultrasonography along with upper extremity segmental blood pressure measurements. It is important to obtain bilateral upper extremity blood pressure measurements to assess for a discrepancy. Ultrasound can reliably detect axillosubclavian stenosis and/or aneurysmal degeneration, as well as downstream occlusion from distal embolization. As with other forms of TOS, a chest x-ray should be performed to evaluate for bony anomalies. CT angiography should be considered to evaluate the patient's anatomy; however, conventional angiography may be necessary to aid in surgical decision making.

Unlike other forms of TOS, aTOS universally requires surgical intervention and frequently mandates surgery beyond thoracic outlet decompression. While surgical decompression of the thoracic outlet remains a fundamental tenet of management in these patients, aTOS requires a tailored surgical approach based on the patient's specific anatomic abnormalities. This may include reconstruction of the axillosubclavian artery, thrombolysis, embolectomy, and/or distal bypass depending on the extent and level of disease.

SURGICAL MANAGEMENT

Although certain aspects of surgical management may vary based on the specific form of TOS, the unifying aspect of all interventions involves surgical decompression of the thoracic outlet. This can be performed using a supraclavicular, transaxillary, infraclavicular, or paraclavicular (infraclavicular and supraclavicular) approach depending on the form of TOS and the patient's unique anatomic characteristics. It is the authors' preference to utilize the transaxillary approach for the majority of nTOS and vTOS cases, which represent approximately 99% of all cases. aTOS, as it frequently requires vascular reconstruction to varying degrees, is typically managed from a paraclavicular approach. Newer methods of treating TOS include robot-assisted first rib resection and video-assisted thoracoscopic surgery.

Transaxillary Approach

The transaxillary approach provides excellent surgical exposure of the interscalene triangle and the costoclavicular space, making it ideally suited for the surgical management of both nTOS and vTOS. Since this technique utilizes a lateral surgical approach rather than anterior, the first rib can be exposed widely. This exposure also provides excellent visualization of the brachial plexus and subclavian vein/artery. Additionally, this incision provides excellent cosmesis by comparison to alternative exposures.

Patients undergo general anesthesia routinely, along with a short-acting neuromuscular blockade. Long-acting neuromuscular blockade should be avoided to enable nerve stimulation and corresponding muscle contraction during exposure and dissection, thereby minimizing the risk for iatrogenic nerve injury. Following anesthesia induction, the patient is positioned in the lateral decubitus position with support from an axillary roll and a beanbag. The body is further padded with foam at pressure points, and pillows are placed between the legs. The arm, axilla, and chest wall are widely prepped. The arm is then suspended within the Machleder retractor, which holds the arm in 90 degrees of abduction and the elbow at 90 degrees of flexion (Fig. 5). Not only does this retractor hold the arm in a stable position, but it facilitates lateral retraction of the arm to open the axillary space and provide adequate visualization during the dissection. The arm is appropriately padded to prevent neurovascular injury during positioning and retraction.



FIG. 5 Positioning for the transaxillary approach. The patient is in the lateral decubitus position with the arm suspended within the Machleder retractor, which affords excellent exposure and maintains stable arm positioning. The post of the retractor is raised and lowered throughout the procedure, to enhance exposure and to minimize traction injury, respectively. *(Courtesy S.A. Chen.)*

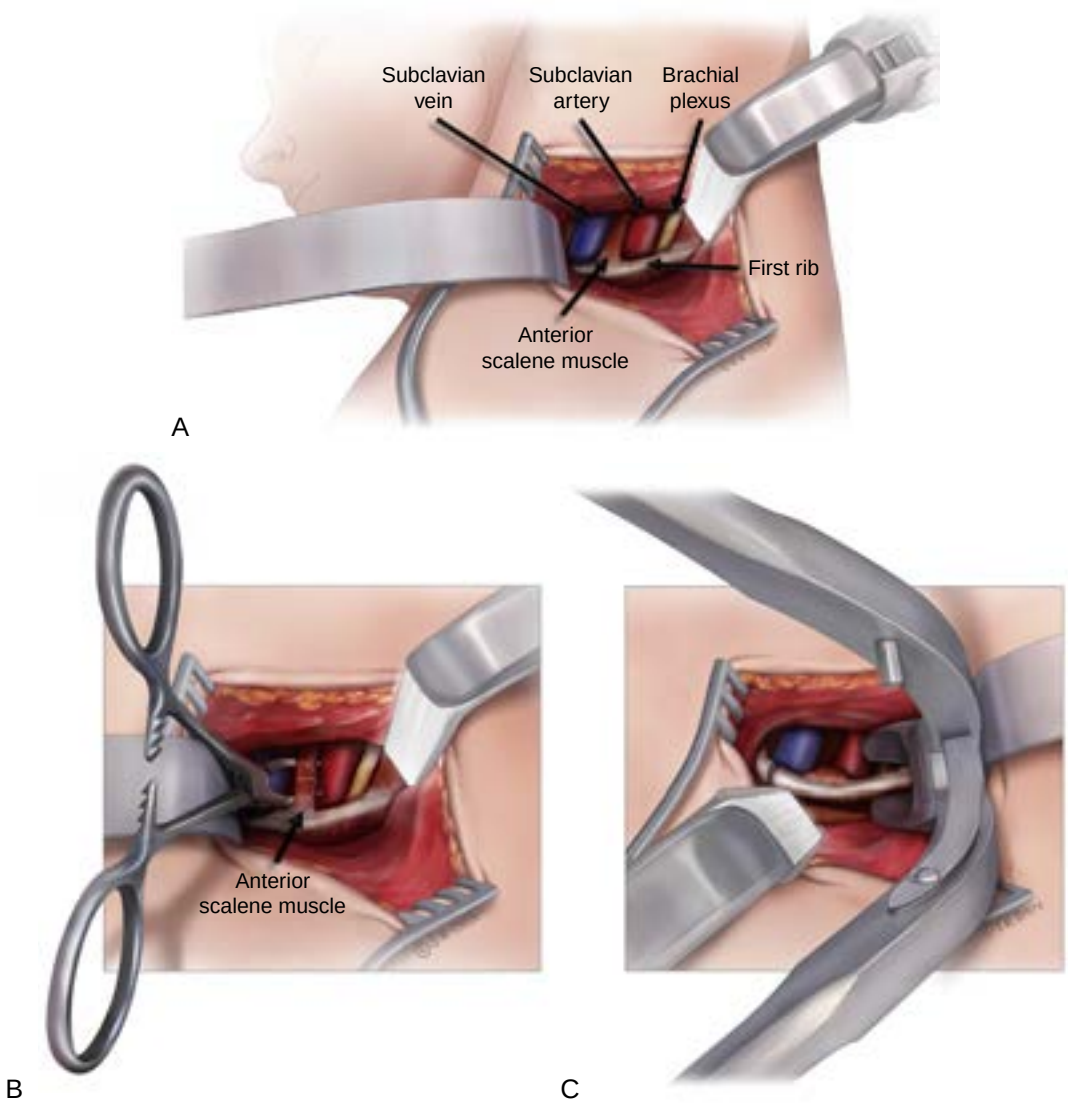


FIG. 6 Transaxillary approach for first rib resection and scalenectomy. **(A)** Anatomic relationships as viewed from the transaxillary approach. A lighted retractor is used to enhance visualization and combined with a Deaver to provide anterior and posterior retraction. **(B)** Division of the anterior scalene muscle is performed with the use of a long right-angle clamp and Metzenbaum scissors. **(C)** Division of the rib, first performed anteriorly then posteriorly. *(Courtesy S.A. Chen.)*

A transverse incision is made within the axilla at the lower border of the axillary hair line, between the pectoralis major muscle anteriorly and the latissimus dorsi muscle posteriorly. Following incision, dissection proceeds with cautery down to the chest wall, being vigilant to avoid injury to the long thoracic and thoracodorsal nerves. Upon reaching the chest wall, the arm is retracted laterally. Blunt dissection ensues within this avascular plane using finger dissection, Kittner dissectors, and/or peanuts. The first rib can be palpated deep in the dissection bed. Additional blunt dissection is performed to identify the subclavian vein anteriorly, the first rib inferiorly, and the subclavian artery and brachial plexus posteriorly (Fig. 6A).

Next, soft tissue attachments and the intercostal muscle bridging the first and second rib are cleared from the lateral/inferior border of the first rib using a periosteal elevator or blunt dissector. The subclavius muscle and tendon are identified anteriorly and carefully, being mindful to avoid injuring the adjacent subclavian vein. The inner table of the rib is then carefully separated from the underlying parietal plural using a spatula or small periosteal elevator. On the lateral outer surface of the rib, fibers of the middle scalene muscle are pushed posteriorly to create a plane between the brachial plexus and the rib. It is important to not transect this muscle sharply to avoid injuring the long thoracic nerve, as it passes through the middle scalene muscle.

A plane is developed bluntly between the anterior scalene muscle and the subclavian artery to facilitate safe division of the muscle. Division of the anterior scalene is performed in several steps, using a right-angle clamp to spread and laterally retract a portion of muscle followed by transection using Metzenbaum scissors (Fig. 6B). Additional passes are performed until the muscle has been divided completely. The rib is then divided with a bone cutter anteriorly, being mindful to avoid injuring the subclavian vein. The right angle is then passed along the inner border of the first rib to remove any additional fibers of the anterior scalene muscle that remain. Next, the rib is transected posteriorly, avoiding injury to the brachial plexus (Fig. 6C). In the presence of a cervical rib, removal of both the first and cervical rib is typically required but poses unique challenges. Often, the nerve is anteriorly displaced by the cervical rib making it difficult to achieve a safe plane for bone transection. Often, the cervical or rudimentary rib has a bony attachment to the rib below, requiring piecemeal removal using a rongeur. Ultimately, a tailored approach is required based on the patient's specific anatomy.

Major complications are rare, with the risk of significant nerve or vascular injury of less than 1%. In the event of an arterial and/or venous injury, it is challenging if not impossible to definitively repair from the transaxillary exposure, requiring an urgent anterior approach for vascular control. Assessment for a pneumothorax is achieved by filling the surgical field with saline before closure and performing a Valsalva, with loss of fluid volume and/or bubbling of air serving as evidence of a pleural defect. This rarely requires placement of a chest tube. Rather, the pneumothorax can be evacuated during closing through application of suction to a red rubber catheter placed within the pleural space, which is removed before final skin closure. The skin and subcutaneous tissue are then closed in standard fashion. A routine postoperative chest x-ray is not required even when a pneumothorax is detected intraoperatively, as it does not change management, provided the patient remains asymptomatic.

Supraclavicular Approach

Another commonly utilized exposure is the supraclavicular approach, which can be used for all forms of TOS (Fig. 7). This is the authors' preferred exposure for the management of aTOS, enabling both arterial reconstruction and first rib resection. This is also our preferred approach for redo operations following previous transaxillary exposure, given the increased potential for vascular complications due to scarring. For patients with either aTOS or vTOS, the supraclavicular approach can be combined with an infraclavicular approach (paraclavicular) to better facilitate vessel exposure, lysis, and/or reconstruction.

Patients are positioned supine with a shoulder roll to allow for neck extension. The head is rotated contralateral to the affected side. The chest wall, axilla, and ipsilateral upper extremity are included in the operative field. A skin incision in the supraclavicular fossa is made 1 to 2 cm cephalad and parallel to the clavicle, extending from the clavicular head of the sternocleidomastoid muscle laterally for approximately 10 cm. The scalene fat pad is divided inferiorly and medially between ties or with electrocautery to facilitate superolateral retraction. Care should be taken to avoid injury to the phrenic nerve as it emerges through anterior surface of the anterior scalene muscle. A nerve stimulator can be employed to aid in identification. Next, the anterior scalene muscle is divided sharply, being mindful to avoid injuring the subclavian artery found deep to the muscle. Some authors suggest full excision of the muscle from its insertion on the transverse process to provide the greatest decompression of the space, which is an advantage afforded by this anterior approach. However, this places the phrenic nerve at risk and has not been conclusively shown to minimize recurrence.

Posterior to the brachial plexus is the middle scalene muscle, which must be cleared from the first rib to facilitate posterior transection of the rib. The long thoracic nerve can be found exiting the middle scalene muscle along its lateral border, injury to which can result in significant disability from a winged scapula and impaired anterior arm elevation. The middle scalene muscle is bluntly cleared from the rib using a periosteal elevator. Sharp division of the muscle

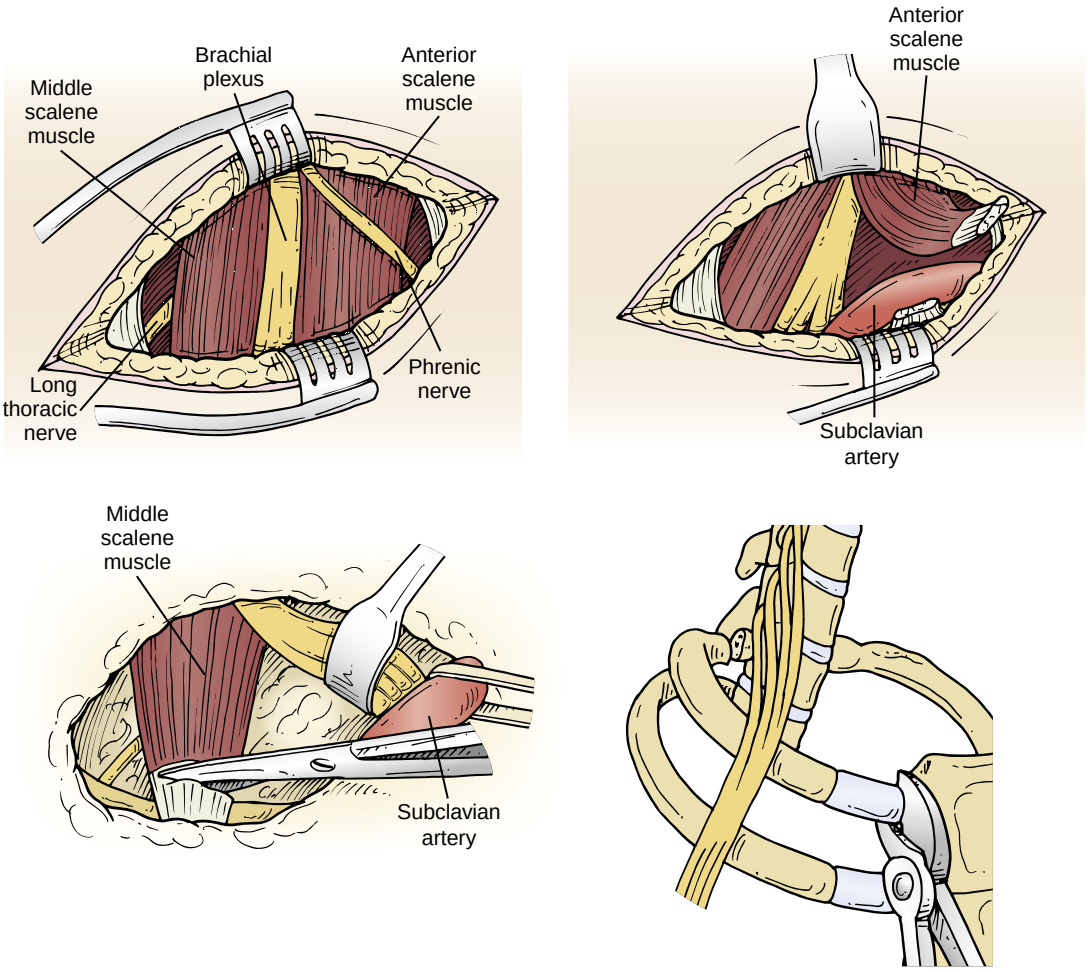


FIG. 7 **Supraclavicular approach for first rib resection and scalenectomy.** *(Modified from Messina LM. Thoracic outlet syndrome. In: Cronenwett JL, Johnston KW, eds. Rutherford's Vascular Surgery, 8th ed. Philadelphia: Elsevier; 2014:1977–1987.e2.)*

close to the rib can be entertained, provided the long thoracic nerve has been identified and protected. Anterior slips of the muscle may be found coursing beneath the plexus, which may require cephalad retraction on the nerves to fully detach the muscle from the rib.

Intercostal muscle between the first and second ribs is dissected. The parietal pleura are then bluntly dissected away from the inner surface of the rib above and below, being careful to not enter the pleural space. Small branches of the subclavian artery may require ligation to facilitate elevation of the artery before transection of the rib. Any residual attachments between the rib and the brachial plexus are then cleared. While anteriorly retracting the plexus, a bone cutter is positioned posteriorly around the rib and the rib is divided. Next, the subclavian vein and artery are elevated and retracted posteriorly to facilitate anterior division of the rib, anterior to the insertion of the anterior scalene muscle. Unlike the transaxillary approach, transection of the rib at the costosternal junction can seldom be achieved from this exposure, but it should be divided as far anterior as possible. Residual bone can then be excised using a rongeur.

Infraclavicular Approach

The infraclavicular approach is an alternative for patients with vTOS, providing access to the costoclavicular space and allowing for more complete anterior resection of the first rib. It also provides excellent exposure of the axillosubclavian vein, allowing for venous reconstruction either with patch angioplasty or interposition grafting. However, there is not a uniform consensus on the need to perform venous reconstruction in the majority of vTOS cases and should therefore be performed selectively. This approach is frequently combined with a supraclavicular exposure, known as the "paraclavicular" approach, enabling both venous and arterial reconstruction, as well as sufficient posterior exposure for complete rib resection.

Patients are positioned and prepped as described for the supraclavicular approach. A transverse skin incision should be made 1 to 2 cm caudal to the clavicle approximately 10 cm in length, beginning at the medial one-third of the clavicle and extending laterally. The pectoralis major muscle will be encountered and is spread to expose the clavipectoral fascia. The pectoralis minor is retracted laterally or can be divided to enable more distal exposure of the subclavian artery and vein, thereby facilitating vascular reconstruction. The subclavius muscle and tendon medially are divided sharply to provide adequate decompression of the vein. The rib can be divided far anteriorly at the costosternal junction.

Robot-Assisted Approach

Robot-assisted first rib resection has grown in popularity for treatment of all types of TOS and can be done via transthoracic or transaxillary approaches. Robotic approaches show promise as an alternative to open surgery, with high long-term patency rates in vTOS, reduced postoperative pain and opioid use, and low rates of brachial plexus injury compared with the supraclavicular approach. Robotic approaches can provide excellent visualization of anatomic structures, yet require unique skill and infrastructure, limiting broader adoption.

For the transthoracic approach, lateral decubitus positioning is employed. Commonly, three port sites are utilized. A variety of instruments can be used, including monopolar cautery hooks and Maryland graspers, among others. Transection of the rib is achieved with a 45-degree Kerrison. A double lumen endotracheal tube is used to facilitate single lumen ventilation. After insertion of a 30-degree camera, the first rib is identified. The periosteum of the first rib is removed from the inner surface of the rib. Next, dissection ensues along the upper border of the first rib anteriorly and posteriorly using blunt dissection. The lower border of the rib is then dissected in a similar manner. Along the upper margin of the rib, the anterior scalene muscle is divided as well as blunt dissection of the middle scalene muscle, with sharp division of the subclavius and the costoclavicular ligament. Once the soft tissue attachments have been cleared posterior to the nerve, the rib is transected posterior to the nerve. Removal of the port is required to introduce the Kerrison rongeur. It is imperative to visualize and avoid injury to the subclavian vein anteriorly and the brachial plexus posteriorly. Once the rib is transected completely, any residual soft tissue attachments are cleared to facilitate removal of the specimen from the chest cavity. A chest tube is typically placed, which can be removed the following day before discharge home.

SURGICAL OUTCOMES

Outcomes following surgery for TOS are inherently linked to the type of TOS being treated. With respect to nTOS, symptomatic improvement following surgery ranges from 60% to greater than 90% across various studies. A recent report from the Johns Hopkins Hospital reviewed their experience with first rib resection and scalenectomy (FRRS) for nTOS over a 10-year period, during which 286 patients underwent 308 FRRS. They reported symptomatic improvement in 89% of patients during the first 5-year period, which increased to 92.8% in the second time period. These improved outcomes were attributed to improved patient selection, a higher percentage of patients with a positive muscle block, and a younger patient cohort. Another study evaluated outcomes in the subset of patients in whom cervical ribs were present and demonstrated sustained symptomatic improvement or resolution in 93%. However, early symptomatic improvement does not guarantee sustained results, with recurrence rates as high as 30% reported. Multiple factors are believed to influence this, including scar tissue, chronic nerve injury, and/or incomplete resection/decompression. Moreover, some patients will fail to have significant symptomatic improvement at all. In a study of 182 consecutive first rib resections (161 patients) for nTOS, 13% of patients were found to have marginal or no improvement in symptoms following surgery. Contributing factors included a poor response to scalene muscle block, the presence of chronic pain syndromes, preoperative opiate use, active smoking, and older age (mean age 45 vs. 38, $P = 0.02$). Additionally, the duration of preoperative symptoms also predicted postoperative outcomes, with an average of 90 months of preoperative symptoms in those experiencing unresolved symptoms postoperatively compared with 48 months in those with resolution of symptoms. In this context, it is important to consider alternative diagnoses due to the frequent nonspecific symptoms in this patient population.

For patients with vTOS or aTOS, outcomes are more easily defined on the basis of objective testing. Arterial and venous patency rates are reported to be greater than 90% after thoracic outlet decompression and vascular intervention, either open reconstruction or endovascular treatment. The authors' stance following transaxillary approach for vTOS is to continue routine systemic anticoagulation postoperatively in vTOS patients for several months, with duration predicated on vessel patency and the need for percutaneous intervention. A routine venogram is performed 2 weeks postoperatively, with approximately 80% to 90% either having a widely patent vein or undergoing successful venoplasty for the presence of residual stenosis. When venoplasty is required, anticoagulation is continued, and a subsequent follow-up ultrasound is performed at 1 month, at which time anticoagulation is discontinued if the vein is widely patent without residual thrombus. A minority of patients will have complete occlusion of the axillosubclavian vein found during the 2-week postoperative venogram and therefore not undergo venoplasty, which justifies continued anticoagulation for up to 6 months. Nonetheless, most of these vessels will either recanalize over time or the patient will develop collaterals sufficient to produce sustained symptomatic relief.

CONCLUSION

The diagnosis and decision making in nTOS is frequently challenging with the subjective nature of its presentation. Conversely,

vascular forms frequently represent a straightforward diagnosis based on history and supported by objective vascular testing. With respect to surgical management, however, nTOS infrequently involves more than FRRS, whereas vascular forms frequently require a more nuanced approach involving adjunctive procedures such as vascular reconstruction or endovascular therapies. For neurogenic patients, excellent results can be achieved with careful patient selection, being mindful to exclude alternate diagnoses for which TOS surgery will afford no benefit. The management of aTOS is driven by the distribution and extent of arterial disease, rarely adhering to a standardized approach. Finally, a protocolized approach to vTOS produces durable results irrespective of the surgical approach and rarely requires extensive vascular reconstruction. Further consensus is needed to determine best practices for diagnosis and management for this group of low-frequency disorders.

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Diabetic Foot

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INTRODUCTION

The pandemic of diabetes mellitus poses an enormous public health challenge in the form of higher medical costs, lost productivity, and premature death. The determinants of diabetes consist of a complex matrix of genetic, epigenetic, and lifestyle factors whose economic burden in the United States in 2012 was estimated at $245 billion in the form of higher medical costs ($176 billion) and reduced productivity ($69 billion). The average medical expenditures for people with diabetes is estimated at approximately $16,750 per year, which is approximately 2.3 times higher compared to those without diabetes.

Diabetes is the leading cause of foot-related pathology, namely diabetic foot ulcers (DFUs). Approximately one in four patients with diabetes will develop a foot complication during their lifetime, and 15% to 20% of DFUs will result in a lower extremity amputation (LEA). It is estimated that approximately 85% of all amputations are preceded by DFU. DFUs are multifactorial in origin and marked by a triad of neuropathy, ischemia, and infection. The optimal management of patients with diabetic foot wounds consist of clinical awareness, glycemic control, periodic foot inspection, custom therapeutic footwear, pressure off-loading, local wound care, treatment of osteomyelitis, and revascularization in cases of peripheral arterial disease (PAD). The development of multidisciplinary care programs has been shown to reduce the rate of LEA in patients with DFUs through early recognition and management of risk factors.

CLASSIFICATION OF THE DIABETIC FOOT AND THREATENED LIMB

DFUs and complex diabetic foot wounds are challenging to diagnose and manage due to the multiple etiologies involved in their development and progression. The etiology of diabetic foot wounds can be characterized as neuropathic, ischemic, or neuroischemic, representing the interplay of diabetic neuropathy and PAD. The detrimental effects of neuropathy and ischemia are potentiated in the setting of immunosuppression (i.e., transplant patients, chronic steroid use, and end stage renal disease) where distal vascular disease not amenable to operative therapy is commonplace. Additionally, altered biomechanics due to structural abnormalities including calluses, bunion deformities, hammer toe, and claw toe deformities allow the foot to become highly susceptible to development of DFU.

Classification of DFUs is of great importance in directing appropriate care. Various DFU classification systems have been developed, including the Wagner, SINBAD, and University of Texas classifications; however, many of these fail to fully account for the interplay of the different etiologies that can affect healing. More recently, the Society for Vascular Surgery developed the Wound, Ischemia, and foot Infection (WIfI) classification system to better predict outcomes of the threatened limb. While meant for all foot ulcerations, including those not related to diabetes, it has been shown to highly correlate with wound-related outcomes and the risk of major amputation.

In our practice, we utilize the WIfI classification system for all patients presenting with DFUs. The WIfI classification is based on the three categories of wound, ischemia, and foot infection, each with a grade from 0 (none) to 3 (severe). This results in 64 possible WIfI permutations predicting the risk of major LEA (Table 1) and the theoretical benefit of revascularization (Table 2). Advanced WIfI clinical stage has also been shown to correlate with prolonged wound healing time, decreased 1-year amputation-free survival, as well as the estimated benefit of revascularization for diabetic patients presenting with chronic limb-threatening ischemia.

When incorporated into daily practice, the WIfI classification provides a framework for both the evaluation and treatment of DFUs with limb threat.

EVALUATION OF THE DIABETIC FOOT

Wound

The evaluation of a patient with a DFU begins with the physical exam of both the foot and the wound itself. Almost all patients with DFUs have some element of sensorimotor polyneuropathy leading to muscle atrophy, structural deformity (claw or hammertoe), and loss of protective sensation (LOPS). This is compounded by the fact that these patients also frequently have autonomic neuropathy leading to decreased sweating and dry skin, which in turn increases the risk of skin cracks, fissures, and ulceration. The physical exam of the foot should include a thorough evaluation of the extent of neuropathic dysfunction, as well as examination for structural deformities that may be contributing to the wound itself. Neuropathy is assessed with a 10-g monofilament and at least one other assessment: pinprick, temperature, vibration, or proprioception.

The examination of the wound begins with local callus debridement. Overriding callus typically hides the wound itself and prevents

TABLE 1 Estimated Risk of Amputation at 1 Year for Each Combination

	Ischemia															
	0				1				2				3			
Wound-0	1	1	2	3	1	2	3	4	2	2	3	4	2	3	3	4
Wound-1	1	1	2	3	1	2	3	4	2	3	4	4	3	3	4	4
Wound-2	2	2	3	4	3	3	4	4	3	4	4	4	4	4	4	4
Wound-3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Foot Infection																

TABLE 2 Estimated Likelihood of Benefit of/Requirement of Revascularization (Assuming Achieving Source Control)

	Ischemia															
	0				1				2				3			
Wound-0	1	1	1	1	1	2	2	3	2	2	3	3	3	4	4	4
Wound-1	1	1	1	1	2	3	3	3	3	4	4	4	4	4	4	4
Wound-2	1	1	1	1	3	3	4	4	4	4	4	4	4	4	4	4
Wound-3	1	1	1	1	3	3	3	4	4	4	4	4	4	4	4	4
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Foot Infection																

Stage 1 Very Low	Stage 2 Low	Stage 3 Moderate	Stage 4 High

both a complete assessment and application of wound care products to the base of the wound. Wounds that are macerated may be related to infection or fluid overload. Differentiating the two should ultimately direct treatment and aid in providing a better environment for wound healing. Wounds are then probed with the back of a cotton swab to assess for depth and penetration to bone.

All patient with DFUs should have a three-view x-ray of the foot not only to evaluate for chronic osteomyelitis but also to identify any structural abnormalities that may be contributing to pressure points and ulcer formation. This can include prior amputations, Charcot deformity, and heterotopic ossification.

Following complete examination, the wound is graded from 0 to 3. Grade 0 corresponds to a lack of a wound or a preulceration. Grade 1 corresponds to a shallow ulcer without exposed bone (except the distal phalanx) and without gangrene. Grade 2 corresponds to an ulcer with exposed bone, gangrene limited to the digits, or a shallow heel ulcer. Finally, grade 3 corresponds to extensive ulcers or gangrene, as well as full thickness heel ulcers.

Ischemia

Physical examination of the foot for ischemia begins with the assessment of pulses. However, this can be exceedingly tricky in the diabetic patient population for three reasons. First, diabetic patients are prone to develop medial calcinosis and "hardening" of the arteries. Patients with significant calcification can have lead pipelike pedal vessels that do not transmit a pulse but still provide adequate blood flow. Second, many diabetic patients with foot wounds have pedal edema precluding an accurate pulse assessment. Finally, small vessel calcification and pedal arch obliteration can lead to poor collateralization and angiosomal ischemia in the presence of a palpable pulse (i.e., a heel wound with a palpable dorsalis pedis artery but a nonpalpable posterior tibial pulse).



FIG. 1 Calcification of tibial and pedal vessels (*arrows*).

An objective assessment of the blood flow is of paramount importance in defining the degree of ischemia. We typically begin with ankle-brachial indices (ABIs) and absolute toe pressures. ABIs may be falsely elevated due to calcification of the arteries (Fig. 1); however, absolute toe pressures are typically preserved in the diabetic patient population. Pulse volume recordings (PVRs) may also provide some beneficial information regarding overall perfusion at different levels of the leg and foot.

Ischemia is then graded from 0 to 3. Grade 0 corresponds to an ABI ≥80 or a toe pressure ≥60 mm Hg. Grade 1 corresponds to an ABI 0.6 to 0.79 or a toe pressure 40 to 59 mm Hg. Grade 2 corresponds to an ABI 0.4 to 0.59 or a toe pressure 30 to 39 mm Hg. Finally, grade 3 corresponds to an ABI <0.4 or a toe pressure <30 mm Hg. It cannot be overstated that toe pressures are more accurate in the diabetic patient population, and we rely heavily on them to assign the ischemia grade and guide our decision for vascular intervention.

Infection

The assessment for infection is likely the most important part of the examination of the diabetic foot due to the fact that infection is the primary component of the WIfI classification that drives amputation. Wound assessment should include examination for odor, drainage, and maceration. Superficial cultures should be obtained using a curette or culture of any puslike drainage itself.

Wounds should then be evaluated for osteomyelitis. Three-view x-rays can assess for bony changes consistent with osteomyelitis; however, this is typically a late finding. We rely on the probe-to-bone test, which has excellent predictive values. Any wound that probes to bone with the back of a cotton swab can be assumed to have osteomyelitis. Finally, MRI of the foot can be ordered in the presence of an equivocal physical examination or a nonhealing wound despite 4 to 6 weeks of maximal wound care and perfusion (<50% size reduction over 4–6 weeks). For patients with metal hardware or implanted cardiac devices that preclude MRI, a three-phase bone scan should be ordered to assess for osteomyelitis.

Infection is then graded according to the WIfI classification. Grade 0 corresponds to no infection. Grade 1 corresponds to a localized infection within 2 cm. Grade 2 corresponds to a local infection beyond 2 cm, abscess, or osteomyelitis. Finally, grade 3 corresponds to signs of systemic inflammatory response syndrome (SIRS).

Glycemic Control

The surgeon should understand that poor glycemic control is associated not only with long-term complications but also poor wound healing. Thus it is imperative to involve the endocrinology team in patients with DFUs and poor glycemic control. As a screening measure, we obtain a hemoglobin A1c every 3 months to assess for glycemic control.

TREATMENT OF THE DIABETIC FOOT

Wound

Once identified and assessed, local wound care is begun. Sharp debridement of any devitalized tissue is performed in the clinic setting. The choice of wound care dressings depends on the characteristics of the wound itself. Healthy wounds are typically prescribed a collagen dressing, while wounds with fibrinous tissue can be dressed with Santyl (Smith & Nephew, Andover, MA) or MediHoney (Integra LifeSciences, Princeton, NJ). Healthy deeper wounds may be best suited to a VAC dressing (3M+KCI, St. Paul, MN). Wounds with local infections are typically prescribed Iodosorb (Smith & Nephew, Andover, MA) or Bactroban (GlaxoSmithKline, Philadelphia, PA). Macerated wounds are dressed with alginate impregnated with silver or other absorptive foams. Wounds that have an adequate base but periwound maceration can be dressed with separate dressings in the base and Calmoseptine (Calmoseptine, Inc, Huntington Beach, CA) to the wound edges. Wounds with exposed bone and osteomyelitis are typically treated with surgical excision and are described later under *infection*.

Lower extremity edema can be due to venous hypertension, lymphedema, or fluid overload, among others. Edema can be exceedingly detrimental to the wound healing process and should be addressed immediately. Multilayer compression is a mainstay of therapy and should be utilized liberally to prevent fluid exudation from the wound bed itself, as this hinders the wound healing process.

Wounds related to pressure need to be offloaded. Multiple offloading devices exist to achieve this goal including wedge shoes, heel-out shoes, and a DH walking boot (Ossur, Foothill Ranch, CA). The best offloading device is the total contact cast, although this requires weekly cast changes, a wound without infection and a reliable patient. The total contact cast transfers all of the weight to the lower leg and tibia, rather than the foot, and has been associated with improved outcomes compared to other offloading devices.

Wounds related to a structural deformity may be healed with local wound care and offloading. However, these are at increased risk of local recurrence. Thus surgical excision of the deformity and rebalancing of the foot may provide the best long-term solution to such wounds.

Ischemia

The original WIfI classification defined a theoretical benefit of revascularization (see Table 2) for each category. Those without ischemia (grade 0, toe pressure ≥60 mm Hg) or those with grade 1 ischemia and smaller wounds or localized infection were not recommended for revascularization. However, the degree of ischemia and contribution of this category to poor wound healing tend to be underestimated in the diabetic population. Although the WIfI classification of ischemia chose an absolute toe pressure cutoff of 60 mm Hg for grade 0, it is generally accepted that the diabetic foot lacks significant collateral pathways due to small vessel disease and pedal arch obliteration. Thus we employ liberal angiography and endovascular intervention for those wounds with an absolute toe pressure 60 to 80 mm Hg that do not heal within 4 to 6 weeks with maximal wound care. Almost all wounds with grade 1 ischemia and above are booked for angiography and possible intervention. If the wound is frankly infected, debridement for source control is performed before angiography. In cases of subacute or chronic infection, angiography should be performed before debridement to minimize the possibility of ischemia-mediated tissue necrosis.

Techniques for infrainguinal revascularization are addressed in other chapters. However, the decision to treat ischemia in an endovascular or open fashion is an area of controversy. Many experts argue that larger wounds with extensive tissue destruction due to infection require open surgical bypass to avoid major amputation. They contend that this may especially be true in the diabetic population where tibial disease predominates, since endovascular therapy below the knee has decreased patency rates compared with open bypass. We have shown, however, that this may not always be the case. In our cohort of 195 predominantly tibial revascularizations, open revascularizations were associated with improved 4-year primary patency but no differences in amputation-free survival compared with peripheral endovascular interventions (PVIs). Furthermore, open revascularizations were also associated with a higher risk of perioperative complications. The improved outcomes in this cohort were felt to be due to an aggressive revascularization and wound care management strategy employed by a closely working multidisciplinary team.

Certain arterial lesions, such as long-segment lesions or heavily calcified are not crossable via endovascular interventions (Fig. 2). For these patients, we recommend open surgical bypass with single segment saphenous vein. In the absence of saphenous vein, arm vein can be utilized with excellent results. Typically, there is a size mismatch given the small nature of the tibial vessels, and thus most bypasses are performed in a translocated, rather than reversed, fashion with valve lysis using a valvulotome.

Patients with severe forefoot ischemia that is not amenable to endovascular or open revascularization are recommended for hyperbaric oxygen therapy as a last resort to avoid LEA. Indications for hyperbaric oxygen include osteomyelitis, gangrene, or an open wound with inadequate perfusion to achieve healing.

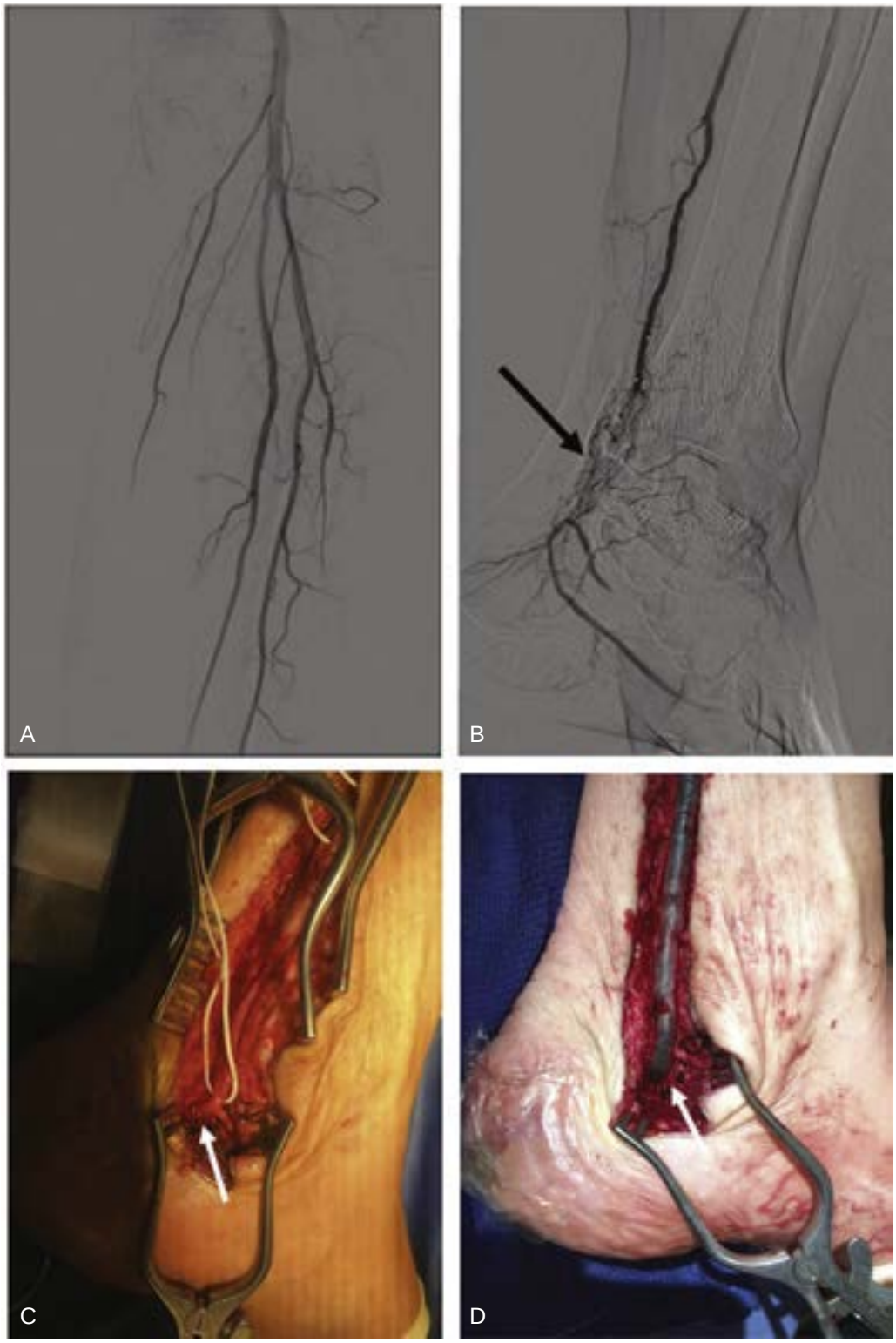


FIG. 2 **(A** and **B)** Preoperative angiograms demonstrating heavy calcific occlusion *(arrow)* of the distal posterior tibial artery with reconstitution of the medial and lateral plantar vessels. **(C)** Operative exposure of distal posterior tibial artery and branching into the medial *(arrow)* and lateral plantar arteries. **(D)** Translocated vein bypass with distal anastomosis onto the medial plantar artery (*arrow*).

Infection

As stated earlier, local wound cultures are typically obtained in the clinic setting for those wounds with any suspicion of infection or chronic wounds. Although we previously prescribed empiric antibiotics based on the wound assessment of foot infection alone, we have stopped this practice as it frequently led to an overprescription of antibiotics that the cultures were not sensitive to. We now prescribe antibiotics based on final cultures and sensitivities sent during definitive debridement.



FIG. 3 **(A)** Calcaneal ulcer with necrotic base. **(B)** S/p debridement with exposed calcaneus bone. **(C)** Placement of Integra (Integra LifeSciences, Princeton, NJ) dermal regeneration template. **(D)** Granular wound base after removal of the Integra silicone layer. **(E)** Healed wound.

Admission for parenteral antibiotics is indicated when there is concern for deep tissue infection (foot infection grades 2 and 3). As with any other acute infection, the primary goal is to achieve source control by means of abscess drainage, debridement of devitalized soft tissue and bone, and, if needed, resection and amputation of the involved bone or digit.

In patients with documented osteomyelitis, we typically recommend surgical resection of the infected bone (Fig. 3). Tissue samples obtained surgically are sent for microbiology to help guide appropriate antibiotic therapy. Simple toe amputations are prescribed a 2-week course of oral antibiotics. In cases where the metatarsal is resected (i.e., partial ray amputation or more proximal), we employ a 4- to 6-week course of prolonged antibiotics regardless of disease-free margins. While the 2012 Infectious Diseases Society of America guidelines suggest prolonged antibiotics are not required when the margins are disease-free, it has been our experience that residual infection leads to further minor *and* major amputation in this group. Thus, the risks of prolonged antibiotics seem to be justified.

In our practice, dirty and infected wounds are left open initially to determine the need for serial debridement and washout of the wound to achieve adequate source control. These wounds are then closed in a staged fashion. In wounds that cannot be closed due to lack of skin or tension and wounds with exposed tendon or bone, we liberally employ coverage with the Integra dermal regeneration template (Integra LifeSciences, Princeton, NJ, Fig. 2C). After a period of 3 to 4 weeks, the silicone layer is removed and local wound care is employed until ready for split-thickness skin grafting. Using this technique, we achieved 12- and 18-month healing rates of 79.0 ± 5.0% and 93.0 ± 3.3%, respectively, in patients who otherwise would have required a LEA.

Glycemic Control

Integration of endocrinology into the treatment team can help with both short-term and long-term glycemic control. While it was previously thought that a hemoglobin A1c ≤7 was necessary for good outcomes, we have shown that an A1c ≤8 was predictive of avoiding a major amputation. Thus, a more liberalized approach in patients with DFUs may be more appropriate than traditional teaching.

MULTIDISCIPLINARY MANAGEMENT, RESULTS OF TREATMENT, AND LONG-TERM PREVENTION

Multidisciplinary teams are now the standard of care for the treatment of patients with diabetic foot wounds. The composition of the multidisciplinary limb preservation service can vary; however, ours consists of vascular surgeons, surgical podiatry, wound care, and endocrinology. Other disciplines including infectious disease, plastic surgery, and orthopedic foot and ankle consultations are involved if the situation warrants their expertise.

We have shown that the multidisciplinary management of the diabetic foot is associated with improved wound healing, lower major amputation rates, decreased readmissions, and excellent long-term profitability regardless of socioeconomic deprivation. And while ulcer recurrence rates remain elevated at 3 years, most new ulcers in patients enrolled in our multidisciplinary service present at a lower WIfI stage, leading to decreased wound healing times and improved overall outcomes.

Patients and their families are educated regarding proper foot care and lifestyle modifications to prevent further complications. In accordance with Comprehensive Foot Examination and Risk Assessment Guidelines, patients follow up on an outpatient basis at regular 3-month intervals for foot inspection and examination, noninvasive vascular testing, and glucose management.

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GANGRENE OF THE FOOT

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INTRODUCTION

Gangrene is defined as the death and putrefaction of a body tissue. Most commonly, it is the result of irreversible ischemia. In the lower extremity, decreased perfusion to the skin and soft tissue, if not reversed in time, will lead to gangrenous changes. The most vulnerable areas tend to be in the peripheral circulation, such as the toes, where collaterals are lacking. Prolonged bed rest may cause pressure necrosis in the heel fat pad. Trauma, sepsis, prolonged use of peripheral vasoconstrictors, or exposure to cold may lead to gangrene. However, in the lower extremity, peripheral arterial disease (PAD) is the most common cause.

Three types of gangrene are recognized: dry, wet, and gas gangrene. In dry gangrene, the soft tissue becomes dry and desiccated, and usually a line of demarcation between viable and dead tissue can be defined (Fig. 1). In wet gangrene, the affected tissue may still be partially perfused and retains some turgor; a line of demarcation is not readily apparent (Fig. 2). Gas gangrene occurs when anaerobic bacteria, such as the *Clostridia* species, invade the tissue and muscle and release gas and toxins locally and systemically (Fig. 3). If not promptly treated, gas gangrene can spread rapidly and be fatal. The clinician's role is to recognize gangrene as a potentially serious problem and initiate a management plan. Surgical treatment of the gangrenous area ranges from simple debridement of necrotic tissue to a major lower extremity amputation. If blood supply to the limb is inadequate, revascularization to improve blood flow should be included in the treatment plan.

EPIDEMIOLOGY

Gangrene is often caused by a chronic disease process called *lower extremity peripheral arterial disease* (PAD). The prevalence of lower extremity PAD is estimated to be approximately 10% of adults older than 55 years of age. Multiple disease processes are associated with the development of PAD and include older age, hypertension, tobacco use, diabetes, and hypercholesterolemia.

Chronic limb-threatening ischemia (CLTI) is present if the patient presents with rest pain, ischemic ulceration, or gangrene. Epidemiologic studies indicate that the annual incidence of PAD in patients older than 40 years of age was 2.35%, and the annual incidence of CLTI was 0.35%. Every year, 11% of patients progress from PAD to CLTI. Risk factors associated with developing PAD include smoking, hypertension, hyperlipidemia, and diabetes mellitus. Although the number of individuals abusing tobacco has decreased over the years, the most recent reported data demonstrated in 2019, 14% (34.1million people) of the US population was still estimated to use tobacco products. The Centers for Disease Control and Prevention (CDC) also estimates that more than 30 million people in the United States are diagnosed with diabetes mellitus, and an additional 84 million qualify as prediabetics. Diabetics are especially vulnerable to the complications of PAD because they often have decreased sensation from neuropathy, making their feet more prone to injury and their wounds are more susceptible to infection. According to the Trans-Atlantic Inter-Society Consensus (TASC) working group, major amputations resulting from peripheral arterial disease range from 12 to 50 per 100,000 individuals per year. The most common indication for amputation is gangrene.

CLINICAL EVALUATION

When examining a patient with gangrene of the foot, a detailed history and physical examination are required. The physician should ask directly about risk factors, and in many cases, a thorough past medical and surgical history will provide clues about the disease process and whether previous revascularization was attempted. Patients with long-standing PAD harbor symptoms for months to years, and a slow progression of the disease process can be elicited. A complete physical examination should be performed, paying particular attention to the presence or absence of bruits or pulses. A diminished or absent



FIG. 1 Clinical appearance of dry gangrene.



FIG. 2 Clinical appearance of wet gangrene.

popliteal pulse will inform the examiner that a superficial femoral or popliteal artery stenosis or occlusion may be present. Conversely, a large pulsatile mass behind the knee is a clue for a popliteal aneurysm that could be the source of distal atheroemboli (trash). After a thorough examination, an experienced clinician should be able to distinguish whether the cause of gangrene is occlusive disease or atheroembolization, although less commonly these two conditions may coexist. Other less common causes of gangrene include myeloproliferative disorders, vasculitides, disseminated intravascular coagulation, and prolonged use of vasoconstrictors.

PAD frequently coexists with coronary artery disease and cerebrovascular disease. The clinical evaluation of the patient should address the potential presence of comorbid conditions that may complicate treatment. A patient with angina or a recent myocardial infarction may require a thorough cardiac evaluation before embarking on a lower extremity bypass. The clinician should also assess the patient's reserve potential and ability to participate in rehabilitation. A bedridden patient who cannot ambulate is better served with a lower extremity amputation than a complicated or futile attempt at saving the foot.

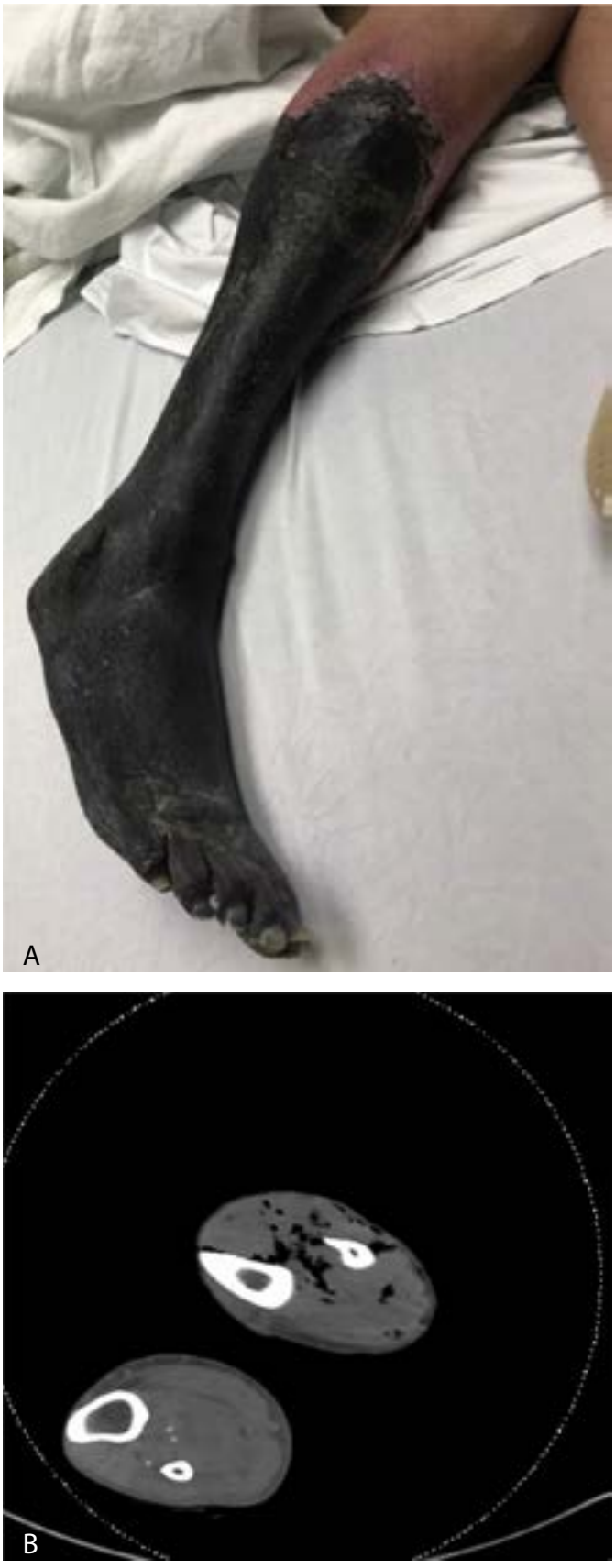


FIG. 3 **(A)** Clinical appearance of gas gangrene. **(B)** CT image demonstrating gas gangrene.

Finally, soft tissue infection may be present with gangrene. Antibiotics, tailored to attack the causative organisms, should be used. However, treatment should not be delayed if the infection does not respond to medical treatment. The surgeon should be vigilant in examining the wound, and especially the sole of the foot where an occult deep space infection may be present. A patient with diabetic neuropathy may not have a normal pain response to infection.

DIAGNOSTICS

Noninvasive Tests

Even with an experienced clinician, the pulse examination can be inaccurate 40% of the time. Therefore, an objective and repeatable non-invasive test is essential to making the diagnosis of PAD. The vascular laboratory should be considered as an extension of the physical examination. The objective of noninvasive testing is to identify the etiology of gangrene and help formulate a rational and expeditious management plan.

Ankle-Brachial Index

The ankle-brachial index (ABI) is the simplest test to assess the peripheral circulation. It consists of recording the systolic blood pressure in both arms and at both ankles (Fig. 4). A proper blood pressure cuff of appropriate size (diameter) should be selected to fit around the arm and the ankle. This is an important detail because an improper cuff will yield a falsely elevated measurement. Using a continuous Doppler probe, the examiner locates the arterial signal, inflates the cuff until the signal disappears, and then allows the cuff to deflate. The systolic pressure is recorded when the first audible signal is detected as the pressure in the cuff is slowly released.

A normal adult with no vascular disease will have a normal ABI (1.0). An ABI less than 0.9 is indicative of PAD, an ABI less than 0.5 correlates with severe disease, and an ABI less than 0.3 is consistent with a threatened limb. A ratio above 1.3 is considered falsely elevated and suggests calcification of the vessels, commonly seen in long-term diabetics or patients with advanced atherosclerosis. A patient may have a normal ABI with toe gangrene in the cases of distal embolization or microvascular disease. Most patients with PAD will have an abnormal ABI. In patients with milder PAD and claudication, the ABI may be normal at rest, but drop with a few minutes of exercise. In this case, exercise ABIs are useful for diagnosis. An exercise ABI will compare a resting ABI to another ABI measurement taken after a predetermined exercise time or when the symptoms of claudication are manifested. A significant drop in measurements will be consistent with a diagnosis of exercise-induced claudication.

Toe-Brachial Index

The toe-brachial index (TBI) is calculated in a similar fashion to the ABI, except that a photoelectrode is placed on the toe instead of a

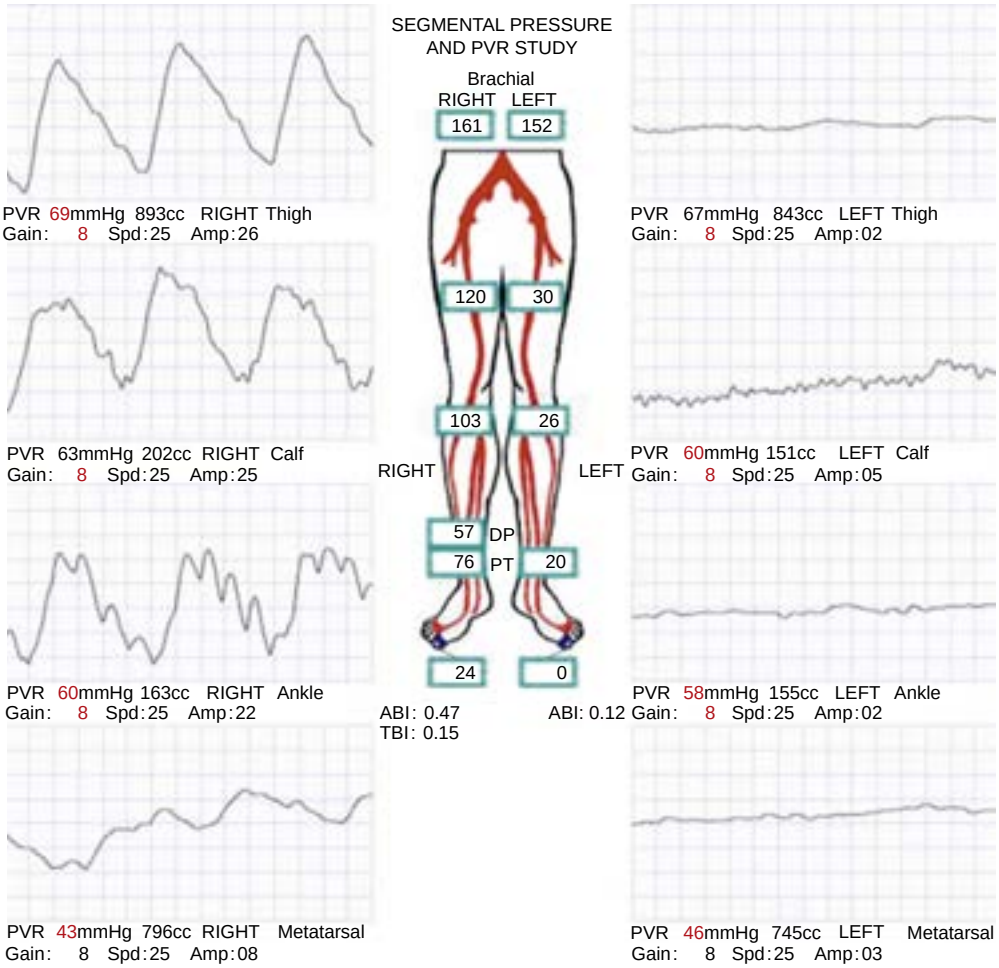


FIG. 4 Ankle-brachial index in a patient with severe left leg ischemia. Note that toe pressure on the left is zero, and the segmental waveforms are all flattened, which is consistent with severe multilevel ischemia. *ABI,* Ankle-brachial index; *DP,* dorsalis pedis; *PT,* posterior tibial; *PVR,* pulsed volume recording; *TBI,* toe-brachial index.

continuous-wave Doppler. The photoelectrode is used to record an arterial waveform that can then be obliterated by inflating the small cuff and signal the return of flow with deflation. There is a natural gradient between the toe and ankle pressures of 20 to 30 mm Hg, so a TBI of 0.7 to 0.8 is considered normal. An absolute toe pressure of 30 mm Hg is the minimum required for healing, and in case of diabetics, a toe pressure of 40 mm Hg or greater is needed.

Segmental Limb Pressures

The ratio of systolic blood pressure to brachial pressure can be obtained at different levels of the lower extremity (thigh, calf). Often, an arterial waveform is also recorded at these levels, allowing the clinician to compare pressure and waveforms at different levels and sides. Generally, a gradient of 20 mm Hg is considered abnormal and can point to the location of significant vascular occlusive disease.

Fluorescence Angiography

Fluorescence angiography, used extensively for eye examinations, is a relatively new technique applied to the evaluation of soft tissue perfusion. It has been used to aid in breast reconstruction and assessing tissue flaps. The viability of tissue flaps is critical for planning the level of amputation. Using a charge-coupled device camera and a low-power laser with indocyanine green (ICG), tissue perfusion can be assessed. Known as ICG fluorescence angiography (SPY system; Novadaq), this technique is being trialed in patients undergoing vascular reconstruction and amputations to guide surgeons in planning vascular reconstruction and extent of tissue resection. This technique may be useful if the surgeon is able to compare objectively an area of adequate perfusion to areas in question.

Transcutaneous Oxygen Measurement

Transcutaneous oxygen measurement ($TcPO_2$) is a noninvasive method of determining local tissue perfusion using small sensors on the skin of the extremity. It is assumed that if an adequate level of oxygen is being delivered to the tissue, normal healing will occur. Sensors can be placed in multiple areas of the body, and either the absolute value of the oxygen tension can be recorded or a ratio between the area of interest and the chest can be calculated. $TcPO_2$ measurements have been shown to have an accuracy of 87% to 100% at predicting wound healing. Values of >60 mm Hg are necessary for absolute wound healing, and values <20 mm Hg are associated with complete failure. Many studies have reported mixed results, and reliance on $TcPO_2$ alone should not supersede clinical examination and other objective testing.

Imaging

Imaging is an important tool surgeons have at their disposal. The diagnostic process should proceed in an orderly fashion, beginning with noninvasive tests and finishing with more invasive tests, if necessary. To plan revascularization, a more extensive imaging protocol may be required.

Duplex Ultrasonography

Duplex ultrasonography combines grayscale imaging (B-mode), Doppler, and color-flow assessment. Initially used to assess carotid arteries, duplex ultrasonography is now widely used to evaluate all vascular beds, including the brain (transcranial Doppler). The ability to assess the diameter of a blood vessel, detect whether it is patent, and measure the speed of the blood flowing through it provides a wealth of information to the examiner. Although not widely used because it is very tedious, arterial duplex mapping of the lower extremities can yield a correct diagnosis in over 90% of cases in experienced hands.

Multidetector Computed Tomographic Angiography

Multidetector computed tomographic angiography (CTA) is now replacing digital subtraction angiography (DSA) as the primary modality to image abdominal and lower extremity blood vessels. The CT scanner is programmed to acquire images in the arterial phase after a bolus of intravenous contrast is administered. CTA is accurate with a sensitivity and specificity of 95% and 96%, respectively, when a lesion is greater than 50%. Drawbacks include increased cost compared with other noninvasive imaging modalities, exposure to ionizing radiation, and the potential for intravenous contrast to cause contrast-induced nephropathy. It is important to note that CTA is limited when attempting to evaluate tibial vessel disease.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) uses radio waves and magnetic fields in conjunction with gadolinium contrast to opacify the vessels and produce detailed three-dimensional images. MRA has not been fully adopted for general use in vascular surgery for several reasons. Typically, it is more expensive than CTA, and it does not provide the spatial resolution necessary to assess small vessels. In addition, it is time-consuming, and some patients cannot tolerate being in the magnet because of claustrophobia or other medical conditions. Furthermore, gadolinium is contraindicated in patients with chronic kidney disease. Newer magnets that use 4 Tesla are being introduced, potentially improving the visualization of small vessels.

Digital Subtraction Angiography

Before CTA, intraarterial injection of contrast agents was the primary invasive diagnostic modality used to evaluate the arterial tree. DSA is now predominantly used in combination with an endovascular intervention such as angioplasty or atherectomy. Less frequently, it is used diagnostically to clarify the runoff status when the CTA is inadequate or specially in cases of tibial vessel disease. It is important to remember this tool when examination and imaging findings do not correlate. DSA is helpful when trying to determine whether there is a distal target for bypass in these situations.

MANAGEMENT

Antibiotic and Medical Management

The extent of gangrene can vary, from localized toe gangrene to more extensive involvement of the whole foot or distal leg. If a soft tissue infection is present, systemic antibiotics are used to prevent further spread and attempt to control it. An empiric regimen can be started after obtaining appropriate tissue cultures. In diabetics, mixed aerobic and anaerobic organisms may be present, and broad coverage is usually necessary. The duration of treatment should be as short as possible as prolonged courses will lead to resistant organisms or other untoward sequelae. Debridement of necrotic infected tissues and drainage of purulent material are the first steps to control infection.

Antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* and resistant forms of *Pseudomonas aeruginosa,* are now being seen with increasing occurrence. Any unnecessary delay in revascularization will complicate the patient's recovery and elimination of infection.

Surgeons are now paying more attention to enhanced recovery protocols that have the benefit of improving outcomes and reducing perioperative complications. While the primary surgical objectives to treating gangrene are removal of necrotic tissue and reestablishing adequate blood flow and tissue oxygen perfusion, the patient's nutritional status and physical-mental condition should not be neglected. Appropriate precautions to prevent bedsores, urinary tract infections, falls, and inadvertent trauma to amputation stumps are to be exercised.

Debridement

The role of debridement is to excise devitalized tissue and promote rapid healing. It is important to have a conservative mindset, that is,

preserving viable tissue while excising necrotic material. Aggressive debridement before proper revascularization should be avoided if possible. Sharp debridement using the knife and cautery, and occasionally a curette, is all that is necessary. Hydroresection or jet lavage can been used to wash out deeper spaces. If the wound is clean and the edges are viable, primary closure can be attempted. However, if the wound is left open for drainage and granulation, a vacuum dressing is very helpful and often well tolerated by the patient. If the debrided site needs frequent inspection, wet-to-dry dressings with saline can be employed. The wet-to-dry dressing will draw immune cells into the tissues and promote healing while acting to debride the tissue when it is removed. A variety of topical enzymes, protease scavengers, and biological wound matrices have been used. However, none have been shown to be superior to surgical debridement and proper revascularization.

Revascularization

The etiology of gangrene is most commonly tissue ischemia caused by peripheral arterial disease. Therefore, the goal of treatment is to restore blood flow to premorbid levels as much as possible. Most patients who develop foot gangrene have some preexisting arterial pathology. It is imperative to evaluate the vascular tree, from proximal to distal, lest the examiner miss a subtle lesion. Often, proximal lesions or inflow are addressed first followed by distal lesions or outflow. Many patients with PAD have multilevel disease, which will often complicate the revascularization plan.

TASC has classified arterial lesions, from the aorta to the ankles, into four categories (A to D) according to disease severity. An A lesion is typically a focal arterial stenosis that is very likely to respond to balloon angioplasty, whereas a D lesion is a long arterial occlusion. In general, TASC A and B lesions can be addressed with an endovascular approach, while C and D lesions respond best to a surgical bypass. Many clinicians will attempt an endovascular procedure for a TASC C or D lesion in a frail patient who is not a good candidate for an open bypass. However, long-term patency is rarely achieved in such cases.

Percutaneous endovascular techniques range from simple balloon angioplasty to complex intentional subintimal dissection of occluded vessels. Balloon angioplasty and stenting is a durable procedure in the iliac arteries. This technique is less durable for superficial femoral and popliteal artery stenosis and occlusion. Drug-eluting stents and drug-coated balloons have been shown to improve the 1-year patency of femoropopliteal interventions. Another endovascular technique is subintimal dissection. In cases with superficial femoral or popliteal artery occlusions, a wire is used to cross the lesion and then reenter the true lumen, with or without a reentry device, beyond the lesion. The diseased vessel is then ballooned and stented. Some interventionalists have added atherectomy, a device that shaves or grinds the plaque to reestablish an adequate arterial lumen. In all percutaneous endovascular procedures performed in the superficial femoral artery and more distally, outcomes are predicated on the diameter of the vessel and the length of the lesion. In general, shorter lesions in larger vessels have the best long-term patency, and conversely, longer lesions in smaller vessels have the poorest patency.

Surgical bypass, with prosthetic material or autogenous conduit, has stood the test of time. The patency of aortobifemoral bypass for occlusive disease is over 80% at 5 years. Similarly, femoropopliteal bypass with an adequate-size autogenous saphenous vein can have a patency of 75% at 5 years. If no vein is available, a prosthetic bypass can be attempted accepting a less favorable long-term patency. Other bypass conduits include cryopreserved artery/vein and bovine carotid. The latter conduits have significant advantages and disadvantages that must be taken into account. A cryopreserved artery/vein is often the conduit of choice in the setting of an infected field when an autogenous conduit is unavailable. Frail and elderly populations are poor candidates for a prolonged open surgical bypass operation. Many patients with PAD do not have an adequate autogenous conduit, especially if they had undergone a previous coronary or leg bypass. In these cases, the clinician is left to choose between inferior options.

Patients with multilevel occlusive disease can undergo hybrid procedures (i.e., a combination of an endovascular balloon and stent with an open bypass). A frequent occurrence is iliac balloon angioplasty with a femoral-femoral bypass or femoropopliteal bypass.

Amputations

Amputations for gangrene in the lower extremity can range from a simple partial toe amputation to a most aggressive hip disarticulation. The goal of amputation is to remove necrotic and infected tissue and allow tissue healing and weight bearing as soon as possible. Often, the patient who requires an amputation is evaluated by a multidisciplinary team that includes the surgeon, physiatrist, physical therapist, orthotist, nutritionist, visiting nurse, social worker, and others. Including the patient's family or support system in the decision process is also an important step in the process. This team participates in planning for the operation and postoperative recovery period, which is often prolonged and complicated in an elderly frail patient with many medical and psychosocial issues.

Toe Amputation

If gangrene is confined to the tip or part of the toe, a partial toe amputation preserving the proximal phalanx can be done. This procedure should have the least impact on the patient's recovery and ambulation. When gangrene affects the entire toe, the surgeon must decide whether there is enough viable tissue to perform an adequate wound closure with or without taking the metatarsal head. The first metatarsal head plays an important role in gait and balance and should be preserved if possible.

Toe amputation preserving the metatarsal head can be performed with a simple curvilinear incision at the base of the toe, either in an anteroposterior or mediolateral fish-mouth fashion or a racquet-like fashion (Fig. 5). The metatarsophalangeal joint is easily identified by flexing the toe and can be disarticulated after sharply incising the joint capsule. A rongeur is used to remove cartilage. Wound closure is done loosely with nylon sutures. In Ray amputations, the proximal extent involves removal of the metatarsal head. The sesamoid bones are also removed. An oscillating saw can be used to transect the bone. Nerves and tendon sheaths should be cut sharply under tension so they retract. Primary closure is done in clean wounds. Sutures can



FIG. 5 Left second and third toe amputation and partial amputation of the fourth toe for gangrene. The wound is left open to heal.

be left for 2 weeks or longer until the wound is completely healed. Proper wound protection and padding is required if a patient is to bear weight on the extremity after the procedure. A plastic, internally lined "ski boot" is helpful in protecting the foot from soiling and unnecessary trauma. Often, toe and foot amputations can be performed with a toe or ankle block, and a tourniquet is not needed.

Transmetatarsal Amputation

In the event of forefoot gangrene or multiple toe ischemia, it is not practical to salvage any toes. In this case, a transmetatarsal amputation is performed. The incision is planned near the heads of the metatarsals on the dorsal aspect and taken in a curvilinear fashion on the plantar aspect to create a flap. The plantar flap is slightly longer to allow easy approximation once the bones are removed. The oscillating saw is used to cut across the metatarsals one by one, progressively shortening the bones proceeding laterally. The toes with the metatarsal heads are peeled away after the tendons have been cut. Hemostasis can be achieved with cautery, but larger digital arteries are ligated or sutured. The plantar flap might require thinning of musculature and subcutaneous tissue to close the wound with undue tension.

Transtibial Amputation

When the entire foot and heel are involved and foot salvage is not possible, a leg amputation is necessary. In emergent cases in which infection is poorly controlled and spreading in a septic patient, a guillotine amputation can be done rapidly. Here the objective is to remove the necrotic infected tissue as quickly as possible without worrying about wound closure. The guillotine amputation should be done as distal as possible. The bleeding vessels are ligated, and either a vacuum or gauze dressing is placed. The most common indication for this is gas gangrene of the foot. This is a temporary and often a lifesaving procedure, and formal amputation usually follows in the next few days. A formal transtibial amputation, commonly referred to as a below-the-knee amputation (BKA), can be technically challenging. It is very important to properly construct the myocutaneous flap so the wound heals and the patient can use a prosthesis. A posterior flap is most commonly used. The incision is started anteriorly about 10 cm below the tibial tuberosity. The anterior circular incision is roughly one-half the circumference of the calf at its largest girth. This can be easily measured using an umbilical tape or suture (Fig. 6). The medial and lateral incisions extend down roughly one-third the circumference, or about 9 to 12 cm. A Gigli or oscillating saw is used to cut the tibia, and the fibula should be at least 1 cm shorter than the tibia. The tibia edge by the shin is beveled so it does not protrude when the patient is ready for a prosthesis. The tibial arteries and veins are suture-ligated, and the nerve is cut sharply and foreshortened to avoid a neuroma. The crural flap can be thinned or debulked so wound approximation is tension-free. Interrupted fascial closure is done with an absorbable suture. The skin can be closed with nylon or staples and is usually left for at least 3 weeks or until the wound is healed (see Fig. 6). A closed suction drain may be used at the surgeon's discretion. A posterior splint is used to avoid a knee flexion contracture. A variety of options are available to keep the knee straight and the wound protected from trauma but accessible for inspection. The posterior flap is the most commonly used flap for a BKA; however, skew flaps can be configured when the viability of the posterior tissue is in question. The most common local complications after a BKA are wound breakdown and infection. Therefore, it is imperative to protect the wound and avoid flexion contraction of the knee. If not properly recognized and managed, these problems will invariably lead to a transfemoral amputation.

Transfemoral Amputation

Amputation of the lower extremity above the knee (above-the-knee amputation [AKA]) is indicated when the ischemia extends proximally enough so it is not possible to obtain adequate viable tissue for closing a BKA. A fish-mouth type of incision is planned just above the knee. The femur is transected with a Gigli or oscillating saw. The

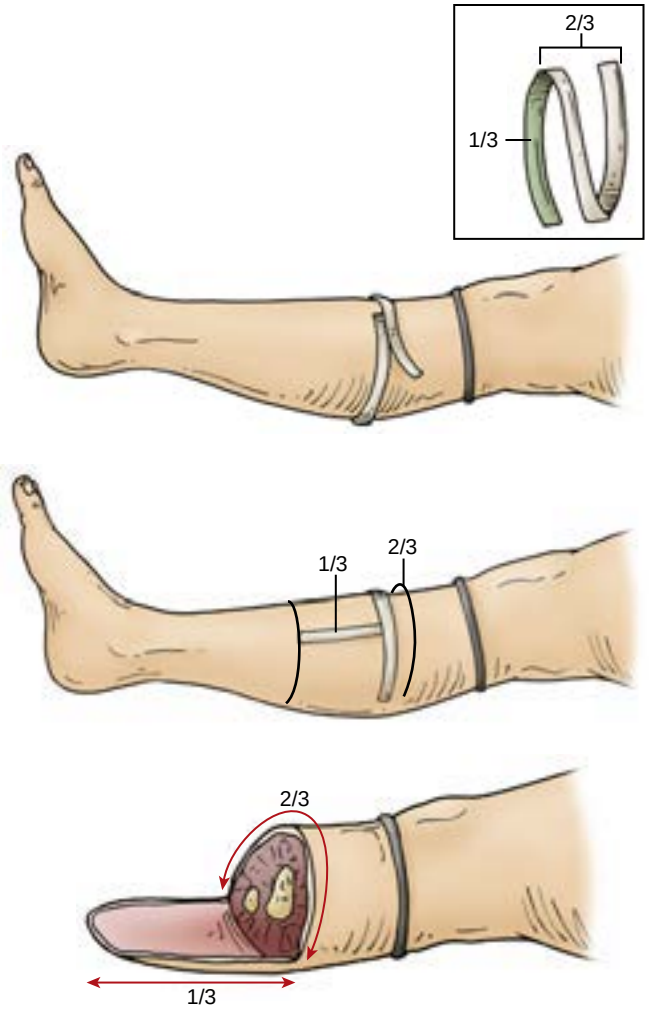


FIG. 6 Using tape to obtain the measurement for a transtibial amputation with a posterior flap. *(From Sanders RJ, Augspurger R. Skin flap measurement for below-knee amputation.* Surg Gynecol Obstet. *1977;145[5]:740–742.)*

superficial femoral/popliteal neurovascular bundle is suture-ligated. The fascia is approximated with interrupted sutures, and the skin closed with nylon or staples (Fig. 7). A protective dressing with gauze and compression with an ace bandage is often helpful. The most challenging issue is to keep the dressing on and the wound protected from soilage.

Cryoamputation

Formalized amputation cannot be performed in all situations. Some critically ill patients who are on multiple vasopressor medications because of septic shock from their infected extremity may be candidates for cryoamputation. This can be performed at the below-the-knee or above-the-knee level. This is performed using a Styrofoam cooler or box that is cut to fit the patient. A warming pack is placed proximal to the cooler on the extremity to avoid further proximal tissue damage. The cooler is filled with dry ice and the patient's nonviable, infected extremity is isolated from the rest of the circulation by way of extreme cold. This will provide bridge therapy until the patient is stable enough to have a formal amputation in the operating room.

Other Amputations

Many modified foot amputations have been devised to address amputations that are more extensive than a transmetatarsal amputation

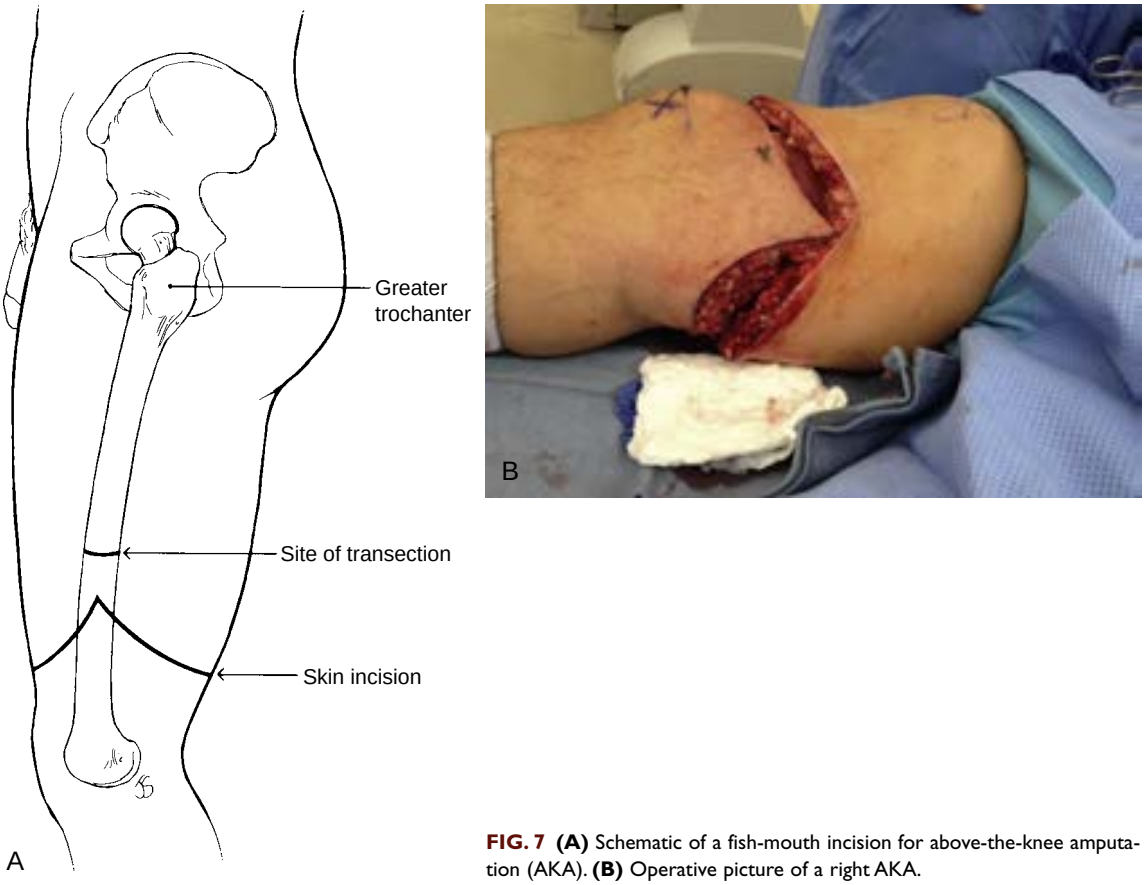


FIG. 7 **(A)** Schematic of a fish-mouth incision for above-the-knee amputation (AKA). **(B)** Operative picture of a right AKA.

but less extensive than a transtibial amputation. These include the Lisfranc, Choppart, and Syme amputations. They are performed infrequently and indicated in very select patients. Similarly, through-the-knee amputations, such as the Gritty-Stokes amputation, are performed less commonly. In very rare situations, a complete hip disarticulation is required if the proximal thigh muscles are not viable. This is a highly morbid procedure and is associated with a high rate of mortality.

SUMMARY

Gangrene of the foot is a well-studied disease process. It is often preceded by PAD, a chronic disease process leading to ischemia of the tissues of the foot. Gangrene can present in three forms: dry, wet, and gas gangrene. It is important to perform a physical examination and ancillary testing to devise a logical therapeutic plan. A wide array of diagnostic tests is available including noninvasive and invasive imaging, which are essential in the diagnosis and treatment of a gangrenous limb. Intervention is multifaceted and includes medical management with antibiotics if needed, medical optimization, revascularization, and amputation. Revascularization can be achieved using endovascular, open, and hybrid methods. Finally, dead necrotic tissue can ultimately be removed with different types of amputations, which are considered based on the clinical scenario.

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Buerger's Disease (Thromboangiitis Obliterans)

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INTRODUCTION/EPIDEMIOLOGY

Thromboangiitis obliterans (TAO), also known as Buerger's disease, is a nonatherosclerotic, segmental, occlusive inflammatory disease that is characterized by diffuse inflammatory thrombosis and recanalization of the small- to medium-sized vessels of the upper and lower extremities. TAO often presents in young male smokers as distal extremity ischemia, ischemic ulcers, or gangrene. In recent years, the incidence of disease in women has increased to nearly 20% and may be the result of increasing tobacco use among women. TAO has a worldwide distribution with the highest prevalence in Eastern European, Mediterranean, and Asian countries.

Although the exact etiology of TAO remains unknown, the disease is strongly associated with heavy tobacco use including cigarette smoking, cigars, smokeless chewing tobacco, and snuff. While a causal relationship has not been established, smoking is closely linked with disease progression. Tobacco use is considered a requirement for diagnosis of TAO, and cessation of use remains one of the mainstays of treatment.

PRESENTATION

Symptom onset in TAO typically occurs in patients younger than 45 years of age with a heavy smoking history. The disease usually starts in the distal small arteries and veins of the hands and feet and later progresses to involve the more proximal vessels. At least two or more extremities are always involved, with 40% of cases affecting all four limbs. Early in the disease course, patients may present with symptoms of distal extremity claudication, cold sensitivity, Raynaud's phenomenon, and superficial migratory thrombophlebitis. Claudication of the foot or arch may often be mistaken for orthopedic pathology and can be helpful in distinguishing from claudication seen in peripheral arterial disease (PAD), which more frequently involves the calves. The most common presentation of TAO in two-thirds of patients is rest pain or, with disease progression, ischemic ulcerations of the distal portion of the fingers, toes, and feet.

The overwhelming majority of cases of TAO predominately involve the small- and medium-sized vessels of the upper and lower extremities. Rarely, instances of large vessel involvement including the cerebral, coronary, pulmonary, mesenteric, and renal arteries have been reported. Mesenteric TAO, although highly infrequent, is associated with poor prognosis and warrants prompt surgical intervention for bowel ischemia. Aortoiliac involvement is also uncommon and is more likely due to PAD in most patients.

DIAGNOSIS

TAO is often a diagnosis of exclusion. Criteria commonly used to describe key diagnostic features of TAO include:

1. Age < 45 years at onset
2. History of tobacco use
3. Distal extremity ischemia in two or more limbs
4. Angiographic findings suggestive of TAO (Fig. 1)

There are no tests that confirm a diagnosis of TAO. Therefore, diagnosis depends on both clinical suspicion and ruling out other etiologies of distal limb ischemia. Workup should include clinical, radiographic, and laboratory evaluation aimed at excluding other etiologies of limb ischemia including embolization, atherosclerosis, diabetes, hypercoagulable states, trauma, connective tissue disease, and autoimmune disorders.

A positive Allen test in a young smoker with distal lower extremity ischemia is suggestive of TAO, but it is nonspecific and warrants further evaluation to exclude other conditions where distal ischemia can be seen in both the upper and lower limbs. Noninvasive studies that characterize the degree of ischemia and assess tissue perfusion such as ankle-brachial index, as well as segmental pressures and arterial waveform analysis, are often helpful for diagnosis in the setting of distal ischemia. Echocardiography and/or computed tomography (CT) with angiography and/or magnetic resonance (MR) angiography can be useful in ruling out proximal embolic sources, particularly in cases of unilateral limb involvement.

No laboratory test confirms TAO. Rather, laboratory evaluation is performed to rule out other diagnoses. When TAO is suspected, laboratory evaluation should routinely include a complete blood cell count with differential basic metabolic panel including electrolytes, blood urea nitrogen and creatinine liver function tests, fasting blood glucose and urinalysis. Acute phase reactants including erythrocyte sedimentation rate and C-reactive protein, a hypercoagulability screening panel with antiphospholipid antibodies in addition to antinuclear antibody, rheumatoid factor, complement and serologic markers for CREST syndrome, and scleroderma should also be obtained.

History and physical exam in TAO often follow characteristic presentation and are sufficient for diagnosis once clinical/laboratory/radiologic workup excludes other possible etiologies of distal ischemia. Vessel biopsy, while rarely necessary, is the only means of definitive diagnosis. Biopsy is typically reserved for patients with



FIG. 1 Lower extremity arteriogram with typical findings suggestive of TOA include absence of atherosclerosis, small- and medium-sized vessel involvement, segmental occlusion, and corkscrew collaterals. *(Image courtesy Drs. Sun-Cheol Park and Jae Cho.)*

BOX 1 Treatment Options for Thromboangiitis Obliterans (Buerger's Disease)

First-Line Therapy and Only Definitive Treatment

Cessation of all tobacco use

Medical

Prostacyclin and its analogues
Aspirin
Selective low-dose intraarterial streptokinase
Bosentan, a dual endothelin-1 receptor antagonist
Cyclophosphamide
Guanethidine sympathetic blocks
Serotonin blockers
Sarpogrelate
Intramuscular injections of vascular endothelial growth factor
Phosphodiesterase type 5 (PDE5) inhibitors

Surgical

Endovascular

Angioplasty of individual tibial and foot arterial obstruction(s)

Open

Sympathectomy
Arterial reconstruction
Omental transfer
Kirschner wire in medullary canal of tibia
Amputation

Experimental Therapies

Intramuscular injection of vascular endothelial growth factor
Autologous whole bone marrow stem cell transplantation by fenestration
Immunoadsorption
Beperminogene perplasmid use

unusual presentation such as large vessel involvement or age greater than 45 years at onset.

In patients with limb-threatening ischemia or those whom a diagnosis of TAO is suspected but not definitive, arteriography is performed. Catheter-based angiography is generally superior to CT or MR angiography for providing the spatial and anatomic detail necessary to evaluate the smaller vessels of the hands and feet. Angiographic findings classic of TAO are highly suggestive but not pathognomonic for the disease. These findings include a tortuous corkscrew appearance of collaterals and abrupt transition between normal and thrombosed segments in absence of features suggestive of atherosclerotic disease (no calcifications, normal vasculature proximal to popliteal and brachial arteries, no identifiable source of thrombus).

TREATMENT

Tobacco Use Cessation

Complete cessation of tobacco use remains the most effective and only definitive treatment for TAO (Box 1). Smoking, including use of smokeless tobacco and even nicotine replacement products, has been closely tied to disease exacerbation and progression. Discontinuation of tobacco use is the only therapy that has been shown to reduce symptoms and decrease the risk of amputation in patients who have not yet developed ischemic ulcers. Even one or two cigarettes a day or use of nicotine transdermal patches and/or nicotine chewing gum is enough to perpetuate the disease. Varenicline or bupropion can be used as nonnicotine aids for smoking cessation. In patients who continue smoking, the risk of amputation has been reported to be as high as 43% at 10 years. Although patients can be reassured that the disease will remit upon smoking cessation, some may still experience symptoms of intermittent claudication and Raynaud's syndrome.

Medical/Adjunct Therapy

In the subset of patients who experience disease progression despite cessation of tobacco use or are unable to quit, therapeutic options are limited. Vasodilators can be implemented for symptomatic management in select patients, but their efficacy overall is limited. Calcium channel blockers can be used in TAO patients with severe vasospasm from Raynaud's phenomenon (Fig. 2). The use of intravenous prostaglandin, Iloprost, has not been as effective or practical for routine use as was initially forecasted in early trials. Preliminary data suggests that Cilostazol, a phosphodiesterase inhibitor often used in the treatment of PAD, may be helpful in mediating the inflammatory lesions of TAO, but further trials are still necessary.

Distal ischemic ulcerations should be managed with debridement and local wound care. Negative pressure vacuum-assisted closure devices can be used in patients with TAO-associated ischemic wounds. Reports of therapeutic hyperbaric oxygen therapy in combination with cell-based therapies in these patients have cited improvement in symptoms. Intermittent pneumatic compression has been helpful in treating ischemic ulcers that result from other small vessel occlusive diseases and may be useful in TAO based on preliminary single study data.

Other investigational therapies that have been tried for TAO include cell-based treatments involving autologous whole bone marrow stem cell implantation and intramuscular injection of vascular endothelial growth factor. In a small case series, the placement of a Kirschner wire into the tibial medullary canal for stimulation of angiogenesis is described for severe disease. While these therapies have shown promising results in healing of ischemic ulcers and pain in TAO patients, larger randomized trials are needed to evaluate their efficacy.

Surgical Therapy

Revascularization is generally not feasible in TAO due to the involvement of small distal vessels and diffuse segmental nature of the disease. Cessation of tobacco use and conservative therapies should be attempted first. However, if medical treatment has failed in patients with severe ischemic rest pain or nonhealing ulcers, revascularization should be considered if possible. If revascularization is unsuccessful or not an option, amputation would be the next most definitive step.

The lack of distal target sites due to the diminutive nature of diseased distal vessels and suboptimal venous conduits from contaminant venous involvement make arterial bypass an unattractive option in the majority of patients. Preoperative evaluation of distal target vessels including arteriography is imperative. Long-term outcomes following arterial reconstruction for TAO patients are relatively poor, particularly if patients relapse or continue to use tobacco. Although long-term graft patency rates are lower than in atherosclerotic disease, the rates of limb salvage in TAO, when feasible, still exceed graft patency by 25% and can lead to healing of ischemic ulcers. Thus, in patients with severe ischemia and favorable anatomy who have failed conservative therapy, arterial reconstruction is an option.

Endovascular options in patients with TAO are particularly limited. Catheter-based interventions have been successfully performed down to the level of the foot in a small number of TAO patients. Although technically feasible in select patients, there is a paucity of data regarding long-term outcomes following endovascular intervention. Like atherosclerotic PAD, endovascular approaches in TAO have lower primary and secondary patency rates when compared with arterial bypass, but amputation rates at 2 years are comparable.



FIG. 2 Before **(A)** and after **(B)** pictures after medical management of gangrenous digital ulcers with phosphodiesterase inhibitor, sildenafil, and calcium channel blocker, amlodipine. *(Photographs courtesy Dr. Deepak Nair)*

Other surgical interventions aimed at symptom control have been described for TAO. Spinal cord stimulation and sympathectomy in the upper and lower extremities have been performed with some clinical benefit. There is still inadequate data to appropriately guide patient selection for these interventions.

PROGNOSIS

Overall, the prognosis for TAO is relatively good but is almost exclusively dependent on whether the patient can discontinue tobacco use. Patients who can stop using tobacco are likely to halt further disease progression and avoid risk of amputation by up to 94%. The prognosis for those who are unable to stop using tobacco is less favorable, with 40% requiring one or more amputations.

Although TAO can be a highly morbid disease with a profound negative impact on quality of life, the average life expectancy against age-matched controls is comparable. Several studies have suggested lower socioeconomic status to be associated with worse outcomes that may be attributable to number of factors including living conditions, income, health literacy, and worse disease severity at the time of presentation. The disease can often have variable periods of exacerbation, and patients should be followed long-term.

SUMMARY

TAO, or Buerger's disease, is a segmental, occlusive, inflammatory vasculitis affecting the distal small- and medium-sized vessels of the extremities. Young male smokers under the age of 45 are predominately affected. The disease has a strong correlation with tobacco use, which is virtually essential for diagnosis. The majority of patients present with late-stage disease involving distal ischemia pain and ulceration of at least two extremities. A third of patients will present with symptoms of early disease including distal extremity claudication, cold sensitivity, Raynaud's phenomenon, and superficial migratory thrombophlebitis. Complete cessation of tobacco use is the primary and only definitive treatment for TAO. Stopping use of tobacco halts disease progression, reduces symptoms, and significantly reduces risk of amputation. In refractory cases, several medical and surgical therapies exist that are palliative in improving pain, ulceration, and limb salvage.

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Takayasu's Arteritis

Sally Schonefeld, MD, NavYash Gupta, MD, Aamir Shah, MD, and Bruce L. Gewertz, MD

Takayasu's arteritis (TA) is an uncommon disorder involving the aorta and its primary branches. Because of its chronic obliterative nature, it is also called *pulseless disease* or *occlusive thromboarteriopathy.* The disease was named for the Japanese ophthalmologist who first identified and described the associated ocular abnormalities in 1908. While Takayasu's arteritis has been diagnosed and reported worldwide, prevalence varies across populations. The incidence seems to be highest in East Asia, and women are much more frequently affected than men (8:1). In the majority of patients, the age of onset is between 10 and 30 years of age. Some studies have detected genetic links to disease susceptibility, specifically identifying distinct markers within the human leukocyte antigen (HLA) region. These findings may be useful in explaining differences in geographic prevalence and understanding the underlying pathways of disease pathogenesis.

The precise etiology and pathogenesis of the disease remains ill-defined; both infection and autoimmune causes have been suggested. The association between TA and rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel syndrome strongly suggest autoimmune mechanisms, although there is presently no experimental model for this form of aortitis.

CLINICAL PRESENTATION

The disease can be broadly divided into two phases: an early "pre-pulseless" phase and a late "pulseless" phase. Initial symptoms include generalized malaise and other nonspecific indicators such as a skin rash, anorexia, myalgia, weight loss, fatigue, and fever. Patients with early disease often have elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels but no other serologic abnormalities. This initial presentation can last from months to years and may not be debilitating, leading to delays in diagnoses.

After the initial interval of vague constitutional symptoms, arterial lesions become evident, and more dramatic symptoms develop. The classic presentation is the absence of one or more peripheral pulses and complaints specific to the extremity or organ rendered ischemic. These symptoms include claudication, neurologic complaints, hypertension, and other symptoms of reduced organ blood flow. Lightheadedness, syncope, or vertigo are frequent complaints when the aortic arch or extracranial carotid vessels are involved. Patients frequently assume a "face-down" posture to prevent the neck extension that would further compromise carotid or vertebral flow. Emotional instability and headache may also be present, along with more serious neurologic signs such as hemiparesis.

Ocular symptoms include blurring, diplopia, progressive blindness, and intermittent impaired vision with physical exertion *(visual claudication).* Ophthalmoscopic examination may demonstrate optic atrophy or retinal vein or artery thrombosis. Exercise-related symptoms can occur in extremities with arterial stenoses; with progression of occlusive lesions, rest pain and tissue loss become evident. Compromise of the external carotid circulation can result in atrophy of the facial muscles and, rarely, ulcerations of the nose, palate, and ear. Abdominal aortic involvement can lead to chronic renal or intestinal ischemia.

Diagnostic criteria for the classification of Takayasu's arteritis were well established by the American College of Rheumatology in 1990 (Table 1) and remain the standard for contemporary TA diagnoses. Criteria include symptom onset before 40 years of age, limb claudication, diminished brachial pulses or asymmetric brachial blood pressures, presence of a bruit audible over the aorta or subclavian artery, and angiographic abnormalities (specifically any stenosis that is not secondary to the more common atherosclerosis, fibromuscular dysplasia, or other causes). When a patient meets at least three of the six requirements, the sensitivity and specificity for the diagnosis exceeds 90%.

Arteriography (Fig. 1) allows classification of Takayasu's arteritis into four main types: type 1 (8% prevalence) is limited to the aortic arch and its primary branches; type II (11% prevalence) includes lesions of the descending thoracic and abdominal aorta; type III (65% prevalence) extends from the aortic valve to the abdominal aorta; and type IV (15% prevalence) includes pulmonary artery involvement and aneurysmal change in any vessel.

In modern practice, noninvasive imaging techniques have contributed to a better understanding of the vascular damage caused by TA and shortened the delay between symptom onset and diagnosis. That said, virtually all patients need definitive assessments of the extent of disease. While classic arteriography was previously the gold standard for imaging, less invasive studies such as CTA and MRA are now the preferred imaging modalities. These studies well demonstrate the extent of vascular involvement and facilitate monitoring of the clinical course and response to treatment. There is an argument in favor of using magnetic resonance angiography (MRA) if repeat studies are anticipated as MRA avoids radiation exposure and iodinated contrast. Additionally, positron emission tomography (PET) is increasingly useful for evaluating large-vessel vasculitis. Although PET is useful diagnostically, the test's usefulness as a reliable measure of disease activity is not well established.

PATHOLOGY

The classic gross appearance of Takayasu's arteritis is a "tree-bark" surface. Patchy involvement with "skip lesions" is the most common pattern, although some patients present with continuous involvement. While TA is properly considered a pan-arteritis, the adventitia

TABLE 1 The American College of Rheumatology 1990 Criteria for the Classification of Takayasu's Arteritis*

Age at disease onset	Symptoms or signs of Takayasu's arteritis before 40 years of age
Claudication	Upper or lower extremity fatigue with exercise
Diminished brachial pulse	Unilateral or bilateral diminished brachial pulse on examination
Asymmetric brachial blood pressure	>10 mm Hg difference between brachial systolic blood pressure
Bruit	Audible over aorta or either subclavian artery
Angiographic abnormalities	Narrowing or occlusion of aorta, aortic branches, or large arteries in upper extremities, usually focal or segmental. Must not be secondary to atherosclerosis, fibromuscular dysplasia, or other causes

*Three of six required to make diagnosis.



FIG. 1 Typical distribution of lesions in Takayasu's arteritis (type I) with severe uniform stenoses of the brachiocephalic and left common carotid arteries. The patient presented with syncope and dizziness.

and outer media usually have the highest degree of inflammation. Active inflammation in lesions is heralded by the presence of lymphocytes, histiocytes, macrophages, and plasma cells. Polymorphonuclear and multinucleated giant cells are consistently observed around the vasa vasorum. TA likely involves a broad cell-mediated autoimmune process involving macrophages and CD4-positive/CD8-positive T cells.

Elastic and smooth muscular portions of the media become eroded by this process, leading to transmural fibrosis and coincident intimal proliferation. As a consequence of this inflammatory cascade, scar tissue and vascular obstruction persist after the active stage of the disease is controlled. In some cases, aneurysmal formation occurs as a result of destruction of the arterial smooth muscle cells of the medial layer.

THERAPY

Glucocorticoids are the mainstay of all initial treatments for TA, particularly in the pre-pulseless stage. For severe and newly active TA, high doses of the drugs are recommended. The addition of nonsteroid immunosuppressive agents, such as methotrexate, can be employed to minimize glucocorticoid toxicity. Other therapies include tumor necrosis factor inhibitors and azathioprine. If remission is achieved, glucocorticoids should be tapered to minimize deleterious side effects. Long-term treatment with low dose glucocorticoids is occasionally employed for patients with frequent disease relapse or poorly controlled disease. If surgical intervention is contemplated, most clinicians require demonstration of satisfactory preoperative control with glucocorticoids and/or immunosuppressive agents.

For patients who have organ ischemia in the pulseless stage, both open surgical reconstruction and endovascular therapy can be useful. This single most important predictor of success is delaying intervention until active signs of the disease have resolved. Indication of quiescence includes normalization of ESR and white blood cell counts. On occasion, it is not possible to delay treatment, especially in patients presenting with life- or organ-threatening manifestations such as stroke, critical limb ischemia, or myocardial ischemia.

Operative therapy focuses on the bypass of involved or occluded vessels. It is vital to identify nondiseased segments proximal and distal to the lesions as there is a higher risk of the development of pseudoaneurysms when anastomoses originate on diseased areas. Miyata et al. followed 91 patients with TA who were treated surgically over 40 years. They reported an incidence of anastomotic aneurysms of 12% at 20 years. As a consequence, some surgeons routinely buttress suture lines with pledgets or place interrupted sutures at regular intervals along a continuous suture line to mitigate this risk. It is also important to limit dissection to these more normal portions of the aorta and distal "target" vessels as the transmural inflammation characteristic of the disease makes inadvertent injury to adjacent structures more likely.

Open surgical repair offers the best durability in most cases. When surgery is too high risk because of other medical issues, PTA is effective as a temporizing strategy to relieve symptoms and prevent limb or organ ischemia. Several studies compared the long-term patency of open versus endovascular treatments for patients with TA. In all studies, there was a significantly higher incidence of restenosis or occlusion in the endovascular therapy group. A small series of patients treated at the Cleveland Clinic suggests that endovascular techniques utilizing stent grafts (rather than uncovered stents) may be associated with lower rates of in-stent restenosis.

SUMMARY

Takayasu's arteritis is a large vessel vasculitis involving the aorta and its major branches. It is diagnosed worldwide but is most prevalent in East Asia. The age of onset is typically between 10 and 30 years, and women are much more commonly affected than men. Patients typically present with vague constitutional symptoms. Once narrowing, occlusion, or aneurysm of affected arteries occurs, ischemic symptoms predominate and reflect the ischemic extremity or organ. Treatment includes glucocorticoids and/or immunosuppressive agents. For patients with symptomatic lesions, open surgical reconstruction and endovascular therapy can both be successful. To date, operative bypass procedures have the advantage of better long-term patency.

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Acute Mesenteric Ischemia

Kristofor A. Olson, MD, PhD, and Pedro G. Teixeira, MD

Acute mesenteric ischemia (AMI) is a rare condition representing 0.1 to 1 in 1000 hospitalizations, yet it is a highly morbid disease with mortality rates upward of 50% when diagnosed early and over 70% in patients admitted to the ICU. It is a disease primarily of the elderly, with a median age of 74, owing to the multiple medical comorbidities that predispose to the condition. The hallmark physical examination finding of AMI is abdominal pain out of proportion to the examination. An elevated index of suspicion is required in patients with atrial fibrillation, mechanical heart valves, peripheral vascular disease, a history of thromboembolic events, or recent myocardial infarction with mural thrombus. In this context, AMI should be assumed until proven otherwise. While a highly elevated serum lactate indicates widespread ischemic injury, mildly elevated or normal levels have a poor negative predictive value and thus are unreliable to rule out AMI. The gold standard for diagnosis remains CT angiography. The findings of pneumatosis intestinalis, superior mesenteric artery (SMA) or celiac occlusion, arterial embolism, superior mesenteric vein (SMV) or portal venous gas, and focal bowel wall nonenhancement all have a specificity of >97% for diagnosing AMI. Prompt surgical attention is required when AMI is high on the differential diagnosis. AMI arises from four etiologies: embolism, thrombosis in the setting of atherosclerotic occlusive disease (AOD), mesenteric venous thrombosis (MVT), and nonocclusive mesenteric ischemia (NOMI).

ANATOMY

The arterial blood supply to the gut arises from the aorta via the celiac, SMA, and inferior mesenteric artery (IMA). When evaluating a patient with acute or acute on chronic mesenteric occlusion, it is important to consider the collateralization and major anastomoses between these visceral arteries, as shown in Figure 1.

TREATMENT

When AMI is suspected, if possible, patients should undergo CT angiography to evaluate the degree of vascular compromise and assist in planning revascularization. Medical management is initiated immediately with nasogastric decompression, heparin infusion, fluid resuscitation, and broad-spectrum antibiotics. Peritonitis requires emergent laparotomy, and delays (such as to obtain imaging) should be minimized before proceeding to the operating room. In general, management of AMI follows the "Four R's" (Table 1). The treatment of MVT and NOMI is predominately nonsurgical, with interventions either under the scope of the interventional radiologist or addressing underlying medical conditions and critical illness; therefore, in-depth discussion of their treatment will not be included in this chapter. Nonetheless, as with embolic and thrombotic AMI, patients suspected of MVT or NOMI and peritonitis warrant operative exploration, and frankly necrotic or perforated bowel should be resected.

The gold standard treatment of AMI remains an open midline laparotomy, including revascularization and resection of grossly necrotic bowel, when required. Diagnostic laparoscopy is of limited utility given the difficulty in adequately and thoroughly assessing all surfaces of bowel. It is easy for the surgeon to become distracted by the presence of ischemic bowel (Fig. 2) and begin resection; however, *revascularization should take priority*, with only frankly necrotic or perforated bowel being resected in a damage-control fashion. In situations where the diagnosis has been made early and without peritonitis, endovascular approaches may be considered. There is no high-quality evidence to support one strategy over another, however, and ultimately the choice will depend on the individual expertise of the surgeon and capabilities of the facility. The following algorithm is useful in identifying suitable patients for an endovascular approach (Fig. 3).

OPEN INTERVENTIONS

Following laparotomy and resection of grossly necrotic bowel, the surgical approach to revascularization in the distribution of the SMA begins the same—the colon is reflected cephalad, and the small bowel is positioned to the patient's right, revealing the root of the bowel mesentery (Fig. 4). Intraoperative Doppler is used to localize the loss of signal and extent of the occlusion. Exposure to the SMA is gained via a transverse incision through the transverse colon mesentery with careful dissection through the perivascular lymphatics and around the superior mesenteric vein. In cases of a proximal occlusion at the ostium or in AOD, the ligament of Treitz may be divided and the duodenum carefully dissected free of the pancreas and retracted to the right to reveal the retropancreatic origin of the SMA. From here, a number of options exist to restore perfusion depending on the clinical circumstances. Following revascularization, a temporary abdominal closure should be placed and the patient brought back for a second-look laparotomy and definitive closure in 24 to 48 hours.

OPEN EMBOLECTOMY

Following identification of the lesion, appropriate exposure, heparinization, and proximal and distal control of the SMA and its colic and jejunal branches, a transverse arteriotomy is made proximal to the embolus (Fig. 5). While the clot may spontaneously evacuate with retrograde arterial flow via this arteriotomy, more commonly the use of a 2- or 3-French balloon catheter is passed in an antegrade fashion to extract the embolus. Smaller catheters are then passed to remove "showered" clot from distal branches. With return of pulsatile flow and distal signals, the arteriotomy is closed primarily using polypropylene suture.

OPEN BYPASS

In the setting of AOD and subsequent thrombosis, bypass is often indicated. Several options exist depending on the extent of disease, availability of a nearby vessel to provide sufficient inflow, and access to fluoroscopy. Antegrade bypass from the supraceliac aorta and retrograde bypass from the infrarenal aorta or common iliac arteries have been debated in the literature with comparable outcomes. Autologous saphenous vein, Dacron, and polytetrafluoroethylene (PTFE) grafts have been utilized; however, the increased operative time required for saphenous vein harvest have led some authors to choose PTFE regardless of degree of intraperitoneal contamination. When synthetic conduits are used, especially in the contaminated abdomen, omental coverage should be performed with a pedicled flap (Fig. 6).

ANTEGRADE BYPASS

Antegrade bypass may be preferred when severe aortoiliac disease is present distally or in the setting of prior endovascular aortoiliac intervention, provided a nondiseased portion of supraceliac aorta can be identified. The left lobe of the liver is mobilized laterally and the left crus divided to expose and gain proximal control of the supraceliac aorta. A side-biting clamp may be utilized to avoid further hypoperfusion distally. An aortotomy is made to facilitate the end-to-side graft anastomosis (Fig. 7). Note, that while the figure depicts a bifurcated graft, which may be suitable for chronic mesenteric ischemia, single-vessel revascularization is typically sufficient

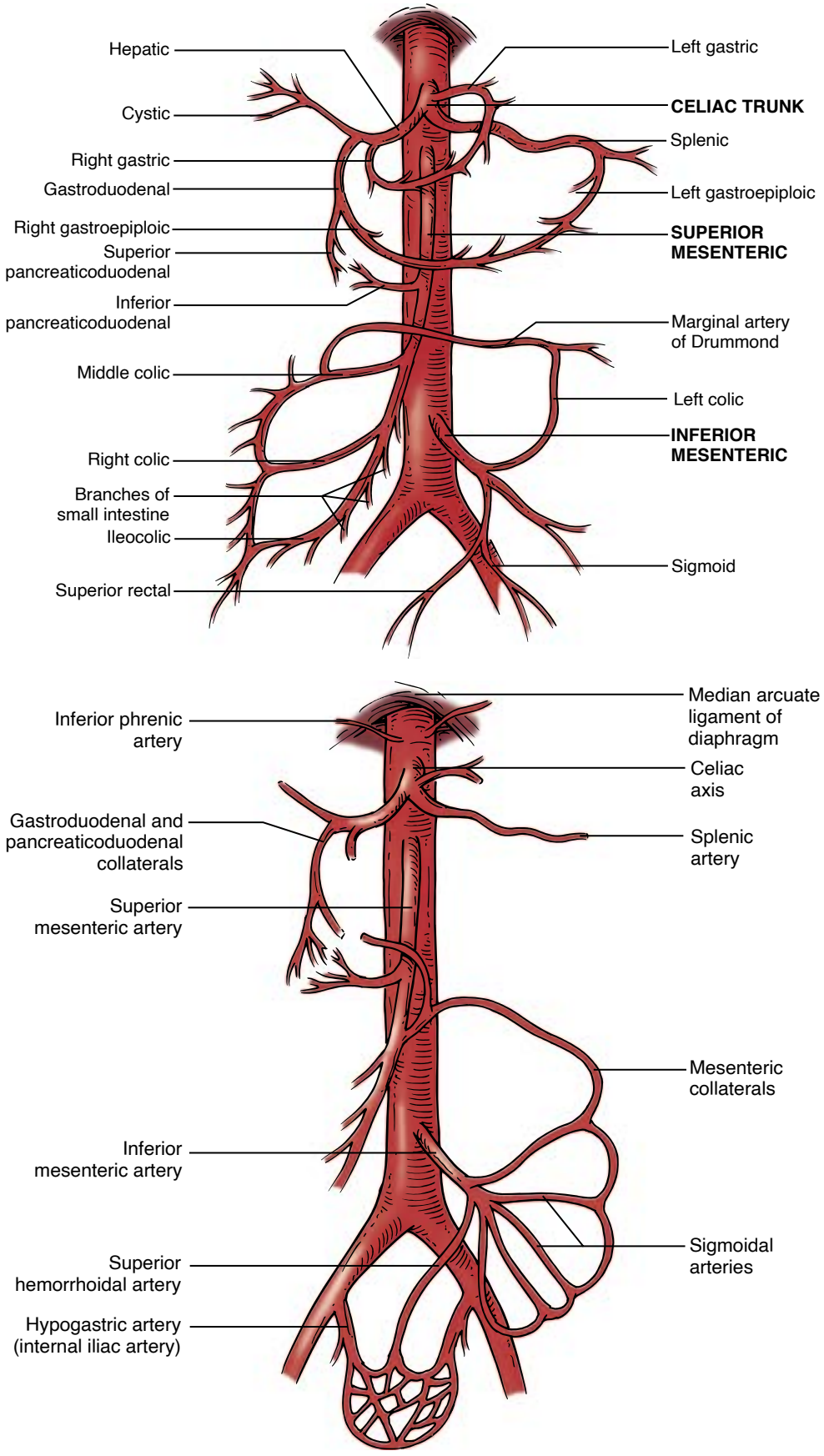


FIG. 1 Blood supply to the visceral organs and their collaterals.

TABLE 1 Four R's of AMI Management

Resuscitation	Fluid resuscitation to restore perfusion to bowel mucosa, crystalloid or colloid.
Rapid diagnosis	High index of suspicion, CT angiography
Revascularization	Open versus endovascular approaches, as discussed later
Reassessment	Second-look laparotomy or laparoscopy depending on initial approach to evaluate bowel viability after revascularization.

From Olson KA, Teixeira PG. Mesenteric Ischemia — How and When to Revascularize. *Adv Surg* 2021;55:75–87.



FIG. 2 Progressive bowel ischemia in a patient with acute SMA embolus in the setting of chronic mesenteric atherosclerotic disease and IMA occlusion. Note the progression from perfused proximal jejunum *(left)* to ischemic terminal ileum/cecum *(right)*.

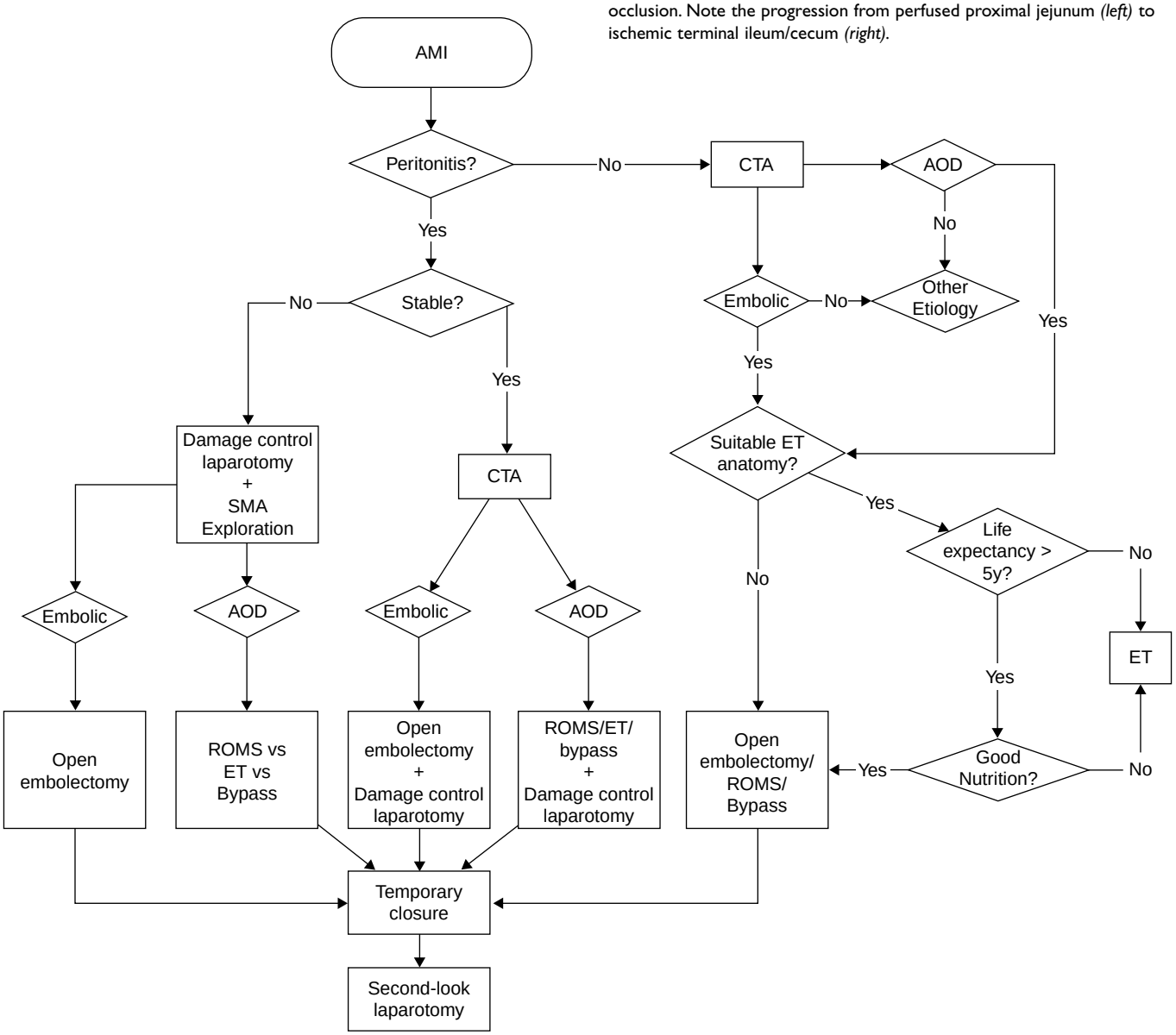


FIG. 3 Algorithm for management of acute embolic/thrombotic mesenteric ischemia via open versus endovascular approach. *CTA*, CT angiography; *AOD*, atherosclerotic occlusive disease; *ROMS*, retrograde open mesenteric stenting; *ET*, endovascular therapy. *(From Olson KA, Teixeira PG. Mesenteric Ischemia — How and When to Revascularize.* Adv Surg *2021;55:75–87.)*

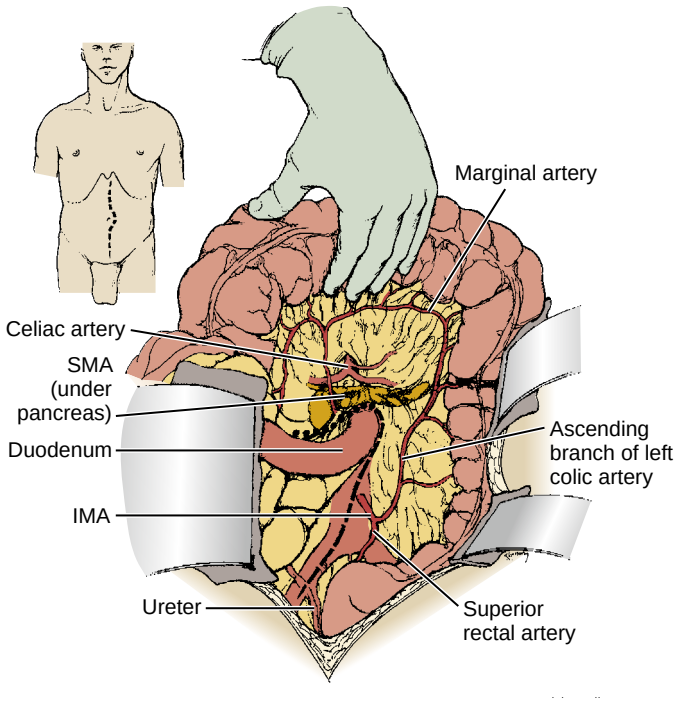


FIG. 4 Operative exposure of the infrapancreatic SMA and IMA. *(From Kazmers A. Operative management of acute mesenteric ischemia.* Ann Vasc Surg. *1998;12:187–197.)*

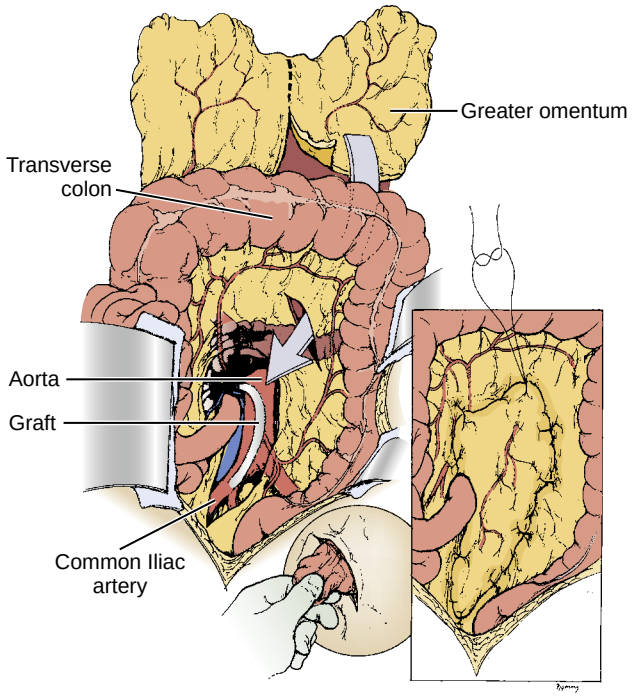


FIG. 6 Omental pedicle flap coverage of synthetic graft via a defect created in the transverse colon mesentery. *(From Kazmers A. Operative management of acute mesenteric ischemia.* Ann Vasc Surg. *1998;12:187–197.)*

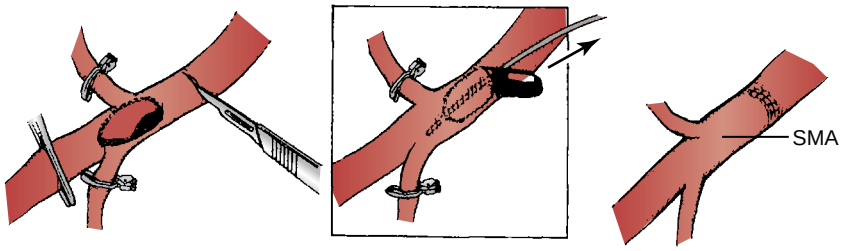


FIG. 5 Transverse arteriotomy for superior mesenteric artery embolism. *(From Cronenwett, Johnston, editors.* Rutherford's Vascular Surgery and Endovascular Therapy, *8th ed. Philadelphia: Elsevier; 2014.)*

for AMI. The graft is then tunneled in a retropancreatic plane to reach an unaffected portion of the SMA, and the anastomosis is created in an end-to-end or end-to-side fashion.

RETROGRADE BYPASS

With suitable distal inflow, either from a nondiseased portion of the aorta or from the iliac arteries, a retrograde bypass may be performed. This approach avoids the added complexity of obtaining supraceliac aortic control and associated renal hypoperfusion. The traditional approach extends the incision in the mesentery used for SMA exposure down the aorta to the common iliac arteries. The use of a C-shaped supported synthetic conduit has been advocated to avoid "kinking" of venous graft (Fig. 8). An alternative approach, called the direct open retrograde revascularization (DORR) method, has been recently described. Rather than dividing the mesentery over the aorta, access to the iliac arteries is gained by incising the white line of Toldt and mobilizing the cecum or sigmoid colon medially. A venous conduit is utilized and an end-to-side anastomosis is performed. The vein graft is then tunneled through the small bowel mesentery, using blunt finger dissection from above and below, directly to the SMA (Fig. 9). This serves the hypothetical advantages of using autologous vein graft, reducing graft redundancy, and decreasing operative time associated with transmesenteric dissection of the iliac vessels despite the time required for vein harvest.

RETROGRADE OPEN MESENTERIC STENTING

A hybrid approach to revascularization has been described for patients undergoing laparotomy using endovascular techniques that can be employed using a C-arm without necessitating access to an endovascular suite. This allows for a thorough surgical exploration of the abdomen without the pitfalls associated with open bypass, particularly in patients with intraperitoneal contamination. After exposing and obtaining proximal and distal control of the SMA and its branches as described earlier, retrograde access via the SMA or a side branch is achieved with a micropuncture kit distal to the lesion. A guidewire and 6- or 7-Fr sheath are placed in a retrograde fashion. The lesion is then traversed, and a balloon expandable bare metal or covered stent is then deployed (Fig. 10). The arteriotomy is either closed primarily or with a vein patch. Success with this approach

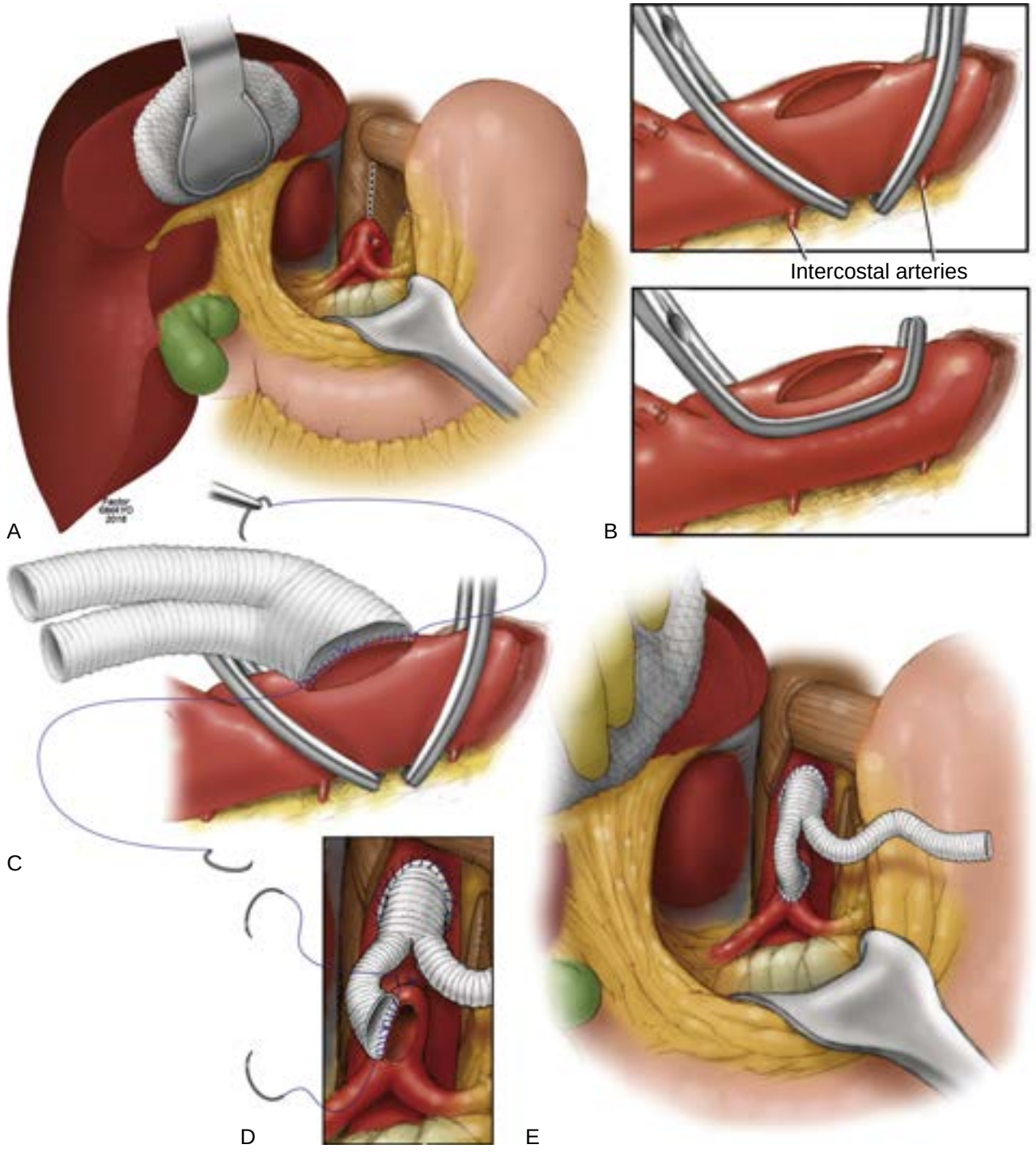


FIG. 7 **(A)** The supraceliac aorta is exposed after division of the diaphragmatic crura. **(B)** Following systemic heparin, the supraceliac is clamped using either two aortic clamps or a Satinsky clamp. **(C)** A slightly oblique aortotomy is made for the proximal anastomosis of the bifurcated graft. **(D)** Note that the graft is gently beveled and that the right graft limb is anastomosed end-to-side to the celiac axis or hepatic artery. **(E)** The left limb of the graft is tunneled behind the pancreas. *(From Sidawy AP, Perler B:* Rutherford's Vascular Surgery and Endovascular Therapy, *9th ed. Philadelphia: Elsevier, 2019.)*

has shown to be similar to other revascularization techniques, with shorter operative times (189 vs. 302 minutes) compared with open mesenteric bypass. Patency rates of 76% were reported at 2 years.

OPEN ENDARTERECTOMY

In patients with extensive AOD, multivessel disease, or acute on chronic mesenteric ischemia, open endarterectomy may be suitable. Access and control of the SMA are described earlier. Meticulous dissection and isolation of the branching vessels is required. A longitudinal arteriotomy is performed over the diseased segment, and endarterectomy is performed in the subintimal plane. Care is taken to remove as much plaque from the branching vessels as possible. Autologous vein or pericardial patch may be used to close the arteriotomy. Figure 11 and Video 1 demonstrate this approach in a patient with SMA atherosclerosis, IMA occlusion, and atrial fibrillation who

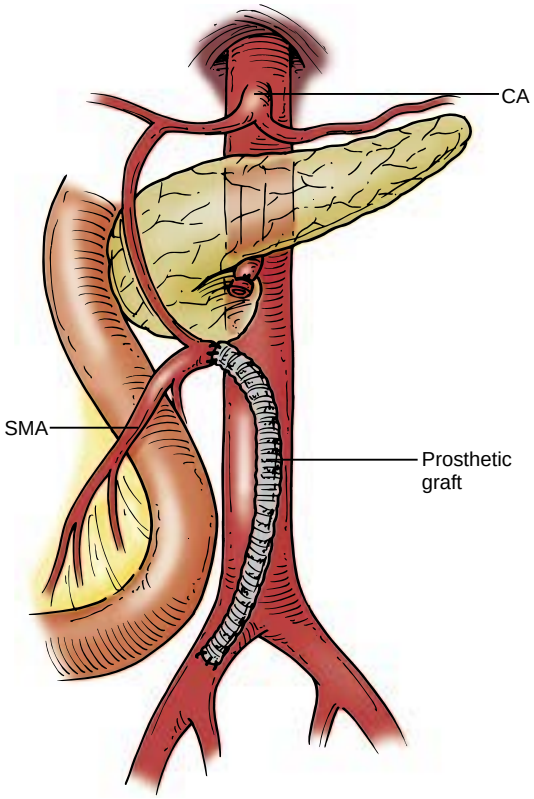


FIG. 8 Retrograde bypass from the common iliac artery *(CA)* to the superior mesenteric artery *(SMA)*.



FIG. 9 Direct open retrograde revascularization (DORR) technique. *(From Huerta et al.* J Vasc Surg. *2020;66:263–271 doi:10.1016/j.avsg.2020.01.019.)*

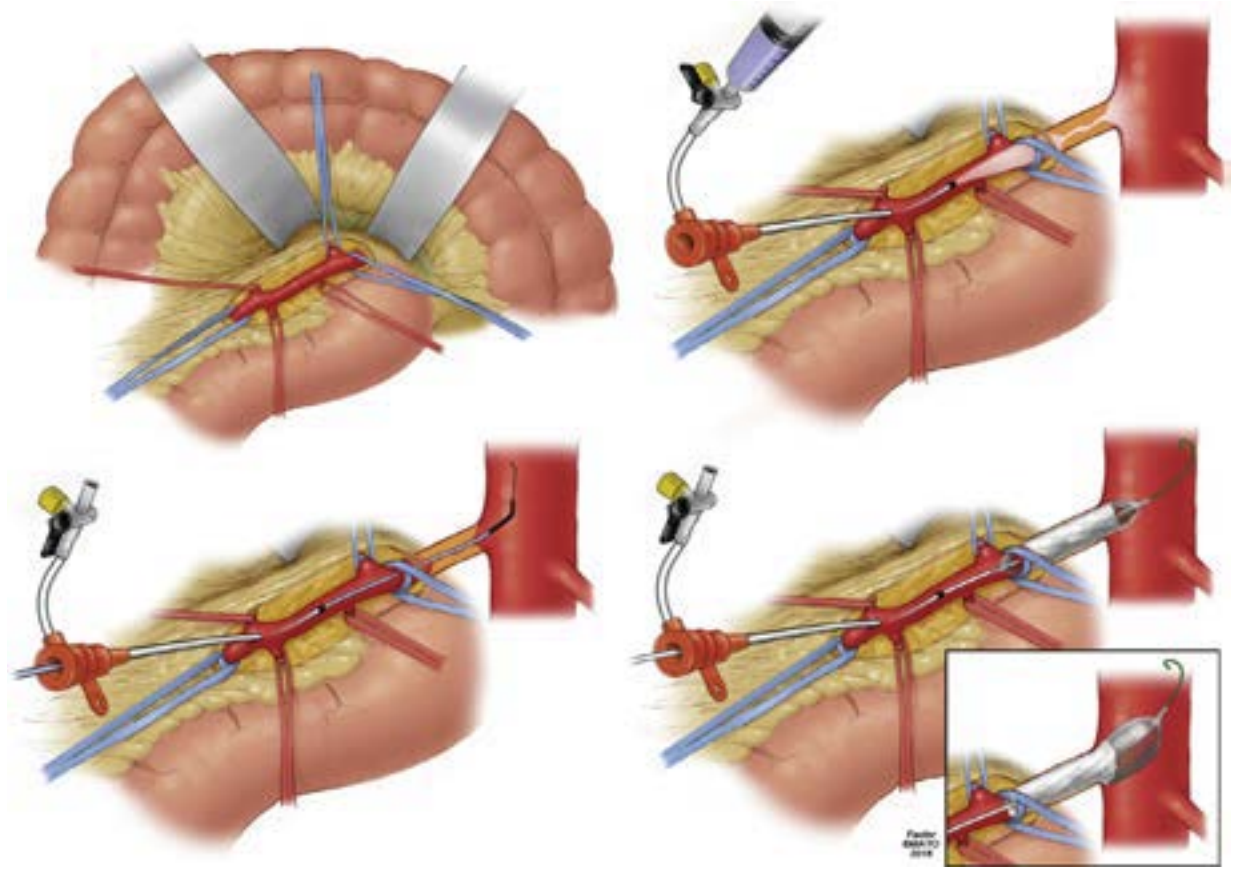


FIG. 10 Retrograde open mesenteric stenting. *(From Sidawy AP, Perler B.* Rutherford's Vascular Surgery & Endovascular therapy, *9th ed. Philadelphia: Elsevier, 2019.)*

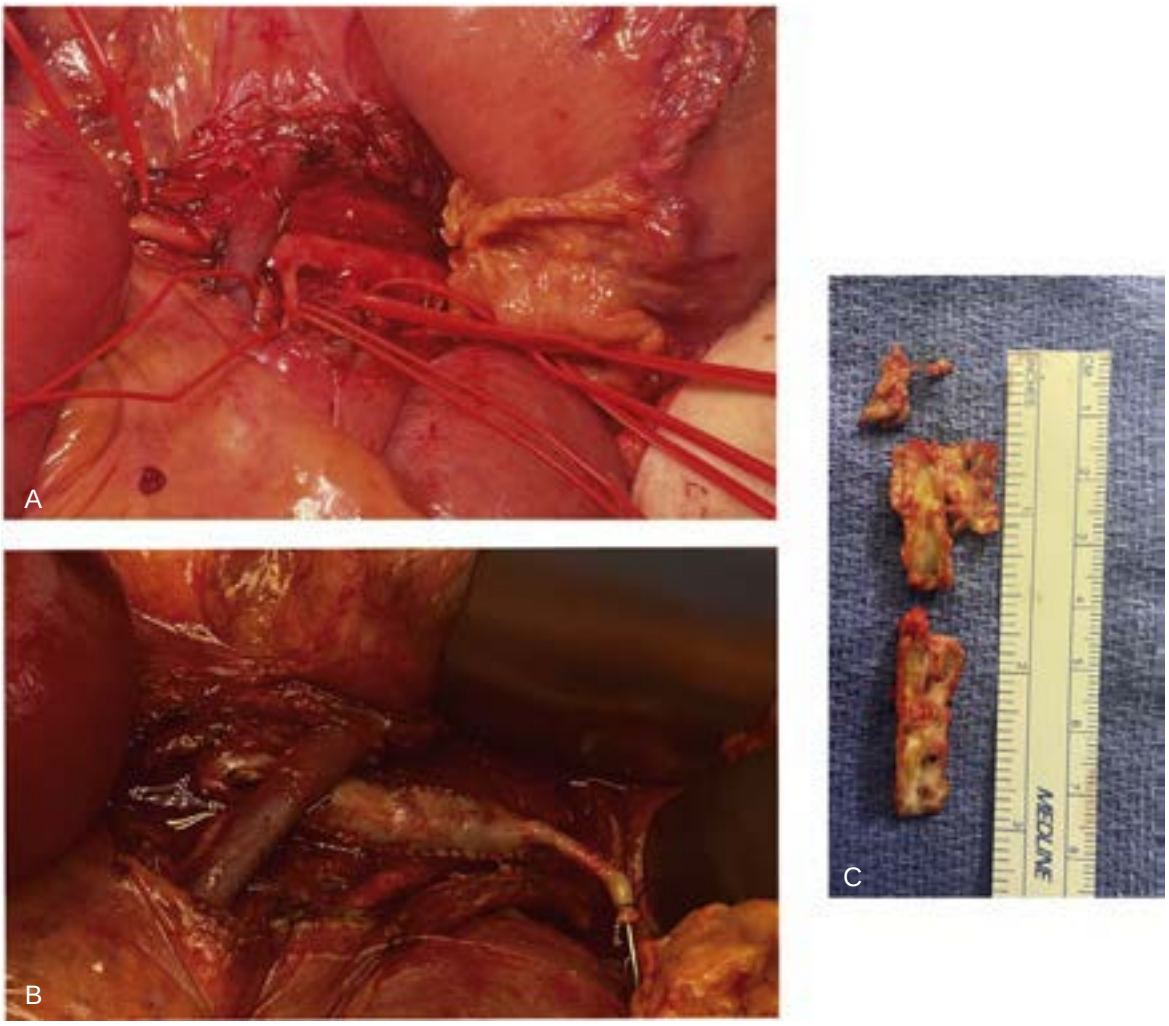


FIG. 11 Patient with acute embolic mesenteric ischemia in the setting of chronic SMA atherosclerosis and IMA occlusion. **(A)** Exposure and control of SMA and its proximal branches. **(B)** Following completion of endarterectomy and saphenous vein patch. A side-branch of the saphenous vein was cannulated with an olive-tip syringe for angiography. **(C)** Atherosclerotic plaque removed from SMA.

developed AMI after discontinuing anticoagulation. The extent of atherosclerotic disease precluded candidacy for bypass.

ENDOVASCULAR APPROACHES

While chronic mesenteric ischemia has been treated by endovascular approaches with some success, limited studies exist to support its widespread use in AMI. Careful selection is needed in identifying patients for endovascular revascularization and forgoing laparotomy (see Fig. 3). Early detection is essential, as extensive ischemia or peritonitis requires open laparotomy. A tortuous or highly angled SMA, proximal and distal landing zones ≤1 cm, and presence of disease at main arterial branches also preclude an endovascular approach. Because patency rates diminish with time, those patients with a life expectancy >5 years, should they survive hospitalization, are better suited for an open revascularization or hybrid technique. Therefore, exclusive endovascular techniques are highly reserved for a subset of patients at select facilities in capable hands. For those who are suitable for endovascular approaches, access via brachial or femoral approach can be used; however, a brachial approach is typically preferable given the difficulty accessing an angulated SMA from the femoral artery. In such cases, an angled guidewire can be used. After directing the guide catheter to the origin of the SMA, a hydrophilic guidewire is used to traverse the lesion. Care should be taken in directing the guidewire to avoid damage to the branching arteries. Thrombosuction, mechanical thrombectomy, pharmacologic thrombolysis, angioplasty, and balloon-expandable stents can then be deployed. If satisfactory revascularization cannot be performed, the patient should be converted to an open procedure. In cases where revascularization is considered successful, a "second-look" diagnostic laparoscopy should be considered.

POSTOPERATIVE CARE

In the acute postoperative period, patients should remain on heparin anticoagulation and broad-spectrum antibiotics, and be resuscitated before definitive abdominal closure. After open revascularization, a second-look laparotomy should be performed in 24 to 48 hours. Given the underlying comorbidities predisposing to AMI, lifetime anticoagulation is necessary. Patients who received endovascular stenting should be placed on dual antiplatelet therapy for 1 to 3 months and subsequently aspirin for life. Aspirin, at a minimum, is

required for patients with bypass grafting, though vitamin K antagonists and novel oral anticoagulants prescribed for comorbid disease are also suitable.

LONG-TERM FOLLOW-UP

Lifestyle modification and addressing the patient's medical comorbidities are essential to minimize disease recurrence. In patients with bypass grafts or stents, surveillance imaging via duplex US or CT angiography is recommended at 1, 6, and 12 months, and then annually thereafter. Early intervention on recurrent disease is paramount to long-term survival.

SUGGESTED READINGS

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Chronic Mesenteric Ischemia

Linda M. Reilly, MD

Chronic mesenteric ischemia (CMI) results from inadequate perfusion of the abdominal viscera. The postprandial pain that is the hallmark of symptomatic CMI causes reduced oral intake, preventing adequate nutrition and leading to progressive weight loss. CMI is also believed to be a precursor to intestinal infarction. Therefore, the goals of treatment are (1) restoration of normal nutrition through durable relief of symptoms and (2) durable protection against visceral infarction. Successful management requires accurate diagnosis, assessment of disease extent, and selection of optimal treatment.

ETIOLOGY

The most common etiology of chronic visceral ischemia is arterial occlusive disease, with atherosclerosis the most frequent form of the arterial pathology. Nonatherosclerotic arterial pathologies such as arteritis, fibromuscular dysplasia (FMD), segmental arterial mediolysis (SAM), or dissection (spontaneous, often in the setting of FMD or SAM, or posttraumatic) may also cause CMI but are fortunately much less frequent. The arteritides that may involve large and medium arteries include Takayasu's arteritis, giant cell arteritis, polyarteritis nodosa, and Behçet's arteritis, the latter to a variable degree. Abdominal pain in the setting of median arcuate ligament compression of the celiac axis is thought to have a component of mesenteric ischemia, although the mechanism is not defined and not easily differentiated from a possible neurologic etiology caused by ganglion tissue compression.

The frequent observation of asymptomatic stenosis or even occlusion of a visceral artery in adults older than 65 years of age (about 20%) and the abundant potential routes of collateral flow to the viscera support the generally accepted belief that involvement of at least two of the three main visceral arteries is necessary to reduce visceral perfusion to the point of symptom development. Although it is clear that compromise of both celiac artery and superior mesenteric artery (SMA) flow can produce CMI, it is less predictable whether compromise of inferior mesenteric artery (IMA) flow and either celiac artery or SMA flow will produce symptoms of visceral ischemia. None of the patients we have treated developed symptoms with involvement of only the IMA and either the celiac artery or the SMA.

The pattern of the flow-reducing lesions is also important in the development of symptoms: the more diffuse the distribution of lesions, the more likely that all potential collateral routes will be affected, and the more likely the patient will be symptomatic. There are three patterns of visceral artery involvement by occlusive processes: lesions involving the orifices and short segments of the proximal main visceral arteries, lesions involving long segments of the main visceral artery trunks (with or without orifice involvement), and lesions involving the branches of the visceral arteries (with or without proximal trunk/orifice) involvement. These patterns of disease determine which treatment method is applicable as well as the prognosis for a successful and durable reconstruction. The importance of establishing the arterial pathology is not limited to knowing the diagnosis but is also important to understanding the implication of a given pathology for successful treatment. For example, typical visceral atherosclerotic lesions are located at the vessel origin, actually representing aortic disease spilling into the visceral artery orifice. The involvement of the visceral artery is usually limited to the first 1 or 2 centimeters of the main trunk. In contrast, unusual pathologic processes involving the visceral arteries, such as an arteritis, generally affect longer segments of the arteries, less commonly involve the orifice, and can involve the main trunk, the branches, or both.

DIAGNOSIS AND EVALUATION

The diagnosis of CMI often challenges the clinician primarily because initial symptoms may be subtle and vague without a recognizable or typical pattern. Progression is insidious, and there are few, if any, physical findings until the onset of weight loss. All too often symptoms are ascribed to anxiety, fed by a gender bias, because there is a 3:1 female-to-male ratio for CMI. The younger age at onset (50–60 years of age) and the low incidence of signs or symptoms of arterial disease in other beds (only about one-third of patients) leads clinicians away from this diagnosis, resulting in an average onset-to-diagnosis delay of 12 months or more. When objective findings do manifest (usually weight loss, hypoalbuminemia, anemia), malignancy is the most common clinical suspicion.

Fortunately, at that point most patients will undergo computed tomographic (CT) imaging. Although this does not provide the best arterial imaging, it is valuable to eliminate many other potential etiologies, particularly malignancy. Once CMI is under consideration, duplex ultrasound (DUS) imaging should be performed to determine which vessels are involved and if any of the lesions are hemodynamically significant (cause a reduction in flow) (Fig. 1). The peak systolic velocity (PSV) threshold for hemodynamically significant disease will vary between imaging centers but is usually ≥200 to 250 cm/sec for the celiac artery, ≥275 to 300 cm/s for the SMA, and ≥200 cm/s for the IMA. Overall accuracy is improved by increasing the PSV threshold to 300 cm/s for the celiac trunk and 400 cm/s for the SMA. The end-diastolic velocity (EDV) threshold

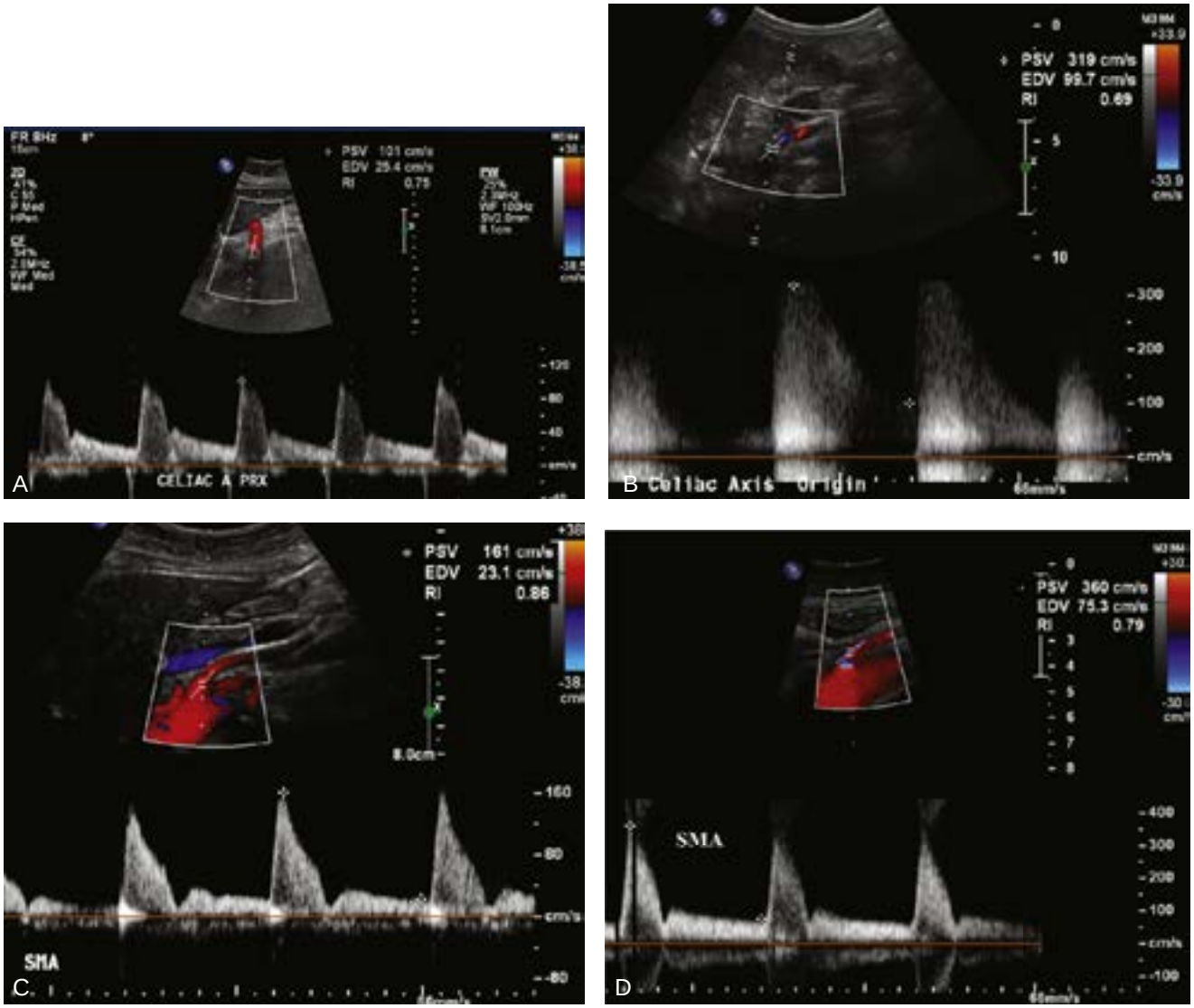


FIG. 1 Duplex ultrasound images. **(A)** Normal CE with normal flow velocities and waveform. **(B)** >70% CE stenosis with PSV = 319 cm/s and EDV = 100 cm/s. **(C)** Normal SMA with normal flow velocities and waveform. **(D)** >70% SMA stenosis with PSV = 360 cm/s and EDV = 75 cm/s. *CE,* Celiac axis; *EDV,* end-diastolic velocity; *PSV,* peak systolic velocity; *SMA,* superior mesenteric artery.

is less variable, generally ≥45 to 55 cm/s. Technician experience and patient body habitus affect the success of visceral artery DUS. Studies should be performed in the fasting state to reduce intestinal air, the most common reason for inadequate imaging. Because patients with CMI have usually lost significant weight, vessel depth is often less of a factor in study quality; however, DUS imaging will be less successful in a patient with a larger body mass index.

Contrast-enhanced computed tomographic arteriography (CTA) provides the best visceral arterial imaging (Fig. 2). Studies should be performed with thin slices (1.25–2.00 mm). Oral contrast should not be administered during a CTA examination. CTA does not provide direct hemodynamic information, but the degree of collateralization provides inferential evidence of hemodynamically significant stenoses. Patients with chronic kidney disease are susceptible to further loss of renal function resulting from the contrast used in CTA. Magnetic resonance angiography (MRA) can also provide very good arterial imaging (Fig. 3) but cannot assess calcification or provide hemodynamic data, and a significant proportion of patients cannot tolerate the claustrophobic setting.

As mentioned earlier, visceral atherosclerotic disease is often present in asymptomatic patients. Therefore, once visceral occlusive disease has been identified, it is still important to be certain there is a causal relationship between the lesions and the symptoms. At this point, other investigations may be helpful (endoscopy, motility studies, malabsorption studies), but should be performed expeditiously because weight loss and physiologic deterioration will be ongoing.

REVASCULARIZATION OPTIONS

There are basically two approaches to reconstruction for visceral arterial occlusive disease: endovascular techniques (angioplasty with or without stenting) and open surgical techniques (endarterectomy or bypass). The pattern of disease plays a major role in the selection of reconstruction technique. Although it is generally agreed that at least two visceral arteries must be involved by the occlusive process to produce symptoms, there is more debate regarding the number of visceral arteries that need to be treated to provide durable symptom relief and protection against visceral infarction. Some argue that durable symptom relief requires *complete visceral revascularization* (involving the celiac trunk and the SMA), whereas others report equivalent results with single-vessel revascularization. Among those who feel that single-vessel reconstruction is adequate, there is further



FIG. 2 Selected CTAs showing different patterns of visceral occlusive disease. **(A)** Focal severe stenosis of the CE *(arrow)* and focal high-grade stenosis of the SMA *(arrowhead)*. **(B)** Occlusion of the CE *(arrow)* with reconstitution at the level of the left gastric branch *(dot)* and critical stenosis of the very proximal SMA *(arrowhead)*. **(C)** Severe long-segment SMA atherosclerosis. The CE is not occluded, just out of plane. *Celiac* celiac axis; *SMA,* superior mesenteric artery.

debate about the optimal single-vessel target, with most favoring the SMA. In fact, if all collateral pathways between the three main visceral arteries are intact, revascularization of any one vessel should be sufficient for relief of symptoms (Fig. 4). Practically speaking, if single-vessel reconstruction is chosen, either the celiac artery or the SMA should be the target artery as long as it is technically feasible. Single-vessel reconstruction to the IMA should be performed only if neither the celiac artery nor the SMA can be repaired. The technique of endarterectomy (transaortic) virtually requires that both the celiac artery and SMA be treated. Bypass can be performed to either single or multiple visceral vessels, but most surgeons will opt to revascularize more than one branch (assuming technically feasible) if for no other reason than to avoid subsequent reoperation. If an endovascular approach is chosen, the selection of the target vessel(s) can be more complicated. The less-invasive nature of the procedure favors treating both the celiac artery and the SMA during the same procedure, but it also allows a staged approach—treating one vessel (usually the SMA) and then waiting to see if intervention to treat the other branch is required. If either the celiac artery or SMA is occluded and the other branch is stenotic, some will reopen the occluded vessel first, concluding that it is lower risk (because generally you cannot worsen an occluded vessel), whereas others might treat the stenotic vessel first, concluding that reopening an occlusion is technically more difficult, more likely to be unsuccessful, and may result in a much longer procedure if considerable time is spent attempting to reopen the occluded branch before accepting defeat and treating the stenotic branch.

Endovascular Techniques

As in other locations, intraluminal endovascular treatment is optimal for focal visceral arterial lesions that are neither bulky nor heavily calcified. The most common visceral atherosclerotic lesion is actually aortic plaque that extends through the mesenteric artery origin and into the visceral artery for a short distance (1–2 cm), stopping before any major branch points. The focal involvement in the visceral branch favors an endovascular approach. Conversely, the aortic component of the plaque, the frequently observed dense calcification, the bulky nature of the lesions, or complete occlusion (especially flush occlusions) are unfavorable factors that may adversely affect procedural success and durability of an endovascular approach. The less-common patterns of visceral occlusive lesions (long segment main artery

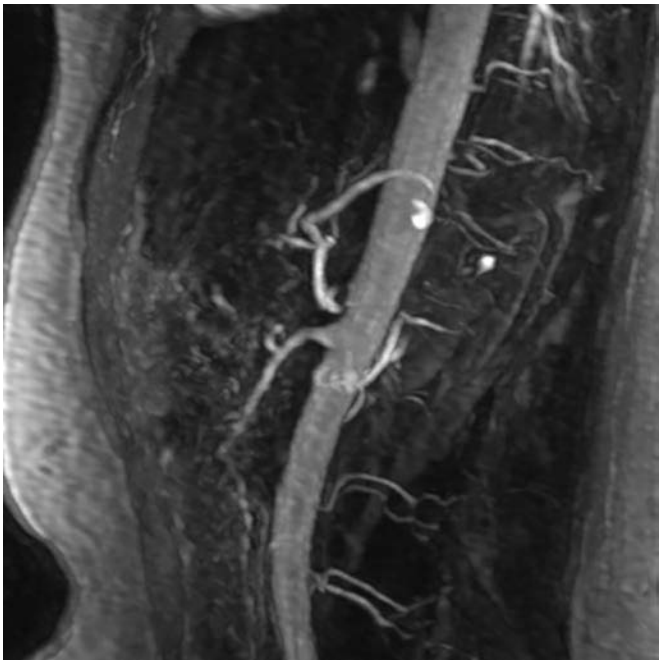


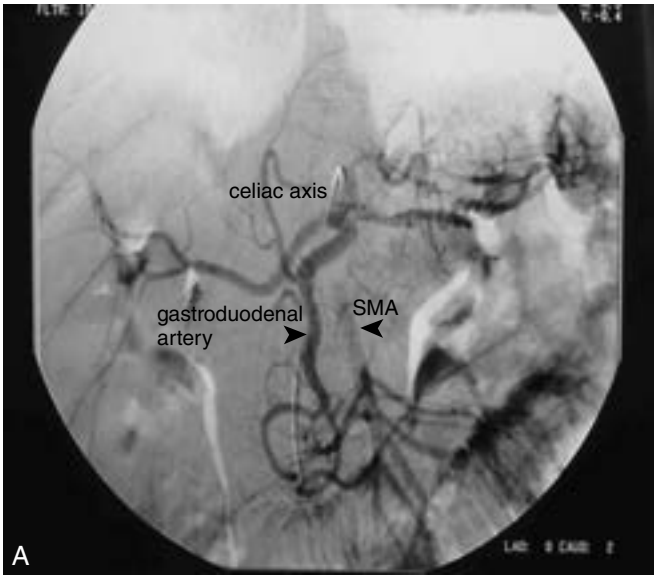
FIG. 3 MRA demonstrating celiac stenosis from compression by the median arcuate ligament.

involvement and/or branch involvement) are less likely to be successfully treated by an endoluminal approach. Compression of the celiac axis (and in rare cases of the SMA) by the very dense median arcuate ligament should not be approached endovascularly unless the ligament is first released. The ligament is too dense and will not respond to angioplasty, even if adjunctive stenting is performed.

Simple angioplasty is rarely used to treat visceral atherosclerotic stenosis. The aortic component of the plaque and the frequent heavy calcification result in a poor response. Angioplasty with stenting is the most common endovascular approach. Balloon-expandable covered stents have become the technique of choice for several reasons. Balloon-expandable stents exert high radial force, which is needed to push against the often heavily calcified, bulky, and circumferential lesions. Covered stents may reduce the risk of vessel injury from the high inflation pressures needed to adequately efface the stenosis. They may also reduce the risk of embolization by trapping the plaque against the arterial wall. Also, the intimal hyperplastic response to angioplasty and stenting can only occur at the distal end of a covered stent (the proximal end of the stent protrudes 1 to 2 mm into the aorta and is not in contact with any arterial wall). The ingrowth of intimal hyperplasia through the interstices frequently seen along the entire length of an uncovered stent is prevented by the fabric of the covered stent (usually expanded polytetrafluoroethylene [ePTFE]). This limits the risk of recurrent stenosis to the distal end of the covered stent. All of these factors may contribute to the reports by some investigators of lower restenosis and reintervention rates when covered stents are used.

The stent should be longer than the stenosis. The stent is positioned to extend beyond the distal end of the plaque and to project into the aorta by 2 to 3 mm (Fig. 5A, B). It is important to "flare" the covered stent in the aorta to adequately treat the ostial aortic plaque (see Fig. 5C) a maneuver that has been reported to improve the midterm patency of mesenteric artery stents. The diameter of the covered stent should be about the same as the target visceral artery. Oversizing is not necessary and risks inflation injury of the branch or, worse still, of the junction of the branch with the aorta. Most currently available balloon-expandable covered stents can be dilated postdeployment to a slightly larger size by using a balloon slightly larger than the delivery balloon. This is far safer than oversizing.

Visceral angioplasty and stenting can be performed from either a transfemoral or a transbrachial approach. The larger size of the common femoral artery reduces access site complications, but the angle of approach into the visceral branch is a disadvantage, particularly because the celiac artery and SMA frequently originate from the aorta at a downward angle. This anatomy can make recanalization of an occluded visceral branch more difficult and may impede tracking of any device (sheath, balloon, covered stent) into the branch. These challenges have been reduced significantly by the development of sheaths with conformable (deflectable) tips that can "aim" down and maintain that orientation, even while devices are inserted. Transbrachial access provides a more natural angle of approach to the



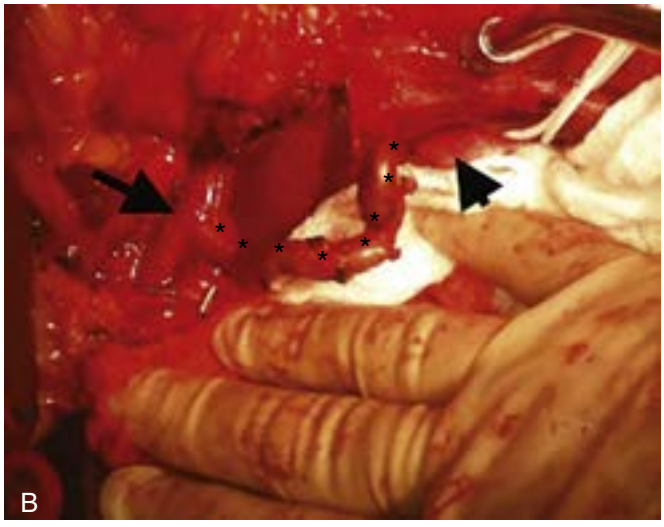


FIG. 4 **(A)** Selective injection of the celiac axis results in opacification of the superior mesenteric artery via a very large gastroduodenal artery. In this case, revascularization of either the celiac axis or the SMA will provide perfusion to the entire visceral circulation **(B).** Intraoperative exposure of the gastroduodenal artery *(asterisks)* from the hepatic artery *(arrow)* to the SMA *(arrowhead)* during a Whipple procedure. A tight celiac stenosis was not recognized preoperatively. Because hepatic artery perfusion was dependent on this collateral pathway, it could not be sacrificed, prompting this unusual complete mobilization. *SMA,* Superior mesenteric artery.

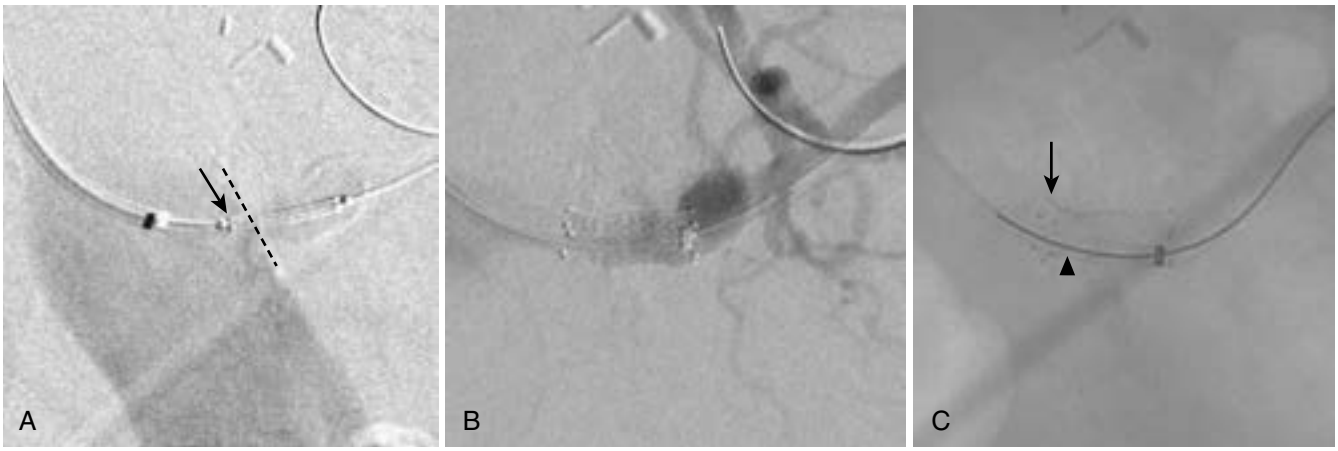


FIG. 5 **(A)** Intraprocedural angiogram demonstrating optimal position of the celiac stent, extending a few millimeters into the aortic lumen. The proximal end of the stent is represented by the *arrow*. The aortic wall is represented by the *dashed line*. **(B)** Angiographic image of the celiac stent after pressure-monitored balloon inflation and stent deployment. **(C)** Angiographic image of deployed celiac stent showing the flared proximal end *(arrow)*. The slight waist *(arrowhead)* represents the location of the aortic wall.

visceral branches. This is particularly important when recanalizing an occluded visceral artery or traversing a critical stenosis in a lesion with significant calcification. The mechanical advantage of pushing in a (more or less) straight line is significant. Using a brachiofemoral wire to stabilize sheath position further increases the in-line force that can be safely exerted to successfully treat challenging lesions or occlusions. In fact, we never conclude that we have failed to recanalize an occlusion or cross a complex lesion until we have tried both the transfemoral and the transbrachial approaches and have used a brachiofemoral wire. Whenever possible, the left brachial artery is used to avoid the disadvantage of traversing the entire aortic arch, with the associated risk of stroke resulting from manipulation across the origins of all the cerebral vessels. Access site complications are of course greater with the transbrachial approach, owing to the smaller size of the artery. One should not hesitate (unless one is a cardiologist) to perform open exposure of the brachial artery to allow safer access.

Plaque fragment embolization is a risk associated with any endovascular procedure, but some arterial beds are more tolerant of this complication than others. The risk of visceral infarction resulting from plaque embolization during visceral angioplasty and stenting has prompted some to use distal embolic protection (filter devices). This adds complexity to an already complex procedure, and currently there are no data showing benefit. One should be aware of the embolization risk, particularly when recanalizing occluded visceral branches. Also, if the clinical scenario suggests subacute visceral branch occlusion (not too likely in patients with CMI), endovascular treatment should be approached very cautiously as the risk of thrombus embolization (as opposed to plaque fragment embolization) is very high. Any recent, relatively abrupt change in symptoms should be concerning. A shower of thrombus fragments can be fatal.

A word of caution about endovascular treatment of the IMA: the IMA is a small and very fragile artery. Unfortunately, whenever there is IMA stenosis, there is always significant aortic plaque that is heavily calcified and circumferential around the IMA orifice and requires significant inflation pressure to overcome. There is often post-stenotic dilation of the IMA with flow-based enlargement (compensating for celiac artery and SMA disease), further increasing the fragility of the artery. Further, the IMA has a very short straight segment before it becomes tortuous. This combination of anatomic features very commonly results in dissection of the IMA when angioplasty and stenting is attempted. This is because the artery distal to the plaque and stenosis will not tolerate the amount of manipulation needed to insert and deploy the stent and efface the stenosis. Because one does not usually treat the IMA unless neither the celiac artery nor the SMA can be treated, dissection of a dominant IMA can be catastrophic.

Hybrid Technique

On occasion, it proves impossible to treat visceral artery stenosis or occlusion using the transfemoral or transbrachial approaches. Usually one then proceeds with an open surgical approach. However, if the patient is too high risk for standard open surgical visceral revascularization, the hybrid approach may provide the best treatment option. Commonly the SMA will be the target artery in this scenario. The artery is exposed through a midline laparotomy and then directly punctured distal to the stenosis or occlusion. Under fluoroscopy, a wire is advanced retrograde, crossing the lesion into the aorta. Angioplasty and stenting are performed in the standard manner. This circumstance is not often encountered with CMI, but is increasingly applied in the setting of acute mesenteric ischemia, particularly when laparotomy for bowel resection or assessment is needed.

Open Surgical Techniques

Endarterectomy

Endarterectomy was the earliest operative technique applied to visceral artery occlusive disease. However, the initial approach utilized the transarterial retrograde approach, through either the celiac artery, SMA, or both to remove the obstructing lesion. This approach resulted from the early failure to recognize the significance of the aortic involvement and was less successful because it did not allow complete removal of the aortic portion of the lesion. Currently endarterectomy is performed through the aorta, and the lesions extending into the visceral artery orifices are extracted by eversion endarterectomy.

Aortic exposure is achieved through a transabdominal approach with medial visceral rotation (MVR) from the left. In this technique, I prefer to keep the left kidney in its anatomic position, while the plane behind the left colon, spleen, pancreas, and stomach is developed to allow displacement of these structures toward the midline. Others prefer to develop the plane behind the kidney as well because it is technically easier and faster. If needed, the entire aorta, from the distal thoracic level inferiorly, can be completely exposed in this manner (Fig. 6). During complete aortic occlusion and with control of any intervening intercostal branches, a U-shaped trapdoor

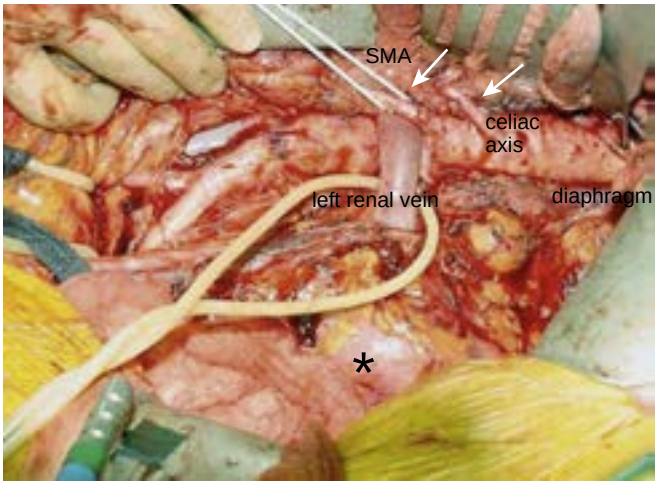


FIG. 6 Aortic exposure provided by a transabdominal approach with medial visceral rotation from the left. Note that the entire abdominal aorta from the diaphragm (under the narrow retractor blades; *arrows*) to the bifurcation of the iliac arteries can be exposed. Note that the left kidney *(asterisk)* remains in its anatomic position. The large vessel loop encircles the left renal vein, which can usually be left intact.

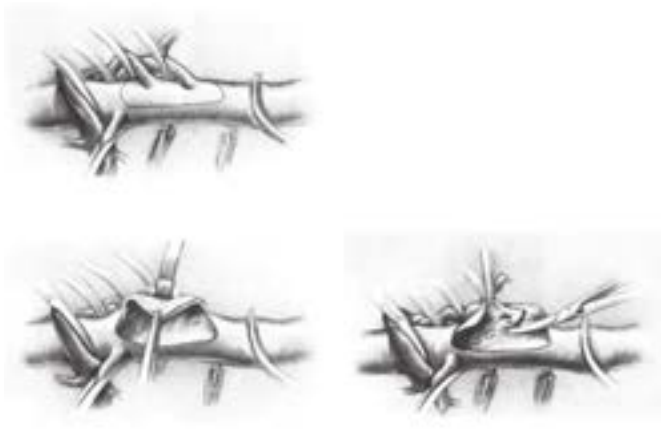


FIG. 7 A trapdoor aortotomy has been created to expose the aortic disease extending into the orifices of the celiac axis and the superior mesenteric artery. *(From Ehrenfeld WK, Qvarfordt PG, Ronald J. Stoney RJ. Surgical techniques for visceral artery revascularization. In: Greenhalgh RM, ed. Vascular Surgical Techniques. Butterworth Heinemann; 1984).*

aortotomy is placed to circumscribe the orifices of the celiac artery and SMA, and an endarterectomy is performed, removing the aortic wall lesion and its extensions into the visceral orifices (Fig. 7). In many cases, the significant aortic atheroma is confined to the ventral surface of the aorta immediately around the celiac artery and SMA orifices, and the aortic endarterectomy can be limited to the trapdoor segment itself. However, more diffuse aortic disease, frequently in the setting of associated renal artery occlusive lesions, requires extension of the aortotomy caudally to allow sleeve aortic endarterectomy and bilateral or unilateral renal artery endarterectomy. In this circumstance, the aortotomy takes the shape of a hockey stick rather than a trapdoor. Following completion of the endarterectomy, the aortotomy is closed with a running suture. If the disease extends well out into the visceral branches, it may be necessary to use a separate longitudinal arteriotomy in the visceral artery itself to allow complete removal of the disease. This visceral artery incision is then closed with a vein patch angioplasty.

Endarterectomy is perhaps the most elegant approach to visceral artery occlusive disease, but it has significant limitations. It is most applicable to visceral artery lesions that are confined to the first 1 or 2 centimeters of the artery. Although longer lesions may be successfully treated with transaortic endarterectomy, in our experience endarterectomy in this setting is less durable. Endarterectomy is not applicable to lesions extending into branches of the visceral arteries. Transmural calcification of a visceral artery should generally be considered a contraindication to endarterectomy. A transmural lesion will force a very deep endarterectomy plane, usually resulting in inadequate integrity of the adventitia. Attempting endarterectomy in this setting usually results in extensive bleeding through the porous adventitia and prolonged visceral ischemia as a consequence of attempts to repair the bleeding artery—an invariably fatal combination. Endarterectomy is particularly appealing when there is occlusive disease involving the renal arteries because it is much faster than individual bypasses to all four arteries (celiac artery, SMA, and both renal arteries). Obviously if there are multiple renal arteries, it is even more attractive. Endarterectomy is often the most appropriate technique for occlusive disease involving the IMA. However, because of the smaller size of this artery and the less predictable location of the endpoint, I favor a longitudinal incision extending out the IMA to a disease-free segment and closure with a vein patch following the endarterectomy.

Bypass

At least theoretically, bypass is the only reconstruction technique applicable to all patterns of arterial visceral occlusive disease. Practically, the more extensive the disease and the more branch involvement, the less feasible bypass becomes. Bypass to the mesenteric arteries may originate from the supraceliac aorta (antegrade bypass) or from the infrarenal aorta or iliac arteries (retrograde bypass).

Antegrade Bypass

Proximal aortic exposure for antegrade bypass can be achieved using a transabdominal, transcrural approach (Fig. 8) or MVR from the

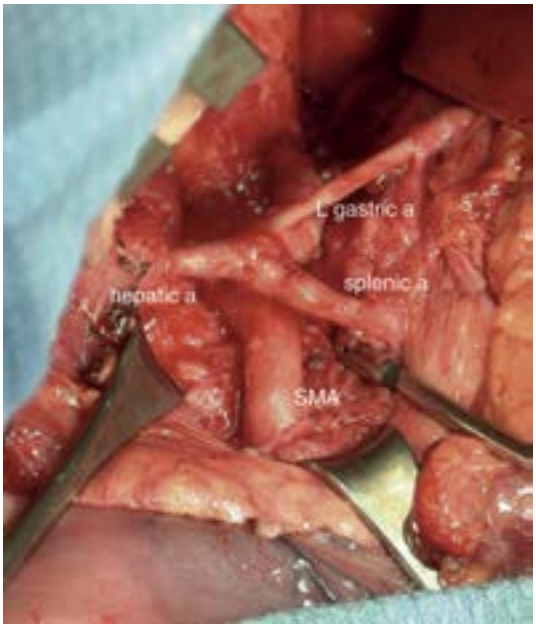


FIG. 8 Transcrural exposure of the celiac axis and its branches (left gastric, hepatic, and splenic) and the superior mesenteric artery *(SMA)*. Note the caudal retraction of the stomach and pancreas. Note also the complete division of the median arcuate ligament and the complete removal of the celiac ganglion and plexus from around the anterior surface of the aorta and the proximal trunks of the celiac axis and the SMA.

left. The transcrural approach is appealing because it is a less extensive exposure. However, it requires a relatively wide costal margin. It also may require a retropancreatic tunnel for the graft that will be anastomosed to the SMA, depending on the extent of the disease in that artery. Finally, the restricted exposure can make the aortic anastomosis somewhat difficult as the space is small, limiting visibility as well as movement. MVR provides much better exposure, but at the cost of a larger operation. Graft length and alignment are easier to determine with the transcrural approach and require more judgment with MVR.

Regardless of the exposure, the proximal anastomosis of the antegrade bypass is placed in the disease-free supraceliac aorta and requires temporary total aortic occlusion. However, circumferential aortic mobilization is not routinely performed. The aortotomy is oriented slightly obliquely and must be of adequate length to allow a low profile for the graft. Sometimes a thin piece of the aortic wall is excised to facilitate wide opening of the anastomosis. The body of the graft should be short, and the bevel on the graft must be long and gradual to allow the graft to assume a low profile on the front of the aorta (Fig. 9). If the graft originates from the aorta with a high profile, it increases the chance of kinking. In addition, the aortotomy must be placed sufficiently proximal on the aorta to allow the graft limbs adequate space to assume a gentle course to the visceral artery. If the distance is too short, the graft limbs will kink. As depicted in Figure 9, we prefer to use a small-diameter bifurcated Dacron graft (12 mm × 6 mm) if both the celiac artery and SMA are to be revascularized. If only one artery requires reconstruction, we prefer to cut one limb from the body of the small bifurcated graft (if available), creating a nicely flanged proximal end to the single graft limb (Fig. 10). If no small-diameter bifurcated graft is available, we anastomose one 8-mm graft end-to-side to another 8-mm graft (or 6-mm graft, depending on the size of the target visceral artery) creating an appropriate customized bifurcated graft (Fig. 11). Whatever

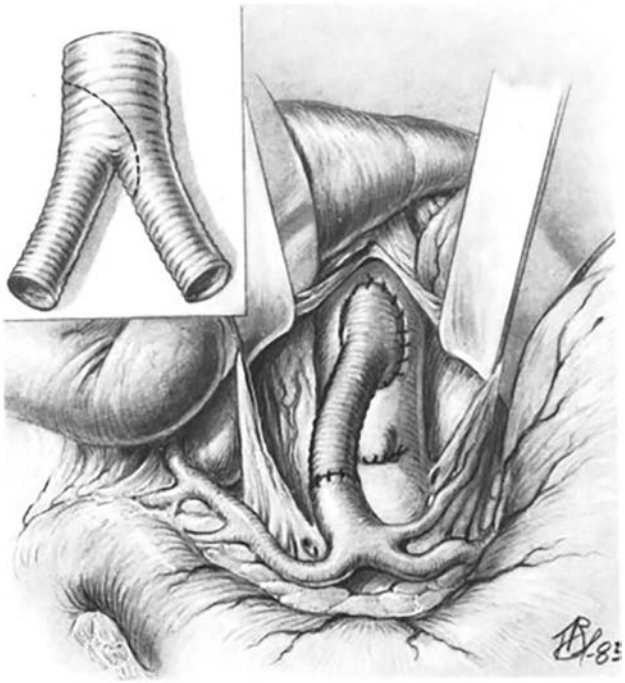


FIG. 10 Creation of flanged conduit from a small-diameter bifurcated graft when only one visceral vessel will be revascularized. *(From Ehrenfeld WK, Qvarfordt PG, Ronald J. Stoney RJ. Surgical techniques for visceral artery revascularization. In Greenhalgh RM, ed. Vascular Surgical Techniques. Oxford, UK: Butterworth Heinemann; 1984).*

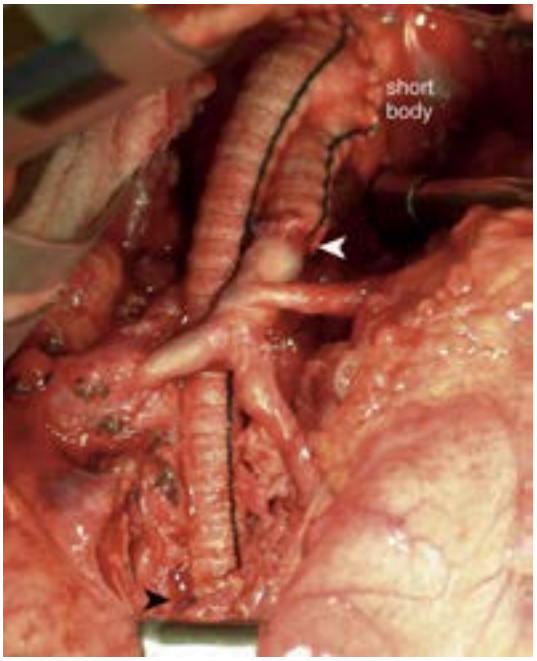


FIG. 9 Completed antegrade bypass to the celiac axis and superior mesenteric artery *(SMA)*. Note the very short body portion of the graft. Note that the orientation of the graft limbs prevents either limb from compressing the other. Also note the inferior retraction of the stomach and pancreas. Celiac anastomosis is indicated by the *white arrowhead,* and SMA anastomosis is indicated by the *black arrowhead*.

the structure of the conduit, after completion of the proximal aortic anastomosis, aortic flow is restored, and an occluding clamp is placed across the limb(s) of the graft.

If the transcrural exposure is used, the celiac artery and SMA are exposed above and behind the pancreas, which requires careful and complete dissection of the visceral arteries from the surrounding celiac ganglion tissue and the median arcuate ligament (see Fig. 8). Usually, the left graft limb will be anastomosed to the celiac axis, and the right graft limb will be anastomosed to the SMA. However, it is always wise to check the relative positions of the two visceral arteries before committing to this arrangement. When the MVR exposure is used, it may be better to *perform the anastomosis to the SMA first.* Usually, the anastomosis to the SMA is performed more distally on that artery than the anastomosis to the celiac axis. This is particularly so when the SMA lesion is more extensive. As a consequence, the SMA anastomosis may actually be performed under the graft limb to the celiac axis, restricting access and/or requiring significant retraction on the graft limb to the celiac axis. To avoid this situation, the anastomosis to the SMA should be performed first. The distal anastomoses are constructed in an end-to-end or end-to-side manner to the individual visceral arteries, beyond the point of atherosclerotic involvement. If the anastomosis is end-to-end, the visceral artery is almost always spatulated, and the conduit almost always has a short bevel. This provides for better alignment and lie for the grafts. The conduit is almost always prosthetic.

Retrograde Bypass

The infrarenal aorta, iliac artery, or a previously placed aortic bypass can also serve as inflow to the visceral arteries. This exposure utilizes the standard infracolic approach. If the SMA is the revascularization target, it is exposed in the root of the mesentery, beyond the disease, in preparation for an end-to-side anastomosis. The celiac axis itself is rarely the target for a retrograde bypass, in part because it is often too short to accommodate the anastomosis and in part because the graft
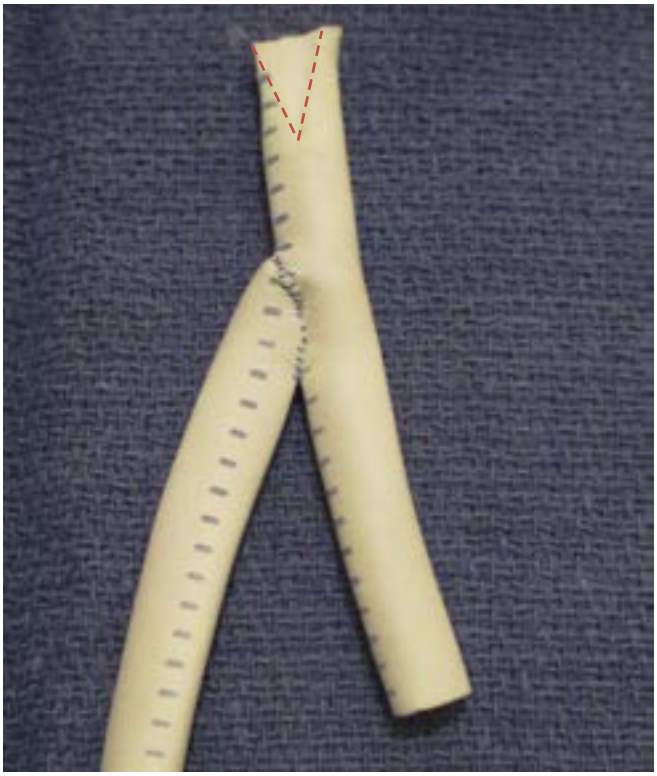


FIG. 11 Physician-constructed bifurcated graft. The dotted red line indicates where the graft has been incised to create a flanged end for the proximal anastomosis.

alignment would be awkward. More commonly, the bypass is anastomosed to a branch of the celiac artery, usually the hepatic artery, since hepatic and gastric perfusion are more important than splenic flow. Positioning and alignment are more difficult with retrograde conduits, making them more susceptible to twisting, kinking, and compression. To minimize this risk, most recommend that the conduit be constructed in the shape of a long, gentle backwards C-curve or candy-cane curve (Fig. 12).

OUTCOMES

Since vascular surgeons began to incorporate endovascular techniques into practice and training, the use of these approaches to treat disease in all vascular beds has rapidly expanded. Mesenteric occlusive disease is no exception. Technical success rates for endovascular intervention (85%–100%) are competitive with but not quite as good as open surgical revascularization (97%–100%). Studies using data from the Nationwide Inpatient Sample (NIS) show that during the first 15 years of this century, between 70% and 80% of patients treated for CMI underwent endovascular intervention. Endovascular treatment surpassed open surgery to become the predominant treatment modality two decades ago. During the same time interval, the total number of patients treated for CMI increased from 1.8 per million to 5.6 per million, while the number of open surgical procedures remained constant. This suggests that the availability of endovascular treatment expanded the pool of patients for whom intervention was determined to be indicated and appropriate.

Open surgery for CMI poses significant risks because the typical CMI patient has medical comorbidities and is malnourished. Even though the mortality of open surgery for CMI decreased by about 50% over the past two to three decades (from about 20% to about 10%), many studies report rates about threefold higher than the mortality of patients undergoing endovascular treatment for CMI

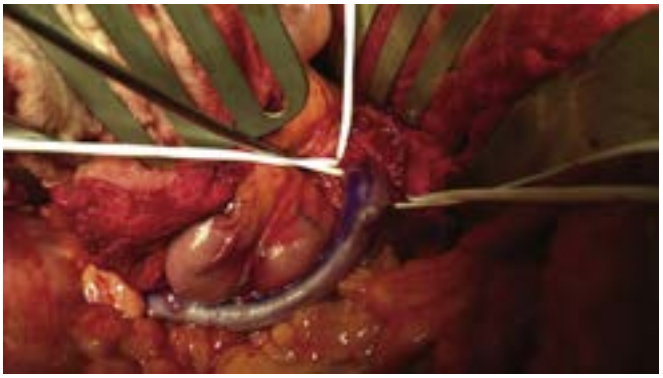


FIG. 12 Retrograde bypass from the left external iliac artery to the superior mesenteric artery (SMA) using cryopreserved femoral vein. The SMA and its early branches are encircled by vessel loops. A tissue conduit was used because the patient underwent segmental small bowel resection at the same operation for a chronically ischemic bowel segment with changes consistent with contained perforation.

(about 10%–13% vs. 3%–5%). Both major adverse cardiovascular and cerebrovascular events and composite in-hospital complication rates are lower with endovascular treatment (major adverse cardiac and cerebrovascular events 8% vs. 16% and composite index 15% vs. 20%), which also has lower median costs and a shorter length of stay. These outcomes are even more notable when one considers that patients undergoing endovascular treatment tend to be older and have more medical comorbidities. For these reasons, most consider endovascular intervention to be the first-line treatment for CMI.

Everything would be perfect in this story of progress if the benefit of reduced in-hospital mortality and morbidity with endovascular treatment of CMI were followed by long-term durability at least equal to open surgery. Unfortunately, this is not the case. Virtually all comparisons of open surgical and endovascular treatment for CMI show higher rates of recurrent stenosis, symptomatic recurrence, and reintervention following endovascular treatment. Reported recurrent stenosis rates are as high as 40%, with reintervention for recurrent symptoms needed in about one-half of that group. Factors associated with an increased risk of restenosis and reintervention include female gender, small-diameter arteries (<6 mm), degree of lesion calcification, long lesions, occlusions, and prior mesenteric interventions. None of these factors can be mitigated. Therefore, efforts to improve the durability of endovascular treatment have focused on technique modifications. About one decade ago, Oderich et al. reported lower restenosis and reintervention rates when covered stents were used instead of bare metal stents, leading to a steady increase in the use of covered stents. Because subsequent reports have not consistently supported the benefit of covered stents, a randomized multicenter trial is currently underway.

An additional benefit of endovascular treatment is its application to the management of patients with failed or failing prior interventions for CMI, whether prior endovascular treatment or open surgical repair. This has always been a difficult clinical situation because reoperative visceral revascularization is technically quite challenging. Endovascular intervention offers the potential for rescue at lower risk, with minimal mortality and morbidity less than 20%. This compares very favorably with redo open visceral operations that have complication rates exceeding 50%.

Amidst the rising tide of endovascular enthusiasm, it is important to remember that open surgical treatment for CMI is a very good modality with very good results. In comparison to endovascular approaches, it has higher technical success rates, has better durability, and is more broadly applicable to all patterns of visceral occlusive disease. It seems intuitively obvious that the less-invasive endovascular approach would offer lower morbidity and mortality, and this assumption is supported by many single-center, retrospective, and

noncomparative reports. But three of four meta-analyses showed no difference in periprocedural mortality between open surgery and endovascular treatment. Furthermore, open surgical mortality and morbidity continue to improve, reflecting progress in preoperative patient assessment and preparation and perioperative management. Evolution in surgical techniques has also contributed to improved outcomes, particularly the increased use of single body cavity exposure (abdominal rather than thoracoabdominal) and the increased use of bypass rather than transaortic endarterectomy. The accumulated evidence that retrograde bypass (usually originating from an iliac artery) produces outcomes equivalent to antegrade bypass (usually originating from the supraceliac aorta) with the advantage of no interruption of aortic flow has also reduced perioperative adverse events.

In summary, CMI remains a therapeutic challenge. Fortunately, the emergence of endovascular treatment has expanded the pool of patients who can be treated with low risk, initial success, and the potential for rescue reintervention using the same low-risk endovascular techniques. In parallel, open surgery has become lower risk, while maintaining durability. This progress offers expanded hope for patients with this life-threatening condition.

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Hemodialysis Access Surgery

Christine Haugen, MD, PhD, and Thomas Reifsnyder, MD

For the past decade, the overall prevalence of end-stage renal disease (ESRD) in the United States has increased at a rate of approximately 2% per year, with the exception of an unusual decrease in ESRD incidence from 2016 to 2017. An estimated 30 million Americans have a diagnosis of chronic kidney disease. In 2018, 131,636 patients initiated dialysis treatment, the highest annual incidence to date, bringing the total number of Americans living on dialysis to almost 500,000. Additionally, the number of older patients with ESRD is increasing, with those aged ≥65 making up 52% of incident hemodialysis patients in 2019. For the vast majority of patients, hemodialysis is the preferred mode of renal replacement therapy. The ability to deliver this lifesaving therapy is dependent on the creation and maintenance of adequate vascular access.

HISTORICAL NOTES

Over the course of approximately a century, end-stage renal failure went from a universally fatal disease to a tolerable chronic illness with reasonable long-term survival. In the United States, a series of events involving science, medicine, and politics led to universally available and undeniable renal replacement therapy.

The concept of dialysis was introduced by the Scottish physical chemist Thomas Graham, whose experiments in the 1850s characterized the movement of water across semipermeable membranes and led to an understanding of the principle of osmosis. It was in fact Graham himself who first applied the term *dialysis* to describe the phenomenon of exploiting osmotic gradients to move solutes across a membrane separating two solutions.

Fifty years later, John Jacob Abel, a pharmacologist at the Johns Hopkins Hospital, first explored the application of dialysis in a clinical setting. Abel, working with Leonard Rowntree and B.B. Turner, described in 1914 the construction of the "artificial kidney," an apparatus that consisted of 32 tubes connected in series and encased in a large glass container filled with a dialysate solution. Using hirudin as an anticoagulant to prevent clotting in the tubes, they tested the invention on anesthetized animals. Using arterial cannulas to channel blood into the narrow tubes of the circuit, they demonstrated that indeed blood could be dialyzed.

The first successful human use of dialysis is credited to Willem Kolff, a Dutch physician who had studied Abel's work. During the German occupation of the Netherlands in World War II, he designed and built, mainly from household items, a dialysis device he named the *rotating drum kidney.* This device consisted of a large drum covered with thin tubing that sat partly submerged in a large tank of dialysate. Blood passed through the series of tubes affixed to the drum that then rotated within the tank, facilitating dialysis of the blood across the tubing. Kolff's first surviving patient was a 67-year-old woman with acute renal failure caused by sepsis. She endured an 11-hour dialysis session in which a measured 60 g of urea were removed. Kolff foresaw many possible applications of hemodialysis and was astutely aware that its implementation for chronic renal failure would require durable vascular access.

The first solution to the access problem was developed by Belding Scribner at the University of Washington. Having been introduced to

a newly engineered material called *polytetrafluoroethylene* or *PTFE* (Teflon) and recognizing its inert and noninflammatory properties, he conceived of using a U-shaped Teflon tube to create an external arteriovenous connection that could be accessed for dialysis. On March 9, 1960, the first dialysis by way of the Scribner shunt was performed. Although this did establish an important proof of principle, Scribner shunts had unacceptably high rates of infection, thrombosis, and hemorrhage, and their functional patency rarely exceeded a few months. Seeking to improve on this, James Cimino and Michael Brescia invented the radiocephalic arteriovenous fistula and described the technique in their landmark *New England Journal of Medicine* article in 1966.

With safe and reliable vascular access technically feasible, widespread availability of hemodialysis had a final major obstacle: its prohibitive cost. Lobbying at local and national levels resulted in government funding for improvements in dialysis machine technology and the construction of more dialysis units. However, because of its cost, most people believed that without federal government support, access would remain limited to the privileged few. In November 1971, a chronic dialysis patient named Shep Glazer and his nephrologist demonstrated a dialysis session before a congressional committee in Washington, DC. This had a tremendous impact on the committee members, which led Congress to act. In October 1972, President Richard Nixon signed into law a bill authorizing Medicare coverage of dialysis.

In this chapter, we review and summarize our current practices for the evaluation, placement, and maintenance of hemodialysis access. In 2002, the Society for Vascular Surgery and the American Association for Vascular Surgery published recommendations for standardized reporting of dialysis access techniques, procedures, and configurations. For purposes of brevity, however, we preferentially use common nomenclature throughout the following discussion.

NATIONAL PRACTICES AND GUIDELINES

The staggering sum of Medicare spending for ESRD patients has been steadily increasing ($29.1 billion in 2010 to $36.6 billion in 2018), accounting for 7.2% of all Medicare claims that year. As healthcare cost containment has become a major national focus, there has been great motivation within the dialysis community to identify best practices that minimize costs and maximize patient benefit. Until recently, most arm accesses placed had been prosthetic grafts. Certainly, some of these grafts were placed out of necessity. Unfortunately, convenience, lack of surgeon experience, and the higher reimbursement rate for prosthetic grafts undoubtedly played a role in their preferential placement. Specifically, in 1990 expanded polytetrafluoroethylene (ePTFE) grafts were placed twice as frequently as autogenous arteriovenous fistulas. According to the Centers for Disease Control and Prevention, in 1995 just over 20% of patients on dialysis were using autogenous access. Clear evidence has since emerged that autogenous fistulas are associated both with more favorable outcomes and lower cost, and this has drawn attention to the unacceptably low proportion of patients in the United States undergoing dialysis through autogenous accesses. The disproportionate and often inappropriate use of prosthetic grafts fueled the National Kidney Foundation's Kidney Disease Outcomes and Quality Initiative (KDOQI). This is a comprehensive analysis of the best practices with regard to the management of ESRD. In 2003, an offspring of KDOQI was The Centers for Medicare and Medicaid Services' *Fistula First Breakthrough Initiative,* which aimed to promote awareness among patients and physicians of the superiority of autogenous access. More recently, there has been pushback from some in the vascular community who believe that there are certain patients who should preferentially have prosthetic access. In 2007, this was been rebranded as *Fistula First Catheter Last.* Although we agree in principle, the best access remains a good arteriovenous fistula. The current national goal is to place autogenous access in at least 65% of new dialysis patients, and the effort seems to be working. In 2017, according to the annual report of the United States Renal Data System (USRDS), there were five times as many autogenous fistulas placed than prosthetic grafts. Unfortunately, the *Catheter Last* effort has not been effective, with the initiation of hemodialysis using a catheter increasing from 60.2% in 2009 to 65.2% in 2018. Additionally, at 6 months post-hemodialysis initiation using a catheter, a staggering 57% of patients were still using the catheter, 33% were using an arteriovenous fistula, and 10% were using a prosthetic graft. In 2019, the KDOQI guidelines were updated to provide a more individualized approach and comprehensive evaluation of dialysis options called ESKD Life-Plan (**P**atient **L**ife-Plan **A**ccess **Ne**eds). The goal of this initiative is to facilitate patient and provider discussions about type of access, complications, and a transition plan for the next access (when needed). Importantly, the planning strategy considers patient survival (<1 year), age, comorbidities, functional status, social support, and patient goals/preferences.

Currently, the three main avenues for hemodialysis access are tunneled central venous catheters, arteriovenous prosthetic grafts, and autogenous arteriovenous fistulas. Clearly, the poorest outcomes are associated with catheter usage; therefore every effort should be made to avoid them. To this end, current KDOQI guidelines stipulate that all patients should be referred to a surgeon for the placement of autogenous access when they reach stage 4 chronic kidney disease (glomerular filtration rate <30). This allows sufficient time for fistula placement and maturation before the commencement of dialysis. The caveat to this scenario is that not all patients have a suitable vein for autogenous fistula creation. Only those with suitable veins should have their access placed far in advance of the initiation of dialysis, and this access should be an autogenous fistula. The most common cause of prosthetic graft failure is stenosis at the venous anastomosis caused by neointimal hyperplasia. This worsens with time, so if a prosthetic graft is required, it should only be placed when dialysis is imminent or has already begun.

The options for dialysis access are frequently affected by treatment options instituted years before the patient reaches ESRD. Patients and physicians alike must be aware that for those with any degree of renal dysfunction, subclavian vein central lines and ports, peripherally inserted central catheter (PICC) lines, and even forearm intravenous catheters (intern vein or distal cephalic vein) should be avoided whenever possible. PICC lines are the curse of the dialysis access surgeon. They not only frequently ruin a typically good access vein (the basilic vein), but they are also associated with rates of central venous stenosis or thrombosis estimated up to 85%, which renders the arm unsuitable for the most common and durable access types.

The algorithm for selecting which fistula to place is fairly straightforward. One should begin distally and work proximally in the nondominant arm: radiocephalic (Fig. 1), brachiocephalic, and



FIG. 1 Mature radiocephalic arteriovenous fistula 6 weeks after surgery.

then upper arm basilic transposition. We believe that the benefits of autogenous access are so great that many exceptions to the standard algorithm are permitted. Although use of the nondominant arm is preferable, frequently the veins are better in the more active dominant arm. In this circumstance, the dominant arm is used without hesitation for fistula placement. If a patient has no suitable vein for autogenous access, then a prosthetic graft may be used. A good prosthetic graft is better than a bad vein. Although prosthetic grafts may be placed between any artery with sufficient flow and any suitable vein with unobstructed outflow, it is best to begin as far distally as possible and reserve more proximal sites for the future. For example, we would consider these configurations in the following order: distal brachial artery to distal brachial vein forearm loop, distal brachial artery to proximal brachial vein or distal axillary vein straight graft, and, finally, proximal brachial artery to proximal brachial vein or distal axillary vein upper arm loop. With education and careful attention to best practices, autogenous accesses can be preferentially placed, and the use of prosthetic grafts can and should be limited.

PREOPERATIVE EVALUATION

End-stage renal disease is rarely an entity that exists in isolation, and dialysis patients have a higher incidence of significant comorbid conditions. According to the USRDS, among hemodialysis patients in 2018, 44% had congestive heart failure, 44% had coronary artery disease, 21% had peripheral vascular disease, and 17% had a history of previous stroke or transient ischemic attack. Briefly stated, these patients are poor operative candidates. The preoperative evaluation revolves around assessing cardiopulmonary reserve and selecting the anesthetic with the least risk. Currently, most of our arm accesses are placed using upper extremity nerve blocks.

Aside from a history of events relevant to cardiopulmonary status and prior dialysis access attempts, it is imperative to inquire as to all previous venous access procedures including dialysis catheters, subclavian lines or ports, PICC lines, pacemakers, and defibrillators. Prior trauma, nonaccess surgery, and intravenous drug use in the upper extremities or clavicles should be noted. The physical examination should include auscultation of the heart and lungs and an evaluation of the extremities to determine the patient's best option for dialysis access. The radial, ulnar, and brachial pulses should be palpated bilaterally. Uncommonly, a radial pulse is present with an occluded brachial artery. An Allen test to confirm adequacy of ulnar flow to the hand should be performed if a radiocephalic fistula is contemplated. It cannot be overemphasized that the preoperative physical examination is incomplete unless a venous tourniquet is used to assess the superficial veins. Arm edema, prominent arm or chest wall venous collaterals, or a history of failed AV access in an extremity should raise suspicion of central venous stenosis.

Duplex ultrasound–based vein mapping before dialysis access surgery was essentially mandated by the KDOQI guidelines. We strongly disagree with this blanket recommendation. Although vein mapping at times may be helpful for operative planning, it is frequently unnecessary, adds cost, and may not always give valid information. In patients already on dialysis via a catheter, we rarely request a vein map. If no suitable vein is found at surgery (see operative techniques below), then the patient will require a prosthetic graft. In patients referred before the initiation of dialysis, vein mapping may be helpful in those who are obese, intravenous drug abusers, or have had prior PICC lines. It may also be helpful in patients with normal-sized arms in whom neither an adequate basilic nor cephalic vein is palpable with a tourniquet in place. Lastly, with the ubiquity of portable ultrasound machines, surgeon-performed vein mapping on the operating room table after successful nerve block anesthesia frequently reveals usable veins that were deemed inadequate on preoperative imaging. This has become our routine.

Venography is an important component of successful dialysis access surgery. Its primary use is not to roadmap the arm veins but rather to confirm central vein patency. Our practice is to use it liberally in any patient with a history of arm swelling, prior central venous cannulation on the side of proposed access, or multiple failed attempts at access. If a hybrid endovascular operative suite is available, the venogram may be obtained at the beginning of the access case, allowing for a combined procedure that is more convenient for the patient.

Last, for the safety of the surgical team, any patient with a history of intravenous drug use should have a plain radiograph of the upper extremity to evaluate for the presence of foreign bodies.

Before surgery, standard blood chemistries and a complete blood count are all that are necessary. The surgeon can assume that uremic platelet dysfunction will always be present, and we have found no utility in checking bleeding times preoperatively. Uncommonly, arginine vasopressin at a dose of 0.3 μg/kg will be needed during surgery to control oozing. Additionally, aspirin use does not seem to affect bleeding significantly, and, considering the cardiovascular risk profile of these patients, we routinely administer a dose of 81 mg in the preoperative area. Clopidogrel does seem to increase oozing is some patients, so this should be held for 5 to 7 days, unless the patient has recently undergone coronary artery stenting. Many patients are also on warfarin. In general, we do not advocate holding warfarin and feel comfortable proceeding with access surgery with an international normalized ratio up to 2.5.

OPERATIVE TECHNIQUES

The best option for anesthesia depends on the patient's comorbid conditions, the anesthesiologist, and the proposed surgery. Although local anesthesia is a viable option for many patients, it works best for patients undergoing radiocephalic or nontransposed brachiocephalic fistulas. Although we have used it successfully for upper arm basilic transpositions, it tends to be somewhat less than ideal for both patient and surgeon because of the relatively large area that must be anesthetized. Over the past decade, we have gone almost exclusively to regional nerve blocks. The blocks are placed in the preoperative area by a dedicated block team while the preceding case is underway. This helps maximize efficiency and shorten turnover time. If the skin incision approaches the deltopectoral groove or the axilla, supplementation of the regional block with local anesthetic may be necessary.

Autogenous Arm Fistulas

The patient is positioned supine with the shoulder of the operative side near the edge of the bed. The arm board should be positioned such that the arm rests in the center of the board. A tourniquet is applied and bedside ultrasound is performed to assess vein size and patency. A standard skin preparation including the shoulder and axilla is performed. If available, an arm board drape is most convenient, otherwise an extremity drape will suffice.

Radiocephalic Fistula

A 3- to 4-cm incision is placed just proximal to the wrist along the lateral or radial aspect of the arm. Once the skin is incised, the surgeon and assistant both lift the skin with Adson forceps to facilitate easy identification of the cephalic vein after some gentle blunt dissection. The vein is encircled with a vessel loop and then sharply dissected out, tying all branches with 4-0 or 5-0 ties. The radial artery is dissected out circumferentially in a standard fashion and controlled with vessel loops. Any side branches are tied but not divided, which helps maintain its orientation. The cephalic vein is divided distally, gently dilated with sequential coronary dilators, and then flushed with heparinized saline solution. After flushing the radial artery, a spatulated end-to-side anastomosis is performed using 6-0 or 7-0 polypropylene suture. Any large proximal vein branches are ligated through separate 1-cm incisions. Closure consists of 3-0 interrupted absorbable dermal sutures and a 4-0 running absorbable

subcuticular suture. On occasion, the vein is so nice that a very short skin line incision can be made over the snuffbox and the anastomosis done there, as described earlier. If a snuffbox anastomosis is used, then we ligate any large distal forearm venous tributaries that are marked at the beginning of the case using ultrasound; this will enhance maturation of the cephalic vein.

Upper Arm Fistula

If there is a potentially good cephalic vein, then a transverse incision is made in the antecubital crease (Fig. 2A), and the cephalic vein is identified (see Fig. 2B). If it is of suitable size, it is dissected out to its confluence with the median cubital vein, ligated distally, and divided. Sequential coronary dilators are gently passed cephalad and should easily pass if there is no intraluminal scarring. Although a sufficient length of vein can be mobilized at this point to easily reach the brachial artery, we frequently convert the incision into a hockey stick–shaped incision (with the handle of the stick along the cephalic vein; Fig. 2C) and mobilize 10 to 15 cm or more of the vein (Fig. 2D, E). This not only allows ligation of the accessory cephalic vein and other small branches, but it also allows superficial tunneling of the vein (Fig. 2), which is necessary in all but the thinnest of arms. With the vein transposed, accessing the fistula can be performed earlier (as soon as 4 weeks depending on vein size), it is easier, and it more consistently enables earlier removal of dialysis catheters. Dissection of the distal brachial artery through the medial aspect of the antecubital incision is done in a standard fashion with control obtained with vessel loops. If the brachial artery appears smaller than expected, the patient most likely has a high brachial bifurcation. In these cases, the more suitable donor artery almost always is the deeper of the two vessels and should be evaluated before proceeding with the anastomosis. The vein is tunneled just beneath the skin making sure that there is no kink or twist at the most proximal site of mobilization (Fig. 2G). Once an arteriotomy is made and the artery flushed with heparinized saline solution (systemic anticoagulation is unnecessary), the vessel loops are replaced with baby bulldog clamps. This eliminates any vessel stretching and makes the end-to-side anastomosis easier to perform. Closure consists of 2-0 absorbable suture in the subcutaneous tissue and 3-0 nylon vertical mattress skin sutures (Fig. 2H). In our experience, subcuticular closures in the upper arm have been associated with postoperative wound problems much more frequently than with interrupted nylon closures. In addition, patients are much more apt to keep their follow-up appointments if they have sutures that need to be removed. If the cephalic vein is not of adequate size or quality, then the median cubital vein is identified near the medial aspect of the incision.



FIG. 2 Brachiocephalic arteriovenous fistula creation. **(A)** Antecubital incision. **(B)** Identification of cephalic vein in antecubital fossa. **(C)** Hockey-stick incision. **(D)** Proximal dissection of cephalic vein. **(E)** Ligation of cephalic vein branches and dissection of brachial artery in antecubital fossa. **(F)** Superficial tunneling of mobilized cephalic vein. **(G)** Completed arteriovenous anastomosis. **(H)** Closure of skin with vertical mattress nylon sutures.

If the median cubital vein is adequate, it is ligated distally, divided, and flushed with heparinized saline solution. We then extend the medial end of our skin incision in a hockey-stick fashion along the medial aspect of the arm nearly to the axilla. The vein is dissected circumferentially over its course toward the axilla as it joins the basilic vein, which subsequently joins the proximal brachial vein.

If the median cubital vein is not adequate, then the basilic vein is used. In this instance, we place two surgical towels under the upper arm to improve positioning and then make a new incision just anterior to the medial epicondyle of the humerus. Once the basilic vein is identified and found to be of appropriate size and quality, the incision is extended proximal and distally until enough vein for a transposition has been exposed. The brachial artery is then dissected out at the antecubital fossa either through a separate incision or through the medial aspect of the antecubital incision if that incision was already made to inspect the cephalic vein. The vein is then tunneled and the anastomosis prepared and performed as described earlier. The fascia and subcutaneous layers are reapproximated with running 2-0 absorbable suture. The skin is closed with interrupted 3-0 nylon vertical mattress sutures. Of note, the above routine is unnecessary if point-of-care ultrasound-based vein mapping is done at the beginning of the case. The decision on which vein to use is made before performing the skin incision. This saves time and potentially can limit the size of the incision(s).

Although the standard brachiocephalic fistula does not typically involve transposing the vein, this is frequently necessary in obese arms. When the patient has a large arm, the surgeon must decide whether to perform the transposition in a one- or two-stage fashion. If the vein is on the small side (3–4 mm), we will plan a two-stage transposition. The first stage is anastomosing the vein to the artery, and after approximately 6 weeks (when the fistula has enlarged to at least 6 mm in diameter) we return the patient to the operating room and superficialize or transpose the fistula so it is easily accessible. This is also true for basilic vein transposition fistulas. If the vein is small, the surgeon can make a two-stage plan: The first stage is creating the fistula, and when of adequate size the patient is returned to the operating room for superficialization or transposition.

At the end of the case, there should be a palpable thrill in the fistula. If there is not, then there is a technical problem, and the incision should be reopened.

Prosthetic Arteriovenous Grafts

If there is no suitable vein, then a prosthetic graft must be placed. The most commonly used graft is 6-mm ePTFE; however, bovine carotid artery, bovine mesenteric vein, and cryopreserved vein grafts may also be used. A transverse incision is made over the brachial artery in the antecubital fossa. The brachial artery and vein (if at least 5 mm in diameter) are isolated and encircled with vessel loops. The vein should be generously dissected out to allow a long venous anastomosis. A second smaller counterincision is made on the lateral volar surface of the mid-forearm on the radial side. Placement of the counterincision in this fashion skews the graft toward the radial aspect of the forearm, and this allows the patient's arm to be in a comfortable position during dialysis sessions. The venous anastomosis is generally performed first when using ePTFE, particularly if the graft has a premade flared end. However, if using a biologic graft, the arterial anastomosis is performed first, as the arterial pressure helps keep the graft oriented during tunneling. The graft is tunneled in a gentle arc to the counterincision and then back to the antecubital fossa. Tunneling is best accomplished with a Kelly-Wick Tunneler (IMPRA), although an aortic clamp may be used. The second anastomosis is then performed, and the incisions are closed. If the brachial vein is too small at the antecubital fossa, then a second incision is made on the proximal medial upper arm, and the proximal brachial or distal axillary vein is used for the venous outflow. Whereas this describes the two most common graft configurations, in reality any suitable artery and vein may be used. We strongly believe in fistula first and therefore do not agree with the use of forearm grafts to help mature upper arm cephalic or basilic veins.

OPTIONS FOR NONCONVENTIONAL ACCESSES

Not uncommonly patients present for dialysis access after many months of catheter usage and have developed upper extremity central vein occlusion or stenosis. Placing brachial artery–based access ipsilateral to this issue will lead to significant arm edema and an unusable access. Long-standing dialysis patients with central vein stenosis or thrombosis pose a particular challenge. Options must be carefully considered in these cases, and there is no room for error. Failure to establish access can quickly turn into a life-threatening situation.

The Hemodialysis Reliable Outflow Graft

The Hemodialysis Reliable Outflow (HeRO) graft is an option for upper extremity access in the setting of central vein stenosis that uses the right atrium for venous outflow. The HeRO graft consists of a standard ePTFE graft and a reinforced single-lumen venous outflow catheter. This device requires that wire access across the stenotic segment of the central vein can be achieved. Once stiff guidewire access to the right atrium is obtained, then the venous outflow catheter is placed over the wire and positioned in the right atrium. The other end of the catheter is then tunneled laterally to the deltopectoral groove and attached to the standard ePTFE graft via a manufacturer-supplied alloy connector. The ePTFE graft is then tunneled like any other graft, and the opposite end is sewn to the brachial artery in the standard fashion. The HeRO graft can also be used to create unimpeded venous outflow to salvage a functioning autogenous arm access in the event that a significant central vein stenosis or occlusion has developed late. After the HeRO catheter has been placed and tunneled to the upper arm, it is connected to the venous end of the fistula using a small cuff of the ePTFE with the attached alloy connector. Last, one can modify the HeRO graft by replacing the graft with an early puncture graft (Acuseal or Flixene) and then attaching it to the HeRO catheter using the Super HeRO adaptor. This allows one to gain wire access to the right atrium using the patient's dialysis catheter. Obviously, there is no catheter for postoperative dialysis, so these patients should be admitted until there is confirmation that dialysis can performed using the early puncture graft. Although the HeRO graft obviates the need to move the access to the leg, it comes with all of the problems associated with nonautogenous access, including graft infection and thrombosis. Long-term warfarin anticoagulation should be considered in patients being dialyzed via a HeRO graft.

Low-Volume Flow Access

Radial or ulnar artery–based accesses have lower volume flows than those from the brachial artery. Not uncommonly, we have seen patients with failed upper arm grafts and ipsilateral central vein occlusion who mysteriously have a usable cephalic or basilic vein. Using forearm artery inflow creates a usable but low-volume flow access and generally does not lead to significant arm swelling despite central venous issues. Admittedly this does not always work, and we have had to ligate the accesses of several patients because of massive arm swelling.

Leg Access

In general, the leg is only used for access once all upper extremity options have been exhausted. However, young women and paraplegics may prefer a primary thigh access, the former to avoid the obvious arm scarring and the latter because they depend on their arms for mobility. The most common leg access is a thigh loop of

ePTFE, although autogenous options exist including saphenous and femoral vein fistulas. Although we have extensive experience using the femoral vein and find it particularly useful when translocated to the upper extremity for home hemodialysis patients, its use for a thigh fistula should be carefully planned and works best in thin legs. The saphenous vein may also be used as a thigh fistula (tunneled anteriorly as a straight fistula and anastomosed to the distal superficial femoral artery), but if the vein is not generous in size (at least 5 mm), failure to mature into a useful access is common. For a prosthetic thigh graft, an oblique skin line incision is made just distal to the groin crease, and either the deep femoral or proximal superficial femoral artery is used for arterial inflow. Through the medial aspect of that incision, the proximal saphenous vein or saphenofemoral junction is preferentially used for venous outflow. The proximal femoral vein may be used, but the dissection is somewhat more difficult.

CAUSES OF ACCESS FAILURE

Stenosis or Occlusion

The risk of access failure caused by thrombosis is more common in prosthetic grafts than in autogenous fistulas. Early failure is generally caused by technical factors but can also be related to hypercoagulability, low-flow states, or use of an inadequate vein. In mature accesses, most problems will be detected by the dialysis unit. High venous pressures, poor arterial inflow (high arterial pressure), recirculation, and diminishing effectiveness of the dialysis all indicate access problems. The anatomic location of the problem usually can be ascertained by physical examination. The lack of bruit and thrill indicates thrombosis. A weak thrill or bruit suggests inflow problems. Pulsatility in a fistula generally indicates an outflow venous problem. Early intervention can often salvage an otherwise threatened fistula or graft. A duplex scan can further pinpoint the area of the problem but is frequently unnecessary. In general, the diagnostic test of choice is fistulography, at which time therapeutic interventions including thrombectomy, angioplasty, and stenting can be carried out. Occasionally open revision is necessary, with many options available to improve either arterial inflow or to relieve venous outflow obstructions.

Infection

Infection is a frequent complication of hemodialysis access and is a major cause of morbidity in the dialysis population. Up to 10% of all deaths in dialysis patients are caused by infections, and most originate from vascular access sites. Compared with autogenous fistulas, the relative risk of infection-related death is 1.8 times greater in those dialyzing through catheters and 1.4 times greater in those dialyzing through prosthetic grafts. The cumulative probability of developing a catheter-related infection is greater than 50% after 2 months of dialysis through a catheter. Risk factors for infection include diabetes, HIV, repeated cannulation, increased age, and lower extremity location. Gram-positive bacterial infections (usually *Staphylococcus* species) predominate, and gram-negative bacterial infections are less common but seen more frequently in patients with leg access. Access-derived infections often (5% rate for arm access infections and 20% for leg access) lead to metastatic infectious complications including bacterial endocarditis, osteomyelitis, septic emboli, and septic arthritis. For catheter-related bacteremia, management consists of culture-directed parenteral antibiotics and removal or exchange of the infected catheter. For infected ePTFE grafts, management must be guided by an attempt to balance the benefits of preserving a functioning access with the severity of infection. Some localized infections can be successfully treated with aggressive intravenous antibiotic therapy combined with resection and replacement through clean tissue of a portion of the graft, though recurrent infection is not uncommon. There is a lower recurrent infection rate when the entirety of the graft is removed, but the operations tend to be more difficult, and access is lost. Lastly, mature autogenous accesses rarely become infected, although patients who access their fistula using the buttonhole technique have a lifetime incidence of cellulitis requiring antibiotics of at least 10%. Because of this, most dialysis units have trended away from this technique.

Arteriovenous Access Steal

Almost all arm accesses create a steal syndrome, but significant steal occurs less than 15% of the time, with brachial artery–based accesses presenting the highest risk. Other risk factors for clinically significant steal syndrome include diabetes, peripheral artery disease, coronary artery disease, female gender, and multiple previous access surgeries. The stages of steal syndrome include: stage 1—steal phenomenon, reversal of flow without complaints; stage II—pain on exertion or during hemodialysis; stage III—pain at rest; and stage IV—tissue loss. Loss of a palpable distal pulse at the time of fistula creation indicates that a significant steal syndrome could develop. Manual compression of the fistula should result in restoration of the distal pulse. Options for improving distal perfusion include ligation, plication, banding, proximalization or distalization of arterial inflow, and distal revascularization with internal ligation (DRIL) (Fig. 3). DRIL has the benefit of leaving the functioning fistula undisturbed, eliminating the physiologic pathway for the steal, and restoring downstream perfusion. We do not routinely perform arm angiography before performing DRIL, but, if the patient has demonstrable atherosclerotic disease in other areas, then this should be considered. Lastly, although use of the saphenous vein for the bypass portion of the DRIL is standard, we have frequently used the basilic vein without consequence.

Other complications that occur with varying frequencies and degrees of morbidity include edema caused by venous hypertension, seromas, wound problems, and carpal tunnel syndrome. Aneurysmal dilation of mature fistulas or pseudoaneurysmal dilation of grafts generally do not need to be addressed with surgery unless there is overlying skin breakdown or impending breakdown as demonstrated by thin, stretched, shiny skin. In general, having a low threshold to investigate and intervene on a fistula that is not performing optimally will minimize the need for repeated access surgeries.

Lastly, two uncommon but catastrophic complications bear mentioning: ischemic monomelic neuropathy (IMN) and acute high output heart failure. IMN presents acutely after placement of a distal brachial artery–based access. The patient typically complains of a painful and weak ipsilateral hand with neurologic findings not confined to a single nerve distribution. These patients will have a warm hand and palpable radial pulse. Prompt clinical diagnosis may be confounded by preoperative nerve blocks, so a persistent neurologic deficit after a block has worn off should not be ignored. Although there may be an associated steal, noninvasive testing usually demonstrates a mild to moderate steal with pain and weakness out of proportion to these results. Treatment consists of emergent ligation or removal of the AV access. Unfortunately, even with prompt appropriate treatment, the nerve damage is not immediately reversible, and it may take months of rehabilitation to regain reasonable function.

Since the last edition of this textbook, we have had two cases of hyperacute high-output heart failure after placement of dialysis access in patients with limited cardiac reserve. If a patient develops sudden unexplained hypotension after the clamps are removed from a new access, acute high-output heart failure should be considered. If it is a possibility, then clamp the new access and the blood pressure should rebound. The hypotension should be reproducible by unclamping the access. If this indeed happens, then the access should be removed or ligated.

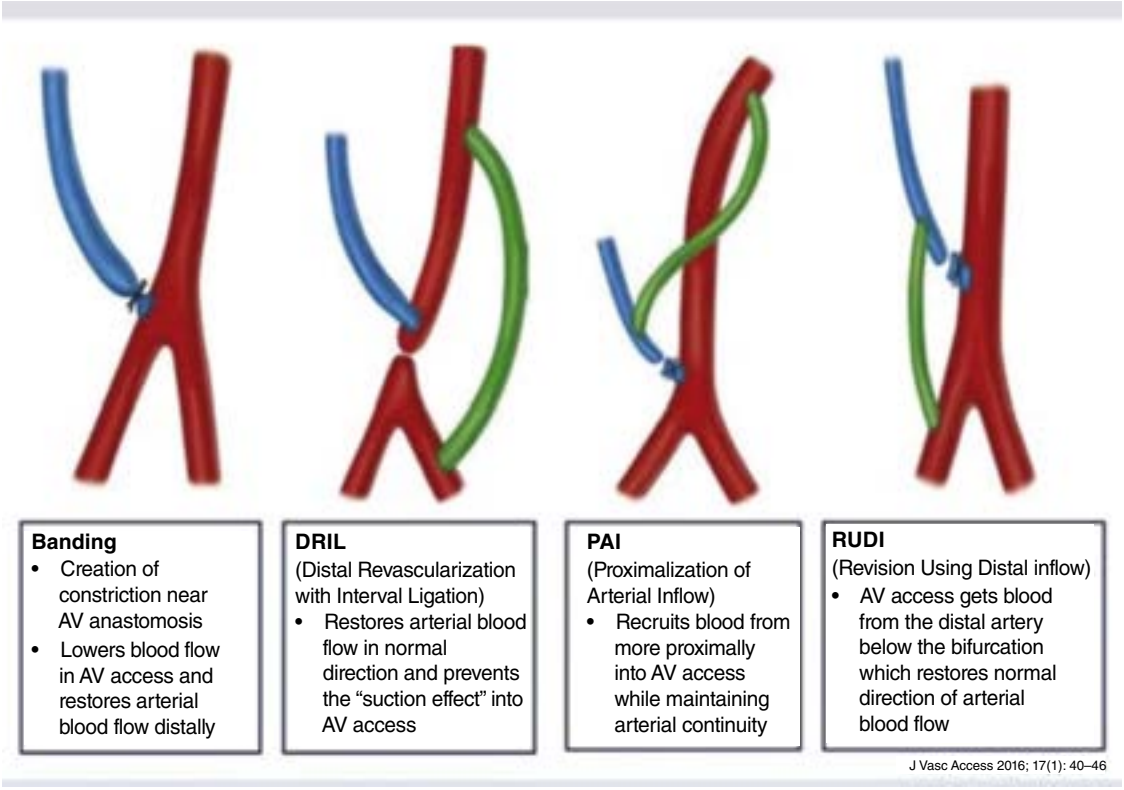


FIG. 3 Surgical techniques to treat dialysis-associated steal syndrome. *(From Al Shakarchi J, Stolba J, Houston JG, Inston N. Surgical techniques for haemodialysis access-induced distal ischaemia. J Vasc Access. 2016;17:40–46).*

CONCLUSION

Assume dialysis is forever, so when performing access surgery, do not jeopardize future options.

Try to avoid all catheters and if possible prosthetic materials; that is to say, fistula first.

Dialysis patient longevity is directly dependent on quality and reliability of access, so fistula dysfunction requires prompt investigation and intervention to maintain patency.

Dialysis access performed properly will be rewarding for the patient as well as the surgeon.

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Venous Thromboembolism: Prevention, Diagnosis, and Treatment

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INTRODUCTION/IMPACT

Venous thromboembolism (VTE), which comprises deep venous thromboembolism (DVT) and pulmonary embolism (PE), is a major contributor to preventable morbidity and mortality in hospitalized patients. VTE affects approximately 10 million patients worldwide and 600,000 to 900,000 individuals in the United States per year, representing the third leading vascular disease after acute myocardial infarction and stroke. This disease results in the death of more than 100,000 people each year in the United States, with one-third of patients dying within 30 days of diagnosis, and an estimated 1 patient dying every 6 minutes as a result of a blood clot. Approximately 50% of VTE events are hospital associated, occurring either in the hospital or shortly after discharge. In addition to patient morbidity and mortality, the socioeconomic impact of VTE is striking, with estimated annual costs ranging from $7 billion to $10 billion in the United States. Economic evaluations have reported doubling of hospital length of stay and annual healthcare costs for patients with VTE equating to $15,000 to $25,000 per patient. Moreover, there are significantly increased hospital readmission rates in patients with VTE. There is increased awareness of the importance of VTE prophylaxis, early diagnosis, and appropriate treatment among hospitalized patients. The Agency for Healthcare Research and Quality (AHRQ) claimed that appropriate VTE prophylaxis is the number-one patient safety initiative that can be employed to prevent in-hospital death, and it is imperative in surgical patients as they represent a unique challenge regarding VTE prevention. In 2008, the US Surgeon General issued "A Call to Action to Prevent Deep Venous Thrombosis and Pulmonary Embolism," with the US Congress dedicating the month of March as DVT Awareness Month given its extensive health impact on Americans. Organizations like the National Blood Clot Alliance (NBCA, www.stoptheclot.org) have continued this effort of advancing the prevention, early diagnosis, and successful treatment of VTE by building programs to enhance public awareness and educate patients and healthcare providers alike. Important public health campaigns like "Stop the Clot, Spread the Word" put on by the NBCA and World Thrombosis Day (www.worldthrombosisday.org) seek to spread the word about blood clot risks and the signs and symptoms of blood clots.

In the context of potentially preventable disease burden, it is important to understand the scope and impact of VTE in terms of patient outcomes and hospital/socioeconomic costs. Specifically, the risk factor profile for each patient, prevention and prophylaxis, tools for screening and diagnosis, and appropriate treatment are important to understand when trying to prevent VTE and manage patients with VTE. All surgical patients are at elevated risk of VTE. Many patient populations treated by surgeons are especially vulnerable to the development of VTE given the physiologic derangements that occur during the perioperative period. Specific disease states such as malignancy, inflammatory bowel disease, trauma, and more lead to increased risk for the development of VTE. Overall, the incidence of DVT has remained relatively constant over time, while hospital admissions for PE have doubled over the past decade, partly as a result of the increased use of sensitive imaging providing for increased diagnosis. Numerous observational studies, randomized controlled clinical trials, reviews, and quality improvement studies are available to help guide surgeons in the prevention and management of VTE.

RISK FACTORS

Virchow's triad of venous stasis, endothelial injury, and hypercoagulability is an important concept in the development of VTE, and diseases that enhance these processes increase the risk for VTE. Although knowledge of risk factors has improved over time, 30% to 50% of VTE episodes do not have an identifiable provoking factor and are classified as unprovoked. Venous stasis can be worsened by risk factors such as surgery (including insufflation during laparoscopy), prolonged immobilization, and stroke. Direct venous injury, whether iatrogenic (i.e., central venous catheter placement) or traumatic leads to endothelial damage and release of coagulation factors, which in turn increases the risk of VTE formation. Diseases such as trauma, malignancy, congestive heart failure, congenital disorders, obesity, and pregnancy contribute to an overall hypercoagulable state, which also increases the risk of VTE (Box 1).

PREVENTION AND PROPHYLAXIS

Before routine VTE prophylaxis was employed, general surgical patients had a high rate of DVT (19.1%) and PE (1.6%) with a high mortality rate relating to PE of 0.87%. In the present era, with routine VTE prophylaxis employed for the vast majority of surgical patients, VTE rates are dramatically lower but still significant with rates of 2% to 3% for some general surgery and surgical oncology cases. It

BOX 1 Risk Factors for Venous Thromboembolism

Strong Risk Factors (Odds Radio > 10)

Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury

Moderate Risk Factors (Odds Ratio 2–9)

Arthroscopic knee surgery
Central venous line
Chemotherapy
Congestive heart or respiratory failure
Hormone replacement therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy/postpartum
Previous venous thromboembolism
Thrombophilia

Weak Risk Factors (Odds Ratio < 2)

Bed rest > 3 days
Immobility caused by sitting (e.g., prolonged car or air travel)
Increasing age
Laparoscopic surgery
Obesity
Pregnancy/antepartum
Varicose veins

Modified from Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I9–I16.

is important to remember the value of VTE prevention in surgical patients as nearly all surgical patients have at least some risk factors that warrant pharmacologic prophylaxis perioperatively.

Evidence has shown that preoperative and postoperative thromboprophylaxis in surgical patients should be employed and that specific regimens should be selected based on individual patient risk factors and type of surgery being performed. Many risk-assessment models (RAMs) have been developed to assist in decision making and weighing the risk of VTE with that of bleeding from prophylactic medications. RAMs are integral to predict and stratify patients' risk of hospital-associated VTE. Many RAMs exist, with currently no consensus as to the best tool. The most common RAMs in surgery are variations of the "three bucket" model, the Caprini score, and the Rogers score. In medical patient populations, the Caprini, Padua, and IMPROVE scores are frequently used. Many hospitals use risk-stratification tools to maximize prescription of risk-appropriate VTE prophylaxis. The AHRQ recommends using clinical decision support tools like The Johns Hopkins Hospital risk assessment model, which increased risk-appropriate VTE prophylaxis from 26% to 80% for surgical patients at that institution. The American College of Chest Physicians (ACCP) previously provided updated guidelines on VTE prevention; however, more recently, the American Society of Hematology (ASH) has been the *de facto* leader in writing guidelines for VTE prevention. Most recommendations consider risk assessment based on the Caprini/Rogers scores in surgical patients when advocating for VTE prophylaxis. Other organizations such as the National Comprehensive Cancer Network (NCCN), the American Academy of Orthopedic Surgeons (AAOS), and the American College of Obstetricians and Gynecologists (ACOG) provide guidelines for specific patient populations.

Whether mechanical prophylaxis, pharmacologic prophylaxis, or both, surgical patients who are considered moderate to high risk should be given prophylaxis to decrease VTE incidence. Mechanical prophylaxis, which includes graduated elastic compression stockings, foot compression devices, and intermittent pneumatic compression (IPC) devices all work by augmenting venous flow and decreasing stasis. IPCs, generally considered the most effective form of mechanical prophylaxis, also stimulate fibrinolytic activity through the release of endothelial tissue-type plasminogen activator (t-PA), prostacyclin, von Willebrand factor, and tissue factor pathway inhibitor. Early ambulation has historically been thought to reduce VTE; however, a recent systematic review did not find any high-quality evidence supporting ambulation alone as an effective prophylaxis for VTE.

In terms of pharmacologic VTE prophylaxis, most guidelines and protocols utilize subcutaneous injections of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) following surgery, with common dosing being 5000 units of UFH three times a day or 40 mg of enoxaparin daily for LMWH for most patients. Alternate dosing regimens are often suggested for patients with morbid obesity. Newer data regarding adjusting VTE prophylaxis in trauma patients suggest that adjusting doses based on thromboelastography (TEG) may be beneficial. Currently no definitive recommendation exists as to which pharmacologic agent is preferred in all surgical patients; some evidence shows that LMWH is more advantageous in the orthopedic surgery, oncology, and trauma patient populations. Many risk-based algorithms exist for implementing thromboprophylaxis for surgical patients in the perioperative setting. Preoperative thromboprophylaxis with a single dose given 1 to 2 hours before surgery reduces the rate of VTE without increasing the risk of major bleeding. The duration of prophylaxis is still a subject of debate and it is routinely discontinued at hospital discharge. Data for extended outpatient prophylaxis report that approximately 50% of postoperative VTE events occur in the outpatient setting (deemed hospital associated), which warrants consideration for extended thromboprophylaxis for high-risk patients. Data exist for extended VTE prophylaxis in orthopedic surgery, inflammatory bowel disease (IBD), and abdominal cancer surgery patient subpopulations, with a 60% reduction in risk of DVT. In orthopedic surgery patients, emerging data from randomized controlled trials and systematic reviews demonstrate non-inferiority of aspirin to LMWH for VTE prevention in both fracture patients and patients undergoing total hip and/or knee replacement surgeries. With its low cost and easy accessibility, aspirin is an attractive option for extended outpatient prophylaxis; however, there is no strong data to make this recommendation outside of orthopedic surgery patients.

Despite the overwhelming evidence that VTE prophylaxis is effective, routine use is surprisingly low. With published compliance rates around 50% to 60% in the United States and worldwide, quality improvement efforts such as electronic tools and reminders have been employed to help increase the utilization of VTE prophylaxis in surgical patients. The goal of care should be perfect prophylaxis to include both prescription and administration of all optimal doses. Missed doses of thromboprophylaxis in hospitalized patients have a significant impact on VTE outcomes. Studies in colorectal surgery, emergency general surgery, and trauma have shown that VTE events are higher in cohorts that missed doses of prescribed prophylaxis. These data have continued to fuel quality improvement efforts of hospital and healthcare systems to engage patients in their care and prevent refusal of prescribed medications, a leading cause of dose non-administration.

DIAGNOSIS

Clinical manifestations of extremity DVT include pain, swelling, redness, tenderness, and/or presence of collateral superficial veins. The Homans sign (calf pain with dorsiflexion of the foot) has historically been thought to be associated with DVT. Unfortunately, it has poor predictive value and should not be used for diagnosing DVT. PE typically presents as sudden onset of dyspnea, chest pain, hypoxia, syncope, dizziness, and/or tachycardia/tachypnea. Up to 10% of PEs present as sudden cardiac arrest; a reminder that PE must be high on the differential diagnosis list for all postoperative or surgical patients with cardiac arrest. About 70% of patients with symptomatic PE have associated DVT; however, PE is present in up to 30% of patients with symptomatic DVT. VTE should be considered and pursued with further diagnostic testing in patients with clinical suspicion for DVT and/or PE. To aid in clinical probability assessment of VTE, there are several published criteria and scoring systems, most notably the Wells score for DVT/PE and the Revised Geneva score for PE, that can help the clinician weigh the risk factors to guide decision making for diagnostic testing.

Historically, DVT was diagnosed with invasive contrast venography; currently the gold standard for DVT diagnosis is duplex ultrasound. This relatively inexpensive and noninvasive test has increased the reporting of overall DVTs identified because it is easily performed, even in patients with a relatively low index of suspicion. Other imaging studies such as contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) can diagnose DVT, although these studies are rarely used for this indication alone.

The most common test for the diagnosis of PE remains CT angiogram of the chest. With improved technology, techniques, and capabilities, multidetector helical scanners have a high sensitivity and specificity, especially when combined with higher clinical probability, allowing for diagnosis of increasingly smaller subsegmental PEs. Although CT angiogram of the chest remains the test of choice, other diagnostic modalities such as ventilation/perfusion (V/Q) scan and echocardiography may be beneficial in certain patient populations. In combination with pretest probability of PE, V/Q scan can be used in patients with renal insufficiency or severe allergy to contrast, which may preclude standard CT angiogram imaging. Echocardiogram findings of a dilated right heart and pulmonary hypertension are relatively specific for PE in the hemodynamically unstable or critically ill patient who may not be able to tolerate transport to a CT scanner. D-dimer levels may be helpful in the emergency department and outpatient settings to rule out VTE. In the perioperative setting, D-dimer levels may be less useful given that these levels are often elevated in patients undergoing surgery. Still, D-dimer levels

should be ordered given the high negative predictive value for VTE with a normal D-dimer level. Regardless of the diagnostic approach, if a high index of suspicion exists for VTE based on clinical signs/symptoms and anticoagulation is not contraindicated, then empiric treatment should be promptly initiated even before a definitive diagnosis is made while further workup is ongoing.

DEEP VENOUS THROMBOSIS TREATMENT

The mainstay of treatment for DVT is largely medical and based on therapeutic systemic anticoagulation. Anticoagulation prevents thrombus propagation to reduce worsening of acute symptoms and sequelae including recurrent DVT, PE, and postthrombotic syndrome (PTS). Most algorithms and protocols involve rapid initiation of either weight-based intravenous UFH or subcutaneous LMWH. Long-term therapy is most often with a direct oral anticoagulant (DOAC) or vitamin K agonist (VKA) therapy. DOACs comprise direct thrombin inhibitors (e.g., dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), whereas VKAs primarily refer to warfarin. The ACCP recommends initial treatment for DVT not associated with cancer with DOAC over VKA therapy given studies citing more rapid onset of action and predictable pharmacokinetic profile, similar risk reduction of VTE, less bleeding episodes associated with DOACs, and improved convenience for patients and healthcare providers. The duration of therapy is dependent on patient characteristics/risk factors and the circumstances surrounding the VTE event. In patients with postoperative trauma-related and/or iatrogenic DVT, known as *provoked,* existing recommendations advise 3 months of anticoagulation therapy. For spontaneous or unprovoked DVT without a clear underlying identifiable cause, patients should be treated for 3 to 6 months with reevaluation for the risk-benefit ratio of extended therapy at 3 months and continuation of anticoagulation if appropriate. For high-risk patients such as those with recurrent VTE, malignancy, and/or inherited hypercoagulable states, lifelong anticoagulation is recommended. Many clinicians routinely repeat duplex ultrasound imaging to ensure resolution of thrombus and help guide duration of therapy, although this practice is not always required.

Some patients have strong contraindications to therapeutic anticoagulation such as high risk of uncontrolled bleeding (e.g., coagulation disorders, severe thrombocytopenia), uncontrollable active bleeding (e.g., gastrointestinal bleeding), acute hemorrhagic stroke, and polytrauma injuries with intracerebral hemorrhage and/or solid organ injury. In these patients who cannot be safely anticoagulated, an inferior vena cava (IVC) filter can be placed to help prevent embolization of the DVT to become a PE.

The role of catheter-directed thrombolysis (CDT) remains controversial in the treatment of DVT. CDT accelerates the resolution of thrombus and can result in increased patency rate in comparison with anticoagulation therapy alone. There is agreement that it should be employed for patients with limb-threatening thrombosis, such as phlegmasia cerulea dolens, or phlegmasia alba dolens. A Cochrane review of patients with acute proximal DVT demonstrated a reduction in postthrombotic syndrome (PTS) in patients treated with CDT plus anticoagulation versus anticoagulation alone. However, CDT did not have any impact on PE, recurrent DVT, or death, and it carries a risk of increased bleeding. The multicenter, randomized ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) trial examined the role of pharmacochemical CDT in patients with proximal lower extremity DVT. The study found no difference in most outcomes for the group as a whole, but there may be a benefit in certain patients with a large iliofemoral clot burden.

PULMONARY EMBOLISM TREATMENT

The management decisions for patients with PE depends on the cardiopulmonary and hemodynamic stability of the patient. Many management algorithms and protocols exist. In hemodynamically stable patients, the treatment and duration of therapy for PE parallels that of the therapeutic management for DVT (i.e., UFH or LMWH) followed by transition to long-term oral anticoagulation. The duration of therapy in PE also mirrors that of DVT, with provoked PEs being treated for 3 months, spontaneous PEs treated for 3 to 6 months, and PEs in high-risk patients (e.g., those with hypercoagulable states, recurrent VTE, and cancer) treated indefinitely.

Patients with submassive PE (with evidence of right ventricular dysfunction without hypotension or elevated troponins) or massive PE (with sustained hypotension, persistent bradycardia, impending cardiopulmonary collapse, and/or cardiac arrest) should be treated aggressively with immediate therapeutic intervention. Specifically, for massive PE, with the signs and symptoms listed earlier, systemic thrombolysis with TPA (alteplase) is indicated assuming no contraindications and acceptable bleeding risk. This recommendation is supported by a double-blind randomized controlled trial demonstrating a significant decrease in primary composite outcome all-cause mortality and hemodynamic decompensation in those treated with systemic thrombolysis in addition to anticoagulation. In patients with absolute contraindications to systemic thrombolysis, percutaneous CDT, surgical embolectomy (Trendelenburg procedure), and/or IVC filter placement should be considered. Newer devices, such as the Flow Triever System (Inari Medical, Irvine, California), offer mechanical thrombectomy options specifically designed to remove a thrombus from large vessels and are approved for the treatment of PE. Studies showing outcomes of this device are small but growing, and they suggest immediate hemodynamic improvements in patients experiencing massive PE.

Overall, PE is a complex disease process with high rates of morbidity and mortality, a broad range of presentations, and complicated management algorithms leading to variations in care among clinicians. To optimize treatment of patients with PE, some hospitals have established multidisciplinary pulmonary embolism response teams (PERTs) similar to those available for trauma, stroke, and cardiac arrest. These teams are often composed of clinicians from varying specialties including pulmonary medicine, critical care, interventional radiology, cardiology, and/or cardiothoracic surgery. The PERT Consortium (www.pertconsortium.org) was established in 2015 to promote adoption of the PERT model in healthcare institutions across the United Sates. Their goals are to ensure the prompt diagnosis and treatment of PE, expand the current body of scientific literature on diagnosis and treatment of PE, and educate the general public and healthcare professionals regarding PE treatment. PERT teams' structure and approaches vary by institution, however they are typically activated via a single contact, available 24/7, and help facilitate real-time discussion and shared decision-making recommendations for the management of acute PE. The team approach allows for rapid evaluation of risks, formulation of treatment plans, and mobilization of resources to adequately care for patients with PE. Recent studies have demonstrated improved outcomes with multidisciplinary PERT teams, including 30-day mortality, with higher-severity PE patients deriving the most benefit from these teams.

INFERIOR VENA CAVA FILTERS

IVC filter placement should be considered in patients with VTE and absolute contraindications to anticoagulation therapy. Specifically, as it relates to DVT, particular attention to IVC filter placement is paid to patients with proximal DVTs and those with free-floating iliofemoral DVTs as they are more likely to embolize compared with occlusive thrombi. The ACCP and other major organizations currently recommend against routine IVC filter placement in patients who are able to be treated with anticoagulation as no data show a benefit of IVC filters in addition to anticoagulation for VTE. Although most current IVC filters are retrievable, placement of an IVC filter is not without short- and long-term risk. Consideration should be made regarding whether the patient has a limited period

of risk, such as major surgery and/or trauma, or whether lifelong risk is present as a result of underlying mechanisms. If a decision for IVC filter placement is made, then ongoing evaluation for the need of the filter is key. It should be removed as soon as possible (when the patient can be anticoagulated) as prolonged IVC filter placement is associated with higher retrieval failure, filter migration, penetration of the IVC wall, embolization of fragments, and filter thrombosis. Poor follow-up is also associated with delayed filter complications. Systems should be implemented to actively follow patients with IVC filters to proactively plan for removal.

CONCLUSION

VTE significantly affects many patients in the United States and worldwide, and it is a major contributor to morbidity and mortality, particularly in surgical patients. Keys to VTE management remain early recognition and appropriate treatment, with the underlying premise that screening and appropriate prophylaxis are paramount in preventing immediate mortality and long-term morbidity. Newer risk-assessment tools and therapeutics to help prevent and treat VTE are constantly evolving; however, the mainstays remain prescribing appropriate prophylaxis, monitoring closely for clinical events, and employing timely therapeutic interventions to treat patients diagnosed with VTE. Given the inherent risk of VTE in surgical patients as well as the potential of missed thromboprophylaxis doses during the perioperative period, it is critical for surgeons to understand these key components of VTE management.

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Vena Cava Filters

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INTRODUCTION

The rationale for filter implantation in the inferior vena cava (IVC) is to prevent clinically significant pulmonary embolism (PE) by trapping venous emboli originating in the pelvic or lower extremity deep veins. Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and PE, is a major cause of morbidity and mortality worldwide. The incidence rate of VTE ranges between 75 and 269 cases per 100,000 persons, as shown by studies in North America, Latin America, Western Europe, and Australia. The incidence of PE is estimated to be approximately 70 per 100,000 persons. The mortality rate can be as high as 30% when left untreated and 8% when appropriately treated. Acute pulmonary embolism is the third leading cause of death in the United States, resulting in approximately 100,000 deaths annually. These figures increased substantially during the COVID-19 pandemic, with reports listing the incidence of PE as high as nearly 2 in 10 hospitalized COVID-19 patients or 14.7%. Patients diagnosed with venous thromboembolism are treated with either systemic anticoagulation and/or IVC filter placement, and occasionally with catheter-directed thrombectomy/thrombolysis or surgery. Even without anticoagulation, patients who receive an IVC filter alone show a significantly decreased PE-related mortality rate.

The concept of IVC interruption for treatment of PE was born from the work of Virchow, Trousseau, and Bottini in the mid to late 1800s. Mechanical prevention of PE has evolved from open surgical ligation of the IVC to the percutaneous endovascular filters used today. Since the advent of a percutaneous approach by Greenfield in 1983, the use of IVC filters has drastically increased. From 1980 to 2000, the number of filters placed increased from 2000 to about 50,000 per year. However, following reports of filter fractures, the US Food and Drug Administration (FDA) issued an initial communication recommending filter removal as soon as protection from PE was no longer needed. This led to a reduction of filter placement by 6.48% over 2010 to 2014. In response, IVC filter registries have been increasingly utilized to increase retrieval rates. When used in a centralized practice, a retrievable IVC filter registry led to a retrieval rate as high as 92%. Overall, retrieval rates increased from 6.9% in 2012 to 22.1% in 2016.

The standard treatment of acute DVT or PE is nearly always immediate, full pharmacologic anticoagulation, barring any contraindications. In addition, catheter-directed thrombolysis or thrombectomy can provide rapid DVT and symptom resolution as well as the potential to prevent permanent valve damage and mitigate the risk of future venous insufficiency. Filters can help save lives and prevent DVT-related morbidity, and although generally accepted as safe devices there are still filter-associated risks. Therefore a pragmatic approach to filter indications, contraindications and placement should be followed. Figure 1 shows nine filter types available in the United States, and Table 1 showcases their features.

INDICATIONS FOR INFERIOR VENA CAVA FILTER PLACEMENT

Indications for IVC filter placement are put in place by expert panels, spanning multiple specialties. Most of these recommendations are based on low-power randomized clinical trials. It is widely accepted that patients with acute DVT or PE and a contraindication to anticoagulation or with severe adverse reactions to anticoagulation should receive an IVC filter. This recommendation is supported by the American College of Chest Physicians (ACCP), the Society of Interventional Radiology (SIR), and the American Heart Association. Contraindications to anticoagulation include uncontrolled active bleeding, acute hemorrhagic stroke, cerebral lesions at high risk of bleeding, coagulation defects, and severe thrombocytopenia (<50,000/μL). For patients without a contraindication to anticoagulation, IVC filters are no longer recommended as an adjunct. The

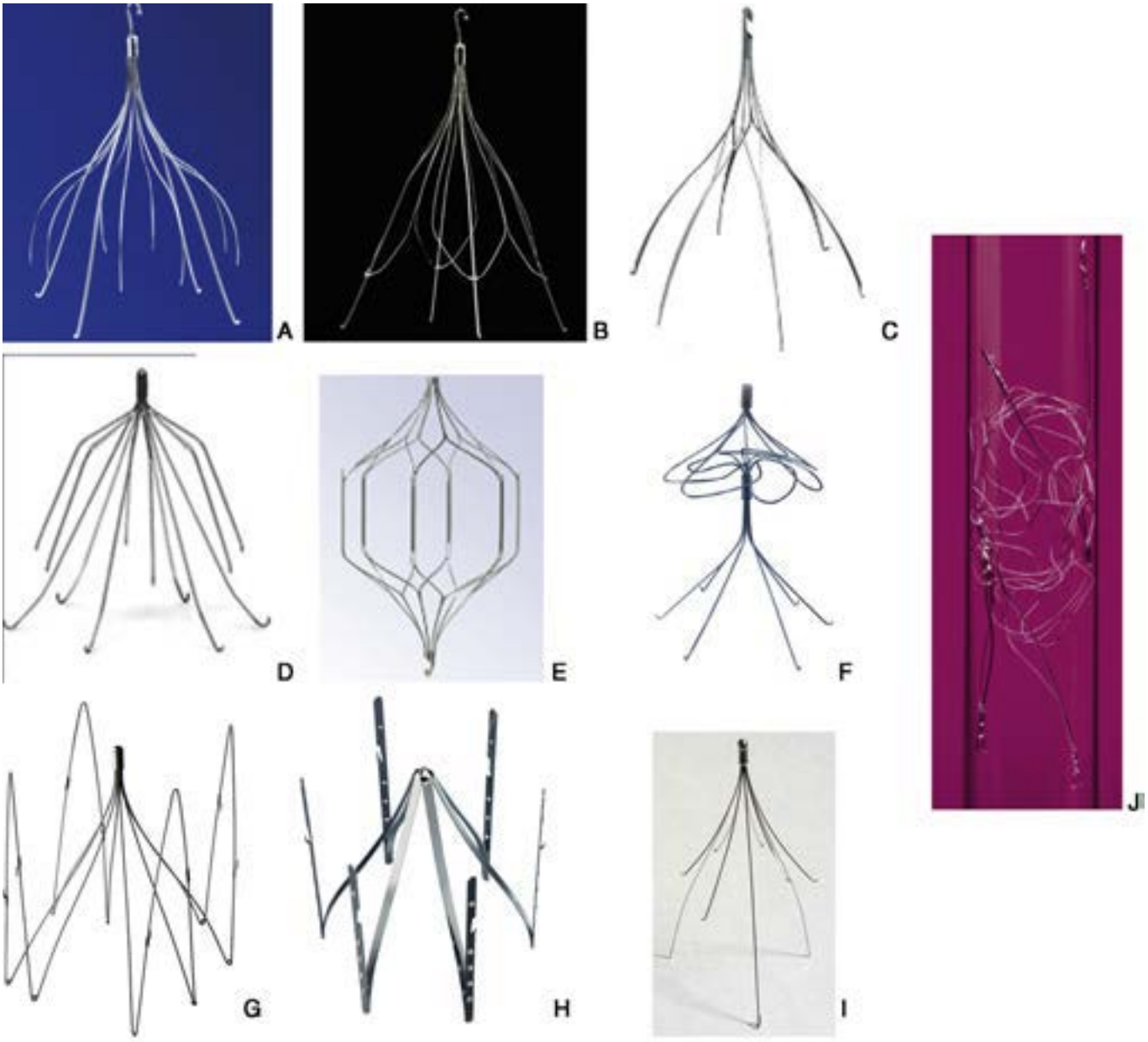


FIG. 1 The nine types of inferior vena cava (IVC) filters available in the United States. **(A)** Celect. **(B)** Günther-Tulip. **(C)** Option. **(D)** Eclipse. **(E)** Optease (retrieval hook). **(F)** Simon-Nitinol. **(G)** VenaTech LP. **(H)** ALN. **(I)** Bird's Nest. There is no prospective, randomized study that compares the safety and efficacy of these filters. Therefore the choice is simply based on operator preference, technical feasibility (diameter of IVC), and the need for a retrievable filter.

PREPIC 2 study showed that IVC filters as an adjunct to anticoagulation compared with anticoagulation alone had no benefit in morbidity or mortality. The slight decrease in PE in the filter group was offset by the increase in DVT.

Newer guidelines suggest a more limited role for the placement of IVC filters for recurrent VTE in the setting of anticoagulation therapy. Evaluation for possible suboptimal medical adherence, drug-drug interactions, inappropriate dosing, and anatomic disorders that predispose to VTE should be addressed first. Additionally, dose escalation or modification of the anticoagulant should be attempted. Only after medical therapy has been clearly exhausted should an IVC filter be placed. For patients with VTE who are undergoing advanced therapies (i.e., thrombolysis, thrombectomy, or embolectomy), IVC filter placement should be considered. Several studies have shown that IVC filter placement in patients receiving thrombolysis or pulmonary embolectomy for hemodynamically significant PE had significantly lower in-hospital mortality than those without an IVC filter. In one study, 141 patients with a DVT who were undergoing percutaneous endovascular intervention were randomized into an IVC filter group and a control group. The study found a significant reduction of PE in the filter group (1.4%) compared with the control (11.3%). However, other studies showed no significant benefit to IVC filter placement in patients with DVT who were undergoing catheter-directed thrombolysis. In our institution, we place IVC filters in select endovascular cases when the proceduralist feels the risk of PE is high.

Prophylactic IVC filter placement has also come under some scrutiny. For example, in trauma patients with a high risk for VTE,

TABLE 1 Filter Features

Filter (Company)	Sheath Size (Fr)	Maximum IVC Diameter (mm)	Material	Notes
Retrievable Inferior Vena Cava Filters				
Denali (Bard Peripheral Vascular)	8.4	28	Stainless steel	Six legs with anchors Placement via jugular (J), subclavian (S), or femoral (F) Retrieval via J
ALN (ALN Implants)	7	32	Phynox	Six shorter anchoring struts with hooks, three longer centering struts Placement via J, brachial (B), and F Retrieval via J
Celect Platinum	7	30	Cobalt-chromium alloy	Four legs with anchors and platinum markers on feet, eight shorter stabilizing wires Placement via J and F Retrieval via J
Gunther Tulip (Cook)	7	30	Cobalt-chromium alloy	Four longer leg anchors with eight secondary limbs J and F placement Retrieval via J
Option Elite (Argon Medical)	5	30	Nickel-titanium alloy	Six leg anchors Allows for antecubital and popliteal access, in addition to J and F Retrieval via J
OptEase (Cordis)	6	30	Nickel-titanium alloy	*Nonconical design* Double basket with side struts and six superior barbs, caudal hook Placement via antecubital, J, and F Retrieval via J
Permanent Inferior Vena Cava Filters				
Bird's Nest (Cook Inc.)	14	40	Stainless steel	Can be used in large-diameter IVC Deployment is operator dependent Has a 7-cm IVC footprint
VenaTech Low profile (B. Braun Medical)	7	35	Phynox	Large-diameter IVC Dual-direction deployment device Less MRI artifact
Stainless Steel Greenfield (Boston Scientific)	12	28	Stainless steel	
Titanium Greenfield (Boston Scientific)	12	28	Titanium	Less MRI artifact
Simon Nitinol (Bard)	7	28	Nitinol	Brachial vein access possible Mild MRI artifacts Filer migration at deployment
TrapEase (Cordis)	6	30	Nitinol	Brachial vein access possible Bidirectional placement Increased risk of caval thrombosis
Convertible Inferior Vena Cava Filter				
VenaTech Convertible Filter	10	28	Cobalt chromium	Can be converted into open configuration when filter is no longer needed

newer studies have shown no significant benefit to the prophylactic use of an IVC filter. In one study, IVC filter placement in patients with proximal femoral fractures showed a significant reduction in PE (2%) compared with patients without a filter (20%). However, this study was performed before the use of chemoprophylaxis, which has shown to reduce the risk of VTE in trauma and surgical patients. The use of chemoprophylaxis in high-risk surgical patients (i.e., bariatric surgery) has likely obviated the need for prophylactic IVC filter placement, though quality randomized controlled trials are needed.

Other possible indications for IVC filters include patients with poor cardiopulmonary reserve, a free-floating iliofemoral or IVC thrombus, pregnancy with high risk for recurrent VTE, and cancer patients with acute DVT as an adjunct to anticoagulation. However, evidence for these indications is limited. Box 1 outlines the indications for IVC filter placement.

BOX 1 Indications for Inferior Vena Cava Filter Placement

Indications

Prevention of PE for patients with acute VTE (i.e., IVC, iliac, femoral-popliteal, DVT, or PE) and one or more of the following:

- Contraindications to anticoagulation
  - Recent major trauma or surgery
  - CNS hemorrhage
  - CNS neoplasm, AVM, or aneurysm
  - Overt gastrointestinal bleeding
  - Massive hemoptysis
  - Significant thrombocytopenia (<50,000/μL)
- Complication of anticoagulation
  - Life-threatening hemorrhage on anticoagulation

Relative Indications

- Failure of anticoagulation
  - Must first confirm proper compliance with anticoagulation and attempt dose escalation and/or changing anticoagulant to obtain optimal medical management
- Patients with VTE who are undergoing advanced therapies (i.e., thrombectomy, thrombolysis, or embolectomy)
- Cardiopulmonary protection in patients with one or more of the following:
  - Massive PE in a patient at risk for further PE
  - Free-floating IVC or iliofemoral thrombus
  - Pregnancy at high risk for PE
  - Cancer patients with chronic, recurrent pulmonary thromboembolism

No Longer Indicated

- Adjunct to anticoagulation for acute VTE
- Prophylaxis in trauma patients
- Prophylaxis in surgical patients (i.e., bariatric) who can be treated with VTE chemoprophylaxis

AVM, Arteriovenous malformation; *DVT,* Deep venous thrombosis; *IVC,* inferior vena cava; *PE,* pulmonary embolism; *VTE,* venous thromboembolism.

FILTER SELECTION

The two most common IVC filters used are permanent IVC filters and retrievable IVC filters. Both types of filters attach to the IVC with hooks or barbs, applying radial pressure. Permanent filters have no built-in design feature, allowing removal, however there are reports of retrieval mechanisms. By contrast, retrievable filters allow for ready removal when no longer needed. Permanent filters have a slightly more favorable risk profile, such as lower rates of tilting (lower rate of >15 degrees off access), perforation (strut extending beyond the IVC by > 3 mm), migration, and thrombosis. However, other studies have shown that the differences in effectiveness and complication rates are not statistically significant. Ultimately, the decision to use permanent or retrievable filters is based on the clinical indication. Patients with chronic disease (i.e., cancer), short life expectancy, and recurrent VTE are better suited for permanent IVC filters. However, patients with acute injuries (i.e., trauma, stroke), single episodes of VTE, and longer life expectancies are selected for retrievable filter placement.

Other types of IVC filters include convertible and temporary IVC filters. Convertible filters can be switched into filter and nonfilter states without removal. Temporary IVC filters do not attach to walls and are attached to the catheter or wire during cases and removed after a short duration. The filter brand inserted is largely based on operator experience and availability. If a megacava (IVC > 32 mm diameter) is encountered, bilateral iliac vein filters or a Bird's Nest type filter (Cook Inc.) may be used.

Special Considerations: Suprarenal Inferior Vena Cava Filter

Clinical scenarios that call for a suprarenal IVC filter are rarely encountered. Indications are related to thrombus location, anatomic variations, and pregnancy. The most common indication is an IVC clot extending above the renal veins, which may occur above a previously placed infrarenal filter. Depending on the extent of the thrombus, thrombolysis or thrombectomy could be considered, with the use of a temporary IVC filter followed by deployment of a retrievable or permanent filter. Suprarenal IVC filters may be considered if either a duplicated IVC or short infrarenal IVC anatomic variants are encountered. Alternatively, bilateral iliac vein filters can be placed in these variants. When filters are indicated during pregnancy, suprarenal filters are preferred because of the caval compression by the gravid uterus and increased incidence of gonadal vein thrombosis. Similarly, large pelvic masses may result in iliofemoral DVT, and these patients may require interruption in anticoagulation for surgical intervention. In addition to caval compression, caval manipulation may occur during surgery. In some instances, isolated gonadal vein thrombosis may be treated with coil embolization. Regardless of the indication for suprarenal IVC filters, short dwelling times and retrievable filters are preferred. Indications for suprarenal IVC filter placement are shown in Box 2.

Contraindications for Placement of an Inferior Vena Cava Filter

Contraindications for IVC filter placement are both technical and clinical. There are no absolute contraindications; however, there are a few relative contraindications. Technical reasons include a thrombosed/occluded IVC, a clot in the intrahepatic IVC, and no available venous access. Clinical contraindications include severe uncorrectable coagulopathy, severe prothrombotic state, and active bacteremia. Although active bacteremia is a contraindication to filter placement, the risk of seeding a filter has not been proven. If a filter is necessary in a patient with active bacteremia, then a retrievable one may be placed, and it should be removed as soon as not needed or replaced as soon as bacteremia resolves. A prothrombotic state increases the risk for in situ filter clot formation. It should not prevent filter placement if protection against potentially lethal PE is necessary. Hematology input is important to screen these patients and have a plan of action related to type of filter used, duration of protection, retrieval, and possibly concurrent systemic anticoagulation.

BOX 2 Indications for Suprarenal Inferior Vena Cava Filter Placement

Thrombus Location

- IVC thrombus to the level of the renal veins
- Large thrombus extending above a previously placed infrarenal filter
- Large gonadal vein thrombosis
- Renal vein thrombosis

Anatomic Considerations

- Duplication of the IVC
- Low renal vein insertion/short infrarenal IVC

Pregnancy-Related Considerations

- Placement during pregnancy

TECHNIQUE

Optimum performance requires catheter expertise, proper venous access selection, and appropriate filter type, as well as proper location and orientation of the deployed filter. Box 3 outlines an approach to IVC filter insertion.

Preoperative Planning

Preoperative planning is crucial to successful IVC filter deployment and clinical outcomes. First, the clinical indication for IVC filter placement should be evaluated, and a proper history, review of records, and physical examination should be performed. As mentioned earlier, the clinical indication, patient factors (i.e., history of recurrent VTE, prognosis), and anatomy will guide filter selection. Laboratory tests should be reviewed for potential severe coagulopathy. Lastly, imaging should be reviewed with special attention on the thrombus location, venous anatomy, and IVC size. Preprocedural measurements are ideal as dehydration and bleeding may underestimate vessel size during venography. Selection of a suitable venous access route on either the right or left side will depend on patient anatomy, operator preference, and the location of the venous thrombosis. Typically, the right femoral vein or internal jugular (IJ) vein are preferred as they provide optimal straight alignment, reducing the risk for tilt. Access via the IJ is often used in an outpatient setting and patients on anticoagulation as it eliminates the need for postprocedural bedrest and allows for easy observation. However, alternative sites may be needed depending on the patient's anatomy or location of the venous thrombosis. For example, to prevent iatrogenic PE, common femoral vein thrombosis precludes use of this vein for access.

BOX 3 Inferior Vena Cava Filter Placement Techniques

Review clinical indication

History, physical examination, laboratory tests, and current imaging studies

Selection of Filter Type

- Retrievable filter for patients with expected temporary use
- Permanent filter in select patients with lifelong indication
- Temporary filter (used during high-risk endovascular cases)

Access

- Internal jugular vein favored
  - Patients with IVC, iliac, or complete CFV thrombus
  - Lower insertion site thrombosis
  - Does not require postprocedure bed rest
- Common femoral vein
- Popliteal vein
- Brachial vein

Inferior Vena Cava Venogram

- IVC diameter and length
  - If > 28–30 mm and < 40 mm, consider a Bird's Nest filter
  - Landing zone must accommodate filter type
  - Final filter selection depending on IVC diameter
- IVC pathology
  - Thrombus
  - Narrowing
  - Consider IVUS when venogram findings are equivalent
- IVC anomalies
  - Duplicated IVC
- Renal vein identification for optimal filter tip position
  - Accessory renal veins

Deployment Pre- and Post-Deployment Check

- Filter location before deployment
- Filter released from device post-deployment
- Filter post-deployment; migration (<1 cm from pre-deployment position), tilt (<15 degrees) and expansion (struts are fully expanded)
- Assess access site hemostasis

CFV, Common femoral vein; *IVC,* inferior vena cava; *IVUS,* intravascular ultrasonography.

Venography

Once the access site has been selected, the patient is prepped and draped, and the skin puncture site is anesthetized in standard fashion. Venous access is obtained using ultrasound guidance and a micropuncture introducer set. If resistance is encountered during the insertion procedure, the clinician should withdraw the guidewire and check vein patency fluoroscopically with a small injection of contrast medium. If fluoroscopic findings are equivalent for a thrombus, intravenous ultrasound can be used to identify the presence of a thrombus and/or degree of narrowing. Regardless of the access site, a standard inferior venacavogram should be performed with 20 to 30 cc of contrast injected below the caval bifurcation in both anteroposterior and lateral views (typically 30 mL of contrast medium at 15 mL/s) through either an access sheath or flush catheter. Ideally a flush venogram, initiated at the level of the left common iliac vein, left of the left pedicle, will elucidate any anatomic variants.

The following factors should be checked on the venogram: caval size, caval patency, position of renal veins, and IVC anomalies. Of course, when imaging is available, these factors should ideally be reviewed pre-procedurally, although a properly performed venogram is more sensitive for variants.

1. Patency**:** If large thrombus is present at the initial delivery site, do not attempt to deliver the filter. Migration of the clot and/or filter may occur. It may be challenging to delineate IVC thrombus from mixing artifact or external compression. In these circumstances, IVUS can be used to evaluate for thrombus. Figure 2 depicts an example of IVUS during IVC filter placement.
2. Position**:** Identify the common iliac vein confluence (typically at L5) and bilateral renal vein ostia (typically at L1–L2). The contralateral iliac vein and the renal veins are recognized by inflow of the unopacified blood or reflux of contrast into them. The ideal location of an infrarenal IVC filter is properly centered (not skewed) in the IVC with its cephalad tip being bathed by the renal vein blood inflow from the lowest renal vein inflow. The blood flow prevents filter tip thrombus formation, enhances endogenous thrombolysis, and may allow for easier filter retrieval. Placing the filter too low may result in a higher rate of IVC thrombosis, which is related to filter-induced turbulent flow. Placing the filter above or across the renal veins may similarly result in IVC thrombosis. Rarely, renal failure may ensue if the filter thromboses and the resulting clot obstructs the renal vein drainage. Clinical scenarios that call for a suprarenal IVC filter are uncommon and are shown in Box 2.
3. Size**:** The IVC typically measures 23 mm. If the vena cava diameter is greater than 28 mm *(mega cava),* an appropriate filter must be selected. Up to 2% of patients have a IVC transverse diameter exceeding 28 mm. A Bird's Nest filter expands to 40 mm; however, it requires a 7-cm infrarenal footprint. Alternatively, bilateral common iliac vein filters may be deployed.
4. Variants: Some anatomic variants such as the duplicated IVC, left-sided IVC, and circumaortic left renal veins should be borne in mind when analyzing the cavogram as well as pre-procedure imaging when available. The filter should be deployed upstream of any accessory renal veins to prevent an embolus bypassing the filter. If either of the iliac veins are visualized on the venocavogram, consider the possibility of a duplicated IVC. For patients

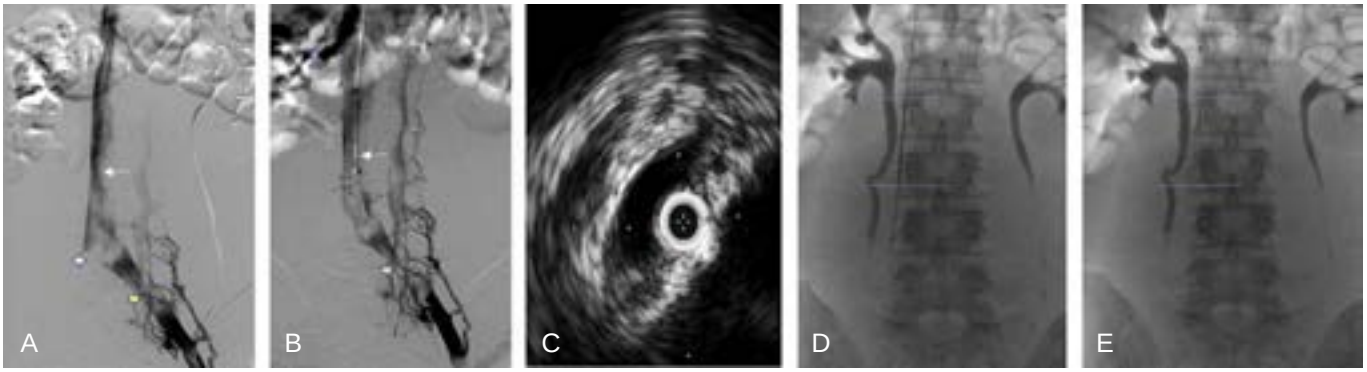


FIG. 2 Intravascular ultrasound (IVUS) used to differentiate a thrombus from external compression in a patient with a known thrombus and metastatic disease. **(A** and **B)** Venograms show a possible filling defect of the infrarenal inferior vena cava (IVC) *(arrows)*, wash-in artifact from the right iliac vein *(white arrowhead)*, and a filling defect with collaterals in the left iliac vein secondary to the thrombus. **(C)** IVUS showing narrowing of the IVC without a thrombus. **(D)** IVC filter deployed with sheath positioned between L2–L3 (marked by horizontal lines). **(E)** The filter is unsheathed and shown in good vertical position without tilt.



FIG. 3 **(A)** Right internal jugular access for inferior vena cava placement. Venogram performed by injecting a omni flush catheter in the left iliac vein. Mixing inflow from the right internal iliac can be seen as a contrast defect *(arrow)*. **(B)** Measurement of the IVC shows acceptable 25 mm diameter. Renal veins are identified by reflux into the right renal vein and mixing inflow from the left *(stars)*. **(C)** Radiopaque marker denotes the tip of the sheath at the edge of the undeployed filter *(lines)*. **(D)** Retraction of the sheath deploys the filter at the L2–L3 levels.

with a duplicated IVC, a filter may be placed in both inferior cavas, or a suprarenal filter may be considered when technically feasible. If a short infrarenal IVC is encountered instead of a suprarenal filter, consider two common iliac filters.

Deployment

Once the venogram has been reviewed, final filter selection can occur. Each filter has its own deployment mechanism dictating a specific technique. Most devices have markings on the sheath and catheter carrying the filter to help guide positioning before deployment. Under fluoroscopic guidance, the sheath is advanced until the tip is at the desired level. Next, the catheter is advanced to the tip (not beyond) of the sheath. The clinician then pins the catheter and pulls back on the sheath slowly under fluoroscopic guidance. The filter is attached to the tip of the catheter, and the unsheathing process will release the filter. In some devices, an additional mechanism is used to release the filter. After deployment, the clinician slowly retracts the catheter under fluoroscopic guidance to ensure that the entire extent of the filter has been safely deployed. Figure 3 shows the critical aspects of IVC filter deployment.

FILTER RETRIEVAL

Any filter that can be retrieved and is no longer needed or effective should be removed as soon as possible. In 2010 and again in 2014, the FDA issued a safety communication to ensure proper follow-up and filter removal in a timely manner. Since 2010, there has been an increasing push to remove IVC filters. Retrieval rates increased from 6.9% in 2012 to 22.1% in 2016. Multiple studies have shown that the use of computerized reminder systems improves retrieval rates, in some cases as much as 92% or by a magnitude of 2.5.

Filter endothelialization is thought to begin at around 3 weeks; therefore, the less time a filter has been in place the higher the retrieval success rate. As indwelling times increase, the rates of filter complications such as DVT, IVC occlusion, filter emboli, IVC penetration, filter migration, filter fracture, and retrieval complications (discussed later) also increase. Meanwhile, the benefit of PE prevention decreases over time. Risk-benefit analyses have shown that in patients for whom the acute risk of PE has passed, the risk of continued filter dwelling begins to outweigh the benefit at approximately 29 to 54 days. Additionally, if the filter itself is ineffective (migrated, kinked, fractured), it should be removed or replaced. In patients with

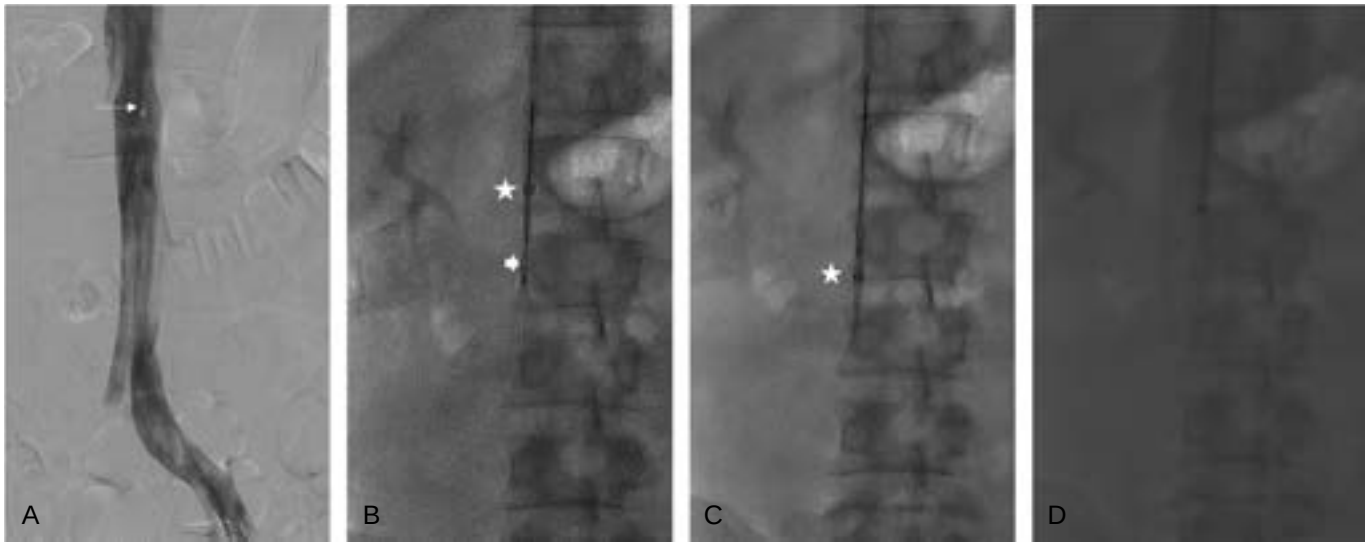


FIG. 4 **(A)** Inferior vena cava (IVC) filter retrieval venography demonstrates patency of the IVC. A hook is noted at the apex of the filter *(arrow)*. **(B)** The snare attaches to the hook *(arrowhead)*. **(C)** The sheath is advanced over the filter *(star)*. **(D)** The ensheathed filter is retracted under fluoroscopy.

active bacteremia and concern for an infected filter, the filter should be removed or replaced. There is no set cutoff time for when a filter should be retrieved. Maximum effort should be made to remove filters while applying good clinical judgment.

Technical success in removing filters is generally very high (>95%) but becomes increasingly challenging with greater dwelling times. Removing the filter during the recommended time frame is usually a simple and safe procedure and does not require pre-procedural imaging. The internal jugular vein is typically accessed, and a hook is used to snare the apex of the filter. A coaxial sheath is then advanced to collapse the filter, and the snared filter and sheath are removed together under fluoroscopic guidance. Figure 4 shows the steps for filter removal using the standard snare technique.

For short-term IVC filters (1–2 months) routine pre-procedural imaging is not required before filter removal. However, for longer indwelling retrievable filters and permanent filters, CT or venogram should be performed to guide planning. When standard techniques fail, advanced techniques using snares, balloons, rigids endobronchial forceps, and thermal lasers can be performed with very high technical success.

FILTER COMPLICATIONS

Complications of IVC filters can be divided into periprocedural or delayed categories (Table 2). Most complications are delayed and related to prolonged indwelling times.

Periprocedural Complications

Most periprocedural complications are not unique to IVC filter placement and include access site thrombosis (most common), venipuncture hematoma, infection, arteriovenous fistulas, and contrast reactions or nephropathy. Periprocedural complications unique to IVC filter placement include filter malpositioning, tilting, incomplete opening, and IVC wall penetration. The rate or periprocedural complications is between 5% and 23%, with a mortality rate of <1%.

Meticulous technique and experience can prevent malpositioning and tilting. Filter tilt, described as >15 degrees off axial midline, may lead to decreased effective trapping of PE. Filter misplacement occurs less than 1% of the time with experienced operators and use of venography, but the rate was significantly higher with inexperienced operators without the use of venography.

TABLE 2 Complications from Inferior Vena Cava Filter and Other Trackable Events

Complications/Adverse Effects	Reported Rates (%)
Periprocedural complications (i.e., access site thrombosis, venipuncture hematoma, infection, AVF)	5–23
Filter migration or embolization	<1
Filter fracture	2–10 (40% after 5.5 years)
Filter thrombosis	2–30
IVC penetration	0–40 (clinically significant penetration estimated has been reported to be <1%)
Breakthrough PE	1.1–6.2 (at 8 years)

AVF, Arteriovenous fistula; *IVC,* inferior vena cava; *PE,* pulmonary embolism.

Delayed Complications

Delayed complications make up the majority of IVC filter–related complications and include DVT, filter migration and embolization, filter fracture, filter thrombosis, and IVC perforation. DVT is the most common complication of IVC filters, with a 2-year incidence of 21% and 36% at 8 years. Filter migration and embolization are perhaps the most feared complication. Defined as a change in original position >2 cm, filter migration has an incidence of <1%. More than 90% of these occur after 30 days. Possible explanations for filter migration include larger than normal vena cava (relative to filter size), filter malpositioning, massive embolization into the filter, and iatrogenic movement from guidewire manipulation. Filter fracture, defined as structural failure or separation of components, occurs in 2% to 10% of patients, and can be as high as 40% after 5.5 years.

Filter thrombosis, defined as thrombus found within the filter, has a widely reported incidence, with an overall range of 2% to 30%.

This significant discrepancy is likely caused by the unclear etiology of the thrombus. This in fact may not be a complication at all but rather evidence of the filter's proper functioning. IVC perforation is defined as filter strut penetration >3 mm beyond the lumen of the IVC. Because these are usually asymptomatic and discovered incidentally, the incidence rate is widely varied, ranging from 0% to 40%.

Although not a complication of filter placement, breakthrough PE (PE despite the presence of an IVC filter) should be discussed with patients. Within the first 12 days, the incidence rate is 1.1%, increasing to 6.2% at 8 years.

DISCUSSION

The standard of treatment for VTE is systemic anticoagulation. A major misconception is that systemic anticoagulation with coumadin, direct oral anticoagulants, heparin, low-molecular-weight heparin (LMWH), or argatroban treats existing thrombi. The goal of systemic anticoagulation is to prevent extension of an existing clot and/or recurrence of DVT or PE. Systemic anticoagulation over 6 months reduces the 2-year risk of recurrent DVT or PE by 50%, from 18% to 9%. However, for patients with acute VTE and contraindications to anticoagulation, IVC filter use reduces morbidity and mortality. Retrospective studies have shown that filters reduce the risk of recurrent VTE to 3% within the first month. In one study, patients with acute VTE and bleeding had a 32% lower 30-day risk of death when treated with IVC filters.

Although the utilization of IVC filters has increased exponentially between 2000 and 2010, FDA warnings and the increased recognition of filter complications have led to new schemata. Indications for IVC filter placement have become more selective. For example, filters are no longer recommended as adjuncts to anticoagulation, for preoperative prophylaxis (in lieu of chemoprophylaxis), or for prophylaxis in trauma patients. Perhaps most importantly, there has been a significant push to reduce filter indwelling time. The use of electronic databases and automated reminders has significantly increased the rate of retrievals. The short dwelling time leads to fewer complications and easier retrievals.

More studies are underway to analyze the effectiveness and appropriateness of IVC filters. The PRESERVE Study is being implemented by the Society for Vascular Surgery, Society for Interventional Radiology, FDA, and several IVC filter manufacturers. When completed, it will be the largest prospective study to investigate outcomes of IVC filter use. Additionally, new filters and the use of convertible and temporary filters are also on the horizon. Hopefully, these studies and improvements will lead to increasing the effectiveness of IVC filters while mitigating their risks.

SUGGESTED READINGS

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TREATMENT OF VARICOSE VEINS

Andrew Schulick, MD, and David R. Whittaker, MD

INTRODUCTION

Superficial venous pathology is common. By age 65 years, the prevalence in the Western population is more than 55%, according to the Edinburgh Vein Study. Clinical findings range from reticular veins and telangiectasias to varicose veins and skin ulceration. Not all superficial venous changes are caused by underlying venous reflux and hypertension, and not all venous reflux manifests as visible physical findings. As a result, evaluation and treatment requires a high level of customization.

Traditionally, treatment of superficial venous disease was based on patient preference and tailored toward symptoms. Modern trends dictate more proactive treatment of venous reflux to mitigate future vein-related morbidity. To aid with treatment, several staging systems have been developed to standardize the classification of venous pathology. The most common are the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification system and the revised Venous Clinical Severity Score (r-VCSS). Using these and other standards, contemporary studies demonstrate that meaningful progression in the severity of venous pathology is more common than previously reported.

Sequelae of venous hypertension may adversely affect quality of life (QoL). In fact, more time is lost from work as a result of vein-related pathology than all arterial pathology combined, including coronary artery disease. Validated venous-specific QoL assessments, such as the Aberdeen Varicose Vein Score, can be used to help distinguish patients who are most likely to benefit from intervention and aid in managing treatment-related expectations.

CLASSIFICATION AND ETIOLOGY

CEAP was introduced in 1994 and revised in 2004. Modeled after the TNM (Tumor/Node/Metastasis) staging system used for cancer, the CEAP system is utilized in clinical decision making and outcomes evaluation (Table 1; Fig. 1). The r-VCSS similarly aids in patient classification and outcomes analysis. The use of these standard classification systems helps ensure optimization of therapy.

Superficial venous pathology is a function of venous hypertension resulting from venous valvular dysfunction. The degree and duration of venous hypertension determines clinical severity. Primary risk factors for valve dysfunction include female gender, family history, activity level, and occupation. The resulting increased lower extremity ambulatory venous pressure (AVP) caused by valve dysfunction contributes to the development of varicose veins and other cutaneous sequelae. Skin manifestations are uncommon with an AVP <35 mm Hg but are almost certain with an AVP >90 mm Hg.

Secondary risk factors for venous valvular dysfunction are less common and include anatomic compressive syndromes such as May-Thurner and Nutcracker syndrome, muscle pump dysfunction, trauma, and postthrombotic changes. Finally, the presence of congenital etiologies, such as Klippel-Trenaunay syndrome, Ehlers Danlos syndrome, and clonal trisomies, must be investigated at the onset of care. Failure to recognize a compromised deep venous

TABLE 1 Revised 2020 CEAP Classification Guidelines

CEAP Classification System and Reporting Standard Revision 2020	
C0	No visible or palpable or reticular veins
C1	Telangiectasias or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophic blanche
C4c	Corona phlebectatica
C5	Healed
C6	Active venous ulcer
C6r	Recurrent active venous ulcer

A, Anatomic distribution; *C,* clinical manifestations; *E,* etiology; *P,* pathophysiology.
From Lurie F, Passman M, Meisner M, et al. The 2020 update of the CEAP classification system and reporting standards (published correction appears in *J Vasc Surg Venous Lymphat Disord.* 2021;9:288). *J Vasc Surg Venous Lymphat Disord*. 2020;8:342–352.



FIG. 1 C6 active venous ulcer. *(Courtesy David R. Whittaker.)*

system before ablative intervention on the superficial system can be a catastrophic mistake.

DIAGNOSIS

Examination and Testing

A detailed history and physical examination is critical to assessment and treatment of the venous patient. Specific signs or symptoms are often clues to etiology and pathogenesis and can help target treatment. Health history helps contextualize recommendations. Alternative diagnoses, such as peripheral arterial disease or musculoskeletal or neurogenic causes of symptoms, should always be considered.

Accurate duplex scanning is an essential part of venous evaluation. Scanning should be protocol driven and is best performed with the patient standing or in the steep reverse Trendelenburg position. This positioning helps ensure that an adequate column of blood is present to pressurize veins, allowing more accurate assessment of venous valvular competency. The lower extremity venous system has many anatomic variants, which can make duplex scans difficult to interpret. The critical component of assessment is to identify the most significant, usually the most central, source of reflux. Pathologic reflux is generally defined as the reversal of flow in a vein segment for a duration of more than 500 ms in perforator veins, more than 500 ms in truncal superficial veins, and more than 1000 ms in the deep veins. Vein diameters greater than 5 mm (3.5 mm in perforators) are important to document as they often correlate with symptomatic reflux (Fig. 2). It is important to correlate the duplex findings with the patient's signs and symptoms. Mild or isolated segmental reflux, especially in a small vein, is not likely to be the source of symptoms and rarely warrants an intervention; these issues should be discussed with the patient to ensure understanding and to manage expectations.

Management of Deep Venous Reflux

Occasionally, venous tributaries that arise directly from a hypertensive deep system can be the source of varicose changes. Although deep vein valve transplantation and valvuloplasty are therapeutic options, these procedures are uncommon and are best performed in specialty centers. Current treatment recommendations are nonsurgical. External graded compression garments (20–30 mm Hg), leg elevation, and activities that increase the muscle-pump remain the mainstays of therapy. Compliance with above-the-knee compression garments demonstrates significant attrition over time. Because the long-term cutaneous changes typically occur below the knee, it is not unreasonable to settle on a recommendation for use of below-the-knee compression garments, regardless of the level of deep reflux.

MANAGEMENT OF SUPERFICIAL VENOUS REFLUX

Superficial venous reflux within the truncal saphenous system is amenable to several different forms of intervention. In each, the fundamental principle is to eliminate the source of symptomatic venous hypertension. Initial therapy should target the most significant contributor of reflux. Subsequent interventions focus on progressively smaller contributors, proceeding in a staged and systematic fashion. In the absence of more central pathology, treatment typically begins by addressing reflux in the truncal superficial veins, the great saphenous vein (GSV), and the small saphenous vein (SSV). Treatment then moves to the accessory systems, tributaries, and superficial varicosities as needed. Finally, cutaneous reticular veins and telangiectasias can be addressed once the underlying venous pathologies have been appropriately managed.

Techniques

Treatment is classified as either endovenous, surgical, or topical. All techniques are designed to functionally remove the treated vein segment from the venous circulation. This redirects flow to functioning venous channels and reduces lower extremity venous hypertension by eliminating congestion-producing reflux.

Thermal Endovenous Techniques

Carlos Boné is attributed with the initial introduction of endovenous laser ablation (EVLA) in 1999. Endovenous options were expanded

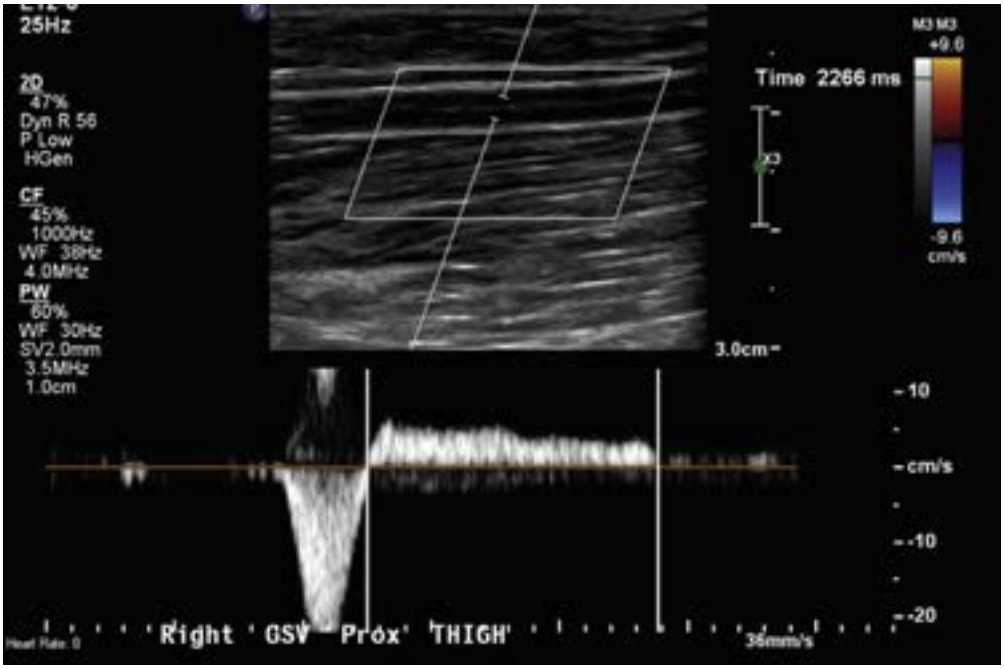


FIG. 2 Significant proximal GSV valvular insufficiency. Note that the reflux velocity is >30 cm/s. *(Courtesy David R. Whittaker.)*

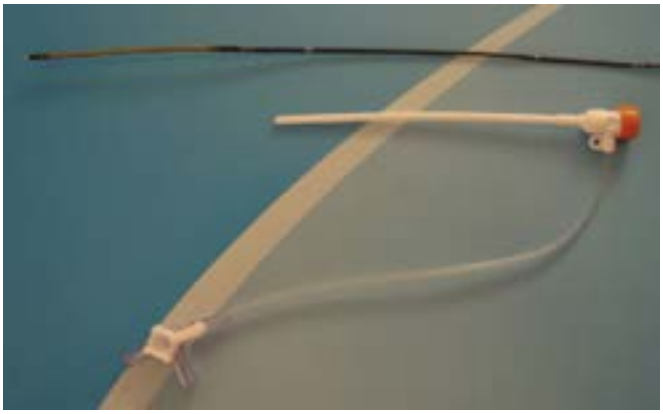


FIG. 3 Radiofrequency ablation treatment systems, ClosureFast (Medtronic). *(From Bauzá Moreno H, Dotta M, Katsini R, et al. Endovascular radiofrequency ablation. Effect on the vein diameter using the ClosureFast catheter.* Cirugia Espanola. *2016;94:353–357.)*

in 2003 to include radiofrequency ablation (RFA). Both RFA and EVLA techniques have long track records of safety and efficacy. The technique for each is generally similar, with some notable exceptions, as highlighted in the following sections.

Radiofrequency Ablation of Truncal Veins

RFA catheters are available in several lengths and styles (Fig. 3). The ClosureFast system is available in 3- and 7-cm thermal tip lengths. In addition, Medtronic offers a dedicated Endovenous Ablation Stylet for management of perforator veins. Each of the catheters is able to use the same generator to produce the appropriate energy profile at the catheter tip. The energy delivered at the catheter tip causes local endothelial and collagen damage that results in closure of the vein lumen and subsequent in situ vein wall degeneration.

The steps for RFA of saphenous veins are as follows:

1. Prep the appropriate leg in the standard, circumferential sterile fashion.
2. Ultrasound scan is performed as the first step of the sterile procedure or before prep; map out the saphenous system and assess the vein for occlusion, aneurysm, exceptionally superficial venous locations, webbing, or other anatomic details that may make the procedure difficult or less successful.
3. Access the vein percutaneously using ultrasound guidance after anesthetizing the superficial skin with lidocaine. Access is routinely initiated just below the popliteal area on the medial calf for GSV. Accessing more distally on the GSV may be indicated for treatment of reflux along the length of the vein in CEAP 5 or 6 patients, but doing so increases the incidence of saphenous nerve injury. Similarly, SSV access is typically in the mid- to lower one-third of the calf as more distal access can result in sural nerve injury.
4. Thread microwire through the needle, and confirm under ultrasound guidance.
5. Remove the needle while keeping the microwire in place.
6. Flush the 7Fr introducer sheath with saline, and place it over the microwire into the vein.
7. Remove the inner dilator and wire. Flush the sheath.
8. Attach the catheter to the generator.
9. Flush the catheter with sterile saline, and cap the Luer port.
10. Insert the catheter through the sheath and advance it.
11. Optional: if the catheter does not advance easily, a 0.025-inch Glide wire (Terumo Corporation, Japan) may be backloaded into the catheter to guide catheter insertion. Alternatively, distal traction on the skin of the leg and stabilization of the vein with the contralateral hand frequently allows for the catheter to be passed though moderately tortuous veins.
12. Confirm tip position with ultrasound guidance to be at least 2 to 2.5 cm inferior to the epigastric vein immediately distal to the saphenofemoral junction (SFJ). The longitudinal view is best used for this measurement. For the SSV, the catheter tip should be positioned in the superficial portion of the SSV and not advanced past the point where the vein dives deep to form

the saphenopopliteal junction (SPJ). This point is typically at least 3 cm from the SPJ. The catheter and veins can be imaged in the longitudinal access, and the distance can be measured and recorded to ensure adequate distance.

13. Move the grommet to the end of the sheath to mark the position.
14. Administer tumescent in the perivenous tissue under ultrasound guidance, striving to create a halo of tumescence around the vein within the saphenous fascia (1000 mg 1% lidocaine, 20 cc 8.4% $NaHCO_3$ in 1000 cc normal saline). Tumescence should extend at least 2 cm proximal to the tip of the catheter to ensure adequate anesthesia and to form a barrier between the heat of the catheter and the deep veins. The catheter tip is equipped with a temperature thermistor. This should register a drop in temperature as the tumescence is infiltrated near its location. Failure to register a drop in temperature is cause to reassess catheter tip position.
15. Position the bed in the Trendelenburg position to facilitate vein collapse.
16. Apply compression over the length of the heating element to facilitate contact between the vein wall and heating element.
17. Press the white device button on the catheter handle to initiate treatment. Watts used during treatment cycle should fall to below 14 at some point during the cycle. Increasing compression can decrease the watts needed to treat the segment of vein. If the patient exhibits any discomfort, immediately press the white button again to disable the energy and infiltrate the catheter tip region with more tumescence.
18. When the treatment cycle is complete, index the catheter to the next shaft mark position. Apply compression over the entire heating element, and start the next treatment. Treat the segment closest to the junction twice. Consider a third cycle near the junction or a second cycle more distally if the vein is greater than 10 mm, if there are large branches or perforators exiting from the segment, or if the wattage does not fall below 14. Do not treat any segment more than three times.
19. Repeat the withdrawal process to sequential shaft marks, compression, and treatment.
20. Remove the sheath over the catheter once the vein is treated over the hashmarks on the catheter.
21. Withdraw until the last index mark is seen. Apply compression over the entire heating element, and start the last treatment. Take care not to withdraw the catheter beyond the three-hash mark area as a more superficial catheter location could possibly get the heating element too close to the puncture site and burn the skin.
22. Remove the catheter and sheath, and apply compression over the access site for hemostasis. A Steri-Strip is usually adequate, but a single 4-0 nylon suture may be used as well.
23. Apply compression from the foot up to the thigh.
24. Review postprocedure instructions.

Endovenous Laser Ablation of Truncal Veins

The EVLA systems also use thermal energy to effect endothelial destruction, vein wall contraction, luminal obliteration, and eventual vein degeneration (Fig. 4). Energy is delivered by treatment fibers, of which there are several different types and configurations. Treatment wavelengths can range from 660 to 1470 nm, but in general, the 1470 nm fibers are more frequently used. A technical review of different fiber characteristics can be found in the Suggested Readings.

The steps for EVLA of saphenous veins are as follows:

1. Once a microsheath is in place as per the standard protocol, advance a 0.035-inch guidewire to the sapheno–deep venous junction under ultrasound guidance.
2. Remove the microsheath, and select a long sheath based in the measured distance from the junction to the access site.
3. Remove the inner dilator and wire from the long sheath.
4. Advance fiber into the sheath.
5. Connect the fiber to the generator, and aim the beam toward the skin.
6. While holding the fiber in place, the sheath is withdrawn to the locking mechanism and locked in place.
7. The tip of the fiber is exposed approximately 2 cm past the end of the sheath.
8. Confirm tip position with ultrasound guidance to be at least 2 cm inferior to the epigastric vein immediately distal to the SFJ. For the SSV, the catheter tip should be positioned in the superficial portion of the SSV and not advanced past the point where the vein dives deep to form the SPJ. This point is typically at least 3 cm from the SPJ. The catheter and veins can be imaged in the longitudinal access, and the distance can be measured and recorded to ensure adequate distance.

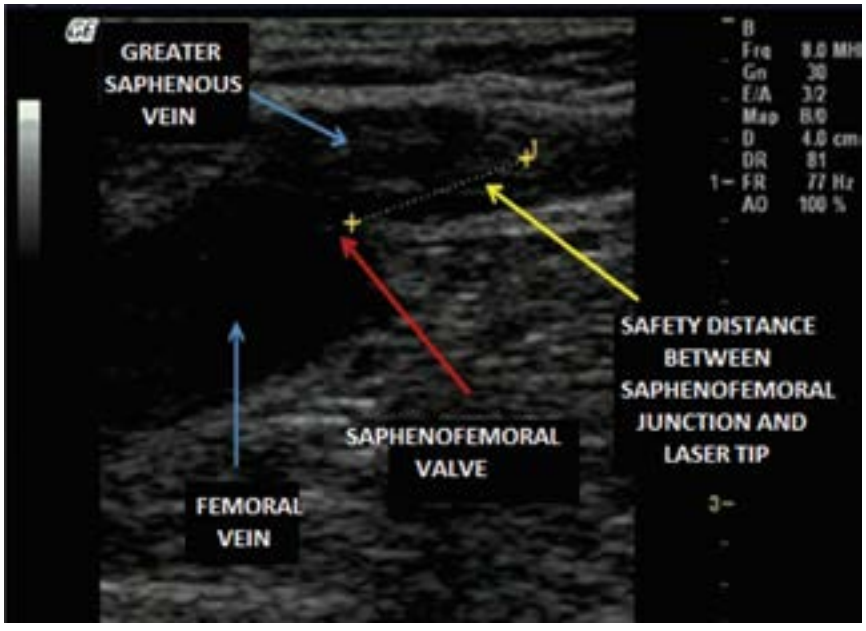


FIG. 4 **Endovenous laser fiber at the proximal treatment location.** *(From Vourliotakis G, Sahsamanis G, Evagelidis P, Aivatidi C. Endovascular laser treatment of incompetent saphenous veins using the 1470 nm diode laser and radial fiber.* Ann Med Surg [Lond]. *2017;25:12–16.)*

9. Administer tumescence as described.
10. Position the bed in the Trendelenburg position to facilitate vein collapse.
11. Once the machine is turned on and set to 5 to 7 W from standby to ready mode, step on the foot pedal to deliver laser energy. Pull back the laser fiber and sheath together 1 cm every 3 to 5 seconds.
12. Treatment energy should be monitored as per recommendations for each laser type; 40 J/cm (1470 nm laser) and 80 J/cm (810 nm laser) are frequently used settings.
13. Stop treatment by releasing the pedal when the laser fiber is 1 to 3 cm proximal to the entry site.
14. Remove the fiber and sheath, and apply compression over the access site for hemostasis.
15. Apply compression from the foot up to the thigh.
16. Review postprocedure instructions.

Nonthermal Endovenous Techniques

Mechanochemical Ablation of Truncal Veins

Mechanochemical ablation offers a nonthermal alternative and is best suited for the truncal veins. This system uses a rotating wire to produce spasm in the vein followed by the concurrent injection of a sclerosant to create chemical endothelial damage and subsequent closure of the vein. A distinct advantage of nonthermal methods of venous treatment is the absence of thermal injury risks to surrounding perivenous structures, obviating the need for tumescent analgesia. The long-term durability of the closure is actively being studied and appears to be on par with thermal-based endovenous treatment solutions.

The steps for mechanochemical ablation of saphenous veins are as follows:

1. The leg is prepped, and the vein is accessed as per the RFA technique. Access can be much lower in the calf than for thermal ablation because there is no risk of thermal nerve injury.
2. Place a 4Fr to 5Fr introducer or a 4Fr angiocatheter into the vein.
3. A syringe is connected to the open end of the microsheath or angiocath while preparing the catheter.
4. Flush the ClariVein catheter (Merit Medical) with saline. Place the stopcock in the closed position on the catheter Luer lock. Have the sidearm face laterally when attached.
5. Attach the 5-mL sterile syringe containing sclerosant (typically 1% polidocanol or 1% to 3% sodium tetradecyl sulfate) to the stopcock. Ensure no air bubbles.
6. Place the catheter into the sheath or angiocatheter.
7. Under ultrasound guidance, place the wire tip at least 2 cm distal (inferior) to the SFJ. For SSV ablation, place the wire tip just distal to the fascial curve, within the straight segment of the SSV. If a gastrocnemius vein connects to the SSV, place the wire tip 2 cm inferior to the insertion.
8. Depress the trigger briefly to test the battery. An LED indicator should turn green.
9. Weld the catheter cartridge to the handle unit.
10. Pull back the cartridge wing further into the handle groove, and turn slightly counterclockwise, clicking into the second stop position.
11. The tip of the fiber is exposed approximately 2 cm past the end of the sheath.
12. The index finger depresses the motor trigger while the thumb delivers sclerosant by pressing the syringe plunger after the stopcock is turned open.
13. Continue the motor for 3 seconds to produce vasospasm with simultaneous pullback for 0.5 cm, and initiate delivery of sclerosant after the 0.5-cm pullback.
14. Continue treatment while pulling back 1.5 mm/s.
15. Treatment is stopped when 3 to 4 cm of catheter is left in the leg. A white mark on the catheter marks 6 cm distal to the catheter tip and alerts that only a short segment of catheter is remaining within the vein. Remember to pull the access device out of the vein and skin over the catheter before the catheter tip reaches the access site to ensure treatment of distal vein segments.
16. Once the vein segment is treated, ultrasound imaging of the vein is performed to assess for vein closure.
17. If the vein is patent, immediate retreatment is accomplished by passing the sheathed catheter tip proximally again for retreatment.
18. If the vein is occluded, the wire tip is resheathed by unclipping the syringe, twisting the cartridge wing clockwise, and moving the handle groove from the second lock position to the first.
19. Withdraw the catheter. Unsheath the wire and inspect.
20. Apply compression over the access site for hemostasis.

Endovenous Closure with Cyanoacrylate Glue

An alternative to using heat or a liquid sclerosant is to use a medical cyanoacrylate-based adhesive glue (VenaSeal, Medtronic) to close the incompetent vein (Fig. 5). This nonthermal technique also avoids heat-mediated nerve injury and requires no tumescent anesthesia. The adhesive glue that is injected into the vein(s) does not dissipate and remains as a foreign body. There is a small population of patients who appear to have a sensitivity to the compound, and a local inflammation or phlebitis has been reported in up to 20% of treated veins or side branches. Caution should be used in any patients with prior reactions to surgical glue–based adhesives that contain cyanoacrylate.

Steps for VenaSeal of the GSV/SSV include the following:

1. Prep the appropriate leg in the standard, circumferential sterile fashion.
2. Optional: a quick, sterile ultrasound scan is performed to mark the skin overlying the targeted treatment vein.
3. Access the vein percutaneously using ultrasound guidance after numbing the superficial skin with lidocaine. Access is routinely initiated at the most distal level of reflux. There is no risk of thermal nerve injury.
4. Insert the microwire and sheath, and remove the wire and dilator.
5. Advance the 0.035 J-wire through the sheath into the vein, and position it just caudal to the junction. Confirm the position under ultrasound guidance.
6. Remove the microsheath over the wire, and advance the 7Fr introducer/dilator from the system over the J-wire to the junction.
7. Remove the wire and inner dilator.
8. Flush the sheath with sterile saline using a flushing syringe. Keep the syringe in place.
9. Position the tip of the sheath 5 cm inferior to the junction under ultrasound guidance.
10. Extract the VenaSeal adhesive from its vial into a 3-cc syringe. Purge air.
11. Connect the 3-mL syringe to the 5Fr catheter. Lock the 3-mL syringe attached to the catheter to the dispenser gun.
12. Prime the catheter by pulling the trigger to advance the adhesive to within 2 to 4 cm of the distal catheter tip.
13. Remove the saline-filled flushing syringe from the introducer.
14. Insert the primed catheter/gun complex into the introducer and advance until the laser mark on the catheter is at the hub of the sheath.
15. Pull the sheath caudal another 5 cm. Advance the catheter cephalad, and lock the sheath to the catheter/gun complex.
16. Verify that the tip is 5 cm away from the junction.
17. Position the ultrasound probe just cephalad to the catheter tip, and apply pressure to compress the junction.
18. Deliver 0.10 mL of adhesive in the vein by pulling the trigger of the gun. Hold the trigger down for 3 seconds.
19. Immediately pull back 1 cm, and deliver another 0.10 mL of adhesive and hold for 3 seconds.
20. Pull back the entire system 3 cm. Hold transverse compression at the junction for a minimum of 3 minutes.
21. Locate the catheter tip position with ultrasound guidance. Apply probe compression caudal to the previous injection and cephalad to the catheter tip, deliver 0.10 mL of adhesive, and then hold the trigger down for 3 seconds.

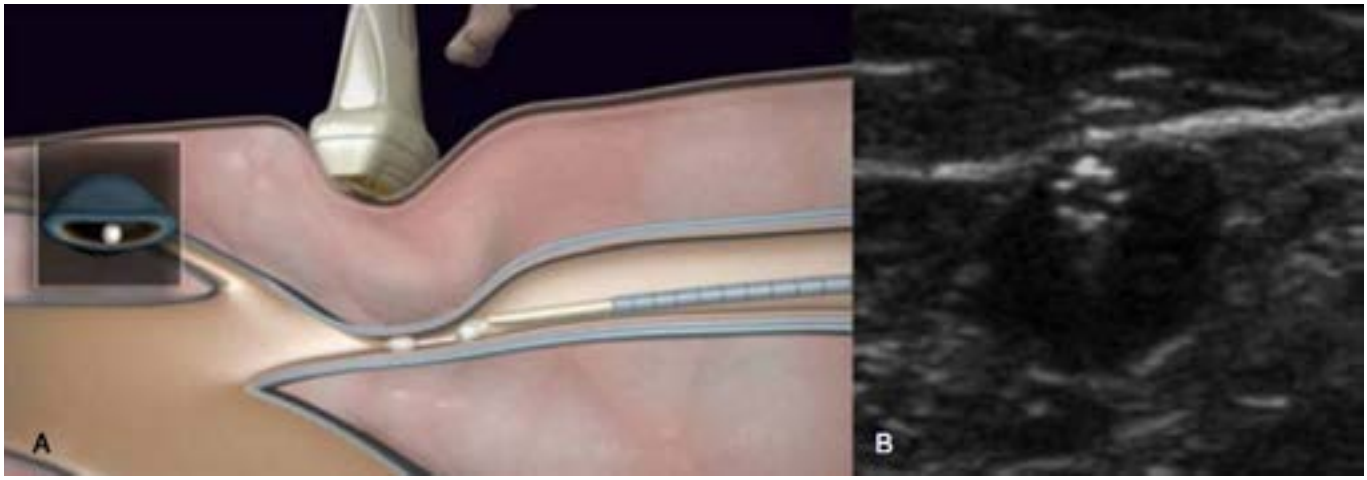


FIG. 5 (A) Artist rendition of cyanoacrylate delivery. **(B)** Transverse ultrasound image of proximal seal zone. *(From Pavlović, MD, Schuller-Petrović S. Endovascular techniques for the treatment of chronic insufficiency of the lower limb's superficial venous system.* Rev Vasc Med *2014;2:107–117.)*

22. Immediately pull back the entire system 3 cm, and hold the probe compression for 30 seconds.
23. Repeat the steps of adhesive injection, pull back, and hold the probe compression for 30 seconds, until 5 cm cephalad from access site.
24. Remove all catheters, and apply manual pressure for hemostasis.

Polidocanol Endovenous Microfoam

Varithena (Boston Scientific, Marlboro, MA) is a commercially prepared 1% polidocanol microfoam that is uniform in density, size, and stability (Fig. 6). The foam displaces blood within the incompetent saphenous vein or tributary, filling the vein, and damaging the endothelium with polidocanol sclerosant. This nonthermal technology does not require venous anesthesia. The microfoam is created with a CO_2 gas formulation that minimizes the air embolism risks associated with physician-compounded foam using the Tessari technique.



FIG. 6 Varithena polidocanol microfoam (Boston Scientific). *(Copyright 2019 Boston Scientific Corporation or its affiliates.)*

The steps for Varithena of the great/accessory saphenous veins are as follows:

1. Prep the appropriate leg in the area of cannulation. An ultrasound scan is performed as previously described, with special attention to marking perforators and large branches.
2. Access the vein percutaneously using ultrasound guidance after anesthetizing the superficial skin with lidocaine. Access is routinely initiated at the most distal level of reflux. There is no risk of thermal nerve injury.
3. Secure the intravenous or micropuncture catheter.
4. Elevate the leg 45 degrees.
5. Generate the foam by connecting the syringe to the canister and activating the canister to release foam into the syringe in 5-mL increments per manufacturer instructions.
6. Inject the foam into the intravenous catheter while compressing the vein distally and compressing any perforators. Inject approximately 1 mL/s in the GSV and 0.5 mL/sec in accessory veins.
7. Monitor the infusion of the foam into the saphenous vein during injection. Once the leading edge reaches 5 cm from the SFJ, occlude the SFJ with an ultrasound probe for at least 3 minutes.
8. At this point, pressure is released from the distal aspect of the treated vein and over large branches. Pressure is continued over the perforators.
9. A maximum of 15 mL of foam is to be given in each treatment session. Patients can be brought back in as little as 24 hours to have repeat treatment as needed.
10. After 3 minutes, confirm with ultrasound guidance that GSV spasm has occurred.
11. Remove the IV. Hold external compression for hemostasis.
12. Additional local injections into untreated varicosities can be performed using a 23-gauge butterfly needle.
13. Keep the leg elevated for 10 minutes while a bandage and compression is applied.

Perforator Vein Treatment Techniques

Perforator veins require a modified treatment approach because of their short length and close proximity to the deep systems. Treatment of perforating veins should generally be reserved for vein diameters greater than 3.5 mm at the fascial level, reflux times longer than

500 ms, CEAP 4 to 6 patients, and those veins directly underneath or in close proximity to ulcers. Radiofrequency, laser, or chemical methods can all be used. Energy-based methods offer the most degree of point control.

Similar steps are used for each treatment technique:

1. Position the perforator vein in its long view.
2. Make a small 2-mm incision in the skin.
3. Through the small incision, access the target vein using either a direct venous puncture and Seldinger technique under ultrasound guidance with a 21 g microneedle, or alternatively, use the treatment stylet to directly puncture the vein.
4. Position the treatment modality 2 to 3 mm from the deep vein or at the fascial level, depending on anatomy.
5. Infiltrate local anesthesia around the perivenous tissue if necessary.

Then:

For EVLA:

A. Thread a 1470-nm or 400-μm microfiber through the needle.
B. Set generator at 6 W, and treat with 50 to 100 J per 2 mm.

For RFA:

A. Direct the endovenous stylet over the wire, or use direct puncture.
B. Withdraw the stylet, and confirm the position of the catheter tip.
C. Treat four quadrants for 60 seconds each.
D. Withdraw the catheter 5 mm, and repeat the four-quadrant treatment for an additional 60 seconds at each quadrant.

Considerations and Potential Complications of Endovenous Procedures

Tailoring treatment modalities to a patient's presentation enhances clinical outcomes. Although all of the discussed treatment options are generally safe and well tolerated, familiarity with the potential pitfalls, complications, and adverse effects of each is necessary.

The most significant risk from endovenous-based therapies is the development of deep venous thrombosis (DVT) or endovenous heat-induced thrombosis (EHIT).

The reported incidence varies among studies but is generally presented as a <1% per procedure risk (Fig. 7). Presuming appropriate catheter location and because treatment-related DVTs have a known etiology and a well-studied natural history, they are managed differently than traditional DVTs, often without the need for formal anticoagulation. Table 2 provides a useful overview of incidence, definition, and treatment recommendations.

Additional risks of thermal-based treatment modalities include the risk of inadvertent injury to surrounding structures from the thermal source. Inadequate tumescent analgesia or anatomic variations can result in intense procedure-related pain. Sural and saphenous nerve injuries are reported with an incidence of 0% to 30%. Although less than the nearly 40% incidence reported with open ligation and stripping, the symptoms can nonetheless be disturbing for both the patient and physician. Of special note, when performing thermal-based procedures for treatment of the SSV, the practitioner must be particularly mindful of the proximal course of the catheter. Anatomic differences may inadvertently place the thermal portion of

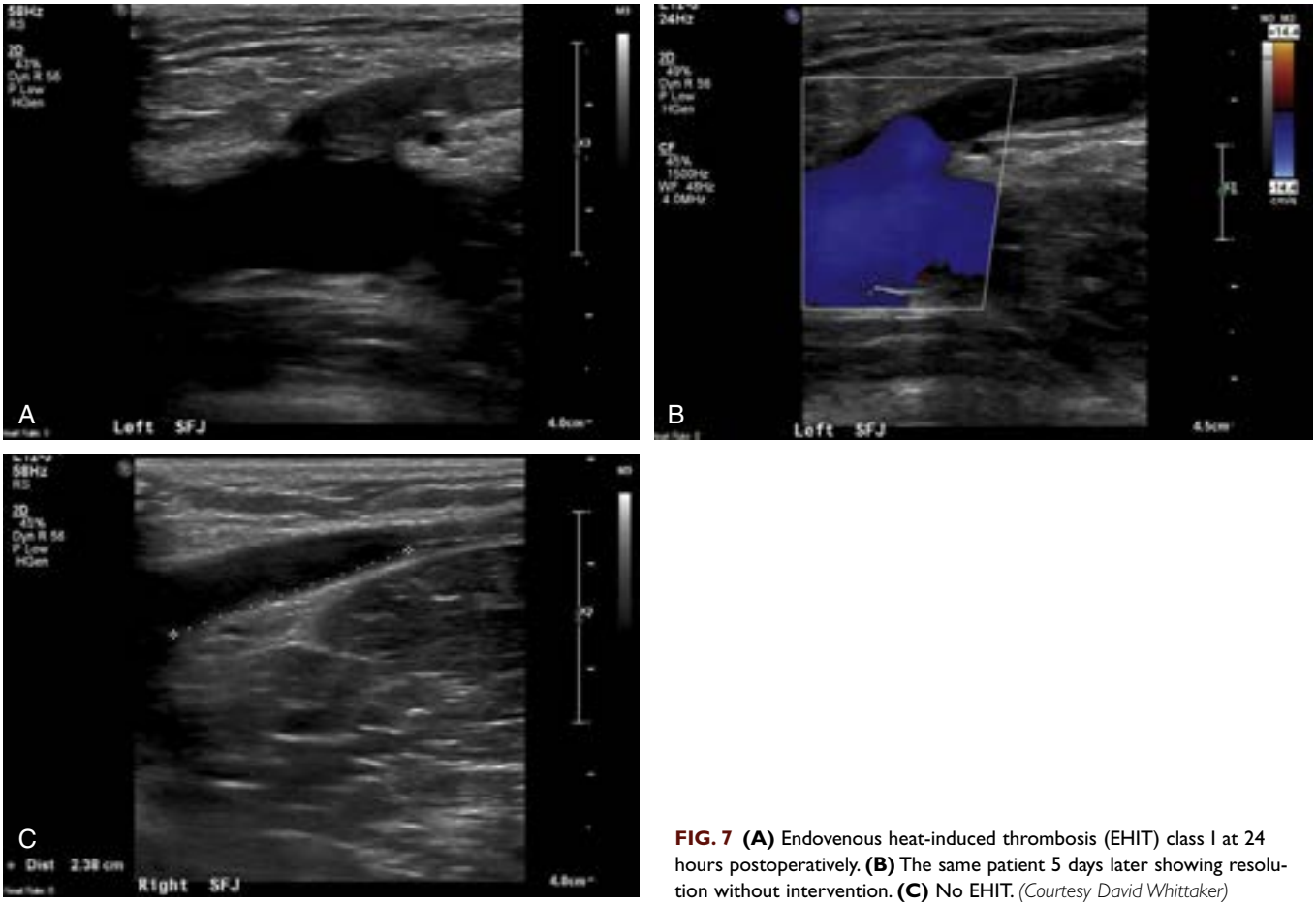


FIG. 7 **(A)** Endovenous heat-induced thrombosis (EHIT) class I at 24 hours postoperatively. **(B)** The same patient 5 days later showing resolution without intervention. **(C)** No EHIT. *(Courtesy David Whittaker)*

TABLE 2 Management Recommendations for the Classification and Treatment of Endothermal Heat-Induced Thrombosis

AVF EHIT Class	Definition	Treatment Recommendation	Strength of Recommendation and Level of Evidence**
I	Thrombus without propagation into deep vein a. Peripheral to superficial epigastric vein b. Central to superficial epigastric vein, up to and including the deep vein junction	No treatment or surveillance	2C
II	Thrombus propagation into the adjacent deep vein, but comprising <50% of the deep vein lumen	No treatment, weekly surveillance until thrombus resolution. In high-risk patients consider antiplatelet therapy vs. anticoagulation. Discontinue treatment following thrombus retraction or resolution	2C
III	Thrombus propagation into the adjacent deep vein but comprising >50% of the deep vein lumen	Therapeutic anticoagulation, weekly surveillance. Discontinue treatment following thrombus retraction or resolution	1B
IV	Occlusive deep vein thrombosis contiguous with the treated superficial vein	Treatment should be individualized, taking into account risks and benefits to patient. Reference may be made to CHEST guidelines for treatment of DVT.	1A

*1, Strong; 2, weak.
**A, High; B, moderate; C, low to very low.
AVF, American Venous Forum; *DVT,* deep venous thrombosis; *EHIT,* endothermal heat-induced thrombosis.
From Kabnick, Sadek M, Bjarnason H, et al. Classification and treatment of endothermal heat-induced thrombosis: Recommendations from the American Venous Forum and the Society for Vascular Surgery. *J Vasc Surg Venous Lymphat Disord.* 2021;9(1):6–22.

the catheter in close approximation to the common peroneal nerve as it exits laterally around the fibular head.

Other potential complications include access site hematoma, skin burns, hypersensitivity reactions, infections, ecchymosis, and postprocedural hyperpigmentation. The risks of linear hyperpigmentation along the course of the treated vein can be particularly disconcerting for patients and should be specifically addressed as a risk factor for all patients considering an endovenous treatment solution. This finding tends to be more common in superficially located veins of larger diameters. Finally, postprocedural symptoms of thrombophlebitis, tightness, and a cordlike pulling sensation are frequently observed by patients and are generally self-limiting.

Postprocedural compression regimens and activity recommendations vary by practice but generally consist of 48 hours of continuous compression to the treated region, using either compression stockings (20–30 mm Hg) or a compression wrap. An additional 5-day period of daytime compression is recommended. Patients are encouraged to resume normal activity immediately but to avoid heavy Valsalva-inducing or vigorous aerobic activity for the first 7 days following treatment.

For procedures in proximity to the SFJ or SPJ, a short duplex at 48 to 72 hours is essential to identify any potential DVT or EHIT formation.

Open Surgical Techniques

Although the vast majority of varicose and insufficient veins are amenable to minimally invasive techniques, there are circumstances in which open surgical management is preferred. Some examples include: (1) extremely tortuous varicosities not amenable to microfoam sclerotherapy, (2) superficial saphenous veins (<1 cm from the skin surface) in which an endovenous therapy might result in skin trauma or a bothersome palpable cord, and (3) aneurysm or extreme dilation of the target vein >2 to 2.5 cm.

Great Saphenous Vein High Ligation and Stripping

A benefit of this surgical approach is the definitive removal of the symptomatic veins with no residual segment at risk of recanalization. Additionally, with definitive control of the proximal vein, there is no risk of EHIT formation, and follow-up ultrasound studies are generally not required. In the long term, however, vein stripping seems to increase unwanted neovascularization, and recurrent venous arborization has been observed. Additionally, surgical incisions and physical vein removal may place the closely adherent saphenous or sural nerve at risk for injury, a possibility that should be considered and discussed with the patient.

Because of the extent of the dissection and the stripping process, this procedure is typically performed with anesthesia support to provide moderate or deep sedation.

The overall steps for GSV high ligation and stripping are as follows:

1. After the standard sterile prep of the affected limb in the supine position, an oblique 2- to 4-cm incision is made over the SFJ, as identified pre-procedurally by duplex ultrasonography.
2. The subcutaneous tissue and saphenous fascia are divided with electrocautery.
3. Placement of a self-retainer retractor will reveal the GSV underneath.

4. The GSV close to the junction to the common femoral vein (CFV) should be dissected.
5. Completely visualize the CFV proximally and distally to ensure that the anatomy is appreciated and that the CFV is not injured.
6. Place two vascular clamps on the GSV: 0.5 cm from the SFJ and the second one distally. Divide the vein with Metzenbaum scissors.
7. Double-ligate the saphenous vein stump with 2.0 silk suture. Imbrication may decrease neovascularity.
8. The stripper is inserted into the distal aspect of the divided GSV and advanced to the upper part of the calf. This can be guided and detected manually or with ultrasound guidance as dictated by body habitus.
9. Stab the skin just above the end of the stripper with a #11 blade.
10. Push the tip of the stripper outside the skin. Dissect the vein and ligate the distal end, and divide the vein after the proximal GSV is securely tied to the stripper with two heavy 2-0 silk ties.
11. The stripper and GSV are pulled out by an eversion technique. Use of the mushroom tip is not required and may increase soft-tissue trauma during the stripping process. The eversion process is adequate and minimizes soft-tissue trauma.
12. Place pressure on the GSV canal, and place a pressure wrap on the leg for hemostasis.
13. Close groin incisions in two layers: 2-0 Vicryl sutures for the fascia and 4-0 Monocryl for the subcutaneous skin.

Small Saphenous Vein Ligation and Stripping

A similar process can be used for the SSV with particular care to identify and avoid trauma to the sural nerve. It is recommended that the SSV only be stripped from the SPJ location to the mid-calf.

Ambulatory Phlebectomy

Superficial varicosities are often managed successfully by addressing the underlying truncal venous insufficiency. Eliminating reflux in the truncal veins decompresses the tributary branches, often resulting in dramatic resolution of varicose veins. In patients with large superficial varicose veins, however, some varicosities may remain enlarged despite seemingly adequate decompression. Occasionally, varicosities without underlying truncal reflux, which are not amenable to endovascular techniques, may need to be addressed surgically.

Phlebectomy can be performed at the time of truncal vein intervention or can be deferred pending the results of truncal decompression. If deferred, a 3- to 4-week period of observation is typically recommended before additional vein intervention. This period allows adequate time to evaluate if decompressed varicosities are going to regress to the extent that additional treatment is not required.

If the residual varicosities persist and are not amenable to directed microfoam sclerotherapy, ambulatory phlebectomy of the varicosities is recommended. This procedure can be accomplished in an outpatient ambulatory setting under local anesthesia.

The steps for ambulatory phlebectomy are as follows:

1. All targeted veins should be carefully marked with the patient standing and well-hydrated before the procedure (Figs. 8 and 9). It is often possible to plan strategic locations for the phlebectomy based on the preoperative marking. Careful attention to the branching nature and size variations of the tributaries can guide procedural treatment and minimize the number of necessary incisions.
2. After the standard sterile prep of the area to be treated, the marked regions are infiltrated with the same tumescent solution used for endothermal procedures (1000 mg 1% lidocaine, 20 cc 8.4% $NaHCO_3$ in 1000 cc normal saline). An 18-gauge access needle and roller pump expedites the tumescent process. In addition to providing adequate analgesia, the tumescence performs a degree of hydrodissection that makes the phlebectomy process more efficient.



FIG. 8 Marking of patient's leg before ambulatory phlebectomy. *(Courtesy David Whittaker.)*



FIG. 9 The same patient in Figure 8 now in the supine position to demonstrate the importance of marking in the standing position with the varicosities fully pressurized. *(Courtesy David Whittaker.)*

3. A small 2- to 3-mm incision is made with a #11 blade directly over the targeted vein. Even large varicosities can be delivered through small incisions.
4. A small vein hook is used to deliver the vein through the incision.
5. The vein is doubly clamped with small snaps and ligated. The snaps are left in place, and the vein is not phlebectomized.
6. This process is then repeated along the course of the target vein until the treatment area is adequately addressed.
7. All vein segments are then rapidly removed, and compression is held along the treated area (Fig. 10). This technique minimizes the overall discomfort and blood loss experienced by the patient.
8. Once hemostasis has been obtained with compression, the incisions are all closed with a single ⅛-inch Steri-Strip. The leg is wrapped in kerlix and ace-wraps.



FIG. 10 Controlled delivery, clamping, transection, and planned phlebectomy minimizes patient blood loss and pain during ambulatory phlebectomy procedures. *(Courtesy David Whittaker.)*



FIG. 11 Corona phlebectatica. *(From Uhl JF, Cornu-Thenard A, Carpentier PH, Antignani PL. Focus on corona phlebectatica: Diagnostic, significance and predictive value in chronic venous disorders.* Rev Vasc Med. *2013;1:38–42.)*

9. The patient is instructed to remove the wraps at 48 hours and switch to compression socks for 5 additional days.

Sclerotherapy

The cutaneous manifestations of venous hypertension include telangiectasias, reticular veins, and corona phlebectatica in addition to the residual sequelae of prolonged venous stasis changes such as lipdermatosclerosis and venous eczema (Fig. 11).

A logical care plan for patients with venous insufficiency and varicose veins often progresses from treatment of underlying truncal reflux to addressing superficial varicosities. Eventually treatment culminates with a discussion regarding therapy for cutaneous telangiectasias and reticular veins. Because these veins are often the initial presenting concern for many patients, it is sometimes frustrating for patients that despite a nearly completed course of truncal and varicose vein treatment, these cutaneous veins are still present. Because treatment for most of these cutaneous sequelae are not covered by standard insurance plans, it is extremely important to discuss telangiectasias and reticular veins during initial patient education. This allows patients to understand their potential financial burdens and helps in managing expectations.

Cutaneous laser techniques can be considered for matting and fine telangiectasias smaller than a 31-gauge needle bore. Discussion of these techniques is beyond the scope of this chapter. Veins that are at least the size of a 31-gauge needle can be considered for sclerotherapy. A variety of different injectable compounds are available, all of which are designed to induce endothelial injury and collapse the vein. Both hypertonic saline and glycerin work as osmotic agents; their use is largely of historic interest. The two most frequently used sclerosants are the detergent-based compounds polidocanol (Asclera 0.5% and 1%) and sodium tetradecyl sulfate (Sotradecol 1% and 3%). Both are approved for use in sclerotherapy, are relatively painless when administered, are minimally allergenic, and rarely result in ulceration, even with cutaneous extravasation. Table 3 provides useful dosing recommendations for sclerotherapy.

Tips for Sclerotherapy

- Document the absence of a cardiac murmur that could suggest a patent-foramen ovale (PFO). Transient TIAs and retinal symptoms have been described during sclerotherapy, particularly with physician-compounded foam using the Tessari method. Although usually self-resolving, these are believed to be related to small, transient microemboli through a right-to-left shunt via a PFO and can be very disturbing. Varithena's CO_2-based polidocanol foam has not been associated with these neurologic events, but it can be expensive to use on a regular basis for telangiectasias and reticular veins.
- Although a minor procedure, obtaining patient consent at the start of treatment is recommended.
- Position the patient as supine as possible during the treatment.
- Preload and label 1-cc TB syringes with 0.5 cc of treatment solution.
- Use a 27- to 31-gauge needle with each syringe, and do not reuse.
- 2 × 2 gauze pads soaked in isopropyl alcohol are used to gently cleanse the skin before treatment.
- Loupe magnification is helpful with a shallow angle of needle insertion.
- A test dose during the first treatment is recommended; the ability to manage an allergic response is important.
- After the test dose, proceed in a regional fashion. Use gentle pressure, and do not hesitate to restick to avoid extravasation.
- Do not exceed the maximum recommended treatment volume per procedure; patients typically require several treatments.
- If extravasation does occur, consider a similar 1-cc syringe to dilute the region with 0.2 cc of sterile saline.
- Small skin wheals and erythematous streaks are common and should not be alarming.
- Immediately compress the treated area with compression garments for 48 hours.
- For larger veins, consider a short interval follow-up in 48 to 72 hours for a trapped blood evaluation. If present, the tip of a 16-gauge needle can be used to make a small nick in the vein accompanied with gentle expression of any trapped thrombus to minimize the possibility of hyperpigmentation areas.
- Avoid treatment below the level of the malleoli.

Treatment Planning and Conundrums

Superficial venous disease and associated symptoms are often accompanied by additional comorbidities that may influence the clinical results. Patient education and a discussion of risks is important in managing expectations and optimizing outcomes. Common planning and treatment considerations are discussed in the following sections.

Unilateral Symptoms with Bilateral Pathology

A patient presenting with unilateral symptoms of venous insufficiency, pain, or varicosities, but with pathologic findings on bilateral lower extremities is best managed by focusing intervention on the symptomatic side only; the contralateral side can be followed for development of future symptoms. Superficial venous disease is not a life-threatening condition, and treatment is generally well-tolerated at all ages, so the concern that a patient may become physiologically unfit for treatment as a consequence of waiting is unfounded. Often a recommendation is made for compression therapies on the untreated

TABLE 3 Sclerotherapy Dosing Guidelines

Agent	Advantages	Adverse Reactions	Manufacturer	Available Formulation	0.5-cc Test Dose	Vessel Size	Concentration	Injection Volume	Max Dose
Polidocanol (Asclera)	FDA approved for intended use Little pain Rare ulceration	Allergic potential Site discoloration Pruritis Neovascularization (matting)	Merz	0.50%	Yes	<1 mm	0.50%	0.1 mL	10 ml of 0.5%/session
				1%	Yes	1–3 mm	1%	0.1–0.3 mL	10 ml of 1%/session
Sodium Tetradecyl Sulfate (Sotradecol)	FDA approved for intended use minimal pain	Allergic potential Site discoloration Requires dilution	Mylan	1%		<1 mm	0.1%–0.25%	0.2 mL	10 ml of 1%/session
						1–2 mm	0.25%–0.4%	0.3 mL	10 ml of 1%/session
						3 mm	0.50%	0.5 mL	10 ml of 1%/session
				3%		*Not for use with telangiectasias			

Data from Merz Prescribing Information. Available at: https://asclera.com/wp-content/uploads/2020/01/Asclera-Full-prescribing-Information-EM00497-04.pdf
Mylan Prescribing Information. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f1756c28-dcd2-4b49-be62-07ca20682018&audience=consumer
Courtesy David Whittaker.

side, although there are little data to support that it alters the natural course of disease.

Bilateral Symptoms with Unilateral Pathology

This presentation is frequently encountered in practice. Symptoms of pain, heaviness, burning, and pruritis often affect both lower extremities, but venous pathology may only be evident unilaterally. This should raise clinical suspicion for alternative etiologies of the patient's symptoms. Alternative disease processes such as congestive heart failure, renal disease, neurologic processes, radiating symptoms from musculoskeletal disorders, and medication effects may be the primary etiology. Failure to identify these possibilities before treatment can result in patient frustration. The patient's response or lack of response to a trial of compression can be a helpful indicator of the likely effectiveness of intervention. If compression does not help, procedures likely will not help.

Isolated Segmental Disease

The physician will often encounter segmental truncal disease of the saphenous systems that seem to correlate with a patient's signs and symptoms. Although there are limited trial data to guide recommendations, some small studies suggest that it is reasonable to consider treating only the pathologic segment to spare the remainder of the saphenous vein. This is particularly applicable to patients with only above-the-knee or below-the-knee segmental reflux in whom future use of venous conduit may be required.

Restless Legs Syndrome

Patients often inquire if treating their venous insufficiency will improve their symptoms of restless legs syndrome (RLS). There have been at least two published studies (see Suggested Readings) that provide some evidence to support that venous insufficiency may have a role in this syndrome. Although it is most likely a multifactorial disorder, addressing severe venous insufficiency may have a positive impact on RLS.

Tobacco Use, Coronary Artery Disease, and Peripheral Artery Disease

The saphenous veins can be important conduits for peripheral artery or coronary bypass procedures. Closure or removal of these vessels to treat underlying venous insufficiency eliminates these conduits as options for use in the future. In patients at high risk for atherosclerotic arterial pathology (active smoker, poorly controlled diabetes, severely hyperlipidemia, history of peripheral artery disease or coronary artery disease), treatment of venous insufficiency must be considered in a different light.

Dilated and serpiginous saphenous veins would be inadequate for most bypass procedures and can be safely ablated. A mildly refluxing, normal diameter (3.5–5 mm) truncal vein that is causing minimal symptoms in a patient at high risk for arterial disease should probably not be treated. Alternatively, the risk versus benefit in a patient with C6 disease and a large 6-mm GSV that pressurizes the area of ulceration would clearly favor treatment of the refluxing vein. There are no known studies that demonstrate the frequency of bypass procedures that are adversely impacted from previous venous treatment procedures.

Simultaneous Versus Staged Procedures

Many patients suffer from multiple levels of venous reflux, many or all of which may be contributing to their clinical signs and symptoms. By starting with the most significant (usually central) level of disease and sequentially addressing smaller and more superficial contributors, the care plan for each patient can be optimized, yielding the best chance to relieve symptoms, while minimizing the performance of unnecessary procedures.

Although there is no studied recommendation of the optimal interval between planned procedures, allowing 48 to 72 hours between truncal reflux procedures results in enough recovery time that the second intervention has minimal impact on the activities of daily living of most patients.

A common question is how long to wait after truncal vein treatment to allow decompressed varicose veins to regress. Studies and reviews vary widely, and no clear recommendation can be made, but a general consensus is to wait 3 to 4 weeks before addressing superficial varicosities and telangiectasias. This should be sufficient time to reach a new baseline. Frequently, given enough time, the treatment and decompression of the underlying truncal venous insufficiency obviates the need for any additional treatment of the superficial varicosities.

Follow-up and Compression Recommendations

Patients undergoing a venous ablation procedure near the confluence of the superficial system with the deep venous system should undergo postprocedure duplex scanning within 48 to 72 hours to evaluate for the presence of EHIT or DVT.

Subsequent postprocedure follow-up is recommended at 6 weeks, 3 months, 6 months, and 12 months. Thereafter, follow-up is recommended for any new signs or symptoms of progressive disease. Although these recommendations vary significantly by location, it is important for the physician and patient to realize that venous disease is a continuous, generally progressive process that may require additional evaluation and treatment in the future.

Recommendations for postprocedure compression vary as well. A reasonable consensus for therapy is one week of 20- to 30-mm Hg graded compression stockings of sufficient length to incorporate the treated vein. Longer periods of compression beyond 1 week are only recommended in patients with components of postprocedure thrombophlebitis.

Postprocedure Thrombophlebitis

Successful endovenous therapies are dependent on an inflammatory response within the treated vein that eventually results in endothelial cell damage, vessel closure, and progressive fibrosis. This inflammatory reaction is pronounced in ~6% of treated patients who demonstrate signs and symptoms consistent with thrombophlebitis. This typically occurs 7 to 10 days postprocedure. Large-diameter veins >1 cm are particularly prone to this reaction. The process is typically self-limiting and managed with patient reassurance, 7 to 10 days of an over-the-counter NSAID dosed three times daily, continued compression for comfort, and gentle activity and stretching.

Future Technologies

The introduction of endovenous technologies has fundamentally changed the practice of venous care. Traditional surgical procedures have essentially been replaced by minimally invasive outpatient interventions.

On the horizon are three technologies of particular interest. The BlueLeaf (InterVene, Inc.) endovenous valve technology allows creation of a native tissue valve within the deep system, allowing in situ treatment of deep vein insufficiency. Results have been promising with excellent technical success and improved r-VCSS.

Steam-generating technology to produce thermal ablation (CermaVein, France) has been undergoing European trials with results equivalent to EVLT and RFA. The small diameter and flexible catheter make this technology amenable to use in both truncal and tributary veins. The simplicity of the catheter and equipment also results in cost savings.

High-intensity focused ultrasound has been used to treat both truncal reflux and superficial tributaries. Through high-speed three-dimensional focusing of ultrasound energy, targeted veins can be treated noninvasively. The latest version of the system, SONOVEIN S (Theraclion, France), completed clinical trials in Europe and received its CE marking for continued clinical evaluation and trials.

CONCLUSION

Venous disease is subtly complex. Although not lethal, it affects a large portion of the population and adversely affects QoL. Endovenous technologies, first introduced in the late 1990s, have transformed the management of venous disease. With current technology, treatment of even complicated venous pathology is often office based, with a low risk of complications and a rapid recovery. Thermal endovascular techniques have the longest track record and proven safety profile. Nonthermal techniques demonstrate similar efficacy to thermal counterparts. Sclerotherapy is especially effective in treatment of cutaneous veins and continues to demonstrate versatility with larger veins. Surgical techniques, although less common, continue to have an important role in the therapeutic armamentarium. Choice of therapeutic modality is determined by patient presentation, patient preference, operator expertise, and clinical setting. Venous therapeutics continues to be an active field of research, and evolving technologies continue to transform clinical practice. A systematic and individualized approach to treatment is necessary to optimize results and manage patient expectations.

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Lymphedema

Joani Christensen, MD, George Kokosis, MD, Halley Darrach, MD, and Justin M. Sacks, MD, MBA

Lymphedema is a chronic and generally progressive debilitating disease of the lymphatic system that results from failure of the lymphatic transport capacity to overcome the lymphatic load. Impairment of lymphatic transport leads to interstitial accumulation of a protein-rich fluid that includes excess water, plasma proteins, extravascular blood cells, and cell products that are normally transported by the lymphatic system from the interstitium into the circulation. In addition, the peripheral lymphatic vessels play a significant role in the immune system and serve to transport leukocytes, function in antigen presentation, and regulate the immune response.

Progressively, lymphatic impairment leads to dilation of the remaining functional lymphatic vessels, failure of valves to maintain unidirectional flow, and eventually stasis. Accumulation of the macromolecules in lymphatic fluid increases the osmotic pressure and leads to an influx of excess water into the interstitium. Persistent stasis and abnormal fluid accumulation lead to an inflammatory process mediated mainly by $CD4^+$ cells that, over time, result in progressive fibrosis of the lymphatic vessels, obliterating the lumen as well as eliminating the lymphatic pump potential. Lymphedema ensues when the capacity cannot overcome the load of lymphatic fluid. Additionally, fibroadipose tissue deposition is promoted in the subcutaneous and subfascial tissues. This progressive underlying pathophysiologic process is reflected by initially soft, pitting edema, followed by induration, hypertrophy, acanthosis, hyperkeratosis, and skin breakdown. Infectious complications follow, with recurrent episodes of cellulitis and lymphangitis. In its rarest form, this process can lead to malignancy, with highly aggressive lymphangiosarcoma (Stewart-Treves syndrome) being a known clinical entity associated with chronic lymphedema. There are several staging systems that have been developed for lymphedema, the most commonly used being the International Society of Lymphology staging system (Box 1).

ETIOLOGY

Lymphedema can be primary or secondary. Primary lymphedema results from a developmental abnormality, requires lack of an offending injury, and frequently is associated with a positive family history. This form of lymphedema may present at birth, during adolescence, or later in life. Primary lymphedema can further be subdivided into congenital lymphedema, lymphedema praecox, and lymphedema tarda. *Congenital lymphedema* or *Milroy disease* (10%–25% of primary lymphedema) is seen within the first 2 years of life. It

BOX 1 Lymphedema Staging

Stage 0: Latent or Subclinical

- Impaired lymphatic transport
- No evident edema, subtle changes in tissue fluid/composition
- Changes in subjective symptoms
- May last months or years before progression

Stage 1: Spontaneously Reversible

- Early accumulation of protein-rich fluid
- Pitting edema
- Subsides with elevation

Stage 2: Spontaneously Irreversible

- Accumulation of protein-rich fluid
- Pitting edema may progress to nonpitting as excess fat and fibrosis develop
- Does not resolve with elevation alone

Stage 3: Lymphostatic Elephantiasis

- Nonpitting
- Significant fibrosis
- Trophic skin changes

Data from the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. *Lymphology*. 2013;46:1–11.

usually affects females (2:1 ratio to males), is bilateral, and involves the lower extremities. It often is not progressive and may improve spontaneously with time. The associated gene is *FLT4,* and inheritance is autosomal dominant. *Lymphedema praecox* or *Meige disease* (65%–85% of primary lymphedema) is seen before the age of 35, typically at puberty. It predominantly affects females (4:1 ratio to males), is unilateral, and involves the lower extremities. The associated gene is *FOXC2*. *Lymphedema tarda* occurs spontaneously after the age of 35 and is the rarest of all primary forms. Many mutations in the VEGFC/VEGFR3 pathway have been implicated in lymphedema.

Secondary lymphedema is an acquired failure of the lymphatic system. Inciting events can be a disease, trauma, radiation, or iatrogenic causes. Worldwide, the most common cause is the infection lymphatic filariasis by the microfilaria *Wuchereria bancrofti,* most commonly transmitted by various mosquito vectors, an entity that affects an estimated 300 million people in developing countries. Adult filarial worms reside in and obstruct lymphatic channels, causing irreversible scarring and fibrosis and often massive edema. In developed countries, most of the cases of secondary lymphedema are related to cancer therapy. In the United States, the most common cause is secondary to treatment of breast cancer. From 20% to 50% of patients undergoing axillary lymph node dissection will go on to have secondary lymphedema. The advent of sentinel lymph node biopsy reduced the prevalence of this disease to 5% to 7%. Adjuvant radiation therapy used for the local treatment of nodal disease can lead to upper or lower extremity lymphedema. Other factors such as trauma, infection, and obesity contribute to secondary lymphedema. Obesity alone can lead to lymphatic dysfunction ("obesity-induced lymphedema"). Obesity-induced lymphedema occurs with increasing frequency above a BMI of 40, with the primary treatment being weight loss.

DIAGNOSIS

The workup for lymphedema starts with a thorough history and physical examination (Box 2). The patients complain of swelling, heaviness, tightness, decreased ability to perform activity, and decreased quality of life. Other causes of edema must be ruled out first, mainly venous insufficiency, deep vein thrombosis, and cardiac, renal, and hepatic failure.

Physical examination maneuvers that can aid with the diagnosis of lymphedema are limb circumference and volume measurement. Limb circumference can be measured at defined anatomic locations—for example, 5 cm above and below the olecranon. Differences of 2 cm when compared with the contralateral limb can be diagnostic; however, their utility is limited by interrater variability and in patients with high body mass index. Volume measurements can be performed with water displacement, with volume differences of 200 mL or 10% considered diagnostic. Stemmer's sign, which is the inability to pinch skin of the dorsal hand or foot at the base of the second digit, is also frequently used to assess for lymphedema. Quality of edema, pitting or nonpitting, is also noted. Bioimpedance spectroscopy measures electrical resistance in tissue to compare fluid content and is used as an additional objective measure of lymphedema.

BOX 2 Diagnostic Workup for Lymphedema

- Thorough history and physical examination
- Rule out causes of edema (basic laboratory tests for renal and liver function)
- Infectious disease workup (in patients with travel history or exposure)
- Lymphatic imaging (lymphoscintigraphy, magnetic resonance lymphatic mapping, indocyanine green imaging)

Imaging studies are an important aid not only in diagnosis but also in planning of surgical procedures. Lymphoscintigraphy uses radionuclide technetium (^{99m}Tc) to assess drainage of the lymphatic basin. Additionally the transport index can be calculated through this study to measure the severity of the disease. Indocyanine green (ICG) near-infrared lymphangiography has proven useful in diagnosis and planning of lymphedema treatment. In an off-label use of ICG, injection in the web space of the extremity digits can help visualize the lymphatic channels and diagnose disruption of lymphatic flow, tortuous abnormal lymphatics, and dermal backflow (diffuse leakage of dye into the interstitium). It is important to note that the limitation on depth of visibility is about 1.5 cm with this modality. Magnetic resonance lymphangiography has gained popularity in assessment of the lymphatic system, as well as the surrounding soft tissue changes and venous anatomy. Intravenous injection of ferumoxytol is used to isolate the contrast enhancement of the venous system to aid with direct visualization of the lymphatic system. High-frequency ultrasound has also been used for intraoperative identification of lymphatic channels. These previously mentioned imaging modalities can help with operative planning and lymphatic vessel anastomosis when the decision is made to use microsurgical techniques.

CONSERVATIVE MANAGEMENT

Conservative therapies are usually used at early stages of lymphedema when fluid accumulation is predominant to prevent development of the cascade of further edema, inflammation, and fibrosis. Conservative management can be burdensome and time-consuming, and the main reason for failure is the need of lifelong treatment and thus noncompliance. It is important to discuss compliance with patients upfront, stressing that individual investment and long-term compliance are central to managing this chronic, lifelong condition. Conservative management includes lifestyle changes, pharmacologic treatments, compressive and decongestive therapy, laser therapy, and, more recently, advancements such as stem cell and growth factor or gene therapy. Additionally, a multidisciplinary team including a physiotherapist, an occupational therapist, and a social worker, as well as psychosocial support can be key to success of conservative modalities.

Lifestyle changes include daily hygiene and skin care to reduce skin breakdown and infection. Weight loss and aerobic exercise have been proven to help decrease the severity of lymphedema in large clinical studies.

Pharmacologic treatments are an area of study in lymphedema. If infection ensues, antibiotics are valuable in immediate treatment. Diuretics have been used historically; however, they are useful only in the case of comorbidities requiring their use. Diuretics may actually lead to further fibrosis and increased interstitial protein accumulation. The use of nutritional supplements such as sodium selenite or vitamin E with pentoxifylline have not demonstrated any significant benefit in patients with lymphedema. Given the importance of inflammation in the pathogenesis of lymphatic changes, antiinflammatory drugs have become targets for study. Ketoprofen inhibits 5-lipoxygenase, which has been shown to be upregulated in lymphedema, and improvements in skin thickness and histopathology have been shown in a pilot placebo-controlled human study, although volume was not reduced.

Compressive therapy with compression garments, multilayered inelastic bandaging, and pneumatic compression therapy are widely used. Compression garments are refitted as swelling decreases. These methods reduce volume of edema by approximately 30% to 45%. External sequential compressive devices also have been used with variable success. Basic range of motion exercises can be a useful strategy as a complement to limb compression and elevation. Contraindications to compression include arterial disease, deep vein thrombosis, and painful postphlebitic syndrome.

Decongestive therapy is a more time-intensive strategy. This modality involves manual lymphatic drainage through massage and

use of compressive garments and intermittent pneumatic pumps. The combination of these therapies has been shown to be more beneficial than each individual approach of decongestive therapy. Additional nonsurgical modalities have been explored in recent years. Low-level laser therapy stimulates tissue changes through nonthermal mechanisms. Autologous bone marrow–derived stem cells injected in the lymphedematous extremities resulted in significant volume reductions reported in recent studies. Growth factors (vascular endothelial growth factor [VEGF]) and gene therapy with adenoviral vectors have been tested in animal models, with promising results in decreasing swelling and increasing lymphangiogenesis.

SURGICAL TREATMENT

Surgical approaches to lymphedema had historically been used as a last resort in refractory cases; however, advances in microsurgical techniques have made surgery useful even in early stages of the disease. There are two main categories of surgical approach to lymphedema: physiologic procedures and debulking or reductive procedures. Physiologic procedures are usually indicated in early stages of lymphedema to restore lymphatic continuity and improve the anterograde flow of lymphatic fluid. In general, these procedures may show less volume reduction than reductive surgery, but they may lead to a greater decrease in need for conservative measures as underlying dysfunction is targeted. Debulking or reductive procedures are more useful in later stages to remove fibro-fatty tissue. These can lead to a larger volume reduction, but underlying dysfunction generally persists, and conservative measures will remain critical postoperatively.

Physiologic Procedures

Advances in technology that led to developing microscopes with higher magnification and instruments to support these "super-microsurgical" approaches was paramount in the evolution of physiologic procedures. Lymphovenous bypass (LVB) and vascularized lymph node transplant (VLNT) have been shown to be effective treatment options in early stages of lymphedema.

LVB

This procedure was introduced in 1953 by Sherman and colleagues. Subdermal lymphatic vessels are anastomosed to adjacent venules most often using ICG near-infrared lymphangiography or high-frequency ultrasound as a guide (Box 3). This creates an artificial shunt to drain lymphedematous fluid into the main circulation and thus improve lymphatic flow and drainage. ICG near-infrared lymphangiography can be performed before surgical planning to help determine patient eligibility for LVB.

BOX 3 Lymphovenous Bypass

1. Begin with lymphatic lymphangiography.
2. Inject 0.01 to 0.02 mL of indocyanine green into the web spaces in the extremity.
3. Visualize fluorescent images and mark visible lymphatic pathways and incision sites.
4. Inject local anesthetic with epinephrine.
5. Inject 0.1 to 0.2 mL of Lymphazurin into the web spaces in the extremity.
6. Take subdermal postobstruction dissection down to venous and lymphatic channels.
7. Use microsurgical connection to reestablish lymph flow with end-to-end anastomoses. End-to-side anastomoses can be used when veins are larger than the lymphatic channel.
8. Confirm that shunts are patent by observing passage of Lymphazurin into the vein.
9. Evaluate postoperative flow and imaging studies.

Chang et al. reported a series of 100 patients undergoing LVB, resulting in improvement of symptoms in 96% of patients and improvement in volume differential in 74% of patients. Volume differential was reduced by 61% at 12 months after surgery for patients with disease stage 1 and 2 and overall by 42%. Whereas this previous study focused more on upper extremity lymphedema, Campisi et al. have reported their experience with more than 2600 patients treated for both upper and lower extremity lymphedema for more than 40 years using LVB or interposition vein-grafted shunts for LVB that resulted in reduction of excess volume of more than 84%, with an average follow-up of 10 years or more. There are, however, articles in the literature reporting variable results in symptomatic and volume improvement, and part of this discrepancy has to do with the lack of validated questionnaires or standardized measurements, respectively, as well as lack of consistent long-term follow up. Importantly, this technique relies on available adequate lymphatics available for bypass and lack of fibrosis overall for volume reduction.

LVB has also been used prophylactically in patients undergoing lymph node dissection. This has been described by the terms immediate lymphatic reconstruction (IRL) and Lymphatic Microsurgical Preventive Healing Approach (LYMPHA), with IRL the preferred terminology. Boccardo et al. reported their experience with 4-year follow up in 74 patients treated with IRL at the same time as axillary lymph node dissection (ALND). Lymphedema developed in only 4%, which compares favorably to the reported prevalence of 13% to 65%. Recent, longer term follow-up, up to 5 years, in a propensity matched cohort of patients undergoing IRL at the time of ALND for breast cancer compared with ALND alone reported a significantly lower rate of lymphedema, 16.1%, compared with 28.6%.

VLNT

VLNT was first demonstrated in rats by Shesol in 1979 and used for a human patient by Clodius in 1982. This procedure harvests healthy fat tissue, lymph nodes, and lymphoid tissue and transfers these into the affected site (Box 4). Two mechanisms have been proposed for the effectiveness of VLNT. The first is the lymphatic "wick," the bridge of proximal and distal lymphatic vessels in the recipient site and a process of lymphangiogenesis stimulated by growth factors produced by the lymph nodes (VEGF) and antifibrotic interleukin-10. The second mechanism is the lymphatic "pump," which stems from lymphovenous communication within the lymph nodes of the transferred flap. Donor sites include the supraclavicular area, submental, lateral thoracic, the groin or superficial lower abdomen, mesenteric, and the omentum. Chang et al. have thoroughly discussed the supraclavicular lymph nodes found inferiorly within the posterior triangle of

BOX 4 Vascularized Groin Lymph Node Transplant

Donor Site

1. Palpate femoral pulse and design elliptical skin paddle lateral to pulse, inferior and parallel to the inguinal ligament.
2. Incise skin superiorly.
3. Dissect from distal to proximal, use fascia of sartorius muscle as deep plane.
4. Harvest the superficial circumflex iliac vessels, lymph nodes, and surrounding fatty tissue.

Recipient Site

1. Make a transverse incision on the recipient site (e.g., wrist).
2. Transfer flap onto the recipient site.
3. Perform microvascular anastomosis to the radial artery and cephalic vein.
4. Consider need for extra coverage of the flap with a split-thickness skin graft.
5. Use a skin paddle for monitoring.

the neck in the bundle of fat between omohyoid and anterior scalene muscles. The fat is supplied by the underlying transverse cervical vessels. The nodes are usually harvested from the contralateral side to avoid any further disruption of the lymphatic flow. On the left side, the surgeon should avoid the thoracic duct during dissection, although large lymphatic leaks have also been reported with harvest from the right side. The groin lymph nodes are another common donor site. It offers the advantage of a concealed scar and the use of a large skin paddle when needed. Preoperative magnetic resonance angiography has been used to identify lymph nodes, and Doppler imaging can confirm the location of the superficial circumflex vessels, which serve as the vascular pedicle. Care must be taken not to dissect further caudally from the inguinal ligament or deep from the muscular aponeurosis, or medial to the femoral bundle, which risks damaging the lymphatic drainage to the lower limb. The benefit of using the groin flap is the opportunity to simultaneously perform an abdominal-based autologous breast reconstruction and treat upper extremity lymphedema. However, other authors suggest staging those two approaches and to perform the groin lymph node transplantation only after the autologous breast reconstruction has been deemed successful; this way, the thoracodorsal vessels are no longer needed for any potential salvage procedure (e.g., latissimus dorsi flap). However, small branches of the thoracodorsal system are often of adequate caliber and match for an anastomosis to the flap pedicle, preserving the latissimus option. Others prefer maintaining the lymph node packet attached to the larger deep inferior epigastric perforator (DIEP) flap, confirming perfusion intraoperatively, and performing a single set of anastomoses to the internal mammary vessels to provider perfusion to the breast flap as well as the lymph node flap.

Dayan et al. have suggested performing reverse mapping of the lymphatic system to harvest only the expendable lymph nodes and to preserve those that drain the extremities, reducing donor site morbidity. Mapping of the lymphatic drainage is done by using technetium injected into the web spaces of the hand or foot and identifying the nodes using a gamma probe. Lymph nodes that drain the trunk targeted for the flap are mapped using ICG near-infrared lymphangiography. In their study of 35 patients treated with VLNT and reverse lymphatic mapping, they had no donor site complications.

Another donor site that has gained popularity the last few years is the free vascularized omental lymph node transplant (VOLT). This is based off the right gastroepiploic vessels most commonly and can be harvested either through an approximately 8-cm upper midline laparotomy or via a minimally invasive laparoscopic approach. The remainder of the omentum is left behind to minimize the chances of donor site lymphatic congestion. The intraabdominal component of this approach does have associated risks, such as hernia development, bowel perforation, and pancreatitis. Nguyen et al. reported their outcomes of 42 patients treated with VOLT and followed up for an average of 14 months, resulting in subjective improvement in 83% and mean volumetric improvement in 22%. The omental flap also has the distinct advantage of being able to generate two separate lymph node flaps, part based on the right gastroepiploic and part based on the left gastroepiploic. These can be transplanted to two different locations on an extremity, for example, in the proximal and the distal/middle aspect in the case of significant edema to maximize the lymphatic flow through the extremity. Importantly, intraabdominal donor sites minimize the risk of donor site lymphedema, which is a concern with superficially located donor sites.

Overall the use of VLNT has been associated with encouraging outcomes. A systematic review of 18 studies in 305 patients undergoing VLNT revealed improvements in swelling (whether measured as limb circumference or volumetric difference) in 86% to 90% of patients with volume difference on average of 22% and no need for postoperative compression garment in about 50%. A recent meta-analysis of cancer treatment-related lymphedema revealed volume reduction in both upper extremity and lower extremity lymphedema, as well as reduction in episodes of cellulitis and demonstrated a greater reduction with non-intraabdominal donor sites.

Debulking Procedures

More advanced stages of lymphedema with significant fluid accumulation or established fibrosis (stages 3/4) require debulking procedures. There are multiple different approaches. Liposuction has been used in the treatment of lymphedema in the recent years , although more aggressive, older approaches such as the Charles procedure and the Sistrunk procedure.

Liposuction was first used for brachial lymphedema in 1987. Since then, the technique was refined in 1993 (Box 5). It is useful in addressing large adipose tissue deposits after fluid has been maximally removed using compression. It is safe and relatively fast and allows for immediate decrease in volume and pressure of the lymph fluid, decreasing the burden and thus promoting better lymphatic flow. It is performed under general anesthesia and using a tourniquet. It is usually indicated when the excess volume is greater than 600 mL. Contraindications include presence of more than pitting edema, metastatic disease, open wounds, coagulation disorders, and reluctance to wear compression garments after surgery. It is assumed that compression use will continue postoperatively as underlying lymphatic dysfunction remains, and a custom garment or low stretch bandaging is performed intraoperatively at the end of the procedure. Risks include lidocaine toxicity, thrombotic and fat emboli, hematoma, seroma, and contour irregularities. Carl et al., in a systematic review of all surgical approaches of lymphedema, analyzed the results of liposuction and found that liposuction achieved an average excess volume reduction (the percent decrease in additional volume of the lymphedematous extremity compared with the contralateral side) of 96.6%, with additional improved overall well-being.

The Charles procedure (described by Charles in 1912) is an aggressive approach including radical excision of skin and subcutaneous tissue down to muscle fascia or epimysium (Fig. 1 and Box 6). Excised skin is used for grafting on the fascia, or other donor sites can be used. The van der Walt modification allows for negative-pressure dressing, with grafting to be done in a delayed fashion. This approach is indicated for severe cases and carries a high risk of complications, including destruction of the remaining lymphatic vessels, infection, ulceration, hyperpigmentation, dermatitis, unstable scars, and a severely altered aesthetic outcome (excessive resection of leg tissues and exacerbated foot lymphedema-bottleneck deformity). The Sistrunk procedure (1918) is a planned, staged excision of the affected subcutaneous tissues. This technique has been modified over the last 80 years and involves burying dermal flaps within skin flaps (Box 7). Long-term results include a reduction of at least half of

BOX 5 Liposuction

1. Mark out the affected area and 2 cm beyond.
2. Choose port sites to effectively reach all areas, both proximally and distally.
3. Inject tumescent solution (1 L lactated Ringer's solution mixed with 1 mL ampule of epinephrine 1:1000 and 30 mL of 1% lidocaine) until blanching is achieved and a moderate amount of turgor is seen.
4. Wait 30 to 45 minutes.
5. Suction with a 4- to 6-mm cannula in a deep plane in all areas, followed by a 2- to 3-mm cannula in a more superficial plane for a smoother contour.
6. Close port sites with absorbable suture.
7. Apply sterile dressings and a pressure garment.
8. Advise the patient not to shower or remove the pressure garment for 72 hours, and encourage the patient to walk at least three times a day.
9. After 3 days, the patient can shower daily and may begin massaging the affected areas.
10. The pressure garment should be worn for 6 to 10 weeks.



FIG. 1 Lower extremity after the Charles procedure.

BOX 6 Charles Procedure

1. Mark the lymphedematous area both proximally and distally.
2. Make an incision both medially and laterally down to the muscle fascia.
3. Excise all tissue superficial to this plane.
4. Remove the skin of the affected area with a dermatome for a split-thickness graft or with a knife for a full-thickness graft. If a full-thickness graft, make sure to remove all fat from the skin.
5. Use this graft to cover the exposed area.
6. Apply petroleum gauze or other nonadherent dressing over the graft.
7. Apply a pressure dressing via a vacuum-assisted device, bolster, or cotton.
8. Splint the extremity in the proper anatomic position.
9. Remove dressing after 3 to 5 days for a split-thickness graft or after 7 to 12 days for a full-thickness graft.

BOX 7 Sistrunk Procedure

1. Mark out the affected area.
2. Plan to excise and debulk sufficient tissue, leaving dermal flaps to bury beneath the skin in the closure. A variation of this is carried out in the Thompson procedure, in which dermal flaps are buried beneath the muscle.
3. Close the incision over drains.
4. Allow 12 weeks to heal before the next serial excision.

the affected tissue in 75% of patients. The Sistrunk procedure is safe, reliable, and predictable. Complications include nerve damage in the affected area, epidermolysis secondary to poor blood supply, wound dehiscence, and infection.

Combination of Procedures

Lymphedema, regardless of the stage, is a complex disease process that requires multiple different modalities. Decongestive therapy and compression are important and are almost always necessary, either alone

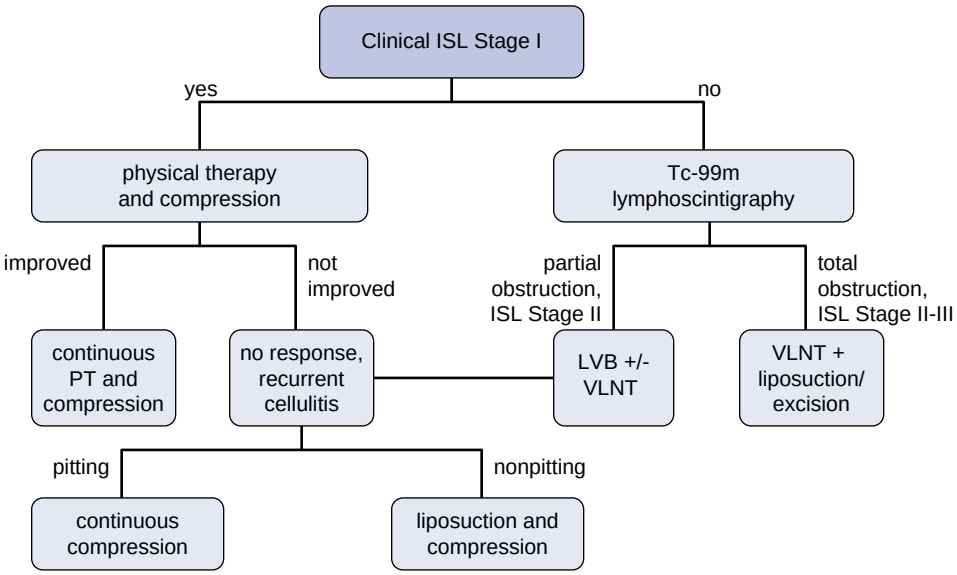


FIG. 2 Lymphedema treatment algorithm. *ISL,* International Society of Lymphology; *LVB,* lymphovenous bypass; *PT,* physical therapy; *VLNT,* vascularized lymph node transplant.

or in combination with surgical procedures. More recently, combining different surgical approaches has become more common. Carl et al. in their systematic review of the surgical treatment of lymphedema identified multiple different procedure combinations, including liposuction with VLNT, VLNT with Charles procedure, VLNT with LVB, and more in a total of eight studies involving 135 patients with variable results. Four of these studies used VLNT and identified the need for additional liposuction or radical reduction in 31.6% to adequately remove lymphedematous and fibrotic tissue. Likewise, in two LVB studies, an average of 16% of patients required liposuction after the LVB to achieve optimal reduction. The authors of this systematic review therefore suggest a thorough algorithm to approach lymphedema, although with increasing management options, high quality evidence with trials comparing techniques is lacking (Fig. 2).

SUMMARY

Lymphedema is a challenging clinical problem that produces significant morbidity in a large population worldwide. All treatment modalities include long-term conservative measures along with support from a multidisciplinary team. Surgical procedures can be a useful adjunct to treatment according to the disease progression; physiologic procedures appear to be more successful in earlier stages of the disease, and debulking procedures are used only for later stages. Regardless of the treatment strategy chosen, patient commitment and lifestyle modifications are of paramount importance to achieving improvement in symptoms and quality of life.

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Lower Extremity Amputation

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Lower extremity amputation, whether caused by peripheral arterial disease or trauma, remains a common method of treatment for many surgeons, including vascular, orthopedic, podiatric, and general surgeons. There are an estimated 150,000 major amputations performed in the United States yearly. Peripheral arterial disease along with diabetes contribute to greater than half of all lower extremity amputations. Although advancements in endovascular limb salvage have led to a significant decrease in the amount of lower extremity amputations caused by arterial disease, they are still an important procedure for the vascular surgeon. Critical limb ischemia first-line treatments include endovascular and open surgical interventions with the goal to avoid tissue loss. However, often tissue loss is beyond salvage, the patient has exhausted all methods of revascularization, or the patient is not a candidate for revascularization, and amputation should be considered for these cases. In these cases, amputation can provide definitive treatment, and some patients may even have an immediate increased quality of life.

Poor selection of the amputation level or suboptimal postoperative care can lead to significant physical and psychological impairment for patients and a significant financial burden for healthcare systems and society through complications, readmissions, and the need for reamputation. As treating physicians, it is important not to think of these procedures as a failure of prior revascularization strategies but instead as another therapeutic option in a person's global rehabilitation. The goals of amputation should be to preserve life and improve quality of life through relief of pain, prevention of infection, return to a functional life, and decreased hospitalizations. These are the same goals used when treating patients with peripheral arterial disease via endovascular interventions or bypass surgery.

Amputation is often performed in the nonemergent setting to remove gangrenous tissue, which may lead to infection and sepsis, or in patients with pain who have no options for revascularization. This is preferred of course to the urgent need for amputation when a patient becomes septic.

INDICATIONS

The primary indications for major amputations are the preservation of life through prevention of ascending infection and tissue loss, relief of ischemic pain, or removal of a neurologically nonfunctioning foot that may lead to decreased function and increased risk of wound development. In patients with chronic wounds or pain, amputation is considered when their limb is deemed nonsalvageable as a result of critical limb ischemia. This can be done using a multidisciplinary approach involving the wound care team, podiatry team, and the vascular surgeon. Salvageability is determined by the amount of remaining healthy tissue as well as options for the alleviation of pain. In this patient population, one should consider whether the patient is nonambulatory or has a nonfunctioning limb that will not recover, even with successful revascularization.

In the acute setting we often encounter patients with irreversible ischemia or those that require urgent amputation as a method of source control in life-threatening ascending infection caused by a lower extremity wound. In a medically unstable patient, one can consider either a guillotine or cryoamputation, which will be discussed later in this chapter. Before patients undergo amputation, patient optimization should be considered such as antibiotics, glucose control, and so on. In patients with skin deterioration caused by cellulitis, treatment with antibiotics initially may improve skin quality for a future amputation flap.

AMPUTATION TYPES

Amputations of the lower extremities can be classified as either minor or major. A minor amputation of the lower extremity can be thought of as one confined to the foot or toes in which patients will likely be able to ambulate without the use of a prosthetic. This includes any digit amputation or transmetatarsal amputation as well as more complex amputations of the foot such as Lisfranc, Chopart, or Syme amputations. Major amputations consist of any amputation proximal to the ankle, including transtibial, transfemoral, through-the-knee, and hip disarticulation amputations. Major amputations will require a prosthetic for future ambulation.

Minor Amputations

A simple digital amputation generally is indicated in the setting of a gangrenous process or chronic osteomyelitis. This disease process should be confined to the distal phalanx, and a ray amputation may be indicated in the setting of a more proximal problem. In general, patients will tolerate the loss of a toe very well with the exception of the great toe, which is responsible for propulsion during ambulation. The most tolerable digital amputation involves the third digit of the foot.

A ray amputation is a more involved procedure resulting in removal of the entire phalanx. It is performed when the disease process is more proximal in the toe, with involvement of the web space or metatarsal head. When faced with the need to perform a ray amputation of the great toe or fifth toe, it is necessary to extend the incision over the medial or lateral border of the foot, respectively. Transmetatarsal amputations are reserved for scenarios in which the infectious process or tissue loss is more extensive into the forefoot or when multiple toes are involved, and leaving a patient with one or two toes is not beneficial. The infectious process or tissue loss should be confined to the distal aspects of the forefoot, however, because success of this amputation relies on the ability to create a viable posterior flap.

The Syme amputation is a less common amputation of the foot in today's practice. It was designed to preserve as much limb length as feasible while also leaving the growth plates intact. An added benefit of this approach is the ability to ambulate without a prosthesis. Typically, this procedure has been used in the setting of severe foot trauma and is relatively contraindicated in patients with neurotrophic ulcers or ischemic vascular disease.

The Chopart amputation is also referred to as a *midtarsal joint amputation* and offers some advantages over the Syme amputation. This procedure is performed at the level of the calcaneocuboidtalonavicular bones and preserves the talus and calcaneus, resulting in less limb shortening. Unfortunately, this also places these amputees at risk for future problems resulting from equinus deformities and a limited weight-bearing surface leading to continued breakdown.

Major Amputations

Transtibial amputation, also referred to as a below-the-knee amputation (BKA), is one of the most common major lower extremity amputations performed and offers improved rehabilitation potential secondary to knee joint preservation and prosthetic options. This is typically performed with a posterior flap, although some suggest that a skewflap leads to better prothesis fitting (Fig. 1). In general, this is the preferred level of amputation if the patient is relatively healthy and has good potential for ambulation with a prosthetic.



FIG. 1 KIWI rigid removable dressing.

Transfemoral amputation, also referred to as an above-the-knee amputation (AKA), usually is reserved for patients who cannot have a transtibial amputation because of tissue loss, muscle ischemia, or poor rehabilitation potential based on their general medical condition.

Through-the-knee amputations are rarely performed as a definitive amputation in patients but are sometimes used as a primary amputation level in patients who require emergent intervention for an ascending infection. These are often converted to transfemoral amputations once the infection has cleared.

Hip disarticulation amputations are reserved for patients with proximal thigh ischemia or trauma and carry a high risk of mortality and morbidity without options for prosthetic rehabilitation. Few surgeons have the experience and expertise to perform this amputation safely and successfully.

SELECTION OF AMPUTATION

The most critical decision regarding lower extremity amputation is the selection of the appropriate level. The ideal amputation level will heal without the need for readmission and reoperation while preserving the best options for rehabilitation for the individual patient. In general, the higher the level of amputation, the greater the chance of healing without complication but also the greater the amount of energy required to achieve ambulation with a prosthetic. The energy expenditure at various levels of amputation can vary considerably among patients. In general, there is minimal increase in energy expenditure to ambulate with any of the minor amputations discussed earlier. However, when comparing major amputations, energy expenditure greatly varies. AKA requires around 50% more energy expenditure for ambulation than BKA. There is also a significant decrease in the walking speed in those with an AKA compared with those with a BKA. The increase in energy can be overcome easily in young, motivated patients, but in the older patient population with multiple chronic comorbidities, ambulation with a prosthetic will not be achieved, even with a BKA. Because of this, in general, traumatic

amputees have a more favorable outcome than those who lost their limb to vascular disease as these populations vary significantly.

Overall clinical assessment of the likelihood of an amputation to heal is achieved through a combination of physical examination findings and some type of diagnostic imaging study. Usually, the presence of a palpable pulse proximal to the level of amputation is a reliable indicator that the site will heal. Assessment of the soft tissue integrity, joint mobility, and muscle strength should be performed as part of the physical assessment. Significant calf soft tissue loss or infection, knee contractures, or muscle wasting would indicate a high likelihood that a transtibial (BKA) amputation would be at risk of failing or of limited value because of an inability to ambulate. Several noninvasive tests have been used to help determine the amount of perfusion and the potential to heal at a specific level and must be interpreted in the setting of the overall health and status of the patient and the surgeon's experience. One of the most widely used diagnostic adjuncts in patients with peripheral arterial disease is lower extremity Doppler imaging in conjunction with ultrasound imaging and evaluating the ankle-brachial index. When used appropriately, it can provide the clinician with both an anatomic and a physiologic assessment of the limb. These studies can be unreliable in the diabetic population who suffer from very calcified vessels deeming them noncompressible on duplex scanning. In these situations, the clinician still can obtain usable information usually in the form of toe pressures or waveforms because these vessels typically are spared from noncompressibility, even in the worst diabetic patients. It has been suggested that absolute pressures of 60 mm Hg or higher at the level of the ankle can accurately predict the healing potential of a BKA in more than 50% of cases. Another commonly used adjunct is the transcutaneous partial pressure of oxygen ($TcPO_2$) measurement. Unfortunately, this modality may not be available to all clinicians. In general, values of 40 mm Hg or higher are strong predictors of wound healing, whereas values of 20 mm Hg or lower almost universally predict failure of healing. To date, there is no measurement that can reliably predict healing 100% of the time. Computed tomography, magnetic resonance imaging, and invasive angiography may all be of help in assessing for underlying infection, vascular supply, and potential for intervention to improve perfusion.

In addition to assessment of the amputation level, significant time and effort should be spent preoperatively to prepare the patient physically and mentally for the procedure and for life after amputation. If possible, nutritional assessment and support should be initiated before amputation to help with healing of wounds and ability to participate in rehabilitation. Involvement of the patient's family in discussions with physical therapy, occupational therapy and rehabilitation specialists, prosthetists, and current amputees can increase the chance of acceptance, understanding, and support for the patient's recovery. Information on local and national support groups for amputees should be made available to help with the transition to amputee living and as a resource for future questions. By starting this dialogue before surgery, many patients will be less fearful and more motivated for their postoperative management.

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

Patients who undergo amputations have risks for postoperative complications similar to those of other patients who undergo major surgery. Patients who undergo a major lower extremity amputation carry estimated mortality risks of 33.7%, 51.5%, 53%, 64.4%, and 80% at 1, 2, 3, 5 and 10 years, respectively. Overall, 30-day mortality after a major lower extremity amputation ranges from 2.3% in lower-risk groups to 17.5% in higher-risk groups. When comparing AKA with BKA, 30-day postoperative compilations are lower in the AKA group, however, 30-day mortality was increased in those undergoing AKA. Independent risk factors for mortality are similar to those associated with a perioperative cardiac event as this is one of the more common causes of death. These risk factors include a history of congestive heart failure, cerebrovascular disease, high-risk surgery, and a creatinine level greater than 2 mg/dL. Beyond these factors, a history of myocardial infarction, postoperative respiratory complications, hemodialysis, preoperative pneumonia, American Society of Anesthesiologists (ASA) class IV or greater, and preoperative total dependence all carry significant risk for early perioperative mortality. It should be noted that diabetes mellitus itself does not confer a higher perioperative mortality risk but does contribute significantly to long-term mortality. Postoperative deep venous thrombosis (DVT), wound infection, and trauma to the amputation site secondary to falls are a few of the more common complications after major lower extremity amputation. For this reason, it is imperative that these patients start taking DVT prophylaxis with either subcutaneous heparin or a low-molecular-weight heparin within the first 24 to 48 hours. Trauma in the immediate postoperative setting is commonplace and can have very deleterious effects on the patient. This trauma is often in the form of a direct blow to the stump itself. Hematoma formation or dehiscence of the wound can occur. Depending on the severity of the trauma and the effect it has on the stump, these inadvertent falls can result in the need for revision or a more proximal amputation in upward of 16% of patients, which can convert some from a below-the-knee to an above-the-knee situation.

The choice of postoperative dressings can play a significant role in reducing the risk of injury as well as promoting healing and reducing discomfort. Soft dressings are composed of a nonadhesive barrier to the staple line, which then is covered with gauze and finally an elastic wrap. They allow easy access to view the limb and evaluate ongoing healing in addition to being relatively inexpensive and easy to apply. However, overzealous application of the elastic wrap can result in ischemia of the staple line, which may result in wound dehiscence or failure. It also can be detrimental if the elastic wrap is applied too lightly, resulting in slippage of the dressing and exposure of the staple line before epithelialization, when it is most vulnerable to bacterial invasion. Also, it has been suggested that softer dressings may lead to contracture formation or lengthen the time before ambulation can occur and that they provide no protection to the stump itself in the event of a trauma (e.g., fall), which occurs not infrequently in new amputees. Rigid dressings use all of the same components as soft dressings but then are covered with plaster. In addition to providing protection to the stump itself if the patient suffers a fall in the immediate postoperative period, these dressings also aid in preventing joint contractures and have been shown to decrease the length of time to ambulation with a prosthetic. Decreased healing time resulting in earlier fitting of a patient's prosthesis and quicker time to ambulation can have a profound positive impact on the patient's overall psychologic state. The downside to such a dressing is the inability to readily access and visualize the staple line to evaluate wound healing and the technical knowledge needed to place one of these dressings without compromising the stump, which most surgeons lack initially. As an alternative to plaster, there are some commercially available removable rigid dressings, such as the KIWI, supplied by many prosthetic companies (Fig. 2). Some commercially prefabricated rigid removable dressings provide the benefits of a rigid dressing but are removed more easily for wound assessment and care. For example, the adjustable postoperative prosthesis (APOP) is composed of a hard plastic that is designed to protect the residual limb while simultaneously preventing a flexion contracture of the knee. These dressings typically are applied by the prosthetist in the immediate postoperative setting in conjunction with a stump shrinker to decrease residual edema. These devices are held in place with Velcro, providing the clinician with easy accessibility to the stump for continued evaluation of healing. If these commercially available devices are used, the person who removes the dressing should have a complete understanding of how to reapply it. Placing the APOP in the wrong configuration could have deleterious effects on the stump and not provide the patient with the intended benefits of its usage.

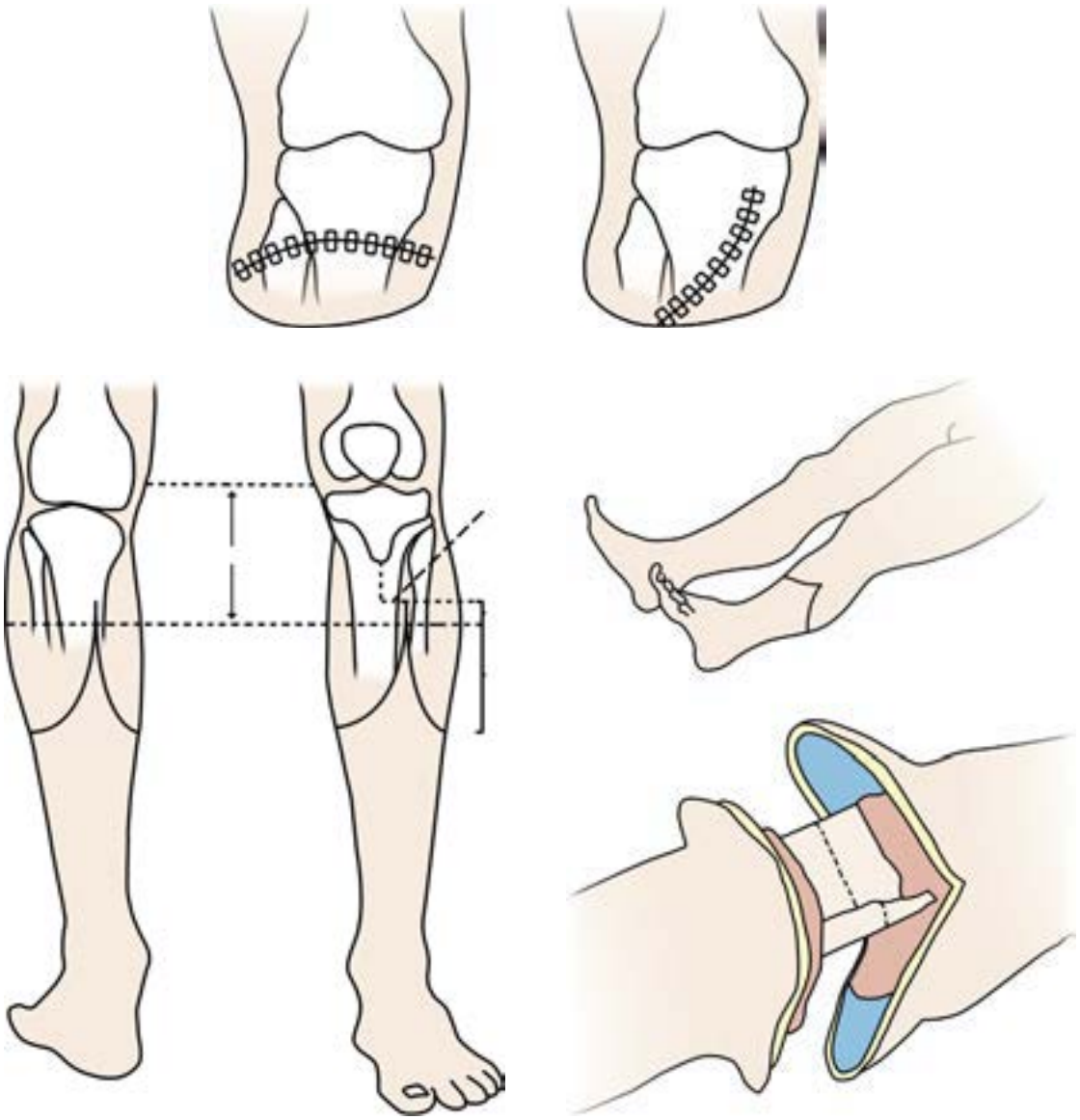


FIG. 2 Below-the-knee amputations. *(Courtesy Maxwell Schwartz.)*

A newer modality for prothesis that eliminates socket-based technology in amputees is osteointegration in which a biocompatible metal device is directly attached to the residual bone to integrate bone with the external prosthesis. This modality has been noted to result in improvement in functional outcomes as well as quality of life. However, these implants also carry an increased risk of soft tissue and bone infection or bone fracture. Closed-incision negative-pressure wound therapy is another adjuvant that may decrease the rates of infection and wound complications after amputation. Although amputation caries multiple risks, it has been described that the risks of wound infection, ICU admissions, and revisions to higher amputation have decreased in recent years.

It cannot be emphasized enough that postoperative rehabilitation therapy must be instituted early in the postoperative course. Close coordination with your hospital's physical and occupational therapists is invaluable in the overall rehabilitation of amputees. These therapists are able to work closely with patients to aid them in learning to manage their activities of daily living (ADLs) and adjust to the life of an amputee. In addition, therapy is geared toward prevention of flexion contractures of the knee in the below-the-knee amputee and improvement of upper body conditioning in all postoperative lower extremity amputees.

Postoperative pain after a major lower extremity amputation is one of the most important morbidities in the eyes of the patient. This pain can be grouped into either residual stump pain or phantom limb pain. Phantom limb pain can be a very debilitating problem for the treating physician and occurs in 45% to 85% of patients after major amputation. The exact cause is unknown at this time, but it is thought to be related to disruption in peripheral axons and neuron circuits. It has been suggested that individuals who suffer from prolonged preoperative pain are at increased risk of suffering from phantom limb pain. Some patients describe episodic discomfort, but as many as 25% may suffer from chronic, unrelenting pain. These symptoms diminish over time for most patients, but they persist for some. Various treatment strategies, including pharmacotherapy, nerve stimulation, and behavioral therapy, have been utilized to manage this debilitating phenomenon. A newer modality for prevention of post-amputation pain is targeted muscle reinnervation (TMR), which involves reattachment of transected nerves into residual muscle tissue. TMR has been associated with decreased rates of

symptomatic neuromas and phantom limb pain. However, more data are necessary to determine the added benefit. Each patient responds differently to each modality, and treatment should be individualized.

OUTCOMES

Postoperative Ambulation

The preservation of one's ability to ambulate is integral to the preservation of one's overall independence. Any minor amputation carries a nearly 100% ambulation rate. The rate of ambulation with a prosthesis after unilateral major lower extremity amputation can be very low, and some studies suggest rates of ambulation outside the home of less than 50% in the vascular population. However, these patients often maintain their independence within the home. ADLs consist of those tasks constituting one's ability to provide even the most basic care to self, including eating, dressing, cooking, and overall mobility with or without assistance. Baseline function includes variables such as age, medical comorbidities, and independence status. Impairment in these simple tasks has been suggested to lead to poorer health, repeated hospitalization, and even death. Advanced age, prolonged hospitalization, history of a stroke, end-stage renal disease, and diabetes all lead to poorer performance of ADLs on discharge, primarily in the nursing home population. Residents who undergo BKA exhibit better performance on ADLs, emphasizing the benefit of limb preservation, even in older adult patients.

Contralateral Amputation

One of the greatest fears an amputee experiences is the risk to the remaining lower extremity after any type of amputation. It has long been identified that those individuals who undergo an amputation are at risk for subsequent amputations or revisions on the ipsilateral leg, in addition to amputations of the contralateral leg. The latter can have overwhelming debilitating consequences for the patient. Independent factors that place the contralateral extremity at risk have been identified and include chronic renal insufficiency or end-stage renal disease, atherosclerosis of the native vasculature with or without diabetic neuropathy, and history of a major lower extremity amputation. Diabetes also has been recognized and is associated with a significantly higher percentage of contralateral major lower extremity amputation. The greatest risk comes from a combination of diabetes mellitus and chronic renal insufficiency. It has been estimated that patients who undergo an initial major lower extremity amputation carry upward of 12% risk for a contralateral major amputation within 5 years, compared with roughly 8.5% risk in patients undergoing an initial minor amputation.

Prosthesis

Not everyone who undergoes an amputation will ambulate successfully with a prosthesis, mainly because of their underlying condition and functional capabilities. For those who can rehabilitate successfully, the advancement in prosthetic limbs makes it possible to resume almost all activities. Computerized controllers for prosthetics allow amputees to navigate uneven terrain, stand safely on boats at sea, and resume many of their presurgical activities that would have been impossible in previous decades. The costs of tailoring even a basic prosthesis for a patient are not insignificant; therefore, it is important to attempt to identify those patients who are likely to ambulate before proceeding with prosthetic development, especially for the more advanced limbs. One tool developed to help in patient selection is the Medicare K-level scale, which assesses functional ability and rehabilitation potential to help guide prosthetic choice. In general, the higher the K-level, the more likely the patient is to benefit from a sophisticated prosthetic limb. Patients with higher K-levels are most likely to benefit from advanced prosthetics.

Prosthetic preparation begins in the immediate postoperative period through use of rigid removable dressings, early physical therapy, and rehabilitation assessments. Some physicians are proponents of an immediate postoperative prosthesis (IPOP), which allows patients to ambulate within a few days. These devices typically are applied in the operating room at the completion of surgery and suspend the limb within the device to avoid pressure on the stump. They are usually cumbersome to don and may increase the risk for falls as patients attempt to use them. Others prefer patients to recover for a longer period and move more toward a traditional prosthetic path.

In the traditional prosthetic path, the amputee undergoes a series of "stump shrinker" applications, rehabilitation, and wound care before being fitted for the initial prosthesis. It may take up to 3 months before the patient begins the initial prosthesis training, and the initial prosthesis may be used for up to 6 months. After this, the permanent prosthesis is fitted and has an overall durability of 3 to 5 years on average before it needs to be replaced. While wearing the temporary (or preparatory) prosthesis, the patient needs continued physical therapy with the ultimate goal of ambulation without the use of any gait aids, including walkers and crutches. As part of this rehabilitation process, the patient is exposed to a schedule of progressive prosthetic wearing time, leading to continuous wearing of the prosthetic. This focuses on learning balance, coordination, weight shifting, and ambulation. As the program progresses, the therapist must work with the patient on overcoming common obstacles, including curbs, stairs, and uneven terrain, in addition to falling in a safe manner and recovering after a fall. Patients also are counseled on weight maintenance. Weight loss is an easy problem to overcome and usually entails padding within the prosthetic, whereas weight gain can lead to problems with the socket fitting and increases the energy requirements to ambulate.

CONCLUSION

Approach to consideration of amputation should be taken in a stepwise fashion. The first consideration is often salvageability. Determining this helps set expectations for the patient early. Next, optimization should be considered before proceeding with surgical amputation. Lastly, appropriate patient assessment for amputation level selection and multidisciplinary involvement should minimize the need for reoperation and allow patients to achieve a better quality of life free from infection, ischemic pain, and dysfunction.

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Initial Assessment and Resuscitation of the Trauma Patient

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INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), unintentional injuries are the leading cause of death in Americans under the age of 45 years, with motor vehicle collisions, firearms, falls, cutting/piercing instruments, and burns among the leading mechanisms. Decreasing mortality in trauma requires an understanding of the trimodal distribution in the timing of death after a trauma. The first peak encompasses over half of all trauma deaths, occurring minutes after the injury as a result of catastrophic central nervous system injuries and major vascular trauma. The initial trauma assessment focuses on identifying ongoing bleeding, managing traumatic brain injury (TBI), and preventing the potentially survivable deaths that occur in the second peak. The second peak occurs hours following the trauma, in which a patient may be transported to a trauma center where interventions can be enacted. The third peak occurs days to weeks after the injury, with deaths resulting from late complications and infections. With the improvement in critical care, there has been a notable decrease in late trauma mortality.

A rapid, systematic, and thorough initial trauma assessment is paramount to providing care to the critically injured trauma patient. Effective trauma care begins with a complete team and facility preparation before the arrival of the patient. Although the basic principles of Advanced Trauma Life Support (ATLS) are taught and used across the country, each hospital has unique considerations in the delivery of care to their region and population. Each trauma team leader should have an understanding of the center's resources, personnel, and limitations in caring for a critically ill patient. The logistic considerations at a level I trauma center will be different from a rural level III or IV trauma center. Level II, III, and IV centers may require more coordination in obtaining equipment and personnel who may be offsite. Additionally, trauma centers should have a good understanding of severe mechanisms of injury and injury patterns that should warrant a transfer to a level I trauma center if able.

The trauma facility should have a designated room for trauma assessment and resuscitation with space for personnel and equipment. Standard available equipment should include personal protective equipment, x-ray and an x-ray–compatible stretcher, and cardiac and vital sign monitors. Necessary ancillary equipment for procedures including airway supplies, chest tubes in a variety of sizes, instrument trays, thoracotomy trays, nasogastric tubes, urinary catheters, central venous catheters, fluid warmers, a massive transfuser, and ultrasound should be available and easily accessible. This equipment list is not comprehensive and should be thoughtfully composed and audited by the multidisciplinary trauma team.

General and trauma surgeons play a critical role on trauma teams as the leaders of the initial evaluation and resuscitation. A trauma team should consist of a prerequisite number of personnel to perform the primary survey and necessary procedures. All team members should have clearly defined roles before reception of the trauma patient. Emergency medicine physicians also play an integral part in triage and assessment. A trauma system requires a strong working relationship between emergency medicine physicians and surgeons to provide coordinated care for injured patients. The role of an emergency medicine physician may be variable including performing much of the primary evaluation and procedures before the availability of a surgeon. Nursing staff are additionally vital to the initial care of a trauma patient. As the team is performing the assessment, nursing staff should be placing intravenous (IV) catheters, drawing blood samples, connecting monitoring, and administering medications. Furthermore, ancillary team members in a trauma team should include respiratory therapists, x-ray technologists, and pharmacists. The immediate availability of consulting services is variable and often a consideration in determination of the necessary level of trauma care. Assigning and understanding the roles of each trauma team member is critical to conducting an efficient trauma evaluation, one in which each person functions in parallel to complete the assessment.

As the patient is in the prehospital setting, the emergency medical services (EMS) team should be working with the emergency department team to ensure transport to an appropriate level of care. In the prehospital triage process, consideration should be given to the proximity of the hospital, availability of higher levels of care, and the needs of the patient based on severity of injury. This process is most optimally coordinated through regional trauma systems with a systematic approach that fits the needs of each geographic and patient environment.

With adequate preparation, triage, and team assembly, each team will be ready to receive the patient and be aware of the facility's limitations and workflow. This will allow for a consistent, complete, and rapid initial assessment of the trauma patient during each new patient encounter. The principles of advanced trauma life support (ATLS) serve as the framework for performing the primary and secondary survey with a goal of identifying and treating immediate life-threatening injuries. Upon arrival of the patient, the EMS providers should have dedicated time to give a brief patient handoff. Although the report should be concise, it often provides important information regarding the observed scene and potential injury patterns. This report should take less than 1 minute as the team intakes and transfers the patient to the stretcher. At this point, the team proceeds to the primary and secondary survey followed by adjunctive diagnostic modalities.

PRIMARY SURVEY

The primary survey is framed to rapidly identify and treat life-threatening injury through a well-established sequence:

A—Airway management with cervical spine immobilization
B—Breathing and ventilation
C—Circulation
D—Disability, assessment of neurologic status
E—Exposure and environment

This sequence allows clinicians to systematically assess and manage injuries in their order of lethality. Beginning with airway management is critical and may lead to death within minutes if an airway is unable to be secured. Although the progression seemingly happens in a discrete fashion, if a patient presents in extremis, a well-functioning trauma team should simultaneously manage the airway, breathing, and circulation under the guidance of a trauma team leader. It is important to realize that the number one cause of *preventable* deaths in trauma patients is hemorrhage. Thus in a patient with brisk external bleeding, prompt control of bleeding (direct compression or tourniquet) must be prioritized. Patients in severe shock frequently have poor mental status, but the underlying problem in this setting is brain hypoperfusion rather than a primary airway or pulmonary issue. Attempting to intubate these patients and starting mechanical ventilation, rather than prioritizing hemorrhage control and resuscitation, can precipitate cardiac arrest (caused by a sharp drop in preload and an abrupt increase in afterload).

Airway

The patient's airway can quickly and easily be assessed by asking the patient to state his or her name and what happened. This will allow for a very rapid assessment of the airway and will also gauge the patient's mental status. If the patient is unable to make a verbal response or has an altered level of consciousness, the airway is at risk and requires a definitive airway. In assessing the airway, trauma providers should be on high alert for injury patterns and objective signs of an airway obstruction. Injuries or burns involving the head, neck, or face should signal the providers to be particularly cognizant of a potential airway compromise. Hypoxia or airway obstruction can manifest in various presentations including agitation, belligerence, anxiety, use of accessory respiratory muscles, or upper airway sounds (stridor, hoarseness, gurgling). Patients require frequent reassessment of airway patency and may require preemptive intubation in the setting of burns or potential obstruction.

Prehospital endotracheal intubation remains a topic of debate, but in patients who are spontaneously breathing, able to maintain adequate oxygen saturation with supplemental oxygen, and have a relatively short prehospital transport time, it is prudent to avoid prehospital intubation. Patients may present to the trauma bay with nasal or oral airways. Inspecting the type of airway the patient has on arrival is paramount to ensure its security. The physical examination is also critical in examining whether a patient appears to have loose teeth, active bleeding into the airway, or vomitus that may have been aspirated during the trauma. Before intubation, the airway should be suctioned with optimization of the view as is required for a successful intubation. Intravenous access should be obtained for administration of drugs and fluids, and patients should be preoxygenated and resuscitated (whenever possible) before attempting intubation. Translaryngeal endotracheal intubation via rapid-sequence induction should be the approach of choice for trauma patients. Providers should be cognizant of the potential for hemodynamic collapse with induction and positive-pressure ventilation. If this cannot be accomplished, a surgical airway (cricothyroidotomy) must be performed. A secure airway should be confirmed post-placement through end-tidal capnography and pulse oximetry to rapidly ensure adequate ventilation and oxygenation, and a chest x-ray should be obtained as soon as feasible.

In the setting of blunt trauma, in-line stabilization of the cervical spine must be maintained while securing the airway. If a cervical collar is removed during the intubation process, the cervical spine stabilization should be held in place by a trauma team member. When spinal stabilization is not required, a patient may benefit from protection of his or her own airway in the upright position.

Breathing

The breathing assessment is a rapid assessment of the patient's ventilation. Ventilation can be impaired as a result of torso trauma or misplacement of an endotracheal tube (ETT). This can be quickly assessed by auscultation of bilateral breath sounds and inspection of chest rise. The ETT should be adjusted if there is a possibility of right main stem tube placement on examination postintubation. Absent breath sounds typically indicate a hemothorax or pneumothorax with a confirmed ETT placement, while the presence of breath sounds does not rule out the presence of a hemothorax or pneumothorax. Ultrasound examination at the bedside can quickly diagnose even a subclinical pneumothorax (absence of pleural sliding). If there are clinical signs of tension pneumothorax (i.e., tracheal deviation, jugular venous distension, cyanosis, hemodynamic instability), rapid decompression of the pleural space using a needle or chest tube insertion is necessary. Pneumothoraces can often expand with the addition of positive-pressure ventilation, which also highlights the importance of an assessment of breath sounds postintubation. Patients presenting in extremis can benefit from bilateral finger thoracostomies for rapid evaluation of the chest. Significant chest trauma including a large flail chest, large underlying pulmonary contusions, or significant aspiration may also require ventilatory support despite an intact airway on presentation.

Circulation

The early recognition, rapid assessment, and management of hemorrhagic shock, is critical and life saving in trauma. Clinicians should have a high index of suspicion for bleeding on evaluation of any trauma patients. Physical examination findings of weak or absent peripheral pulses, cool or pale skin, and decreased capillary refill are signs of hemorrhage. The peripheral pulses can provide an estimate of the patient's systolic blood pressure. Although previously suggested that palpable dorsalis pedis pulses correlated with systolic blood pressures over 100 mm Hg, femoral pulses 70 to 80 mm Hg, and carotid pulses over 60 mm Hg, small studies have shown that these numbers may overpredict the patient's blood pressure. Thus as pulses are examined, a noninvasive blood pressure should be obtained and correlated.

Shock is defined as hemodynamic collapse with impaired end-organ perfusion. In a trauma patient, the most likely cause of shock is hemorrhagic, which should be recognized in an expedited fashion. The severity of the patient's hemorrhagic shock can be classified by the class of hemorrhage I to IV (Table 1). As evidenced by Table 1, the patient's systolic blood pressure is not an early indicator of hemorrhagic shock and should not be a sole indicator for ongoing bleeding. The physiologic manifestations of shock including tachycardia and systolic blood pressure should not be waited on before initiation of management. The shock index (SI) [heart rate (HR) divided by systolic blood pressure (SBP)] is a better predictor of shock than either HR or SBP alone. A SI >0.9 is highly suggestive of critical bleeding. Although the majority of shock in a trauma patient is hemorrhagic, a clinician should continue to evaluate for additional possible etiologies of shock. Differential diagnoses, evaluation, and management of shock are listed in Table 2. Differentiating the cause of shock dictates the appropriate management for the patient.

TABLE 1 Classification of Hemorrhage*

Parameter	Class I	Class II (Mild)	Class III (Moderate)	Class IV (Severe)
Approximate blood loss	<15%	15%-30%	31%–40%	>40%
Heart rate	↔	↔/↑	↑	↑/↑↑
Blood pressure	↔	↔	↔/↓	↓
Pulse pressure	↔	↓	↓	↓
Respiratory rate	↔	↔	↔ / ↑	↑
Urine output	↔	↔	↓	↓↓
Glasgow Coma Scale score	↔	↔	↓	↓
Base deficit†	0 to –2 mEq/L	–2 to –6 mEq/L	–6 to –10 mEq/L	–10 mEq/L or less
Need for blood products	Monitor	Possible	Yes	Massive transfusion protocol

*From the American College of Surgeons. *Advanced Trauma Life Support Student Course Manual.* American College of Surgeons; 2018.
†Base excess is the quantity of base (HCO_3^- in mEq/L) that is above or below the normal range in the body. A negative number is called a *base deficit* and indicates metabolic acidosis.
Data from Mutschler A, Nienaber U. Brockamp T, et al. A critical reappraisal of the ATLS classification of hypovolaemic shock: Does it really reflect clinical reality? *Resuscitation* 2013, 84(3):309–313.

Treatment of hemorrhagic shock requires a simultaneous double-armed approach: resuscitation and definitive hemorrhage control. It is imperative to realize that resuscitation is an adjunct to hemorrhage control, and *not a substitute*.

Resuscitation

The initial resuscitation strategy depends upon multiple variables, such as: (1) degree of blood loss, (2) whether there is ongoing bleeding, (3) presence or absence of TBI, (4) mechanism of trauma, and (5) age and comorbid status of the patient. Two large-bore IV lines should be placed in all trauma patients and blood sent for type and crossmatch. If IV access cannot be obtained promptly, intraosseous or large-bore central venous access is required for transfusion of fluid and blood.

In adult patients who may have stopped bleeding, 1 L of warmed isotonic fluid can serve as the initial fluid resuscitation. Response to this fluid bolus (sustained response versus no/transient response) can differentiate the patients who have already stopped bleeding from those who either have ongoing blood loss, lost more blood than anticipated, or have other reasons for shock. Aggressive resuscitation in the absence of hemorrhage control does not improve survival and can, in fact, worsen outcomes by causing additional bleeding ("pop the clot") and creating hemodilution, hypothermia, thrombocytopenia, coagulopathy, acidosis, and edema. A controlled resuscitation strategy (250-mL boluses to target a systolic blood pressure of 70 mm Hg or palpable radial pulse) with permissive hypotension has been shown to decrease mortality compared with a standard resuscitation strategy (2-L bolus to target systolic blood pressure of 110 mm Hg). Thus prehospital providers and transport teams should allow for permissive hypotension until definite hemorrhage control can be achieved.

Following initial administration of crystalloid fluids, blood products should be used if any additional resuscitation is required in the acute phase. Blood that is type-specific but not crossmatched can be used in an emergency setting. Type O negative blood should be used in pregnant females and is preferred in females of childbearing age if available. In patients with active bleeding who are in shock, the principles of *damage control resuscitation* should be followed (Box 1). In patients with large-volume (or ongoing) blood loss, early transfusion of balanced blood products (red blood cells, plasma, platelets, and clotting factors) using a structured massive transfusion protocol is the most logical approach (Fig. 1). There is strong evidence to support transfusion of packed red blood cells, fresh-frozen plasma, and platelets in a 1:1:1 ratio. The role of prehospital plasma administration in patients with early signs of hemorrhagic shock have been investigated in two randomized controlled trials: Prehospital Air Medical Plasma (PAMPer) and Control of Major Bleeding After Trauma (COMBAT). Although there remain logistical challenges to full implementation in the civilian sector, prehospital plasma has been demonstrated to be safe and improves survival, particularly when longer transport times are required. Tranexamic acid (TXA) is a procoagulant hemostatic adjunct that has also been shown to reduce the risk of death in trauma patients with bleeding and TBI. TXA should be given as soon as possible and no later than 3 hours postinjury.

Military studies provided the first investigations of utilizing whole blood in trauma resuscitation. With promising results suggesting there may be an improved mortality and decrease in blood product utilization, some civilian level I trauma centers have begun testing the use of whole blood. Additional ongoing studies examine the use of vasopressors in trauma. Although there is typically no role for

BOX 1 Principles of Damage Control

- Apply direct pressure to the bleeding site, or a tourniquet proximal to the site of hemorrhage in the extremities; pack junctional wounds with hemostatic dressings.
- Facilitate early transfer to the operating room or angiography suite for definitive hemorrhage control.
- Minimize crystalloid infusions, and utilize a controlled resuscitation strategy with permissive hypotension until time of definitive hemostasis.
- Utilize a massive transfusion protocol early to ensure that sufficient blood products are in appropriate ratios rapidly available.
- Transfuse blood products using a balanced resuscitation strategy with plasma, platelets, and red blood cell transfusions.
- Use functional laboratory measures of coagulation (e.g., thromboelastography or rotational thromboelastometry) to transition from empirical transfusions to targeted therapy.
- Selectively administer pharmacologic or procoagulants adjuncts (e.g., tranexamic acid, prothrombin complex concentrate) to reverse anticoagulants.

Modified from Cannon JW. Hemorrhagic shock. *N Engl J Med.* 2018;378(4):370–379.

TABLE 2 Differential Diagnosis and Management of Shock in Trauma

	Signs/Symptoms	Diagnostic Studies	Management
Hemorrhagic shock	Tachycardia Hypotension		
Chest	Respiratory distress Absent breath sounds Flat neck veins Dullness on percussion Flail chest/rib fractures	CXR eFAST Chest CT Finger or tube thoracostomy	Chest tube thoracostomy Thoracotomy
Abdomen	Peritonitis Abdominal distension Seat belt sign Flank bruising	FAST CT abdomen/pelvis DPA	IR embolization (hemodynamically stable, solid organ injury) Laparotomy
Pelvis	Pelvis instability Blood at urethra Scrotal hematoma Lower extremity length discrepancy or rotation	FAST CT abdomen/pelvis	IR embolization Laparotomy
Extremity	Swelling of extremity Trauma near major vascular supply Closely associated long-bone fracture Hard signs of vascular injury (bruit/thrill, loss of pulses, active pulsatile bleeding, expanding hematoma) Soft signs of vascular injury (decreased/mismatching blood pressure distal to the injury site, decreased pulse strength, hematoma, neurologic deficit)	Clinical CT extremity angiogram Angiogram	Angiogram Open vascular repair/bypass/ligation
Cardiogenic shock (blunt cardiac injury, myocardial infarction, air embolus)	Tachycardia/dysrhythmias Chest pain	CXR (associated injury-sternal fracture) EKG Continuous telemetry Troponin Echocardiogram	Supportive care Cardiac catheterization (if myocardial infarction)
Cardiac tamponade	Beck's triad (muffled heart sounds, jugular venous distension, hypotension) Tachycardia Narrow pulse pressure Electrical alternans	Ultrasound	Subxyphoid periocardial window if ultrasound is equivocal Sternotomy, repair of cardiac injury
Tension pneumothorax	Tachycardia Jugular venous distension Subcutaneous emphysema Respiratory distress Tracheal deviation Tympanic to percussion Absent breath sounds	Clinical diagnosis eFAST CXR	Chest tube thoracostomy (needle decompression could be a temporizing step)
Neurogenic shock	Cervical and upper thoracic cord injuries Hypotension (without tachycardia) Nonresponsive to fluid	Clinical; other causes must be ruled out before diagnosis	Fluid resuscitation and vasopressors Supportive care
Septic shock	Peritonitis Fever Tachycardia Symptoms and timeline consistent with sepsis (e.g., delay of diagnosis of abdominal injuries, infection leading to later fall)	Clinical Laboratory findings (leukocytosis, inflammatory markers) Urinalysis Blood cultures CXR	Fluid resuscitation Broad-spectrum antibiotics Supportive care Treatment of the underlying etiology

CT, Computed tomography; *CXR*, chest x-ray; *DPA*, diagnostic peritoneal aspiration; *eFAST*, extended focused assessment with sonography for trauma; *EKG*, electrocardiogram, *FAST*, focused assessment with sonography for trauma; *IR*, interventional radiology.

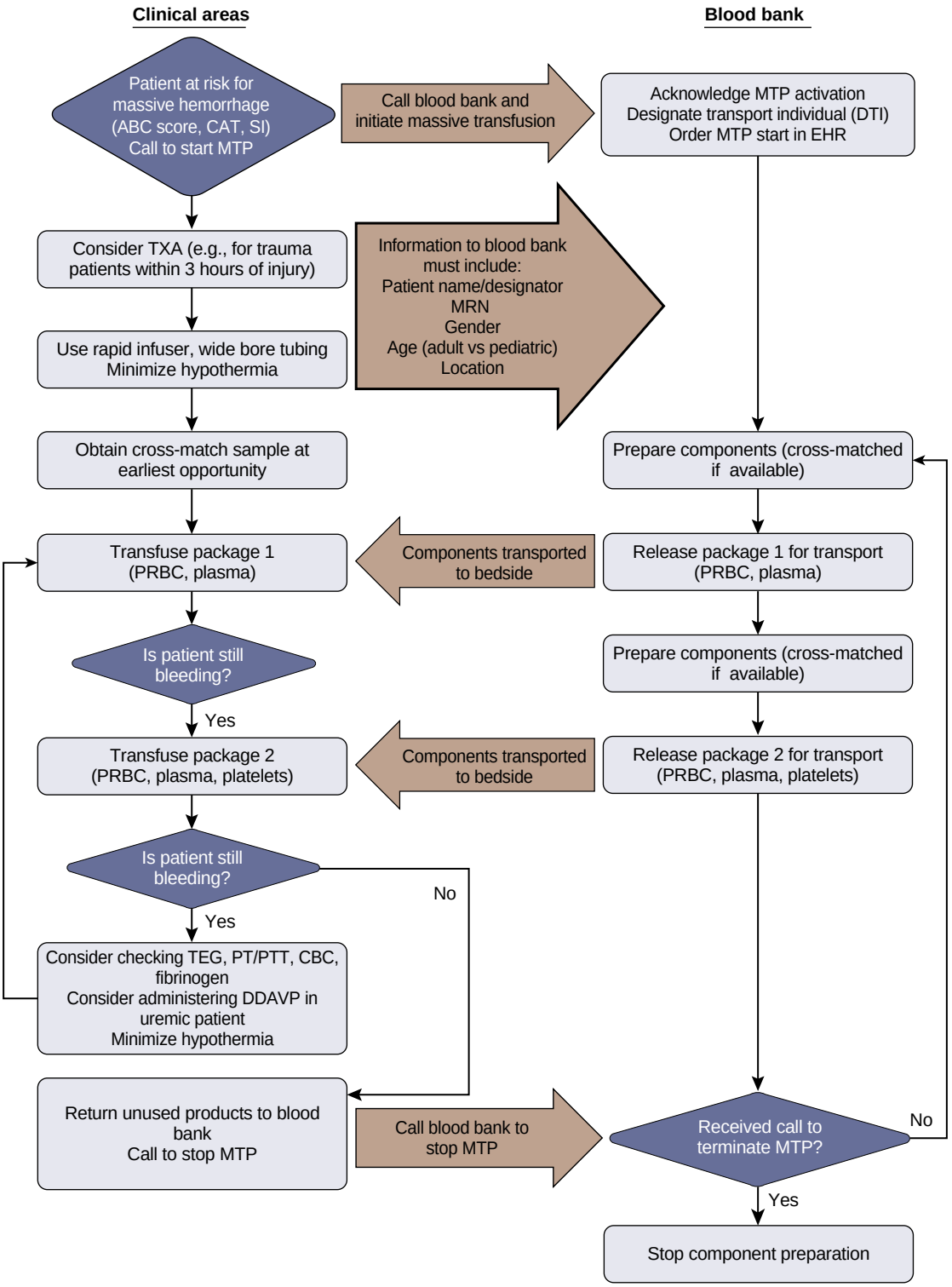


FIG. 1 Typical massive transfusion protocol. *(From Abuzeid AM, O'Keeffe T. Review of massive transfusion protocols in the injured, bleeding patient.* Curr Opin Crit Care. *2019;25:661–667.)*

vasopressors in hemorrhagic shock, animal studies have suggested a potential role for vasopressin in improving tissue perfusion and decreasing blood product requirements. The 2019 AVERT-shock trial demonstrated that the use of low-dose arginine vasopressin in hemorrhagic shock decreased blood product requirement without increasing complications or mortality. Currently, the utilization of vasopressin or other vasopressors remains a topic in need of further studies.

Definitive Hemorrhage Control

Hemorrhagic shock must be managed by rapidly pursuing hemostasis as delays have been linked to increased mortality. The sites of hemorrhage in a patient are the chest, abdomen, pelvis, long bones, or externally. Diagnosis of the location of hemorrhage drives the following steps in management, namely to stop the ongoing bleeding. Obvious external signs of bleeding can be managed with

manual pressure, packing, or a tourniquet if feasible. The American College of Surgeons (ACS) Stop the Bleed campaign provides community outreach, teaching the principles of controlling external hemorrhage in a stepwise approach to decrease preventable prehospital deaths from external, particularly compressible, extremity hemorrhage.

Numerous modalities and clinical examination findings can assist in differentiating the source of bleeding. Diagnostic adjuncts including imaging and procedures should be performed to rapidly localize the body cavity with bleeding (Table 3). Once the source of bleeding is identified, the patient should quickly be moved to the operating room for hemorrhage control. A patient in extremis may ultimately require an emergency thoracotomy or resuscitative endovascular balloon occlusion of the aorta (REBOA) to temporize bleeding before proceeding to the operating room.

Disability

An assessment of disability and neurologic status begins with the Glasgow Coma Scale (GCS). A preliminary GCS score should be calculated on initial assessment of the patient. A GCS score of 8 or below suggests that the patient is unable to protect his or her own airway and requires intubation. However, unless apneic, this intubation should be carefully planned and executed with deliberate attention to adequate preoxygenation, pre-intubation resuscitation, and judicious use of vasoactive agents to prevent secondary brain injury (e.g., caused by hypotension, hypoxia, or hyperventilation). This is also the time to evaluate for spinal cord trauma and other signs of TBI including lateralizing signs. The mental status should be continuously reevaluated throughout the primary and secondary survey.

The GCS score has long been used as an initial determinant of disability; however, the score also has utility in predicting outcomes post-TBI. It has also become a component of numerous other trauma outcomes prediction scoring systems including the Trauma and Injury Severity Score (TRISS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the Revised Trauma Score (RTS).

If TBI is suspected, prevention of secondary brain injury should be a priority. Prevention of hypoxia, hypercarbia or hypocarbia (target CO_2 35–40 mm Hg), maintenance of adequate perfusion, correction of coagulopathy, and management of intracranial hypertension should be integrated in the management of patients with a TBI.

Exposure and Environment

To perform a thorough examination of a trauma patient, the patient must be fully exposed. All clothing must be removed to perform a complete examination and minimize missed injuries. Upon completion of the physical examination, the patient should be covered with warm blankets to minimize hypothermia, which should be aggressively avoided, particularly in the setting of likely coagulopathy of trauma in hemorrhagic shock. Use of forced-air warming blankets, warmed intravenous fluids, and an elevated room temperature are measures that should be implemented in a hypothermic patient.

SECONDARY ASSESSMENT

The secondary survey is a complete history and physical examination of the patient following the primary survey. The secondary survey should be performed only when there is normalization of patient vital signs. A systematic head-to-toe assessment of the patient should ensue to gain a full understanding of all of the patient's injuries, particularly when patients are altered or sedated. Additionally, a full patient history should be obtained including past medical history, allergies, and medications when able.

Imaging Adjuncts

Imaging has become a critical adjunct in the diagnosis and management of surgical and trauma patients. A variety of rapid and accurate imaging modalities can significantly guide management of trauma patients.

Plain Radiography

Plain radiographs are an important adjunct to the initial assessment. In the optimal setting, trauma stretchers should be x-ray–compatible allowing for placement of the x-ray cassette without further mobilization of the patient. This will facilitate anteroposterior (AP) chest and pelvis x-rays, which can be immensely beneficial in the initial diagnostics and resuscitation. As noted in Table 3, a chest x-ray (CXR) can quickly diagnose many life-threatening injuries. Additionally, a CXR should be performed after intubation and chest tube placement to confirm placement of tubes. The role of routine CXRs has been questioned and will remain a source of debate. In patients who are hemodynamically stable and have a mechanism of injury that will warrant a CT scan of the torso, there may be minimal added benefit to performing a CXR. However, we feel that CXRs should be liberally obtained as most trauma patients will not be candidates for CT. In fact, available data suggest that with a normal physical examination of chest and thoracic spine along with a normal CXR, yield on chest CT is extremely low. Clinicians should use clinical judgment to decide on the necessity of CT, keeping in mind the radiation exposure and hospital costs associated with CT. A pelvic x-ray (PXR) should be used as an adjunct when there is clinical suspicion of hemodynamic shock as a result of pelvic bleeding. In a hemodynamically stable patient who otherwise meets criteria for obtaining a CT abdomen and pelvis, there is little utility to a PXR in the trauma bay.

One indication to plain radiography that should not be overlooked is the ability to detect retained radio opaque foreign objects quickly. Gunshot wounds are often highly variable in course because of the significant amount of kinetic energy. A CXR, abdominal x-ray (AXR), and PXR before going to the operating room can reveal retained bullets and potentially guide the surgeon to the body cavity requiring exploration.

Ultrasound

Ultrasound has inherent advantages in imaging trauma patients. It is a noninvasive, radiation-free, rapid, and accurate diagnostic modality that has become readily available in nearly all trauma resuscitation rooms. As a result, focused assessment of sonography in trauma (FAST) scan has become a staple in trauma training. A FAST examination entails using ultrasound to investigate four locations in which there may be hidden bleeding. The views to examine are the pericardium, the right upper quadrant, the left upper quadrant, and the pelvis. The strongest indication to perform a FAST examination is in hemodynamically unstable patients with blunt trauma. When free fluid is seen on FAST, particularly in a hemodynamically unstable patient, it can be presumed that there is blood in the cavity in question.

The sensitivity and specificity vary significantly in the literature because of differences in patient cohorts, injury patterns, and study variations. In a 2018 meta-analysis, the sensitivity and specificity of FAST in abdominal trauma were 68% and 95%, respectively, and there was a 96% sensitivity and 99% specificity in thoracic trauma. The results across numerous studies have shown that although a positive FAST examination is likely trustworthy when clinically correlated, a negative FAST examination does not rule out the possibility of intraabdominal or pelvic bleeding. Additionally, the FAST examination is limited by the experience level of the ultrasonographer and the body habitus of the patient.

TABLE 3 Common Imaging Indications in Trauma

Imaging Modality		Indications
X-RAY		
	Chest x-ray	Abnormal chest physical examination Decreased breath sounds To confirm endotracheal or chest tube placement As part of routine trauma evaluation
	Pelvis x-ray	Pelvic instability Signs of pelvic hemorrhage Unexplained hypotension
ULTRASOUND		
	FAST eFAST	As part of routine trauma evaluation Abnormal chest physical examination Decreased breath sounds As part of routine trauma evaluation
CT SCAN		
	Brain	Altered mental status Headache External signs of head trauma Loss of consciousness Penetrating head trauma Blunt trauma on anticoagulation CSF leak from nose or ear
	Cervical spine	Midline neck pain Inability to clear cervical collar (altered mental status, distracting injury)
	Neck angiogram	Penetrating anterior or posterior zone I–III neck injuries (in conjunction with CTA chest) Cervical spine fracture Neurologic symptoms or deficits (lateralization) Le Fort fractures Cervical bruit Horner's syndrome Raccoon eyes (bruising around eyes, sign of basilar skull fracture)
	Maxillofacial	Periorbital ecchymosis Evidence of eye trauma, extraocular eye movement derangement Crepitus Bony displacement Facial instability Motor or sensation deficits to face
	Chest, angiogram	Penetrating neck injury Penetrating injury near subclavian and axillary artery Posterior chest penetrating wound Mechanism with risk for blunt aortic trauma (rapid acceleration/deceleration, sudden compression of chest) Suspicious chest x-ray findings (widened mediastinum, left apical cap, large left hemothorax, indistinct aortic contour, depression of left main bronchus, deviation of trachea or nasogastric tube to right)
	Chest, IV contrast	Abnormal chest physical examination Hemothorax or pneumothorax Flail chest Significant mechanism of injury Scapular fracture Multiple rib fractures or sternal fracture Clinical suspicion for thoracic spinal injury Suspicion for diaphragmatic injury

Continued

TABLE 3 Common Imaging Indications in Trauma—cont'd

Imaging Modality	Indications
Abdomen/pelvis, IV contrast	Abdominal pain or tenderness Seat belt sign Abdominal distension Flank bruising Abnormal FAST in a hemodynamically stable patient Pelvic fracture Lower rib fractures Suspected lumbar or sacral spinal injuries
Extremity, angiogram	Soft sign of vascular injury with penetrating trauma near major vessel (see Table 2) Long bone injury pattern with associated possible vascular injury (posterior knee dislocation, supracondylar femur fracture, supracondylar humerus fracture)

CSF, Cerebrospinal fluid; *CTA*, computed tomography angiography; *eFAST*, extended focused assessment with sonography for trauma; *FAST*, focused assessment with sonography for trauma; *IV*, intravenous.

Ultrasound has now been expanded to use in identifying pneumothoraces through an extended FAST (eFAST) examination. The eFAST examination has also been shown to have variable sensitivities and specificities. Similar to the FAST examination, there is a consistently higher specificity than sensitivity, suggesting that a negative eFAST should be confirmed if there is clinical suspicion for thoracic trauma. eFAST examination also has variable sensitivity in comparison to chest x-rays. Again, the eFAST examination is limited by operator experience and patient body habitus. The role of eFAST examination has yet to be fully delineated in the trauma assessment.

Computed Tomography

Cross-sectional imaging has become a highly valuable imaging adjunct to surgeons including in the setting of trauma. CT is rapid and accurate in the diagnosis of pathology in both blunt and penetrating trauma. CT allows for classification and characterization of solid organ injuries, which has improved prognostication and intervention in blunt abdominal trauma. Administration of CT contrast can opacify different structures and improve visualization of bleeding or extravasation. Intravenous contrast is beneficial and should be utilized in trauma scans. The contrasted scans can be performed to visualize arteries (CT angiography) with smaller cross-sectional slices or in portal venous phase as a standard CT with IV contrast. With the improvement in CT technology, there is also a decreased need for traditional angiography for solely diagnostic purposes. Given the invasive nature of angiography, noninvasive CT angiography has allowed for a more judicious use of angiography for intervention for those who have a higher likelihood of vascular injury. In general, oral and rectal contrast have fallen out of favor in CT for trauma. However, rectal contrast may have some use in select cases with penetrating flank injuries for evaluation of the retroperitoneal colon.

CT is not an appropriate diagnostic modality in a hemodynamically unstable patient. A patient in the CT scanner is relatively poorly monitored and has an increased risk of aspiration when lying flat for the examination. More importantly, in case of worsening hypotension, airway compromise, expanding pneumothorax, or other acute life-threatening events, CT scan suites typically lack the tools and resources for appropriate interventions. There also remains a risk of radiation exposure. The radiation exposure in a whole-body CT scan is approximately 3 times that of the average background atmospheric radiation exposure. Although the benefit often outweighs the small risk of radiation exposure, the future cancer risk from a CT scan is difficult to quantify and increases with a larger number of CT scans performed in a lifetime. In special populations (i.e., children and pregnant women), a CT scan in trauma should be obtained only when clinically indicated.

SUMMARY

Trauma care requires standardized and coordinated care to continue decreasing potentially survivable injury-related deaths. Moreover, work should continue in the prevention of trauma, injuries, and violence as the only way to prevent the majority of trauma deaths is to prevent the occurrence of trauma. As we pursue quality improvement in trauma resuscitation, implementation of trauma video review has increased in trauma centers across the country over the past decade. Reviewing trauma resuscitation videos can allow for improvement in communication, team dynamics, and coaching at all levels of providers.

Future directions and innovations in early hemorrhage prevention are the use of novel pro-survival drugs and preserved plasma products in the prehospital setting and development of hemostatic agents or local hemorrhage control.

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Prehospital Management of the Trauma Patient

Zaffer Qasim, MBBS

Trauma remains a leading cause of death and disability worldwide. The epidemiology of mortality traditionally followed a trimodal distribution, with the majority of deaths occurring within minutes of injury from either hemorrhage or devastating traumatic brain injury (TBI); a second peak occurring within hours of hospital arrival as a consequence of the severity of their injuries; and a third peak occurring days or weeks after the initial insult secondary to organ failure and sepsis. However, with advances in care, a bimodal distribution is more common in modern trauma systems, with death occurring either immediately or within a few hours of injury; late deaths have dramatically diminished.

A key component of an effective trauma system of care is the prehospital care provided from the point of injury to hospital arrival. This can be delivered by bystanders as well as trained members of a trauma system's Emergency Medical Services (EMS). These elements create a chain of survival from the point of injury to delivery to in-hospital care.

LEVELS OF PREHOSPITAL CARE DELIVERY

Basic Life Support—Spontaneous Responders

There exists a period of time, sometimes termed the *disaster gap,* from the initial incident to the arrival of trained help. Members of the public who are near the point of injury can be termed *spontaneous responders.* They may be able to provide critical first aid, including simple measures such as opening of the airway or control of bleeding through application of direct pressure or a tourniquet, if available.

The fact that this group of individuals can provide critical support in the period before skilled help arrives and could reduce potentially preventable mortality was recognized in 2013 as part of a multiagency review by the Joint Committee to Create a National Policy to Enhance Survivability from Intentional Mass Casualty and Active Shooter Events convened in the wake of the Sandy Hook Elementary School shooting the year before. The committee's recommendations were published in a report termed the *Hartford Consensus.*

This directly resulted in a call for implementing bleeding control training. Although initially aimed at the management of mass-casualty incidents, this was extended to include smaller incidents. Programs such as the American College of Surgeons Committee on Trauma (ACS-COT)–sponsored Stop the Bleed campaign and the American College of Emergency Physicians (ACEP)–sponsored Until Help Arrives course are designed to empower members of the public to be effective spontaneous responders by training them in basic hemorrhage identification and control techniques, scene safety, and effective communication with emergency medical dispatchers. Public spaces such as airports and schools are now more likely to have bleeding control kits, often alongside automated external defibrillators.

Basic Life Support—Emergency Medical Responders and Technicians

Emergency medical responders and emergency medical technicians (EMTs) form critical parts of a trauma system's prehospital response capability. The National Registry of Emergency Medical Technicians defines the curriculum to credential prehospital clinicians at each of these levels. They are trained to safely assess scenes, provide basic trauma life support, and transport patients expediently to hospital-level care. They can support the care provided on scene by working alongside advanced life support teams.

Advanced Life Support Personnel

Broader trauma care can be provided at the scene by appropriately trained advanced life support clinicians. Interventions include advanced airway management such as drug-assisted endotracheal intubation, hemorrhage control, splinting including pelvic binder application, needle or open thoracostomy, intravenous access, and fluid administration. Typically, in the United States this level of prehospital care is provided by EMTs who undergo more extensive training to the paramedic level. Many international systems as well as some in the United States also incorporate specialty-trained prehospital physicians as part of their prehospital care system. Such physicians can provide an even higher level of procedural skill and clinical decision making on scene in specific circumstances such as complex trauma and delayed extrications.

Medical Direction

Oversight of a trauma system's prehospital response (including training, communications, protocol development, clinical response, and quality assurance) is the remit of the EMS medical director. Increasingly, this person is an EMS–board-certified emergency medicine physician, though trauma surgeons and other allied specialties may also carry out this role in some systems. The medical director also acts as a crucial liaison between EMS and other prehospital services (including police and fire departments) and hospital specialists. Local protocol development should include input from those specialties involved in trauma management.

INITIAL PREHOSPITAL MANAGEMENT OF THE CRITICALLY INJURED PATIENT

Prehospital trauma evaluation and management generally follows principles used during in-hospital care. One approach has been codified in the Prehospital Trauma Life Support (PHTLS) course created

jointly by the ACS-COT and the National Association of Emergency Medical Technicians. This framework promotes critical thinking and standardized patient evaluation and treatment, and it includes a primary survey addressing airway (with cervical spine control), breathing, circulation, disability, and exposure/environmental control. Scene assessment and safety precedes this evaluation. A momentum to rapidly and safely transport to the most appropriate treatment facility should underline prehospital management.

As a direct result of experience from the military conflicts in Iraq and Afghanistan, the approach to time-critical priorities in trauma assessment has been revised. The ABCDE principles are arranged in a different mnemonic: MARCH (Massive hemorrhage, airway management, respiratory support, circulation, head injury and hypothermia). An alternative mnemonic that follows the same premise is (C)ABC: Control of exsanguinating hemorrhage, Airway, Breathing, Circulation.

Scene Assessment and Safety

On arrival, the prehospital responder should initially determine whether the scene poses any ongoing threat to themselves, their colleagues, or the patient. Threats can include structural instability, traffic, fire or environmental challenges, electrical hazards, hazardous materials, or the presence of a violent offender. Information can be gathered from personal observation, bystander reports, technical specifications, and allied agency responders. Scene safety may be dynamic, and the prehospital responder must maintain situational awareness and open communication with colleagues regarding evolving threats.

Massive Hemorrhage Control

The principal mechanism of potentially preventable mortality from trauma is hemorrhage. Rapid identification and temporary control of massive, exsanguinating hemorrhage is life saving. Sources may be obvious, such as a bleeding extremity, but can also be less obvious, such as the junctional areas (groin and axillae), scalp, and the back. Rapid removal of clothing may help facilitate identification of these injuries. Bleeding may be managed through the use of direct pressure, wound packing (including the use of hemostatic agents and dressings), and tourniquets.

Hemostatic agents have evolved over time, with civilian use being informed from military practice. These typically incorporate chitosan, zeolite, or kaolin. Examples include HemCon bandages, QuickClot combat gauze, X-Stat sponges, and Celox gauze. They can be used to pack wounds and can be incorporated into pressure dressings. Civilian studies have reported largely favorable outcomes with minimal complications.

Similar civilian adoption has occurred with tourniquets. Although initially a controversial adjunct, extensive experience from recent military conflicts has demonstrated safety and survival benefit without increasing amputation rates directly resulting from tourniquet use itself. Recent civilian data demonstrated an almost six-fold mortality reduction when utilized in peripheral vascular injury.

Tourniquets are indicated in extremity injuries if bleeding is not controlled by direct pressure; the source here is usually arterial. They should be placed as proximal as possible on a part of the limb with a single bone (upper arm or thigh) to allow direct compression, and then tightened until hemorrhage stops. The time of application should be clearly documented, and this information is given to the hospital team on arrival.

Splints (including box, vacuum, and traction splints) and pelvic binders can be applied in the prehospital setting. These devices not only reduce pressure on skin and neurovascular structures, but they also can decrease bleeding by stabilizing fractured bones.

Airway Management

The prehospital clinician should actively evaluate for signs and symptoms of airway compromise and respiratory distress. Simple airway maneuvers such as a jaw thrust, in conjunction with supplemental oxygen and, when required, basic airway adjuncts such as oral or nasal pharyngeal airways can allow support of the airway, oxygenation, and ventilation.

Advanced airway management through endotracheal intubation (including drug-assisted rapid sequence intubation) has been controversial in prehospital trauma management. Although this is deemed a definitive airway, the success of prehospital intubation is dictated by type and intensity of training and skill maintenance. This can vary widely from one EMS system to another. In both retrospective and prospective studies of prehospital intubation, often in the setting of TBI, patient-centered outcomes such as neurologically intact survival have been variable and likely dependent on multiple variables including the development of hypoxia or hypotension during intubation, inadvertent hyperventilation, prolonged scene times, and aspiration events. Systems in which clinicians are appropriately trained and have a high frequency of procedural use likely have more favorable outcomes. Therefore, in many EMS systems, basic airway maneuvers en route to the hospital may be more appropriate. This can be supplemented by the use of supraglottic devices such as a laryngeal mask airway.

Surgical airways may be required in situations where oxygenation and ventilation are impossible. However, many prehospital clinicians lack significant experience in this technique. EMS systems seeking to include this in the clinician's scope of practice must pay close attention to training, protocol development, and quality assurance.

End-tidal carbon dioxide monitoring (capnography) should be considered the standard of care in confirming the correct placement of an advanced airway. Both colorimetric and waveform capnography devices exist. Waveform capnography allows for continuous monitoring of ventilation and is particularly useful in identifying significant hypoventilation or hyperventilation. Both of these can be detrimental in the setting of prehospital trauma, in particular TBI.

Respiratory Support

Life-threatening pathologies such as a tension pneumothorax should be actively looked for by prehospital personnel. Clinical signs can include diminished breath sounds, deviation of the trachea, presence of subcutaneous emphysema, and distended neck veins, especially when accompanied by hemodynamic instability. Several recent studies measuring chest wall thickness have found that there is a higher incidence of successfully reaching the pleura in adults with a standard 2.5-inch (5-cm) needle when placed in the fifth intercostal space, anterior axillary line, as opposed to the traditionally taught second intercostal space, midclavicular line. Longer (8-cm) needles are also commercially available and useful in larger adults. In children, the second intercostal space, midclavicular line is still recommended, with depth of insertion guided by the patient's body size and response to insertion. Complications include inadequate drainage of the pneumothorax caused by not reaching the pleural, kinking of the catheter leading to reaccumulation of the pneumothorax, and damage to surrounding structures, including the neurovascular bundle of the rib, the lung, and nearby great vessels.

An alternative to needle thoracostomy is open thoracostomy. This utilizes steps similar to surgical chest tube insertion except for the actual placement of a chest tube. This technique has been incorporated successfully in some EMS agencies. Although more training is required, open thoracostomy is more likely to lead to successful decompression of the pneumothorax. There is further potential of injury to the neurovascular bundle of the rib if care is not taken with dissection technique.

Open thoracic wounds causing a simple pneumothorax can be managed by early application of a chest seal. This can be through the use of a three-sided dressing, although in clinical practice these are not very effective. Commercially available vented chest seals such as the Asherman chest seal are more efficacious, allowing for the release of accumulated air without allowing reentry. Thus, progression to a tension pneumothorax can be prevented.

If intubated, consideration should be made of using a transport ventilator. All ventilators, regardless of complexity, allow a set rate and tidal volume to be delivered. This has the benefit of preventing inadvertent hypoventilation or hyperventilation and reduces the risk of barotrauma through delivery of set tidal volumes. These factors can be beneficial in the injured patient, especially in the setting of TBI.

Circulation

In addition to managing massive hemorrhage, the prehospital clinician can attempt to obtain vascular access. This is preferentially obtained through placement of two short, large-diameter intravenous catheters (size 14- or 16-guage) in the upper extremity veins. Although large-volume resuscitation is no longer recommended, obtaining venous access in the field may be easier as the patient is encountered at an earlier stage of shock, when veins are more prominent than by the time they arrive to hospital. However, the prehospital clinician should be mindful of the time spent on scene and consider performing this task en route.

If venous access is not possible after two attempts, EMS personnel can attempt to place an intraosseous (IO) line. IO access was once reserved only for children, but it has gained importance in all age groups when intravenous access is challenging or impossible. Newer devices allow rapid placement. Typical sites include the proximal tibia and the humeral head, although the distal femur and the sternum are also options. Sternal IO access requires a needle specific for this site. The IO route has similar plasma kinetics to intravenous medications and fluids. Recent cadaveric study has demonstrated mean flow rates of normal saline of 93.7 mL/min via the sternal route, 57.1 mL/min via the humeral route, and 30.7 mL/min by the tibial route when the fluid was administered under pressure.

The infusion of (often cold) normal saline in particular presents challenges from both worsening hypothermia as well as acidosis secondary to its high chloride content. Therefore, if a crystalloid is to be administered, a more balanced solution such as lactated Ringer's is preferred. However, there has been a significant move away from large-volume crystalloid volume resuscitation over the past several decades. Several studies have demonstrated that patients may have higher mortality when large volumes are administered in the field, especially in the setting of uncontrolled hemorrhage and penetrating trauma. The development of acute respiratory distress syndrome, coagulopathy, and pneumonia are all associated with large-volume fluid resuscitation.

Targeting a "normal" systolic blood pressure should be avoided in the setting of uncontrolled hemorrhage. Rather, a systolic goal of 80 to 90 mm Hg is preferable and may decrease mortality. This goal avoids excessive arterial pressure and venous dilation at bleeding sites and the disruption of an establishing clot. This systolic blood pressure goal should be increased in the setting of TBI to 100 mm Hg to allow maintenance of cerebral perfusion. Small fluid boluses (250–500 mL) can be administered if necessary to achieve these goals.

Waveform capnography is a useful adjunct to determine adequate perfusion. Both hospital and prehospital studies show that low or decreasing levels of end-tidal carbon dioxide correlate with increasing mortality in trauma. A recent, retrospective prehospital trial showed that capnography was at least as useful if not more predictive of mortality or of the need for massive transfusion than systolic blood pressure or shock index.

Circulation: Use of Blood Products

Blood being lost from a victim of major trauma should be replaced by blood. The survival benefit of early blood product administration has been reiterated in the recent military conflicts in Iraq and Afghanistan, but was in fact common practice in major conflicts predating this. As a result, several civilian studies have reviewed the benefit of prehospital blood products. The Prehospital Air Medical Plasma (PAMPer) trial investigators showed significantly lower mortality and median prothrombin-time ratio in their 230 trauma patients randomized to receive plasma as opposed to usual care (typically crystalloid). However, this benefit is likely most apparent when transport times exceed 20 minutes. This was demonstrated by the Control of Major Bleeding After Trauma (COMBAT) trial carried out in urban systems with short transport times to a level I trauma center. In this study, there was no significant difference in 28-day mortality between the two groups.

Secondary analysis of the PAMPer trial patients showed that, when compared with patients who received only crystalloid, only plasma, or only packed red blood cells (PRBCs), the group that received both plasma and PRBCs showed the most significant mortality benefit, with a hazard ratio of 0.38. This aligns with the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial evaluating a 1:1:1 ratio versus a 1:1:2 ratio of plasma, PRBC, and platelets for civilian trauma patients in the hospital. The 1:1:1 group showed improved hemostasis and fewer deaths resulting from exsanguination.

In an attempt to further achieve optimum replacement of blood lost, low-titer cold-stored whole blood has been proposed as a more ideal blood product in civilian trauma. Whole blood offers the advantage of having a smaller volume, higher hematocrit and platelet content, and lower citrate content when compared with equivalent amounts of component therapy. Military data have shown a mortality benefit with the use of whole blood. Several observational civilian trials have shown an indication to improved mortality, especially early in resuscitation, as well as a lower overall need for blood products. Some EMS agencies have therefore started incorporating whole blood in their systems.

Inclusion of blood products in prehospital systems requires consideration of training, cost, coordination with local blood banks, and specific protocol development. Duration of storage may be a limiting factor. European and military systems have incorporated freeze-dried plasma, which can be reconstituted. This has a longer shelf life, but it is awaiting approval by the US Food and Drug Administration.

Circulation: Tranexamic Acid and Calcium

Tranexamic acid (TXA) is an antifibrinolytic drug that can be utilized as an adjunct to resuscitation of massive hemorrhage. The randomized controlled Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial studied its use compared with placebo in 20,211 civilian trauma patients internationally. They showed significant reductions in all-cause mortality in the TXA group (14.5% vs. 16.0%, number needed to treat of 67) as well as mortality secondary to hemorrhage (4.9% vs. 5.7%). The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERS) trial retrospectively evaluated 293 consecutive admissions with combat-related injuries who received TXA. The authors showed significantly lower unadjusted mortality in the TXA group (17.4% vs. 23.9%), with the largest benefit in those who required a massive transfusion (14.4% vs. 28.1%). The more recent Study of TXA During Air Medical and Ground Prehospital Transport (STAAMP) trial, while underpowered to show an overall mortality benefit, did show a trend to benefit in patients with severe shock and also demonstrated that prehospital TXA could be safely administered.

TXA shows most benefit when given early after injury. Initial recommendations advise administration of 1 g as a loading dose within 3 hours of the injury, followed by 1 g infused over 8 hours. Administration later than 3 hours postinjury is not recommended. The Committee on Tactical Combat Casualty Care has, however, recently changed its prehospital dosage to a single 2 g dose. Prehospital guidelines supported by ACS-COT and ACEP recommend incorporating objective measures as guides to when to administer TXA, such as heart rate >120 beats/minute and/or systolic blood pressure <90 mm Hg. While showing improvements in measures of coagulopathy, TXA may also increase incidence of venous thromboembolism. Therefore, protocol development should ensure documentation of administration to allow outcomes to be tracked.

Hypocalcemia has recently been noted to be a common finding in trauma patients suffering from hemorrhagic shock. Several studies have highlighted that patients with hypocalcemia have a higher associated mortality and suggest that calcium should be administered early (with the first unit of blood as opposed to after several units have been administered as previously recommended) in an attempt to address the coagulopathy of trauma.

Head Injury and Neurologic Concerns

Impact brain apnea is an underappreciated contributor to morbidity and mortality in trauma. Following a concussive head injury, there is a short period of apnea. In severe impacts, recovery from this apnea does not occur spontaneously, resulting in direct neuronal injury from hypoxia and hypercapnia. Concurrently, massive catecholamine release causes hypertension, which worsens vasogenic edema secondary to hypercapnia and results in elevated intracranial pressure. Unless rapidly recognized and managed, this can lead to early death. Opening the airway and correcting hypoxia and hypoventilation can lead to favorable neurologic outcomes.

TBI is a significant cause of mortality in the injured patient. The primary goals of the prehospital clinician are to prevent secondary brain injury through the management of hypotension and hypoxia. Hyperventilation is detrimental to cerebral perfusion and should be avoided. Performing a prehospital rapid neurologic assessment provides useful information that the hospital treatment team can utilize in their management and prognostication. Validated scoring systems like the Glasgow Coma Scale (GCS) should be utilized.

Blunt trauma patients were often immobilized using rigid cervical collars and long spinal backboards because of concern for spinal injury. True spinal immobilization, however, does not occur with these techniques, and a growing body of evidence has shown significant complications from these measures including the development of pain, pressure injuries, and respiratory compromise. Thus, the routine use of long spinal backboards should be discontinued. The ACS-COT, ACEP, and the National Association of EMS Physicians recommend the term *spinal motion restriction* and provide guidance on its use in blunt trauma. These include (1) acutely altered level of consciousness (such as GCS score <15 or evidence of intoxication), (2) midline neck or back pain and/or tenderness, (3) focal neurologic signs and/or symptoms (such as numbness or motor weakness), (4) anatomic spinal deformity, and (5) distracting circumstances or injury that impairs the patient's ability to contribute to a reliable exam.

Validated clinical decision rules, such as the National Emergency X-Ray Utilization Study (NEXUS) or the Canadian Cervical-Spine Rules, can be utilized by prehospital personnel to clear cervical spines. The criteria utilized in these two decision rules are illustrated in Figure 1 and Table 1. However, there have been mixed results in studies comparing interrater reliability for these rules between prehospital and in-hospital clinicians.

For patients with penetrating trauma, the Eastern Association for the Surgery of Trauma issued a practice management guideline recommending against using cervical spine immobilization. In their systematic review, they found no benefit and higher mortality in patients who underwent spinal immobilization, even in the setting of direct neck injuries. The presence of a cervical collar may also delay the identification of critical injuries.

Hypothermia

Hypothermia complicates approximately two-thirds of civilian trauma patients arriving to the emergency department. Hypothermia is defined as a body temperature <35°C (<95°F) and is a contributor to trauma-induced coagulopathy. Correction of hypothermia is difficult once it is established. Therefore, early anticipation, identification, and management is important. Patients can be rewarmed in the prehospital setting by using blankets, increasing the ambient temperature in transport vehicles, and incorporating the use of fluid warmers when infusing fluids and/or blood products.

PREHOSPITAL PAIN MANAGEMENT

Several studies have demonstrated insufficient pain management in the prehospital setting. Adequate prehospital pain management not only is compassionate to the patient, but it assists with additional pain management in the hospital. Multiple agents exist to provide prehospital analgesia. If the patient is able to take oral medications, acetaminophen can be administered. Short-acting opiates such as fentanyl are efficacious and less likely to cause hemodynamic compromise when compared with morphine. Fentanyl's short duration may necessitate repeat dosing, and prehospital personnel should monitor for respiratory compromise. Ketamine can be given by intramuscular and intravenous routes and provides effective prehospital analgesia. It has the potential to cause a dissociated state. Despite prior practice based on poorly conducted studies, there is no convincing evidence that ketamine raises intracranial pressure.

PREHOSPITAL TRIAGE

Triage involves the process of quick and accurate patient evaluation to determine the extent of their injuries and the most appropriate level of medical care needed for those injuries. There has been a significant improvement in in-hospital and 1-year mortality in the United States through the management of injured patients in trauma centers as opposed to non-trauma centers. The ACS-COT divides trauma centers into different tiers based on capability, with level I centers having the resources for multidisciplinary trauma care including the presence of subspecialists, education, research, outreach, rehabilitation, and injury prevention. Appropriate prehospital triage is needed to ensure expedient transfer to the appropriate level of care within individual trauma systems. In achieving the balance of transporting patients to the appropriate level trauma center without overburdening them with lower severity injuries, the ACS-COT allows for an under-triage rate of 5% or lower and an over-triage rate of up to 50%.

Triage decisions vary depending on whether prehospital personnel are managing a single incident or a mass-casualty incident. For single incidents, the Centers for Disease Control and Prevention (CDC) Guidelines for Field Triage of Injured Patients provides a step-by-step algorithm to identify severity of anatomic or physiologic derangement that would warrant transfer to a higher-level trauma center (Fig. 2). These variables include abnormal vital signs (such as systolic blood pressure <90 mm Hg or a GCS score <14), anatomic problems (including penetrating injuries to the torso, head, or proximal limbs; two or more proximal long bone fractures; paralysis; and pelvic fractures), or significant mechanisms of injury (such as falls >20 feet in adults, ejection from a motor vehicle collision, pedestrian struck by an automobile). Other contributing factors that can drive triage decisions include elderly patients, advanced stage of pregnancy, head injuries in patients taking anticoagulant medications, and the clinical judgment of the prehospital clinician.

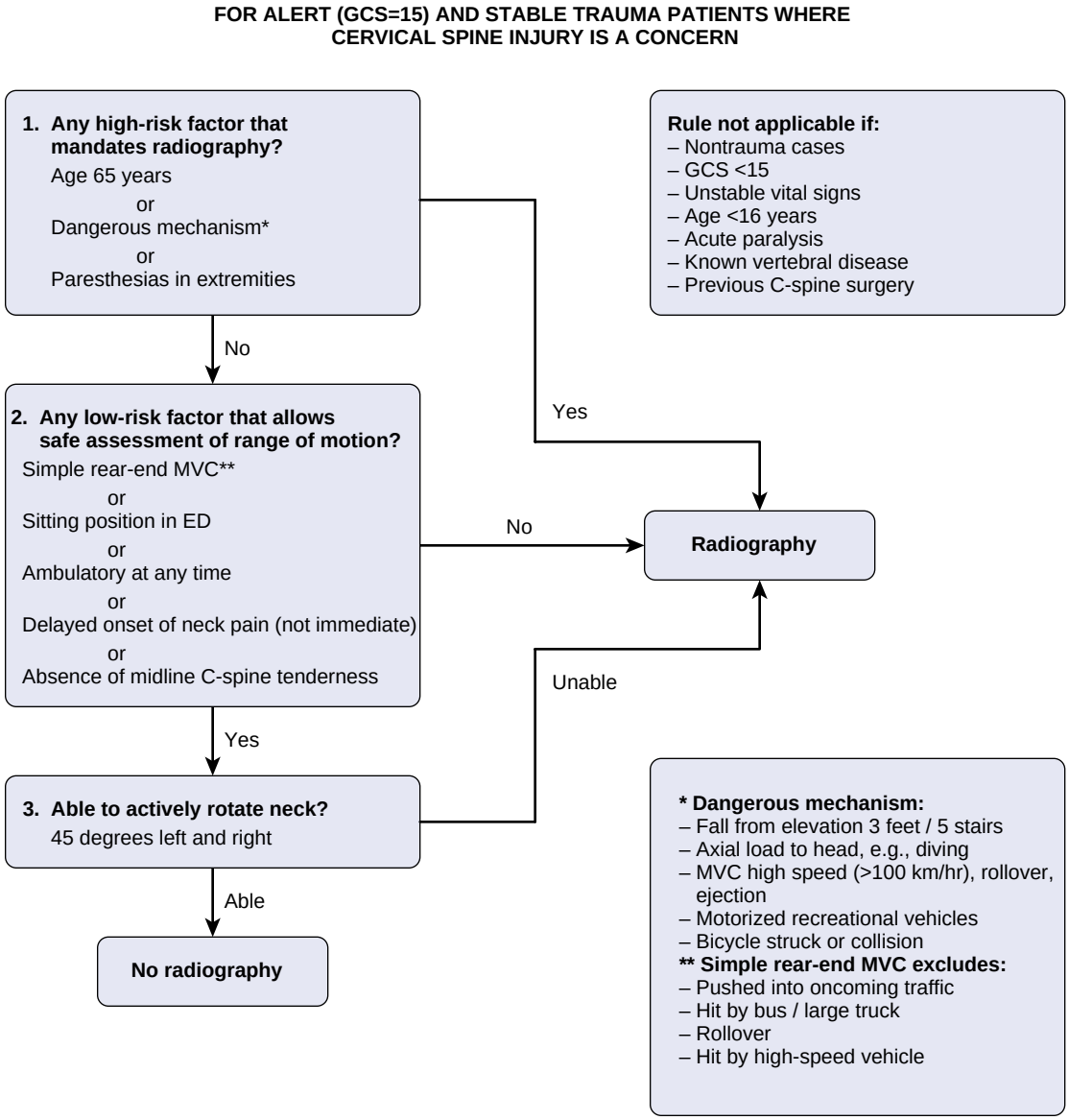


FIG. 1 Canadian cervical spine rule. *ED,* Emergency department; *GCS,* Glasgow Coma Scale; *MVC,* motor vehicle collision.

TABLE 1 NEXUS Criteria for Low Probability of Cervical Spine Injury

1	No Midline Tenderness
2	No focal neurologic deficit
3	Normal alertness
4	No intoxication
5	No painful distracting injury

NEXUS, National Emergency X-Ray Utilization Study.

Priorities are different when prehospital clinicians are managing a MCI. Such incidents run the risk of overwhelming available resources, and priority is placed on focusing care on those victims most likely to survive so as not to disproportionately allocate resources to those with lower likelihood of survival. Planning for MCIs is key, and these plans should be activated and executed when required. They will take into account preparation, planning, incident command, interoperability with other agencies, triage, communications, response to hazardous, chemical, or biological agents, management of special populations, and recovery.

The triage tool here must be simple, rapid, and have good interrater reliability. The CDC has developed the SALT approach (Sort, Assess, Lifesaving interventions, Treatment/transport) based on expert consensus and best available evidence (Fig. 3). Other systems in use include START (Simple Triage and Rapid Treatment) and RAMP (Rapid Assessment of Mentation and Pulse). Using SALT, patients are divided into five categories (dead, expectant, immediate, delayed, and minimal) using a color-coding scheme. Expectant patients (gray) are highly likely to die imminently despite attempts to address an immediate life threat. These patients are still deserving of comfort and compassion. Immediate patients (red) are often nonambulatory and have derangements of their respiration, perfusion, and/or mental status requiring immediate attention such as opening of the airway, application of a tourniquet or other control

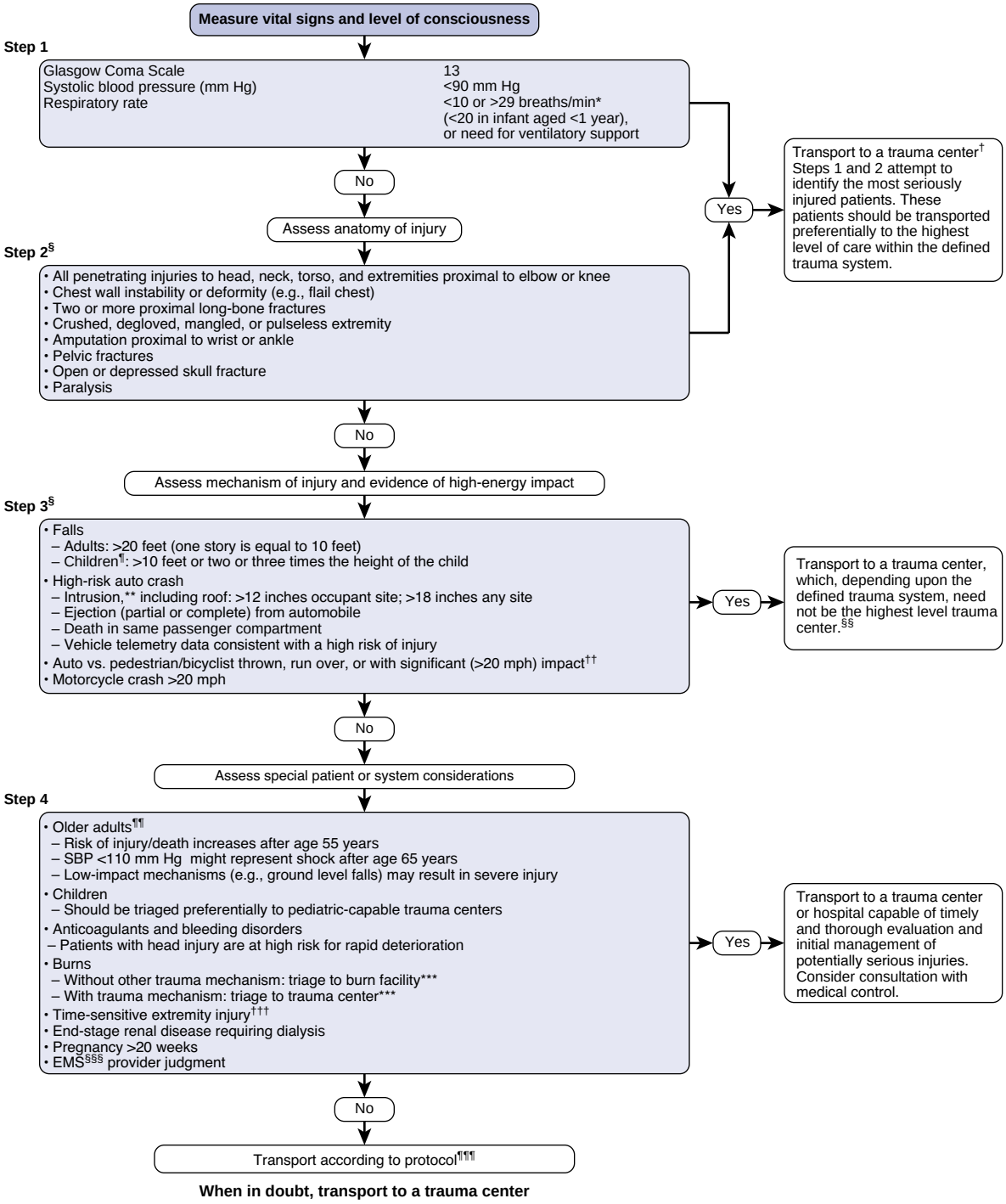


FIG. 2 Centers for Disease Control and Prevention Guidelines for Field Triage of Injured Patients. *EMS,* Emergency medical services; *mph,* miles per hour; *SBP,* systolic blood pressure. *(From Sasser SM, Hunt RC, Faul M, et al. Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011.* MMWR Recomm Rep. *2012;61:1–20.)*

*Upper limit of respiratory rate in infants is >29 breaths/min to maintain a higher level of overtriage for infants. †Trauma centers are designated Level I to IV, with Level I the highest level of trauma care available. §Any injury noted in steps 2 and 3 triggers a "yes" response. ¶Age <15 years. **Intrusion refers to interior compartment intrusion, as opposed to deformation, which refers to exterior damage. ††Includes pedestrians or bicyclists thrown from or run over by a motor vehicle or those with estimated impact >20 mph with a motor vehicle. §§Local or regional protocols should be used to determine the most appropriate level of trauma center; appropriate center need not be level I. ¶¶ Age >55 years. ***Patients with both burns and concomitant trauma for whom the burn injury poses the greatest risk for morbidity and mortality should be transferred to a burn center. If the nonburn trauma presents a greater immediate risk, the patient may be stabilized in a trauma center and then transferred to a burn center. †††Injuries such as an open fracture or fracture with neurovascular compromise. §§§Emergency medical services. ¶¶¶Patients who do not meet any of the triage criteria in steps 1 to 4 should be transported to the most appropriate medical facility as outlined in local EMS protocols.

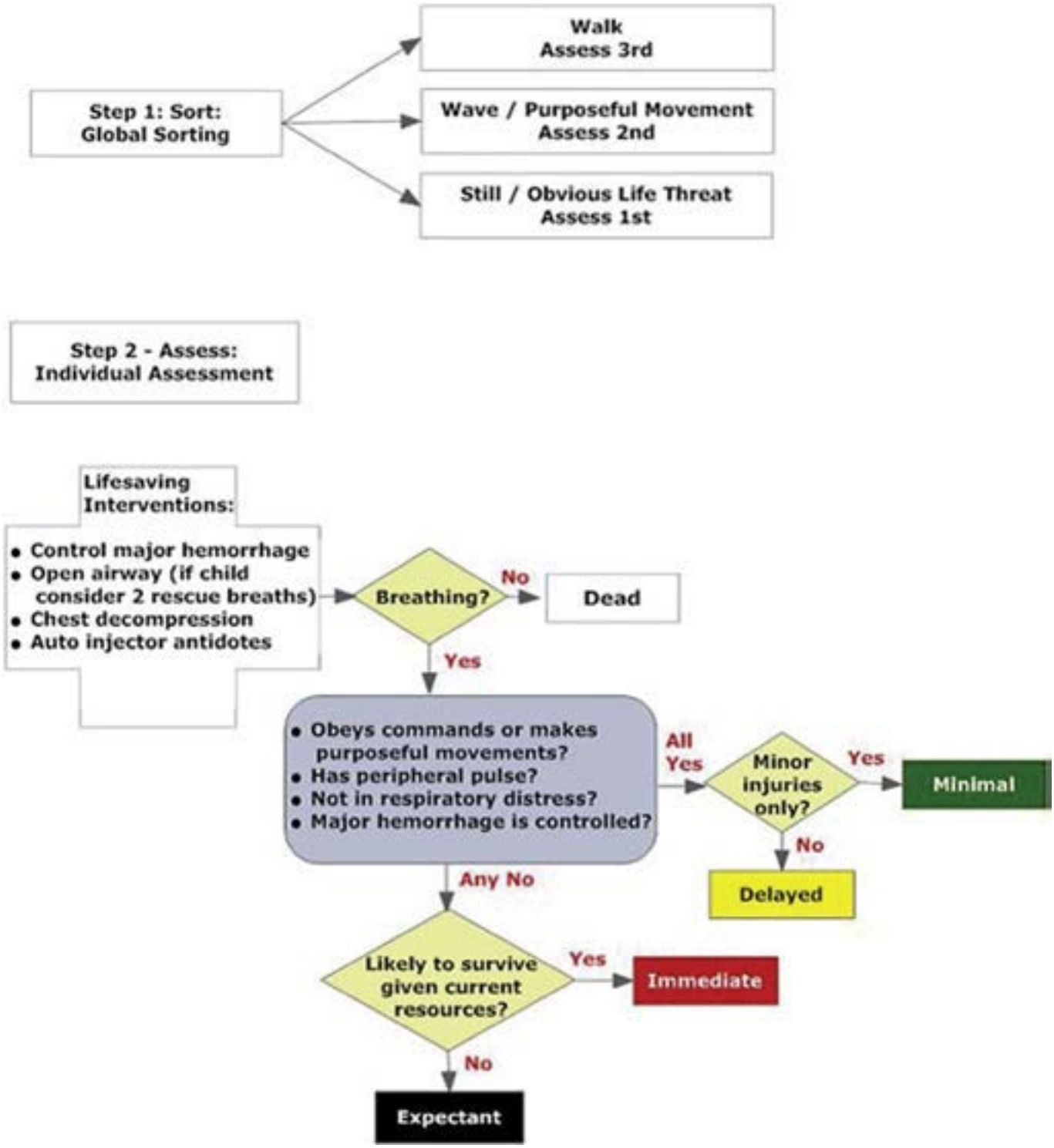


FIG. 3 SALT mass casualty triage. SALT, Sort, Assess, Lifesaving interventions, Treatment/Transport. *(From Brown J, Sajankila N, Claridge, J. Prehospital assessment of Trauma.* Surg Clin North Am. *2017;97:961–983.)*

of major hemorrhage, or chest decompression. Delayed patients (yellow) may also have significant injuries, but their care can be deferred for up to 1 hour. Minimally injured patients (green) are often ambulatory and may require very minor attention. Victims are often moved to a casualty clearing area, where they should undergo a repeat triage assessment to determine the transport mode and destination.

MODE OF TRANSPORTATION

The choice of transportation mode (whether ground or air) is dependent on multiple factors including distance, the patient's clinical condition, cumulative weight of the patient and treating personnel, weather conditions, availability of landing zones, and availability of prehospital resources. Equally important as the mode of transport is the skill set of the personnel providing that transport.

The benefit of helicopter EMS (HEMS) over ground EMS (GEMS) has been difficult to determine because of significant methodologic problems of studies attempting to answer this question. A recent retrospective study from Denmark dispatched HEMS or GEMS assets based on availability resulting from weather conditions, but found no significant difference in 1-year mortality for either critical illness or injury. Of note, the crews on both forms of transport were trained to a similar standard. It is important to understand that in the United States, HEMS and GEMS are not uniform, homogenous entities, and multiple economic and regulatory issues govern the education, training, and use of both teams. Therefore, individual trauma systems must determine the availability and capabilities of their various EMS assets and work with the EMS medical director and associated specialties to determine appropriate utilization and dispatch criteria.

Two studies recently compared alternate modes of transport for patients with penetrating trauma. Utilizing National Trauma Data Bank information, a study compared 103,029 patients transported by either GEMS or private vehicle within urban trauma systems and determined that private vehicle transport was associated with a higher survival (odds ratio of 0.38). The authors also separately studied 88,564 penetrating trauma patients transported either by EMS or police vehicle and found similar mortality rates between these two modalities.

EMS PATIENT HANDOFF

Handoffs are a critical process of patient care involving the transfer of information and responsibility from the prehospital to the hospital team. Several studies have highlighted the varying quality of EMS handoffs, including content delivered and information received. Competing priorities including patient transport from EMS to hospital stretcher and initiation of patient assessment by the trauma team may mean that essential information is missed. Therefore, a standardized process is recommended. This can take the form of a structured D-MIST report (comprising Demographics, Mechanism of injury, Injuries sustained or suspected, Signs, and Treatment given). If there are no immediate life threats to be managed, the trauma team should give EMS teams 30 to 60 seconds of uninterrupted time to provide their handoff. To aid information retention, the handoff information should be documented in the medical record.

PREHOSPITAL TRAUMATIC ARREST

Prehospital traumatic arrest unfortunately carries an overall poor prognosis. In both blunt and penetrating trauma, the cause often revolves around hypoxia, hemorrhage, or an obstructive pathology such as pericardial tamponade or tension pneumothorax. Unless a termination of resuscitation protocol exists within a prehospital system, most prehospital traumatic arrest patients will still be brought to the hospital. However, durations of arrest of greater than 10 minutes in blunt trauma and greater than 15 minutes in penetrating trauma are generally thought to have a very poor chance of regaining return of circulation, let alone meaningful neurologic recovery.

The pathophysiology can be described as a low-output state in trauma, secondary to the aforementioned mechanisms. This will often manifest as pulseless electrical activity before deteriorating into asystole. The prehospital clinician should address hypoxia, obvious external hemorrhage, and tension pneumothorax as previously discussed. Notably, external chest compressions may be ineffective in the setting of hypovolemia or an obstructive pathology and can unnecessarily delay a life saving intervention such as needle or open thoracostomy. If blood products are available, they should be administered.

FUTURE DIRECTIONS

The use of point-of-care ultrasound (POCUS) has significantly changed the diagnostic and management approach for critically ill or injured patients in the hospital, and it can be utilized in the prehospital setting. Several studies have demonstrated that, following focused training, paramedics can utilize POCUS effectively for a number of clinical indications. For the trauma patient, these include identification of a pneumothorax and the performance of the focused assessment with sonography in trauma (FAST) exam.

The approach to noncompressible torso hemorrhage remains challenging. Despite significant advances in hospital care, a significant proportion of patients with torso hemorrhage die before they can reach that care. The peak time of death from high-grade torso hemorrhage occurs within 30 minutes of injury, with a second early peak within the first 1 or 2 hours. Both urban congestion and rural geography in the United States can preclude shortening prehospital transport times, resulting in significant periods of time elapsing from the point of injury to definitive hemorrhage control (a median time of 128 minutes in one multicenter study). Thus, in-hospital hemorrhage control may be applied after the establishment of irreversible hemorrhagic shock. Alternative approaches may therefore be considered including the development of advanced prehospital resuscitation teams, similar to those utilized recently by the military. These may provide advanced trauma critical care, deliver blood products, and employ evolving techniques such as resuscitative endovascular balloon occlusion of the aorta (REBOA) to temporarily control subdiaphragmatic hemorrhage, all while maintaining a trajectory to hospital care: "scoop and control" as opposed to "scoop and run." REBOA has been utilized by physician-staffed prehospital teams in London and Paris, and data are evolving to support a survival advantage if utilized with strict indications within the right system of care.

Bypassing the emergency department and transporting patients directly from the field to the operating room based on predefined criteria may also shorten time to definitive hemorrhage control. This has been adapted from the military into some civilian centers in the United States. Early studies have demonstrated mortality benefits, in particular for the most severely injured and those sustaining penetrating trauma, in both adult and pediatric populations. Such policies require careful consideration and coordination between prehospital personnel and hospital teams.

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Use of Resuscitative Endovascular Balloon Occlusion of the Aorta in Resuscitation of the Trauma Patient

Adam Nelson, MD, and Bellal Joseph, MD

INTRODUCTION

Advanced Trauma Life Support (ATLS) emphasizes the rapid control of hemorrhage in the injured patient. The application of direct pressure or an extremity tourniquet is sufficient in many situations. However, noncompressible hemorrhage requires aortic occlusion for hemostasis. Noncompressible torso hemorrhage (NCTH) requires timely definitive hemostasis, equipment, and blood resources. To prevent immediate exsanguination before hemorrhage control, obtaining proximal aortic control remains the benchmark for survival in NCTH. For patients in extremis, this is typically achieved through emergency surgery coupled with resuscitative thoracotomy (RT) and descending aortic clamping. The use of resuscitative endovascular balloon occlusion of the aorta (REBOA) was first described in 1954 by Colonel Hughes to address the challenges of military traumatic hemorrhage during the Korean Conflict. Other attempts were described in the 1980s, but the technique fell out of favor because of undeveloped equipment and poor outcomes.

The past decade has witnessed an evolution in resuscitation paradigms with escalating extracorporeal capability and the introduction of precise technology. More specifically, the use of endovascular techniques to treat hemorrhage has increased significantly in civilian trauma care. REBOA is being adopted at many trauma centers as a supportive adjunct to resuscitation in the exsanguinating patient. Although the use of REBOA in trauma is relatively new, REBOA has been increasingly utilized for a more diverse patient population with hemorrhagic shock such as patients with ruptured abdominal aortic aneurysms, aortic-enteric fistulas, postpartum or abdominal/pelvic surgery hemorrhage, hemoperitoneum following splenic artery aneurysm rupture, gastrointestinal hemorrhage, and vascular injuries.

Despite emerging indications and potential in resuscitation, the true efficacy of REBOA as a temporizing hemostatic measure in hemorrhagic trauma is not yet established and the hemostatic effect may not be as profound as its hype. Currently, no high-grade empirical evidence demonstrates improvement in survival when REBOA is compared with the standard of care for severe hemorrhage. The risk-benefit ratio of this technology is still being investigated in different patient populations. Before widespread adoption, a rational and evidence-based evaluation of this tool is needed to identify its correct indications.

INDICATIONS

Proximal aortic control using REBOA is theoretically an ideal intervention to temporize life-threatening bleeding. However, these theoretical benefits are not proven empirically. To this day, REBOA protocols are derived from expert opinion and are not supported by quality data. These protocols must also be adapted to each institution depending on local trauma team facilities, resources, and strengths hindering widespread applicability. The Eastern Association for the Surgery of Trauma (EAST) issued recent practice management guidelines regarding the use of REBOA in hemorrhage control. They concluded that based on the very low quality of evidence, they could not recommend for or against REBOA.

The use of REBOA in patients with NCTH is primarily based on the patient's physiologic status in the prehospital setting and at the time of admission. Currently reported REBOA indications and algorithms are based on the presence or absence of signs of life on admission. While some reports emphasize that patients who arrive with cardiopulmonary resuscitation (CPR) in progress should strictly undergo RT, others have highlighted the potential role of REBOA in this setting. One advantage of RT is both diagnostic and possibly therapeutic in the setting of penetrating chest trauma. REBOA does not address other etiologies of traumatic cardiac arrest such as tension pneumothorax or cardiac tamponade, both of which can be treated with RT.

In patients who present without a pulse, the decision to utilize REBOA is based on the mechanism and pattern of injury, duration of CPR, presence of an organized narrow complex cardiac rhythm, and/or organized cardiac activity by an ultrasound exam. The Joint Theater Trauma System Clinical Practice Guideline: REBOA for Hemorrhagic Shock was established in June 2014 to guide the use of REBOA in trauma. This guideline includes the Traumatic Arrest Algorithm (Fig. 1) and the Algorithm for the Management of Profound Shock (Fig. 2).

For trauma patients arriving with loss of vitals, the potential use of REBOA is primarily restricted to patients with blunt trauma with organized rhythm detected on an EKG or FAST. Also, patients with penetrating trauma who underwent CPR for less than 15 minutes with a potential source of bleeding in the abdomen/pelvis/extremity and absent devastating head injury may also be candidates for REBOA placement (see Fig. 1).

For trauma patients presenting with signs of life on admission in profound shock, the potential use of REBOA is determined by vital parameters, the response to resuscitation, the likely pattern of injury, and the source of hemorrhage. All of these parameters are equally important in determining the need for REBOA. In a recent study, it was reported that 55% of patients with potential anatomic indications for REBOA did not ultimately have physiologic indications once we account for response to resuscitation. Such information is readily obtained from the patient's primary survey, clinical assessment, and imaging modalities such as focused abdominal sonographic examination for trauma (FAST), chest, and pelvic x-ray. In those patients, it is argued that REBOA may be inserted for transient responders or non-responders to resuscitation upon verification of the subdiaphragmatic source of the hemorrhage. The limitation of this argument is that there is no consensus on the definition of the transient response to resuscitation (see Fig. 2).

The major determinant for survival in the management of hemorrhage associated with pelvic fractures is timely hemorrhage control before exsanguination and cardiovascular collapse. An important step in the management of these patients is definitively excluding other sources of major hemorrhage. FAST and/or diagnostic peritoneal lavage (DPL) or diagnostic peritoneal aspirate (DPA) are performed to identify patients with hemoperitoneum who require immediate laparotomy. In hemodynamically unstable patients with pelvic fractures and negative FAST/DPA who have no evidence of significant thoracic bleeding or an aortic injury, the focus becomes stopping pelvic hemorrhage with options including angioembolization, REBOA, preperitoneal packing (PP), or emergent pelvic fixation.

Currently, high-quality data verifying the efficacy of zone 3 REBOA for the treatment of unstable patients with pelvic fractures does not exist. Randomized study designs are needed to verify the proposed indications and algorithms. Given that REBOA is a less invasive procedure compared with PP, its role in the management

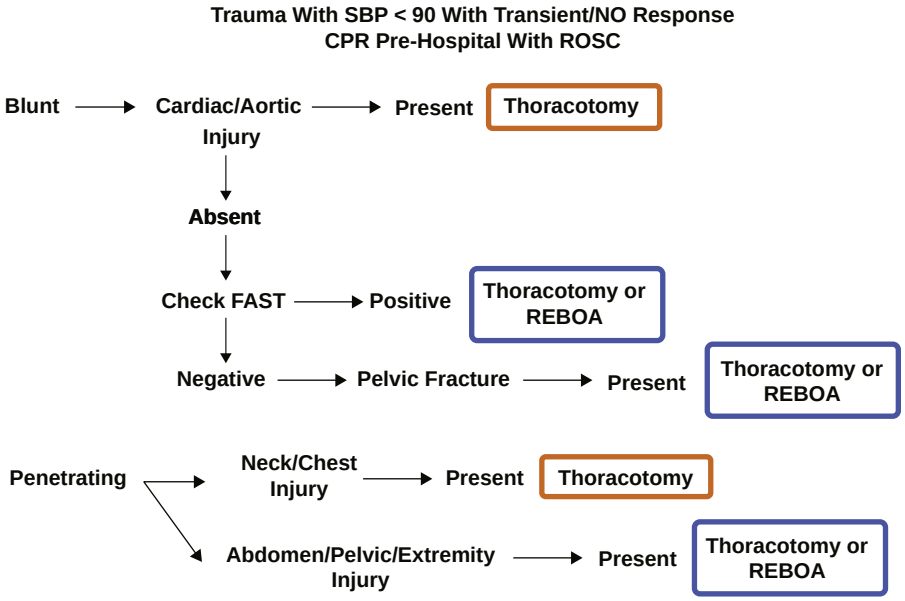


FIG. 1 Traumatic arrest algorithm for RT or REBOA for hemorrhagic shock.

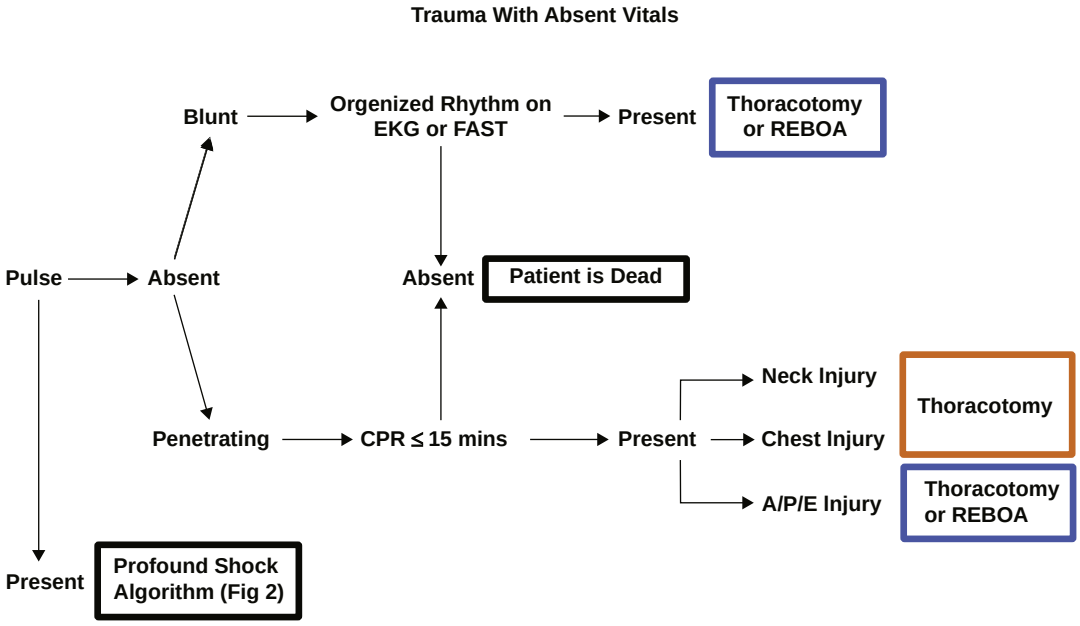


FIG. 2 Profound hemorrhagic shock algorithm for RT or REBOA.

of NCTH, specifically hemorrhage from isolated pelvic fractures, merits consideration.

CONTRAINDICATIONS

REBOA is strictly contraindicated in patients with traumatic aortic injury, hemorrhage proximal to zones of occlusion including areas of the neck, axilla, and superior mediastinum. Patients with extremity bleeding should have attempted hemorrhage control with the application of direct pressure or a tourniquet before REBOA placement. REBOA is also hazardous in traumatic brain injury, blunt cardiac, penetrating neck, or chest trauma where RT may have an advantage in the provision of definitive hemorrhage control. Relative contraindications include elderly age (age >70 years), pulseless electrical activity arrest longer than 10 minutes, presence of terminal illness, or profound comorbidities.

Patients with penetrating thoracic trauma who present in profound shock should undergo prompt RT. Upon accessing the thoracic cavity, definitive hemorrhage control can be directly performed and the descending thoracic aorta can be clamped above the diaphragm to augment myocardial and brain perfusion. The deployment of REBOA in the setting of thoracic hemorrhage is contraindicated and hazardous because of the potential to exacerbate hemorrhage from great vessel injury. Of particular concern are patients with

penetrating injuries having a thoracoabdominal trajectory. In those patients, REBOA may be considered only after ascertaining the subdiaphragmatic source of the hemorrhage and ruling out thoracic hemorrhage using a chest x-ray and a FAST exam. Chest radiography showing a widened mediastinum in the setting of blunt trauma may indicate thoracic aortic injury, which is another contraindication for REBOA since balloon inflation could worsen the injury and cause an aortic rupture.

RISKS

Assessing the risk of a procedure requires a standardized application. REBOA as an intervention is rapidly evolving and its current indications remain speculative, are based on expert opinion, and lack complete consensus. Outcomes are also confounded by the variations in catheter sizes, occlusion strategies, and occlusion durations. Quality data are limited, yet they are portrayed wrongly as being high in quality, contributing to a dazzling mirage. Selective emphasis on improved outcomes and concealing complications contributes to an illusion of improved outcomes. In addition, the excessive number of REBOA publications without standardization of outcomes and controls makes identification of risks more difficult. The greatest risk of this new technology is the potential for portraying disinformation and misinformation as facts.

The Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) registry is the largest prospective observational dataset examining the utility of aortic occlusion for those patients suffering from hemorrhagic shock. A 5-year retrospective analysis of this registry approved by the American Association for the Surgery of Trauma (AAST) was conducted between January 1, 2014, and November 6, 2018. During the study period, REBOA increased from 39% to 47.2% with a decreasing utilization trend in zone 1 and an increasing trend in zone 3. The catheter size also changed from a 4 to 5 French sheath (Fr) to a 7 Fr in later procedure years. The study concludes that REBOA survival increased significantly but fails to expand on the points we raise next. Procedure-related complications in the open aortic occlusion were stable; however, distal embolism, acute kidney injury, and pneumonia/acute lung injury were more frequent in the REBOA group and increased annually as the study progressed. Concerning mortality differences between REBOA over open aortic occlusion, the two groups were very different, making a direct comparison between these two cohorts unrealistic. However, while open aortic occlusion patients were more likely to expire in the emergency department or operating room, REBOA patients had a greater likelihood of expiration in the ICU or other parts of the hospital. Despite increasing expertise in REBOA, both the time from admission to hemodynamic stability and definitive hemorrhage control was lower in patients requiring open aortic control.

Thrombosis and distal embolization leading to limb ischemia are known complications from femoral arterial cannulation. This risk increases with larger catheters and with the cannulation of smaller arteries. Assessment of distal limb perfusion after REBOA placement is important to identify and mitigate ischemic complications. Suspicion of limb ischemia requires further diagnostic imaging and consultation with vascular surgery. Cannulation of the common femoral artery (CFA) rather than the SFA is a key step in avoiding ischemic complications as the CFA is larger in diameter and therefore has less risk of thrombosis. Proficient and consistent cannulation of the CFA with ultrasound guidance (if possible) is a requirement for providers placing a REBOA catheter. Inadvertent venous cannulation is another described complication of REBOA placement that underscores the importance of ultrasound guidance.

TECHNICAL POINTS

The challenging and rate-limiting step of REBOA is gaining access to the CFA. Even before the patient is deemed eligible for REBOA, establishing CFA cannulation is attempted. Reliable access proves important in avoiding limb ischemia and subsequent complications.

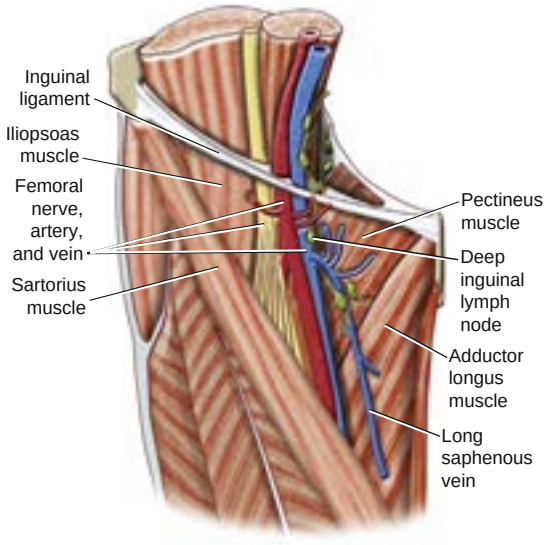


FIG. 3 Common femoral artery (CFA) anatomy in the groin. *(From Mauro M, Murphy K, Thomson K, et al.* Image Guided Interventions, *3rd ed. Philadelphia: Elsevier; 2020.)*

Familiarity with the CFA anatomy in the groin is fundamental (Fig. 3). The inguinal ligament runs from the anterior superior iliac spine to the pubic tubercle. The external iliac artery becomes the CFA as it crosses underneath the inguinal ligament. The CFA then bifurcates into the SFA and the deep femoral artery 3 to 4 cm distal to the inguinal ligament. To note vascular landmarks in the groin crease are not reliable.

Effective cannulation of the CFA is dependent on the surgeon's level of experience, the clinical situation, and the availability of ultrasound. One of the following three methods may be used: open cutdown, ultrasound-guided percutaneous, and blind percutaneous. Percutaneous access can be challenging in the setting of ongoing CPR, and the current practice for these patients is cannulation after open surgical exposure. Open cutdown begins with a vertical groin incision to identify the CFA as it emerges beneath the inguinal ligament and ends with cannulation under direct visualization. Even in experienced hands, blind percutaneous access has resulted in the cannulation of the wrong vessel. Blind access entails entering the vessel within 2 cm of the inguinal ligament, and this requires a skin entry site superior to the typical femoral arterial line access site. Data shows that blind access is easier to perform when a femoral pulse is present, but this is seldom the case in the exsanguinating trauma patient. If percutaneous access is desired, we highly recommend ultrasound guidance to ensure CFA cannulation, given that ultrasonography is readily available and will not delay time to hemorrhage control.

At this point, the insertion of the arterial line in the CFA does necessarily imply that we are committed to the path of REBOA insertion. One of the benefits of REBOA's hype is that it increased comfort in inserting arterial lines in hemorrhagic trauma patients. Once the decision made is to proceed with REBOA, the catheter (arterial line or micropuncture) used for initial CFA access must be upsized to a larger sheath depending on the device being used. To this day there is neither consensus on the optimal REBOA catheter nor one standardized catheter available across all trauma centers. Devices being used range from 4 to 14 French with new devices being promoted and released regularly. Note that while external landmarks are utilized to estimate insertion lengths of the device within the aorta, this proves to be much more difficult in patients with obese body habitus. While upsizing and inserting devices, the catheter should always move liberally within the sheath and dilator. If resistance is encountered, extreme caution is required to prevent severe injury. If the utilization

of tactile feedback and imaging in experienced hands fails to resolve the resistance met, the procedure should be aborted.

When we speak of REBOA, we divide the aorta into three zones (Fig. 4). Zone 1 extends from the left subclavian artery to the celiac artery. Zone 2 is between the celiac artery and the lowest renal artery, and zone 3 extends from the lowest renal artery to the aortic bifurcation. The balloon should never be inflated in zone 2 to avoid the occlusion of visceral vessels. Occlusion at this level impedes retrograde flow and perpetuates a prothrombotic state. Ultimately, the goal is to inflate the REBOA catheter in zone 1 or zone 3. Choosing the location of balloon inflation requires determining the most likely source of bleeding. Such information is derived from the patient's primary survey, clinical assessment, and imaging modalities such as FAST, chest, and pelvic x-ray. In theory, balloon inflation should occur as distally as possible but proximal to the site of bleeding. However, this does not always translate clinically. Upon verification of the subdiaphragmatic source of hemorrhage using the aforementioned modalities, effective balloon inflation at zone 1 ensures occlusion proximal to the site of hemorrhage. If the bleeding is deemed to originate from an isolated pelvic fracture, balloon inflation at zone 3 ensures occlusion of the aorta proximal to the bleeding site. In both cases, the focus should shift immediately to providing definitive hemorrhage control interventions. Whether patients in arrest who arrive with CPR in progress should strictly undergo RT or REBOA to enhance cerebral and coronary perfusion while temporizing distal hemorrhage is yet to be determined.

To arrive at the desired aortic zone for balloon inflation, the following surface landmarks are used to estimate the required depth of catheter insertion. The inferior border of zone 1 and zone 3 corresponds to the xiphoid process and the umbilicus, respectively. Placing the inferior edge of the balloon just above these desired landmarks and measuring the distance to the end of the introducer sheath all while tracing the path of the iliac artery and aorta may serve as a guide to the catheter's depth of insertion. This technique is utilized for standard, over-the-wire balloon catheters. The balloon of the ER-REBOA and ER-REBOA PLUS catheters (Prytime Medical) is set back from the tip of the catheter. This allows one to estimate the required depth of catheter insertion by measuring from the sternal notch to the end of the sheath for zone 1 and from the xiphoid process to the end of the sheath for zone 3.

The depth of balloon insertion has now been determined and the distance should be labeled in the trauma flow sheet. Depending on the make and model of the catheter, it may either have distance markers on it or require manual marking with tape. If a Coda-type balloon (Cook Medical) is used, then the balloon is inserted over the guidewire and into the sheath. Alternatively, if an ER-REBOA catheter is used, then the catheter is inserted directly into the sheath without requiring a guidewire. The catheter is advanced to the previously determined depth and secured with a catheter clip, occlusive dressing, or suture. It is imperative to use imaging (x-ray or fluoroscopy) to ensure proper positioning of the catheter before balloon inflation (Fig. 5). The use of ultrasound to visualize the balloon inflated in zone 3 has been reported and requires a high level of experience. However, ultrasound visualization of zone 3 placement remains technically challenging.

The placement of REBOA in the aorta has now been confirmed and balloon inflation with saline or dilute contrast material should begin. Full strength contrast is avoided because it is viscous and will clog the balloon lumen. Different occlusion times and strategies have been practiced at different institutions, the most common of these being complete balloon occlusion in REBOA practicing centers. Partial occlusion (pREBOA) or intermittent deflation/inflation of the balloon (iREBOA) is used at some centers to minimize complete occlusion time. This is difficult to achieve without continuous monitoring of the blood pressure both above and below the balloon along with a clinical assessment of the rate of bleeding. There are presently insufficient data to guide this practice, the pREBOA and iREBOA can potentially prolong occlusion times while mitigating occlusion-associated physiologic derangements. However, the question of whether these findings are translatable to clinical settings remains unanswered. For this section, we will restrict the technical pearls to complete occlusion of the aorta.

The balloon is slowly inflated until the contralateral femoral pulse is lost. While this is not an easy task in the hemorrhagic trauma patient, the presence of an arterial pulse waveform monitor can guide the volume of inflation. In the ER-REBOA catheter, the waveform is proximal to the balloon and similar to a floating pulmonary artery catheter. Therefore, inflation continues until a rise is noted on the tracing. If the waveform is distal to the balloon, inflation should stop when the arterial waveform disappears. If these waveform monitors are not available, some experienced endovascular surgeons stress

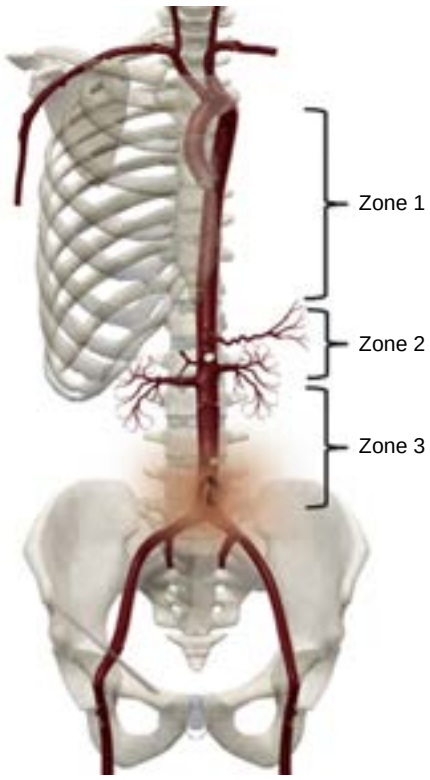


FIG. 4 **Zones of the aorta.** *(From Bogert JN, Davis KM, Kopelman TR, et al. Resuscitative endovascular balloon occlusion of the aorta with a low profile, wire free device: a game changer?* Trauma Case Rep. *2017;7:11–14.)*

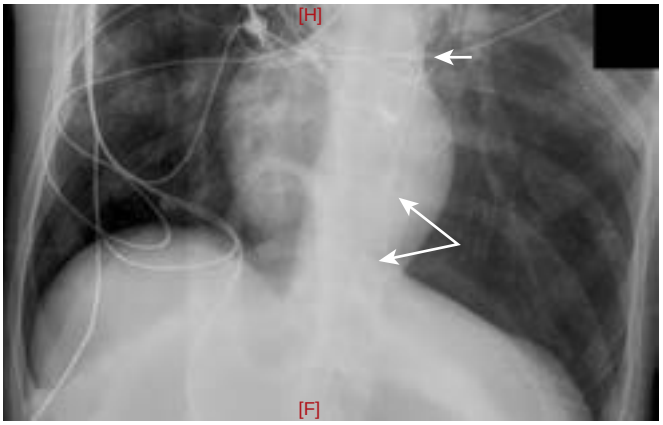


FIG. 5 Chest radiograph confirming REBOA placement before inflation.

the cessation of balloon inflation if subtle increases to resistance are encountered during inflation. How effectively this subtle increase can be detected by experienced surgeons, let alone inexperienced ones, is yet to be determined. Real-time fluoroscopic visualization as the balloon expands against the walls of the aorta can reliably determine adequate inflation. Inflation should stop once the balloon stops widening and elongates with added volumes. Similarly, portable radiography can reveal adequate aortic occlusion based on the shape of the balloon. If overinflation has ensued, the balloon will resemble an oversized oblong shape with an extension of the balloon beyond its edges.

At this point, complete occlusion of the aorta has been achieved. Establishing timely definitive hemorrhage control via surgical and/or endovascular interventions becomes the next step. According to the literature, the most frequent location of REBOA insertion is the ED followed by the operating room. If the patient is in the ED, they should be immediately transported to the operating room or angiography suite. The time to intervention should be minimized at modern trauma centers with advanced interventional facilities. If there is doubt that REBOA in the ED will significantly delay transfer to definitive management, then the rationale behind its insertion should be reconsidered. Safe duration of complete aortic occlusion is unknown, but the American College of Surgeons Committee of Trauma (ACS-COT's) joint statement recommends complete balloon occlusion given that definitive control is within 15 and 30 minutes for a balloon inflated in zones 1 and 3, respectively. These time restraints are seldom adhered to in REBOA practicing centers. While some studies report tolerance to longer occlusion durations, it is the surgeon and his team's responsibility to obtain definitive hemorrhage control and deflate the balloon at the earliest time possible. The aforementioned partial balloon inflation strategies in either zone 1 or 3 may extend the maximum occlusion time; however, this is not well studied and can lead to issues with intimal injury and balloon migration. Additionally, partial occlusion is difficult to accomplish in practice because small changes in balloon volume create large changes in distal blood flow.

Complete occlusion of the aorta reduces dramatically the intravascular space. This reduction rapidly and dramatically increases afterload whose effects on the heart, lungs, brain, and other proximal organs may prove deleterious. At this point, continuous monitoring of arterial pressure is mandatory and adjustment in resuscitation products may be required. With the mirage of "normal"-appearing vital signs during aortic occlusion it is easy to forget that with every minute of balloon occlusion, distal organs are experiencing ischemia.

Balloon deflation is a critical step in restoring distal tissue perfusion, but this step is not without risk. It can lead to highly labile vitals because of acidic blood washout from ischemic tissue and the abrupt fall in cardiac afterload. Hypotension ensues because of sudden vasodilation and relative hypovolemia. At this point, communication between the surgeon and anesthesiologist is necessary to ensure prompt administration of pressors and volume expanders to reverse these entities. Balloon deflation may require 15 minutes or more. It should be deflated slowly over the course of 3 to 5 minutes initially, never removing more than 1 mL from the balloon at a time. It is important to note that very minute changes in balloon volume result in large changes in blood flow distal to the balloon. For this reason, the surgeon should be extremely careful not to remove more than 1 mL at a time from the balloon. The surgeon should also make sure to assess and treat any physiologic aberrations that arise between withdrawals.

Increasing sheath dwell time predisposes to increased ischemic complications to the limb. At this point, definitive hemostasis has been established and the balloon has been successfully deflated. Standard of care mandates documentation of lower limb perfusion. This can be achieved by angiography (gold standard) illustrating patent flow to the foot or with Doppler signals symmetric to the contralateral leg. In the setting of distal flow limitations, prompt angiography and vascular surgeon consultation are necessary.

If the CFA cutdown approach is used, then surgical repair of the artery is necessary. To ensure arterial patency, a Fogarty balloon should be used to clear the proximal and distal vessel of any suspected thrombus. Documentation of lower limb perfusion, described above, is required. If CFA percutaneous approach is used, then the sheath may be pulled and pressure held for 30 minutes. Documentation of lower limb perfusion is also required. For the first 12 hours after sheath removal, lower extremity neurovascular examinations should be done every hour. Vascular ultrasound of the CFA puncture site may also be considered at 72 hours to identify possible access site complications.

PITFALLS

At present, we do not have high-quality Level I evidence for REBOA efficacy in the treatment of traumatic hemorrhagic shock, and additional research is warranted. Furthermore, none of the proposed guidelines or algorithms adopted at trauma centers are backed by empirical evidence demonstrating a clear survival benefit when REBOA is used in comparison to the standard of care. The current indications for REBOA remain speculative and are based on expert opinion with no complete consensus.

The rate-limiting step for REBOA is obtaining safe and accurate CFA access after determining that the patient may benefit from aortic occlusion. This step is difficult and time-consuming, especially in the hemorrhagic trauma patient. We recommend early CFA access in all patients with hypotension secondary to hemorrhage. This intervention provides a more accurate systolic blood pressure measurement and secures access for REBOA if deemed necessary. Using this strategy, once the physician decides that the patient qualifies for their definition of nonresponder to transfusions, REBOA may be inserted without delay.

The aortic diameter at zone 1 varies between 15 and 38 mm and at zone 3 between 6 and 28 mm. Most balloons can tolerate large inflation volumes but will only require a fraction of their maximum volume to achieve complete occlusion. The surgeon must remain aware of these two knowledge points while managing the patient in duress. Even with close attention to signs of aortic occlusion, balloon overinflation occurs. This predisposes to intimal injury that may progress to dissection once the device is removed. The balloon may also rupture and complicate and delay valuable hemorrhage control time. The worst scenario is balloon overinflation leading to aortic rupture and immediate patient exsanguination.

In the hypotensive patient, arterial blood is not pulsatile and looks dark, similar to venous blood. Venous placement of REBOA may occur without the surgeon's ability to discriminate because of these characteristics. This results in ongoing hemorrhage and may injure the vein after balloon inflation. Inadvertent venous access underscores the importance of using ultrasound to obtain initial vascular access. Similarly, malposition in the aorta can lead to ineffective hemostasis, continued hemorrhage, intimal injury, and injury to the origins of visceral vessels or injury to smaller iliac arteries depending on location. We recommend the use of radiographic or fluoroscopic imaging to identify and correct balloon malposition. More so, failure to secure the sheath and balloon will lead to distal migration of the balloon. This can cause a similar injury pattern to balloon mispositioning.

Aortic occlusion in an exsanguinating patient will cause a rapid and marked increase in the measured blood pressure. Vital signs may even appear normal after balloon inflation despite the significantly altered physiology. In the setting of RT, there are obvious external cues that the patient is exceptionally ill and requires emergent intervention. Due to the less invasive nature of REBOA, those external indicators are absent, and it is possible that less experienced trauma teams fail to recognize the ongoing urgency to proceed with the next phase of care. It is imperative that trauma team leaders educate all members of the team regarding the physiologic alterations and time constraints created by aortic occlusion.

COMPLICATIONS

REBOA is not without complications, and the risk can be substantial if this tool is used inappropriately. Studies ensuring the safety of this intervention or demonstrating an acceptable risk-benefit ratio are also lacking. The complications associated with the use of REBOA are partially attributed to the limitations of currently available devices. These limitations include the size of the catheter and the introducer sheath and catheter stability. Technical complications are divided into several categories: issues associated with arterial access, challenges associated with balloon positioning, inflation, and deflation, and difficulty with sheath removal.

Reported femoral access complications include arterial disruption, dissection, pseudoaneurysms, hematoma, thromboembolism, extremity ischemia, and the problem of prolonged occlusion time and delayed definitive control. As previously stated, reliable CFA access is paramount in reducing complications arising from vascular access. Aortoiliac injuries have also occurred; these include intimal tear, dissection, thrombosis, and rupture, which may be fatal or cause limb loss. Balloon rupture may occur with over-inflation of the balloon relative to the aortic diameter. Unintended inflation of the balloon in the iliac vessels may lead to rupture or thrombosis. In the elective setting, thrombotic complications associated with arterial cannulation are mitigated by heparin infusion. However, this is not an option in the bleeding trauma patient. Thrombus formation can occur anywhere along the length of the catheter or access site. It is crucial to check for Doppler signals after balloon deflation. Additionally, angiography should be performed before sheath removal to evaluate for distal thromboembolism. Any concerns for limb ischemia should prompt consultation with vascular surgery.

Other limitations common to endovascular occlusion of the aorta include occlusion time and physiology postrelease. Even if one's technique is impeccable, prolonged occlusion results in significant distal ischemic reperfusion injury, predisposing the patient to organ dysfunction, cardiovascular collapse, and spinal cord ischemia. In as little as 15 minutes, the metabolic derangements can be irreversible, thus emphasizing the importance of proximity to definitive hemorrhage control, which is feasible with RT.

Recently, to mitigate the risk associated with occlusion times, pREBOA or iREBOA has been introduced. These practices utilize the same catheter, to allow limited blood flow past the balloon. Theoretically, allowing some flow may limit complications of ischemic reperfusion injury. Currently, REBOA is primarily utilized as an all-or-none flow occlusive device. Several animal studies indicate this is potentially feasible in limiting ischemic burden; however, partial occlusion is difficult to achieve without continuous monitoring of the blood pressure both above and below the balloon along with a clinical assessment of the rate of bleeding. Besides, determining and maintaining a consistent degree of partial inflation is difficult to achieve given the complex physiologic environment. Thus, at this point, there is presently insufficient data to guide this practice.

CONCLUSION

REBOA is a novel minimally invasive method to achieve proximal bleeding control in trauma patients with noncompressible torso hemorrhage. The catheter continues to evolve, balloon sizes are not final, device application (pREBOA vs. iREBOA vs. complete occlusion) is still under investigation. The ease of safely performing this procedure is a concern as well. Even the complications associated with this device have not been adequately recognized. REBOA's utilization currently surpasses its indications and requires certification before use. Its utilization must be adapted to the individual institution's available resources, and logistical familiarity is needed, as is greater practice with this procedure. There needs to be a well-defined population delineated before providing any strong recommendations for REBOA use. This, too, will require time and controlled prospective studies.

Suggested Readings

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Airway Management in the Trauma Patient

Samuel M. Galvagno Jr., DO, PhD, and Thomas M. Scalea, MD

Early, aggressive, definitive management of the airway is emphasized as a crucial initial priority for trauma patients because hypoxia and airway obstruction are closely linked to preventable morbidity and mortality. Airway management in trauma patients is frequently complicated by cervical spine instability, brain injury, hemodynamic instability, lack of patient cooperation, risk of aspiration, time pressure, and facial injuries. For these reasons, airway management is an essential skill given the well-defined adverse clinical outcomes that ensue when trauma patients develop acute respiratory insufficiency and hypoxia caused by delays in securing the airway. This chapter will describe techniques that can be employed to rapidly establish and maintain a patent airway, with an emphasis on the importance of providing adequate oxygenation and ventilation throughout all phases of airway management.

RAPID CLINICAL AIRWAY ASSESSMENT: INDICATIONS FOR MANAGEMENT

A patient who is alert, oriented, and speaking normally in the absence of any observed injuries to the head or neck has an adequate airway. Any change in voice, complaint of a sore throat, dyspnea, tachypnea, use of accessory muscles, noisy breathing (snoring or stridor), or unexplained agitation may be ominous signs of imminent airway compromise.

For patients who are not able to safely maintain a patent airway, a focused examination should be performed while preparing the necessary equipment. The majority of the anesthesiology literature suggests that a combination of airway parameters found during an airway examination will provide the best chance for predicting a potentially difficult airway. A systematic approach to airway assessment should be employed, following the line of sight of the anesthesia provider from the upper incisors to the vocal cords, with a focus on the inside of the mouth and pharynx, concluding with examination of the mandibular space, neck, and chest. Box 1 and Figures 1 and 2 describe clinical tests that can be used to determine if a patient is likely to have a poor view of the vocal cords during direct laryngoscopy.

Of utmost importance during airway management is the ability to ventilate a patient with a mask. Independent risk factors for impossible mask ventilation include male sex, a history of sleep apnea, Mallampati 3 or 4 status, and the presence of a beard. Ultimately, few will argue that having an armamentarium of skills to manage the difficult airway is the most important aspect of management, especially considering the myriad factors that may preclude a thorough airway assessment in the trauma patient.

OXYGEN THERAPY AND AIRWAY ADJUNCTS

Initial interventions for airway management include provision of supplemental oxygen and a variety of noninvasive airway maintenance techniques. Complicating this process is the fact that the spinal cord must be protected until the possibility of a spinal cord injury has been excluded. Oxygen therapy should be provided to maintain the SpO_2 above 92%. A logical first step is to apply a non-rebreathing mask, which provides an FiO_2 >90%. High-flow humidified oxygen via nasal cannula is an increasingly popular mode for oxygen delivery (i.e., 60 L/min at 100% FiO_2) and may be delivered beneath the mask to provide additional oxygenation and some degree of positive end-expiratory pressure (PEEP). Oxygen therapy can then be deescalated accordingly after the patient has been assessed and stabilized, to a simple face mask (FiO_2 35%–55%), a Venturi mask (FiO_2 24%–60%), or a nasal cannula (FiO_2 24%–44%).

If the airway is compromised and the patient is not ventilating and oxygenating adequately, rapid noninvasive interventions are indicated during the interval preceding preparation for establishing a definitive airway. Bag-valve mask (BVM) ventilation with 15 L/min of oxygen should be initiated (FiO_2 90%–100%). Addition of a nasal cannula beneath the mask is advised when available to provide additional high-flow (>10 L/min) oxygen throughout the intubation procedure. This technique may help prevent desaturation during intubation by improving preoxygenation while also providing apneic oxygenation during the intubation attempt. Oropharyngeal or nasopharyngeal airways can be inserted to alleviate airway obstruction by the tongue. The most reliable technique for properly sizing an oral airway is to measure from the midpoint of the incisors to the angle of the mandible. Nasopharyngeal airways should not be used if the patient has a suspected craniofacial injury for fear of inserting the devices intracranially. The length of a nasopharyngeal airway should be selected based on the distance from the tip of the patient's nose to the tip of the earlobe. The chin-lift maneuver, which is performed by gently lifting the mandible without hyperextending the neck, may help open the airway. Alternatively, the jaw-thrust maneuver can be performed by displacing the mandible forward while applying

BOX 1 Airway Parameters That May Predict Poor Visualization of the Vocal Cords During Direct Laryngoscopy

- Prominent incisors or abnormal dentition
- Mandibular protrusion (see Figure 1)
- Mouth opening (>3 fingerbreadths, or 5–6 cm is normal)
- Mallampati classification (see Figure 2)
- Thyromental distance (>3 fingerbreadths, or 5–6 cm is normal)
- Cervical range of motion (should *NOT* be tested in any patient with a suspected C-spine injury)
- Anatomic abnormalities (masses, swelling)
- Thickness of neck
- Length of neck (shorter neck associated with difficult intubation)

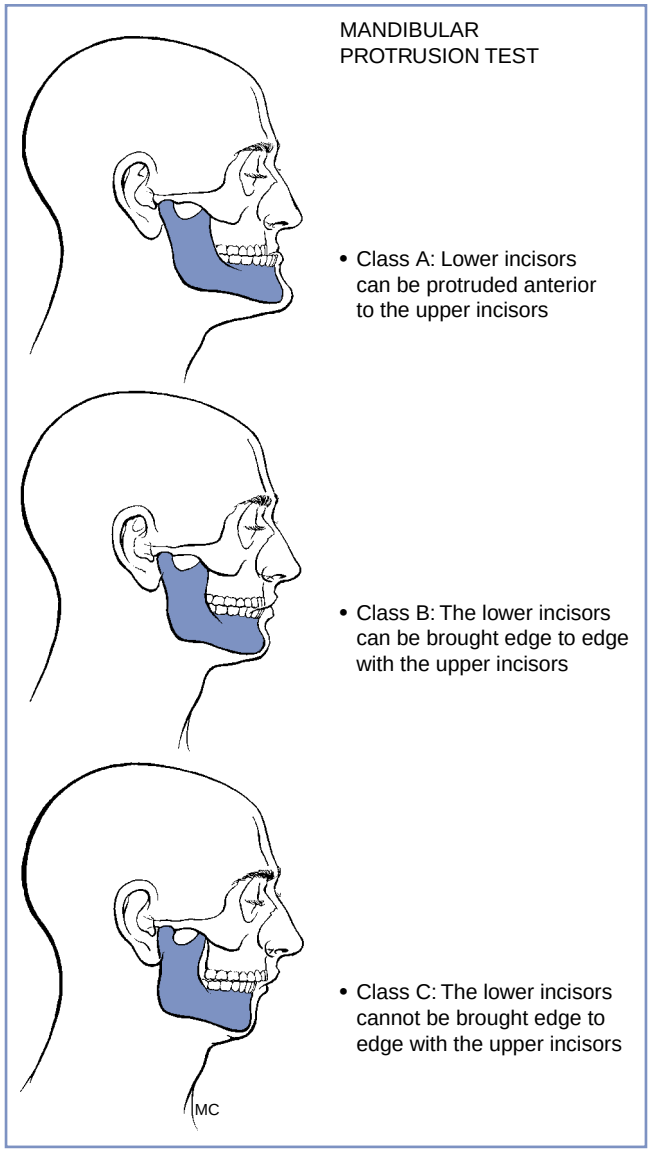


FIG. 1 The mandibular protrusion test. The test assesses jaw mobility. Class A portends better vocal cord visualization during direct laryngoscopy than Class B or C. (Modified from Munnur U, de Boisblanc B, Suresh MS. Airway problems in pregnancy. *Crit Care Med.* 2005;33:S259-S268.)

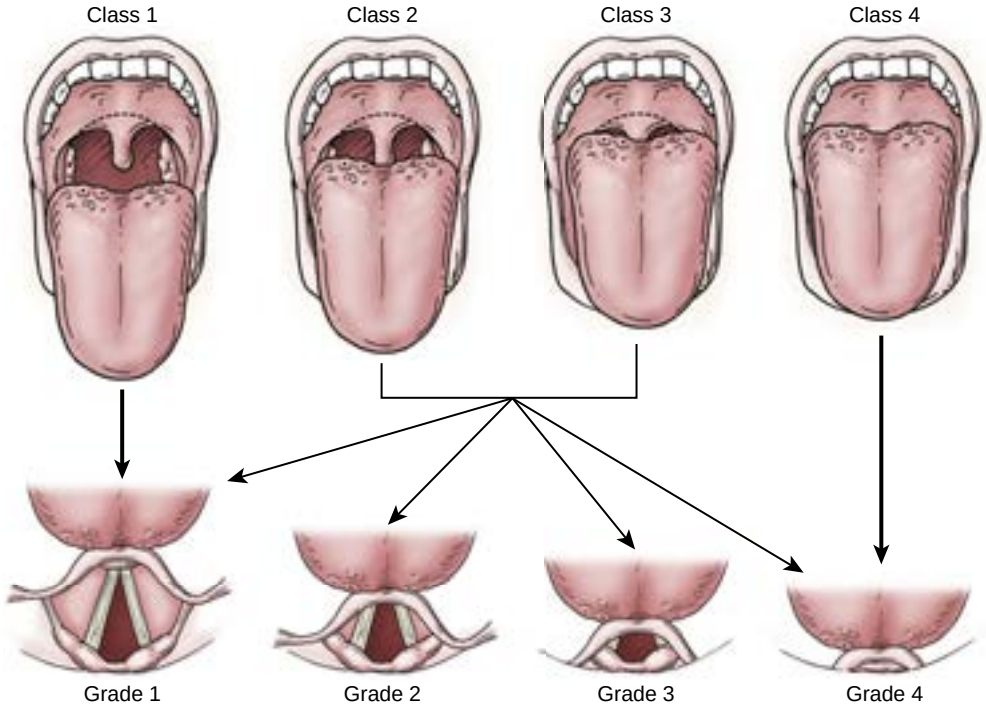


FIG. 2 The Mallampati classification. The higher the class, the worse the Cormack-Lehane view of the vocal cords during direct laryngoscopy. *(From Lalwani AK, ed. Current Diagnosis and Treatment in Otolaryngology: Head and Neck Surgery. 2nd ed. New York: McGraw-Hill; 2007.)*

pressure to both angles of the mandible. Either technique is preferable for trauma patients because both techniques can be performed during in-line cervical stabilization.

RAPID-SEQUENCE INDUCTION AND INTUBATION

A definitive airway in a trauma patient is defined by the placement of a cuffed tube in the trachea, attached to a source of oxygen and properly secured. Endotracheal intubation, nasotracheal intubation, cricothyroidotomy, or tracheotomy can be performed to establish a definitive airway. In the majority of trauma patients, rapid-sequence induction and endotracheal intubation (RSII) is used to establish a definitive airway.

RSII is predicated on the fact that the trauma patient has a full stomach, and excessive bag-valve mask ventilation will cause gastric insufflation with aspiration of gastric contents. RSII involves a highly organized sequence of events starting with preoxygenation for at least 3 minutes. The "6 *P*'s" of RSII describe the recommended sequence (Table 1). During the preparatory stage, a suction catheter is prepared and tested, an adequate source of oxygen is established and readied for connection, a pulse oximeter is attached to the patient, pharmacologic agents are prepared, and airway equipment is organized. It should be noted that proper performance of RSII ideally requires at least four providers: one to apply cricoid pressure or laryngeal manipulation, one to maintain in-line cervical stabilization, one to ventilate with a BVM and intubate, and one to administer drugs and assist with airway devices (Fig. 3).

Although avoidance of BVM ventilation has been the traditional recommendation in RSII, many practitioners find that gentle mask ventilation (inspiratory pressure <20 cm H_2O) is acceptable during the induction sequence. Gentle mask ventilation may help prevent hypoxemia in obese, pregnant, pediatric, and critically ill patients, and it also allows testing for the adequacy of mask ventilation in the event that intubation attempts fail. Additionally, to help prevent desaturation, a nasal cannula can be applied before intubation at a high flow rate (10–15 L/min) to both help with preoxygenation and to provide some degree of apneic oxygenation during intubation attempts. If a high-flow humidified nasal cannula device is available, higher rates (up to 60 L/min) can be used at higher FiO_2 (100%).

Before paralytics are given, an induction agent is administered. A review of induction agents is provided in Table 2. Paralytics are recommended as part of RSII because omission of neuromuscular blockade has been shown to result in suboptimal intubating conditions. Either succinylcholine (1–1.5 mg/kg) or rocuronium (0.8–1.2

TABLE 1 The "6 *P*'s" of Rapid-Sequence Induction and Intubation

RSII Step	Time Interval	Pharmacologic Agents
Preoxygenation	0–3 minutes	Oxygen, including addition of nasal cannula
Premedication	3 minutes	Induction agent +/– fentanyl, lidocaine, atropine, defasciculating agents (vecuronium, rocuronium; usually 1/10 the induction dose)
Paralysis	3.5–5.5 minutes	Midazolam, ketamine, etomidate, propofol, or other induction agents *FOLLOWED BY* succinylcholine or rocuronium
Placement	6–6.5 minutes	Oxygen
Performance	7–7.5 minutes	Oxygen
Post-intubation management	7.5+ minutes	Oxygen, sedatives, analgesics, and so on

RSII, Rapid-sequence induction and endotracheal intubation.

mg/kg) is administered for paralysis. Succinylcholine can be administered intramuscularly if an intravenous line is not established, but an increased dose of 3 to 4 mg/kg is recommended for this route. In the majority of patients, both succinylcholine and rocuronium provide optimal intubating conditions by 60 seconds when dosed appropriately. Priming doses of nondepolarizing agents are usually not considered for trauma patients because these agents must be administered at least 3 minutes before the loading dose of muscle relaxant is administered, and in elderly or debilitated patients, pretreatment with a small dose of muscle relaxant may predispose to aspiration. Succinylcholine is contraindicated in patients with burns, open globe injuries, neuromuscular disorders, hyperkalemia, pseudocholinesterase deficiency, severe crush injuries, or chronic paralysis. Rocuronium, a nondepolarizing agent, is an alternative when succinylcholine is contraindicated, but this agent cannot be administered intramuscularly, and the duration of action is much longer (typically up to 45 minutes) than succinylcholine (6–10 minutes).



FIG. 3 Four providers are recommended for securing the airway. Providers are assigned to (1) ventilate with the bag-valve mask and intubate, (2) maintain in-line cervical stabilization, (3) administer cricoid pressure, and (4) administer drugs and assist with airway devices.

Pharmacologic adjuvants, such as opioids, may be considered during RSII, but these agents are frequently omitted because of time pressure. If administered, fentanyl (2 mcg/kg), alfentanil (20–30 mcg/kg), or remifentanil (1 mcg/kg) may help attenuate hemodynamic responses to intubation, but opioids alone do not provide adequate amnesia and are usually not recommended as sole induction agents for RSII because of a higher incidence of patient recall. Midazolam is a short-acting benzodiazepine with excellent amnestic properties that may also be given intramuscularly, but this agent may take 2 to 3 minutes to work. Following preoxygenation, intravenous lidocaine may be considered (1.5–2 mg/kg) for the theoretical benefit of preventing increases in intracranial pressure (ICP), although evidence to support the use of lidocaine is tangential and largely extrapolated from nontrauma populations. Lidocaine may precipitate hypotension—a undesirable side effect in patients with traumatic brain injury.

ENDOTRACHEAL INTUBATION

In many trauma centers, cricoid pressure has historically been used to prevent regurgitation. Cricoid pressure involves backward and upward application of pressure to the cricoid cartilage to occlude the esophagus; 3 to 4 kg of pressure is recommended to occlude the esophagus. The use of cricoid pressure remains controversial because the technique is often incorrectly applied, may impede laryngoscopic views, is biomechanically difficult during laryngoscopy, can cause airway trauma, and could impair bag-valve mask ventilation. If cricoid pressure is used, pressure should be released if the laryngoscopic view is poor.

Approximately 1.5% to 4% of all trauma patients may have an undiagnosed cervical spinal cord injury; hence, cervical immobilization is obligatory. Manual in-line stabilization has been shown to be superior for preventing inadvertent movement of the cervical spine during intubation compared with a cervical collar alone. During intubation, one provider is dedicated to maintaining manual in-line stabilization.

Figure 4 demonstrates the correct placement of a MacIntosh or McGill laryngoscopic blade. The laryngoscope should be held in the

TABLE 2 Induction Agents Commonly Used for Rapid-Sequence Induction and Endotracheal Intubation

Induction Agent	Dose for RSII	Onset	Duration of Action	Comment
Propofol	1–3 mg/kg	10–30 seconds	8–10 minutes	Dose usually reduced, sometimes by as much as 1/10 the recommended induction dose; causes decreased systemic vascular resistance and hypotension
Ketamine	1–2 mg/kg IV 2–4 mg/kg IM	30–60 seconds	5–20 minutes	Acceptable for use in patients with increased ICP; direct myocardial depressant but has indirect stimulatory effects (best avoided in patients with coronary artery disease)
Etomidate	0.2–0.3 mg/kg	30–45 seconds	10–20 minutes	A single dose causes adrenocortical suppression; recent evidence supports safety in septic shock
Remifentanil	1 mcg/kg	30–60 seconds	<10 minutes	250 times more potent than morphine; may cause hypotension; not a reliable amnestic; does not accumulate; broken down by nonspecific esterases
Midazolam	0.3–0.6 mg/kg	2–3 minutes	20–30 minutes	When combined with opioids, can cause marked hypotension and respiratory depression

IV, Intravenously; *IM*, intramuscularly; *RSII*, rapid-sequence induction and endotracheal intubation.

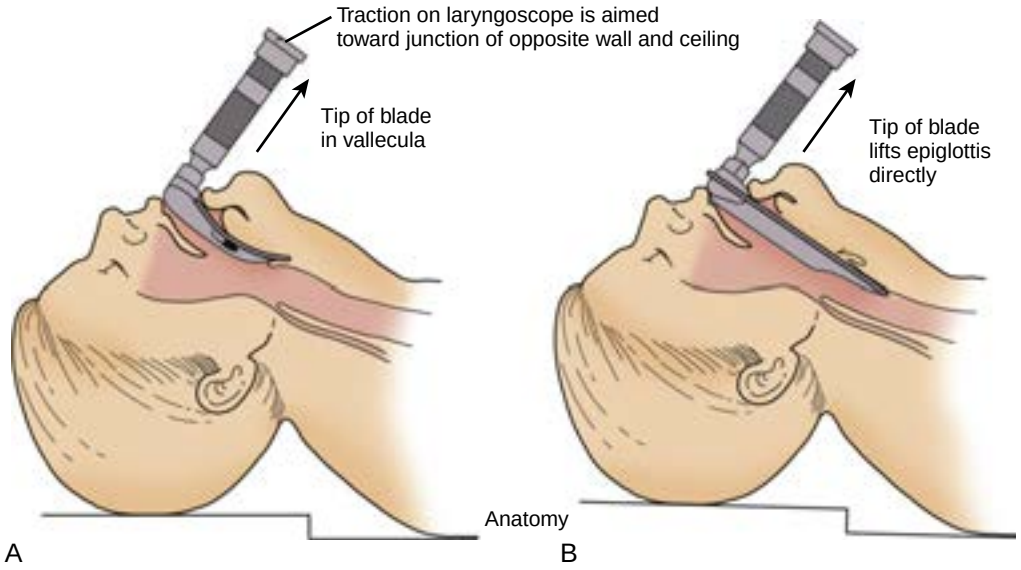


FIG. 4 **(A)** MacIntosh blade. **(B)** McGill blade. It should be noted that the patient in this figure does not have cervical spine precautions; in the majority of patients, manual in-line stabilization must be performed during intubation attempts to prevent exacerbation of neurologic damage.

left hand and inserted into the right side of the patient's mouth, displacing the tongue to the left. Video-laryngoscopes are increasingly used as alternatives to traditional laryngoscopic blades. Video-laryngoscopy offers the advantage of additional situational awareness for the trauma team and the ability to record for postprocedure quality assurance review. During laryngoscopy, the airway structures are lifted into view, avoiding using the blade as a fulcrum on the teeth, and the epiglottis and vocal cords are visualized. The endotracheal tube should be gently inserted with the cuff past the vocal cords and inflated with enough air to provide a good seal (<30 cm H_2O). In general, intubation attempts should not take more than 30 seconds. Verification of tube placement is accomplished by auscultation of bilateral lung sounds, observation of chest rise, absence of epigastric/gastric gurgling or distension, and presence of end-tidal carbon dioxide with either a colorimetric device or continuous capnography. If a colorimetric device is used, the color indicator should change from purple to yellow, and at least six ventilations with an appropriate color change should be observed to avoid potential false positives. A chest radiograph should be obtained to confirm the position of the tube.

In patients with suspected cervical spine injuries, the laryngoscopic view may be impeded by the requirement of in-line cervical stabilization. For patients with a Cormack-Lehane grade 3 or 4 view, the gum elastic bougie may used to introduce the endotracheal tube. The bougie is a flexible, 60-cm, 15F introducer with a Coude tip angled at 40 degrees, 3.5 cm from the distal end (Fig. 5).

The bougie is lubricated and inserted with the Coude tip directed anteriorly, advancing until at the level of the tracheal rings. The endotracheal tube is then advanced over the bougie into the trachea.

Video laryngoscopy has evolved as a technology that allows direct visualization of the airway by all airway team members. Studies have been mixed regarding advantages for use in patients with difficult airways, but some research has shown that video laryngoscopy results in a higher success rate at first attempt compared with direct laryngoscopy, especially for less experienced airway providers. Video laryngoscopy can be used at all stages of intubation, including initial laryngoscopy, awake intubation, and to help confirm proper endotracheal tube position.

SUPRAGLOTTIC AIRWAY DEVICES

A variety of supraglottic devices exist for use when attempts at endotracheal intubation or BVM ventilation fail. Various versions of the laryngeal mask airway (LMA) are the most commonly used

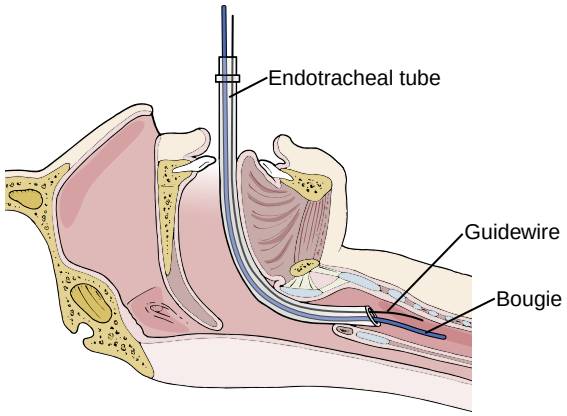


FIG. 5 Gum elastic bougie insertion. See text for explanation. (From Sandberg MD et al. *The MGH Textbook of Anesthetic Equipment*. Philadelphia: Elsevier; 2010.)

supraglottic airway devices currently in use. Although these devices enable ventilation, whether by providing a seal around the laryngeal inlet or occluding the esophagus, none of these devices represents a definitive airway. Each of these devices requires additional training, and all must eventually be replaced with a definitive airway in the trauma patient. In cases of traumatic arrest during prehospital management, immediate endotracheal intubation may not be feasible or safe. In these instances, placement of a supraglottic airway may be considered to prevent unacceptable pauses in chest compressions and to decrease the time to ventilation.

AWAKE FIBER-OPTIC INTUBATION

When patients are suspected of having cervical spinal cord injuries but do not require *emergent* intubation, awake fiber-optic intubation (AFOI) is one method that can be used to secure the airway. The term *awake* is a misnomer; the patient will maintain spontaneous ventilation throughout the procedure under sedation with amnestic agents. This method may be advantageous in patients with injuries to the cervical spine because cervical spine movements can

be minimized, thus preventing neurologic impairment. Careful titration of sedation is mandatory for AFOI because abolition of spontaneous ventilation obviates any advantage when using this technique. Monitors are applied, and oxygen is delivered via a nasal cannula. Patients are premedicated with glycopyrrolate (0.2–0.4 mg) to attenuate secretions barring any known cardiac conditions in which tachycardia must be avoided. Sedation is achieved by careful administration of midazolam (0.5 mg, titrated to effect). Opioids are avoided because of the synergistic respiratory depression that occurs when these agents are coadministered with benzodiazepines; however, opioids may be used instead of benzodiazepines, keeping in mind that these opioids do not provide reliable amnesia. Alternatively, a dexmedetomidine infusion (0.2–1.5 mcg/kg/h) may be considered, but for trauma patients, this agent is seldom used because of the preparatory time required and onset of action (more than 10 minutes). For topicalization, 2 to 3 mL of 5% lidocaine ointment is applied to the posterior tongue via a tongue depressor to anesthetize the glossopharyngeal nerve. Next, 1 to 2 vials of 4% lidocaine are emptied into a specimen cup, and cotton balls (with strings attached to ensure easy retrieval from the airway) are soaked in this solution. Using either Magill forceps or a right-angle tonsil holder, the cotton balls are gently introduced deep into the pyriforms and held in place for 60 to 90 seconds. The process is repeated for each side, effectively anesthetizing both branches of the superior laryngeal nerve. Finally, an oral airway is inserted (to prevent biting of the fiber-optic scope), and the fiber-optic scope is introduced. Once the vocal cords are visualized, 1 to 2 mL of 1% or 2% lidocaine is sprayed through the injection port on the fiber-optic scope directly on the vocal cords. This anesthetizes the recurrent laryngeal nerve. Once all three nerves are anesthetized, the endotracheal tube can safely be inserted with either a video-laryngoscope (i.e., "awake" video laryngoscopy) or over a fiber-optic bronchoscope. Careful attention must be paid to the amounts of lidocaine used because a dose greater than 5 mg/kg may result in anesthetic toxicity. The technique can be modified accordingly for nasotracheal intubation with use of topical vasoconstrictors as well as anesthetics to anesthetize and mitigate bleeding in the nasal passages. It should be noted that this technique is not recommended for patients who are deemed to be at increased risk for aspiration.

AIRWAY MANAGEMENT DECISION MAKING

For patients in need of an immediate airway, Figure 6 provides a decision algorithm. Initial priorities always include adequate preoxygenation and in-line cervical immobilization. In trauma patients, the option to awaken the patient, as one would do for an elective surgical procedure, is not feasible. After a third failed attempt at intubation by an attending anesthesiologist, an LMA can be inserted to facilitate the transition to a definitive airway via fiber-optic intubation or intubation through the LMA. However, if the airway cannot be expeditiously secured after the third laryngoscopy attempt, a surgical

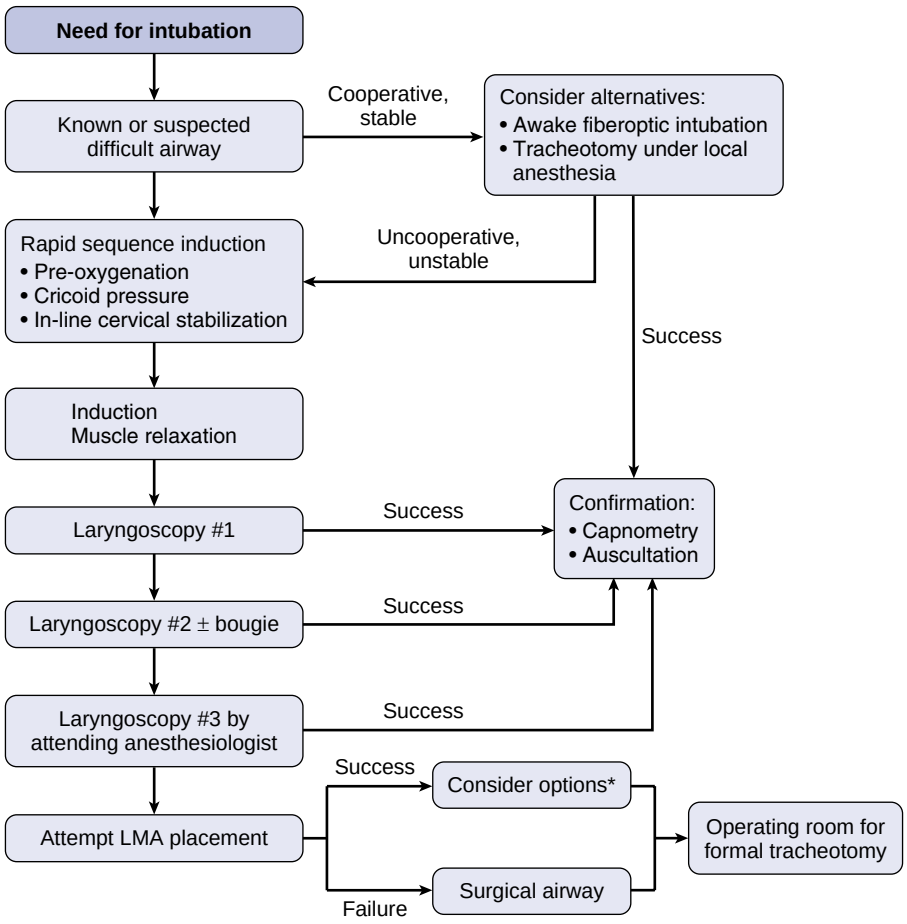


FIG. 6 Airway management algorithm at the R Adams Cowley Shock Trauma Center. Laryngoscopy may include the use of a video laryngoscope such as the GlideScope or Ranger (Verathon, Bothell, Washington) at multiple steps. *(From Stephens CT, Kahntroff S, Dutton RP. The success of emergency endotracheal intubation in trauma patients: A 10-year experience at a major adult trauma center.* Anesth Analg. *2009;109:866–872).*

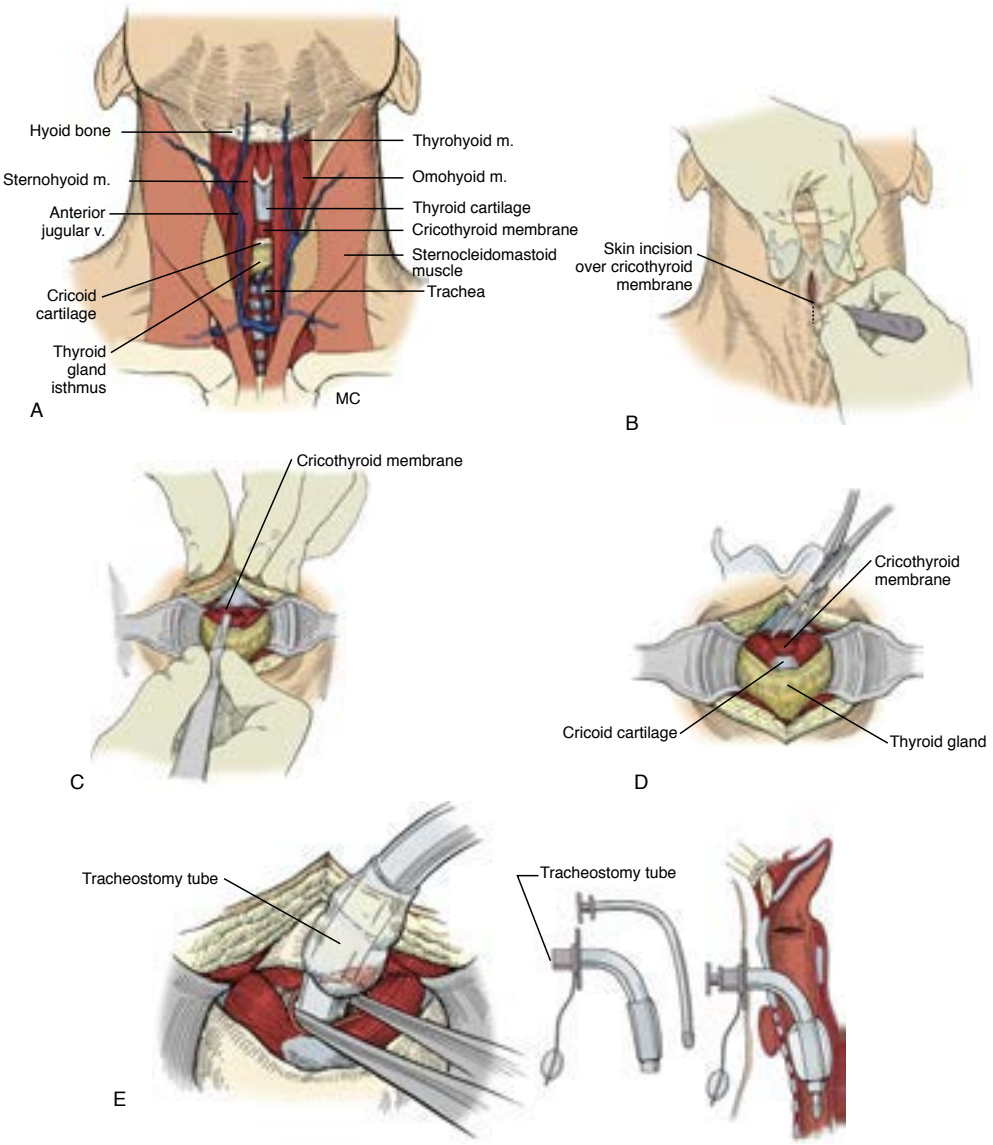


FIG. 7 Cricothyroidotomy. **(A)** The cricothyroid membrane is located between the thyroid cartilage above and the cricoid ring below. **(B)** The operator's nondominant hand holds the thyroid cartilage, while the other hand performs the procedure. A vertical skin incision avoids the anterior jugular vein to minimize bleeding. **(C)** The cricothyroid membrane is incised transversely. **(D)** The opening is widened with a small hemostat. **(E)** The tracheostomy tube is placed into the airway, and the cuff is inflated. *(From Haut ER. Evaluation and acute resuscitation of the trauma patient. In: Evans SRT, ed.* Surgical Pitfalls: Prevention and Management. *Philadelphia: Elsevier; 2009: 757–771.)*

airway is necessary. It should be noted that in the hands of experienced trauma airway experts, the rate of conversion to a surgical airway has been reported to range from 0.2% to 2%.

SURGICAL AIRWAY

A patient committed to RSII (i.e., paralyzed), who subsequently cannot be ventilated or intubated, requires a surgical airway. Options include a surgical cricothyroidotomy or tracheostomy; cricothyroidotomy is preferred as the surgical technique of choice (Fig. 7). The patient is placed in the supine position with the neck in a neutral position. After the neck is prepped and draped, the thyroid notch, thyroid cartilage, cricothyroid membrane, cricoid cartilage, and trachea are identified by palpation. Stabilizing the thyroid cartilage with one hand, a 2.0- to 2.5-cm vertical incision is made over the cricothyroid membrane with a #10 or #11 surgical blade. A hemostat or tracheal spreader is introduced into the incision and rotated 90 degrees to open the airway. Either a cuffed endotracheal tube (5.0 or 6.0 size) or tracheostomy tube is inserted through the cricothyroid membrane incision. Alternatively, a gum elastic bougie can be inserted into the opening, and an endotracheal tube or tracheostomy tube may be passed over the device into the airway. The cuff is inflated, and placement of the tube is confirmed by lung auscultation, chest rise, and end-tidal carbon dioxide detection.

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Surgeon's Use of Ultrasound in the Trauma and Critical Care Settings

Alisa Cross, MD, and Grace F. Rozycki, MD, MBA

INTRODUCTION

For over 30 years, surgeons in American trauma centers have successfully performed, interpreted, and taught ultrasound examinations for patients who are injured or critically ill. According to the Rogers Diffusion of Innovations Theory, surgeons are considered to be early adopters of the technology, and their presence in so many areas of the hospital helped promote ultrasound as a useful tool for the evaluation of patients in the elective and emergent settings. Real-time imaging allows the surgeon to receive instantaneous information about the clinical condition of the patient and therefore helps expedite the patient's management. In many trauma centers, ultrasound machines are standard equipment in the trauma resuscitation rooms. Although diagnostic peritoneal lavage (DPL) and computed tomography (CT) scanning are still valuable diagnostic tests for the detection of intraabdominal injury, ultrasound is faster, noninvasive, painless, and well tolerated by adults and children. Moreover, the portability of the ultrasound machine allows for an evaluation of the patient in multiple settings, including the trauma bay and intensive care unit (ICU).

As an extension of the physical examination, surgeons routinely use ultrasound in the acute setting to determine the presence or absence of fluid in the peritoneal cavity, the pericardium, and the pleural cavities. Additional uses of this modality include the detection of pneumothoraces and sternal fractures. What follows is a discussion of the use of ultrasound in blunt and penetrating thoracoabdominal trauma with an additional discussion of the use of ultrasound in the ICU.

THE USE OF ULTRASOUND IN TRAUMA

FAST

Developed for the evaluation of injured patients, the *F*ocused *A*ssessment for the *S*onographic Evaluation of the *T*rauma Patient (FAST) is a rapid diagnostic examination to assess patients with potential injuries to the thorax or abdomen. The test sequentially surveys for the presence or absence of fluid in the pericardial sac and in the dependent abdominal regions, including the Morison pouch of the right upper quadrant (RUQ), the left upper quadrant (LUQ) behind the spleen and between the spleen and kidney, and the pelvis posterior to the bladder.

The FAST is performed in a specific sequence; the pericardial area is visualized first so blood within the heart can be used as a standard to set the gain. Most modern ultrasound machines have presets so the gain does not need to be reset each time the machine is turned on. Occasionally, if multiple types of examinations are performed with different transducers, the gain should be checked to ensure that intracardiac blood appears anechoic. This maneuver ensures that hemoperitoneum will also appear anechoic and will be readily detected on the ultrasound image. The abdominal part of the FAST should begin with a survey of the RUQ, which is the location within the peritoneal cavity where blood most often accumulates and is most readily detected with the FAST. In a multicenter trial of 275 blunt and penetrating trauma patients, investigators found that regardless of the injured organ (with the exception of those patients who had an isolated perforated viscus), blood was most often identified on the RUQ image of the FAST. This can be a timesaving measure because when hemoperitoneum in the RUQ view is identified on the FAST examination of a hemodynamically unstable patient, then that image alone, in combination with the patient's clinical picture, is sufficient to justify an immediate abdominal operation. In a hemodynamically stable patient, following the examination of the RUQ, the LUQ and pelvis are visualized as discussed in the following sections.

Technique

Ultrasound transmission gel is applied on four areas of the thoracoabdomen, and the examination is conducted in the following sequence: the pericardial area, RUQ, LUQ, and pelvis (Fig. 1). Abdominal structures are best imaged with a lower-frequency transducer, which allows for deeper penetration into tissues (sacrificing some resolution). Most ultrasound transducers are now capable of imaging in multiple frequencies, which allows the sonographer to achieve the best balance of resolution (higher frequency) and tissue penetration (lower frequency) based on a patient's individual body habitus.

To begin the examination, a 3.5-MHz curvilinear transducer is oriented for sagittal or longitudinal views and positioned in the subxiphoid region to identify the heart and to examine for blood in the pericardial sac. The normal and abnormal views of the pericardial area are shown in Figure 2. The subxiphoid image is usually not difficult to obtain, but a severe injury to the chest wall, a very narrow subcostal area, subcutaneous emphysema, or morbid obesity can prevent a satisfactory examination. Both of the latter conditions are associated with poor imaging because air and fat reflect the wave too strongly and prevent penetration into the target organ. If the subcostal pericardial image cannot be obtained or is suboptimal, a parasternal ultrasound view of the heart should be performed.

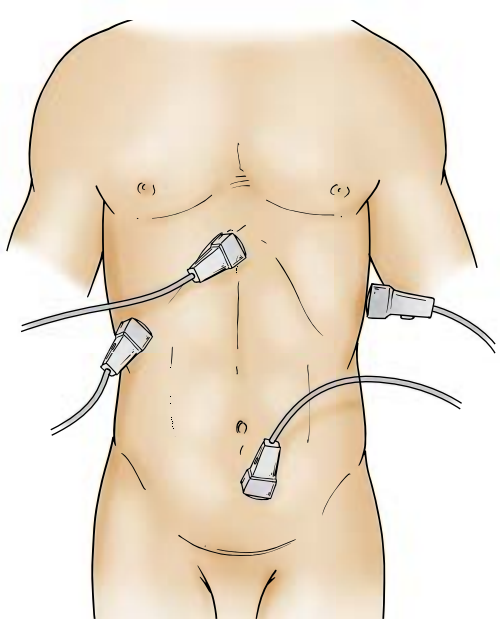


FIG. 1 Transducer positions for FAST: pericardial, right upper quadrant, left upper quadrant, and pelvis.

Next, the transducer is placed in the right anterior or mid-axillary line between the eleventh and twelfth ribs to identify a sagittal section of the liver, kidney, and diaphragm (Fig. 3). The presence or absence of blood is sought in Morison's pouch and in the right subphrenic space. Next, attention is turned to the LUQ. With the transducer positioned in the left posterior axillary line between the tenth and eleventh ribs, the spleen and kidney are visualized, and blood is sought in between the two organs and in the left subphrenic space (Fig. 4). The splenic window is often the most difficult to obtain as the presence of gas in the stomach may interfere with the imaging. To ensure the best imaging, the stomach may need decompression with a nasogastric tube. Further, the transducer should be placed significantly more posterior (posterior axillary line) and superior (one to two rib spaces higher) than with the RUQ window.

Finally, the transducer is directed for a transverse view and placed about 4 cm superior to the symphysis pubis. It is swept inferiorly to obtain a coronal view of the full bladder and the pelvis examining for the presence or absence of blood (Fig. 5).

Accuracy

Improper technique, inexperience of the examiner, and inappropriate use of ultrasound have long been known to adversely affect ultrasound imaging. More recently, the etiology of injury, the presence of hypotension on admission, and select associated injuries have also been shown to influence the accuracy of this modality. Failure to consider these factors has led to inaccurate assessments of the accuracy of the FAST by inappropriately comparing it to a CT scan and not recognizing its role in the evaluation of patients with penetrating torso trauma. Both false-positive and false-negative pericardial ultrasound examinations have been reported to occur in the presence of a massive hemothorax or mediastinal blood. Repeating the FAST after the insertion of a tube thoracostomy improves visualization of the pericardial area and decreases the number of false-positive and false-negative studies. Notwithstanding these circumstances in which false studies may occur, a rapid focused ultrasound survey of the subcostal pericardial area is a very accurate method to detect hemopericardium in most patients with penetrating wounds in the "cardiac box." In a large multicenter study of patients who sustained either blunt or penetrating injuries, the FAST was 100% sensitive and 99.3% specific for detecting hemopericardium in patients with precordial or transthoracic wounds. Furthermore, the use of pericardial ultrasound has been shown to be especially helpful in the evaluation of patients who have no overt signs of pericardial tamponade. This was highlighted in a study in which 10 of 22 patients with precordial wounds and hemopericardium on ultrasound examination had admission systolic blood pressures >110 mm Hg and were relatively asymptomatic. Based on these signs and the lack of symptoms, it is unlikely that the presence of cardiac wounds would have been strongly suspected in these patients; therefore this rapid examination provided an early diagnosis of hemopericardium before the patients underwent physiologic deterioration.

The FAST is a focused examination for the detection of fluid in dependent areas of the abdomen and is designed to answer the simple question of "fluid or no fluid." Therefore, its results should not be compared with those of a CT scan because the FAST does not readily identify intraparenchymal or retroperitoneal injuries. Therefore select patients considered to be at high risk for occult intraabdominal injury should undergo CT of the abdomen regardless of the results of the FAST examination. These patients include those with fractures

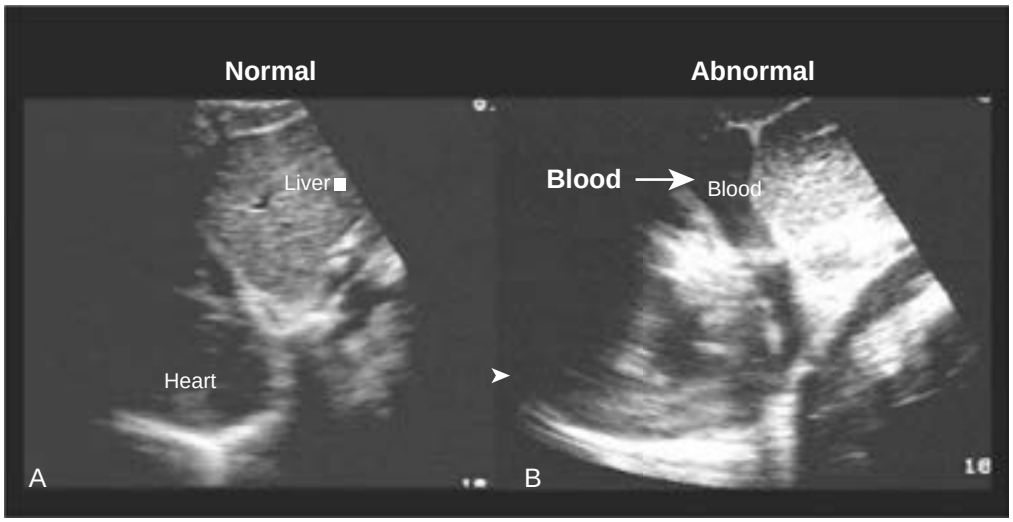


FIG. 2 **(A)** Normal sagittal view of pericardial area showing pericardium as single echogenic line. **(B)** Abnormal sagittal view of pericardial area showing separation of visceral and parietal areas of pericardium with blood *(arrow)* that appears anechoic.

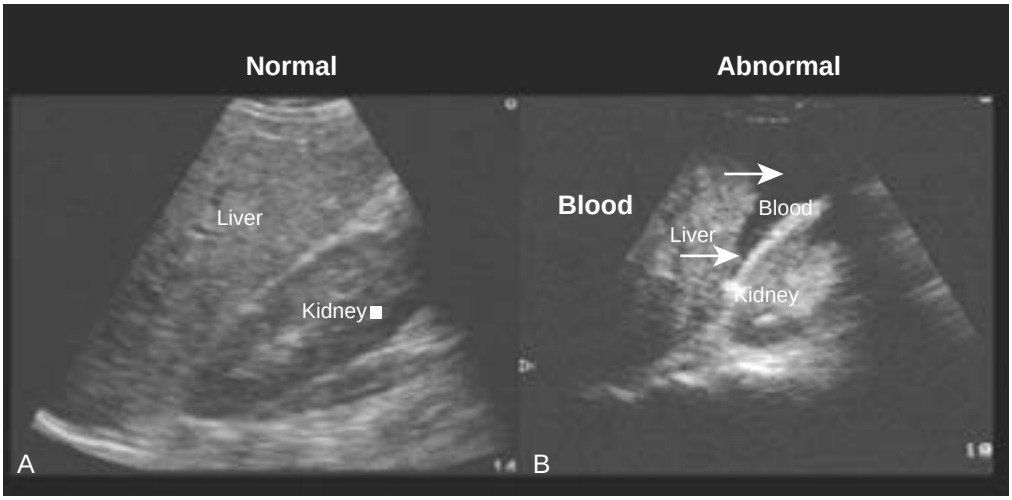


FIG. 3 **(A)** Normal sagittal view of liver, kidney, and diaphragm. Note Gerota's fascia is hyperechoic. **(B)** Abnormal sagittal view of liver, kidney, and diaphragm. Note fluid (blood) between liver and kidney *(arrows)*.

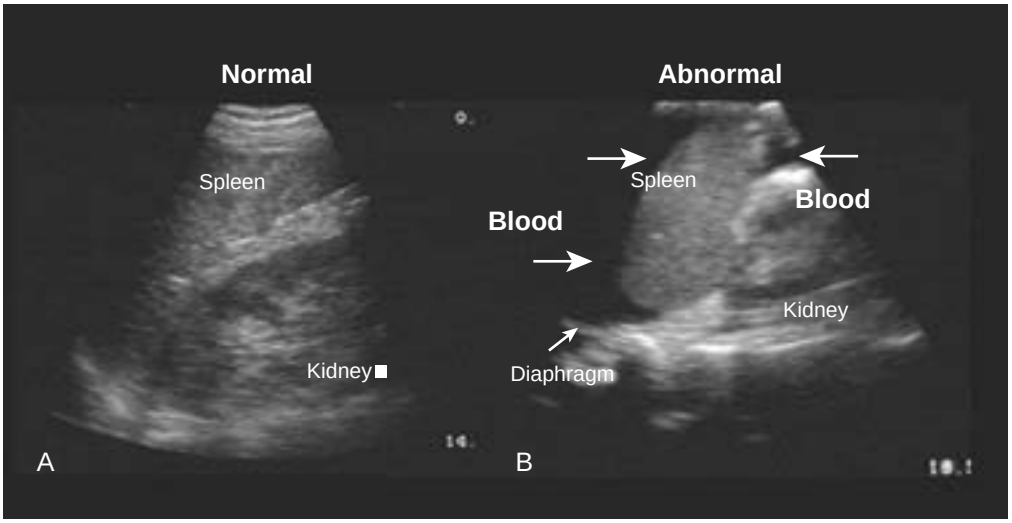


FIG. 4 **(A)** Normal sagittal view of spleen, kidney, and diaphragm. **(B)** Abnormal sagittal view of spleen, kidney, and diaphragm with fluid (blood) between spleen and kidney and above the spleen in the subphrenic space *(arrows)*.

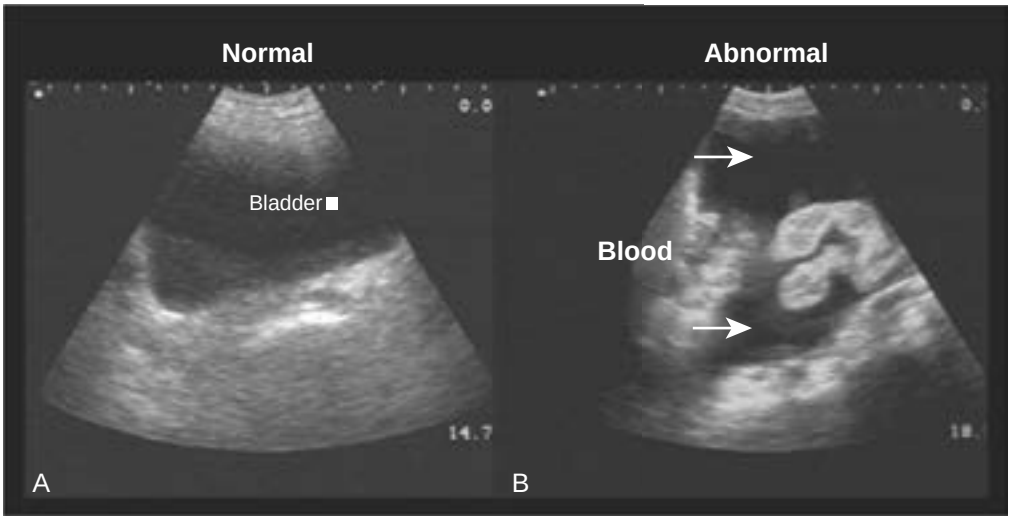


FIG. 5 **(A)** Normal coronal view of full urinary bladder. **(B)** Abnormal coronal view of full bladder with fluid in pelvis. Note the bowel floating in fluid *(arrows)*.

of the pelvis or thoracolumbar spine, major thoracic trauma (pulmonary contusion, lower rib fractures), and hematuria.

Traumatic Hemothorax

A focused thoracic ultrasound examination was developed by surgeons to rapidly detect the presence or absence of a traumatic hemothorax in injured patients. This examination is worthwhile because it dramatically shortens the interval from the diagnosis of a hemothorax to the insertion of a thoracostomy tube.

Technique

The technique for this examination is like that used to interrogate the upper quadrants of the abdomen in the FAST and uses the same type and frequency transducer. With the patient in the supine position, it is performed one to two rib spaces higher than the RUQ and LUQ FAST views. Ultrasound transmission gel is applied to the right and left lower thoracic areas in the mid to posterior axillary lines between the ninth and tenth intercostal spaces (Fig. 6). The transducer is slowly advanced cephalad to identify the hyperechoic diaphragm and to interrogate the supradiaphragmatic space for the presence or absence of fluid (Fig. 7), which appears anechoic. In the positive thoracic ultrasound examination, the hypoechoic lung can be seen "floating" amidst the fluid. The same technique can be used to evaluate a critically ill patient for a pleural effusion.

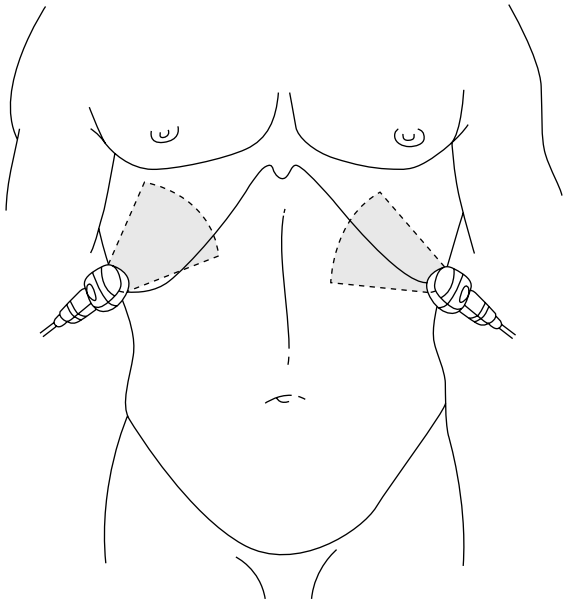


FIG. 6 Transducer positions for thoracic ultrasound examination (detection of hemothorax).

Accuracy

A study that compared the time and accuracy of ultrasound with that of the supine portable chest x-ray found both to have similar high sensitivities and specificities for the detection of hemothorax, but performance times for the thoracic ultrasound examinations were statistically much faster ($P < 0.0001$) than those for the portable chest x-ray. Although it is not recommended that the thoracic ultrasound examination replace the chest x-ray, its use can expedite treatment in many patients and decrease the number of chest radiographs obtained.

Pneumothorax

Ultrasound examination for the detection of a pneumothorax is unique in that there is an absence of two findings. The first is a refraction artifact called a *comet tail* that results from the interaction of air with the lung tissue (Fig. 8). The second finding is pleural sliding, which indicates that the visceral and parietal layers of the pleura are in normal apposition. Hence a pneumothorax is not visualized on ultrasound but rather diagnosed by the absence of these two normal findings.

Technique

A 5.0- to 7.5-MHz linear array transducer is used to evaluate a patient for the presence of a pneumothorax. The examination may be performed while the patient is in the erect or the supine position. Ultrasound transmission gel is applied to the right and left upper thoracic areas at about the third to fourth intercostal space in the mid-clavicular line, and the presumed unaffected thoracic cavity is examined first. The transducer is oriented for longitudinal imaging, placed perpendicular to the ribs, and slowly advanced medially toward the sternum and then laterally toward the anterior axillary line. When a pneumothorax is present, air becomes trapped between the visceral and parietal pleura and does not allow for the transmission of the ultrasound waves. Therefore, the visceral pleura is not imaged, and pleural sliding and the comet tail artifact are not observed. If desired, the examination may be repeated with the transducer oriented for transverse views, with images obtained with the probe parallel to the ribs.

Accuracy

Several studies have documented the sensitivity and specificity of ultrasound for the detection of a pneumothorax. Dulchavsky and colleagues showed that ultrasound can be successfully used by surgeons to detect a pneumothorax in injured patients. Of the 382 patients (362 trauma; 18 spontaneous) evaluated with ultrasound, 39 had pneumothoraces, and ultrasound successfully detected 37 of them, yielding 95% sensitivity. Pneumothoraces in two patients

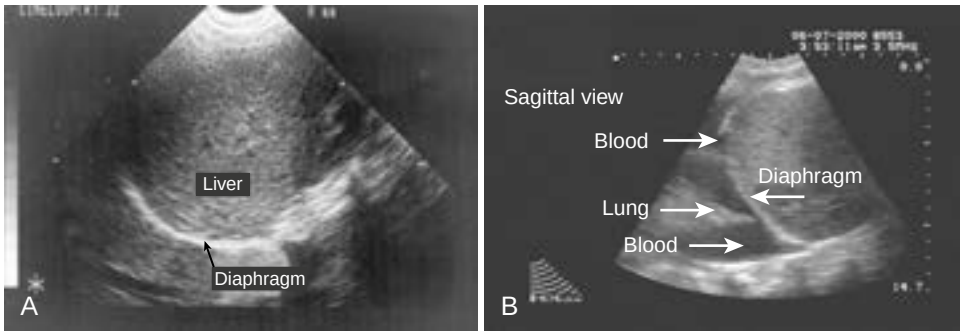


FIG. 7 **(A)** Sagittal view of liver, kidney, and diaphragm. Note supradiaphragmatic (lung) area but absence of pleural effusion. **(B)** Sagittal view of right supradiaphragmatic space. The right hemithorax contains fluid (blood), which appears anechoic.

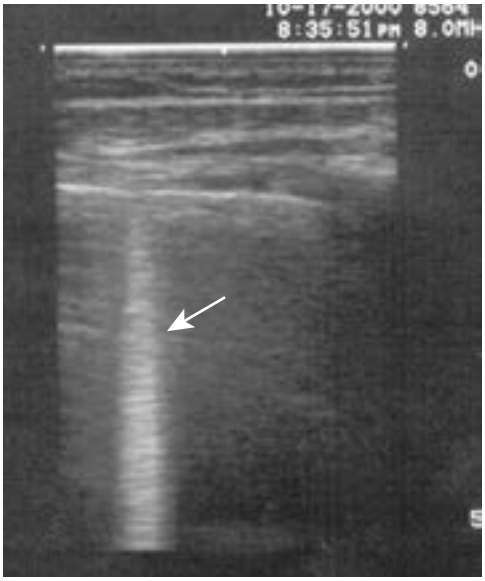


FIG. 8 Comet tail artifact *(arrow)*.

could not be detected because of the presence of significant subcutaneous emphysema. The authors recommended that when a portable chest x-ray cannot be readily obtained, the use of this bedside ultrasound examination for the identification of a pneumothorax could expedite the patient's management.

Sternal Fracture

Fractures of the sternum are visualized on a lateral x-ray view of the chest, but this film may be difficult to obtain in a multisystem injured patient. Therefore, an ultrasound examination of the sternum can rapidly detect a fracture while the patient is still in the supine position, thus avoiding the need to obtain a lateral x-ray of the chest wall.

Technique

With the patient in the supine position, the ultrasound examination of the sternum is performed using a high-frequency linear array transducer that is oriented for sagittal or longitudinal views. Beginning at the suprasternal notch, the transducer is slowly advanced in a caudad direction to interrogate the sternum for a fracture, and then the examination is repeated with the transducer oriented for transverse views. The examination of the intact sternum is shown in Figure 9. A sternal fracture is identified on the ultrasound examination as a disruption of the cortical reflex (Fig. 10). Investigators have found that the use of ultrasound for this diagnosis is as accurate (and much more rapid) than a lateral view x-ray examination of the chest.

Special Situations

Ultrasound would seem to be an ideal method of evaluating an injured pregnant patient, but the data do not support it to be a very sensitive test for the detection of intraabdominal fluid because of the anatomic changes of pregnancy.

Ultrasound for diagnosis of injuries after penetrating trauma has been studied much less extensively than its use in blunt trauma. Ultrasound has a high sensitivity and specificity for the diagnosis of hemopericardium in patients with penetrating injury to the "cardiac box." But, when compared with local wound exploration of a stab wound to the abdomen, the sensitivity is poor. A report by Murphy et al. examined the utility of ultrasound to diagnose fascial penetration after anterior abdominal stab wounds. In this study, 35 patients underwent ultrasonic evaluation of their anterior abdominal fascia with an 8.0-MHz linear array transducer followed by a local wound

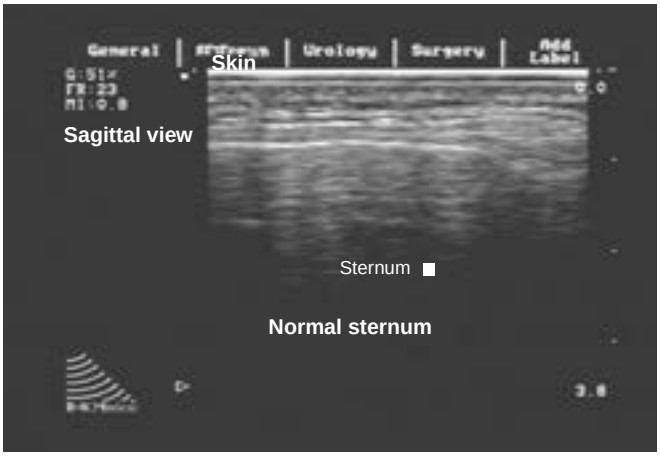


FIG. 9 Sagittal view of sternum illustrating normal findings.

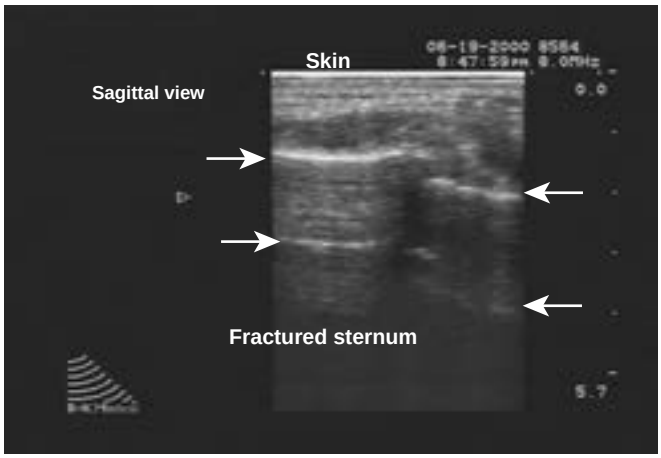


FIG. 10 Sagittal view of sternum illustrating fracture (interruption of hyperechoic line).

exploration. Although ultrasound had only a 59% sensitivity (13/22 patients), it did have 100% specificity with no false-positive studies. Thus, if fascial penetration is noted on ultrasound, a more invasive wound exploration is probably not needed. However, under these circumstances, a negative ultrasound evaluation is clearly less helpful and does not preclude peritoneal penetration.

USE OF ULTRASOUND IN SURGICAL CRITICAL CARE

With technologic advancements, ultrasound has been shown to be a valuable tool for the evaluation of critically ill patients. Performed by the intensivist at the bedside, these focused examinations are useful for a number of diagnostic dilemmas and procedures, including the detection and drainage of a pleural effusion, rapid evaluation of hypotension of unknown origin, diagnosis of deep vein thrombosis (DVT), and rapid diagnosis of central venous line complications immediately after placement. In several studies, ultrasound findings have contributed to a change in the patient's management and, consequently, to a decrease in morbidity and length of stay.

Pleural Effusion

The superiority of ultrasound over plain radiography for the detection of pleural fluid is well documented. On ultrasound examination,

pleural effusion is identified as an anechoic area surrounded by the chest wall, lung, and diaphragm. Diaphragmatic motion with respiration and the movement of the lung in the surrounding pleural fluid effusion aid in the diagnosis. Once diagnosed, ultrasound-guided drainage optimizes the location, ensures complete drainage, and minimizes the complication of a pneumothorax.

Technique

The patient is placed in the supine position, and the head of the bed is elevated 45 to 60 degrees. A 3.5- or 5-MHz curvilinear transducer, oriented for sagittal sections, is placed at the 9th to 10th intercostal space in the mid to posterior axillary line. The transducer is advanced cephalad until the hyperechoic diaphragm, the subdiaphragmatic organs (liver or spleen), chest wall, lung, and effusion are seen. A felt-tipped pen is used to mark the spot where the needle will enter the chest. The image is frozen, and the distance is measured from the mark to the mid-portion of the effusion to choose the correct needle length. The needle is attached to a syringe and advanced superior to the rib (to avoid the neurovascular bundle) while aspirating until pleural fluid is returned. Using the same principles, the pleural effusion can be easily drained via a thoracostomy tube using the Seldinger technique via a wide variety of commercially available drainage kits.

Venous Interrogation for Deep Vein Thrombosis

Venous thromboembolic disease is a common cause of morbidity and mortality in the critical care population and has a reported incidence of 5% to 60% in high-risk injured patients. The use of a focused ultrasound examination performed at the bedside by critical care physicians can provide valuable information to potentially support or exclude the diagnosis of DVT. In 2010, Pierre and colleagues reported their results of a multicenter retrospective study of critically ill patients suspected of having a DVT. They compared a focused intensivist-performed ultrasound evaluation with the standard duplex study and found that their focused examination compared favorably with the duplex study, showing a sensitivity and specificity of 88% and 98% versus 85% and 100%, respectively. In addition, the intensivist-performed focused examination confirmed the diagnosis of DVT 14 hours sooner than the duplex study.

Technique

The patient is placed in the supine position with the leg externally rotated and the knee flexed. A high frequency, 7- to 12-MHz linear transducer is placed in the transverse position just inferior to the inguinal ligament, where the common femoral vein is identified. Compression is applied while sliding the transducer distally along the common femoral vasculature until the deep femoral vein and superficial femoral veins are visualized. The examination is repeated with the transducer oriented in the sagittal position (Fig. 11). If the vein is well visualized, it is followed distally to the popliteal area. Although this focused examination does not include flow dynamics, it covers the most common areas where DVT is found, that is, common, deep, and superficial femoral veins and popliteal veins. The findings consistent with a DVT are inability to fully compress the vein and the presence of hyperechoic intraluminal material (i.e., clot; Fig. 12).

Placement and Confirmation of Central Venous Lines

In 2001, the Agency for Healthcare Research and Quality recommended the use of ultrasound guidance for the placement of central venous lines, and these recommendations were subsequently endorsed by the American College of Surgeons. The benefits of using ultrasound for central line placement are ease of venous cannulation and fewer complications, especially arterial puncture and pneumothorax. This description is limited to internal jugular venous access as the visualization of the subclavian vein is more difficult as a result of bone artifact.

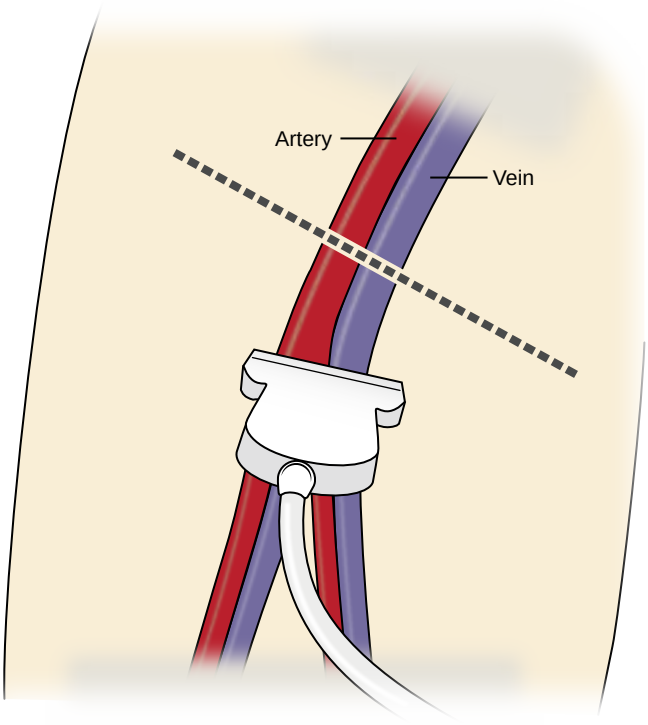


FIG. 11 Transducer positioning to interrogate the femoral vein.

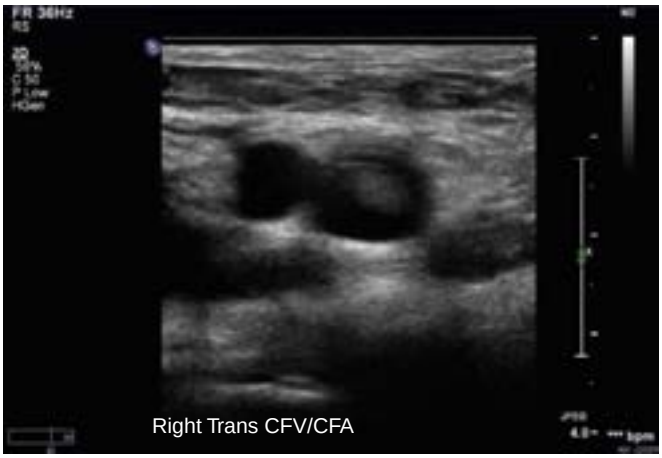


FIG. 12 Transverse image of hyperechoic material consistent with clot within the femoral vein. *CFA,* Common femoral artery; *CFV,* common femoral vein.

Technique

Before prepping the patient's neck, anatomic landmarks (sternal notch, trachea, earlobe) should be marked and the internal jugular vein scanned to ensure ease of compressibility and absence of a clot.

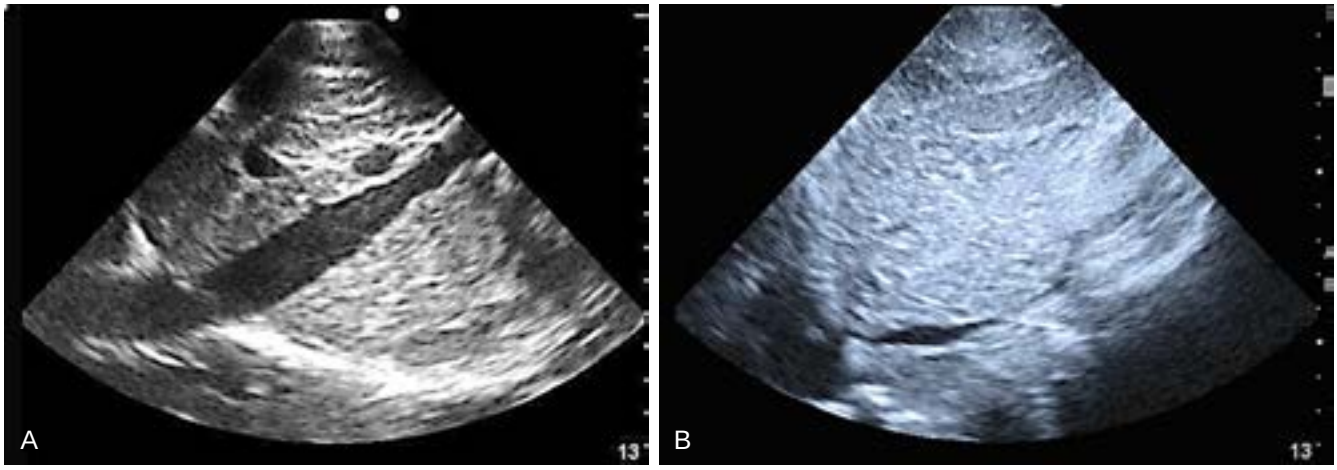


FIG. 13 **(A)** Longitudinal image of full vena cava. **(B)** Longitudinal image of collapsed vena cava.

The patient's head should be elevated about 30 degrees and slightly extended and rotated to the contralateral side. A high-frequency linear transducer is held in the nondominant hand, placed in the transverse position (i.e., perpendicular to the long axis of the neck), and oriented so the left side of the transducer correlates with the left side of the ultrasound screen. The ipsilateral carotid artery and patent internal jugular vein are identified. The insertion site is determined, and the depth to the internal jugular vein is measured. The needle (attached to a syringe) is inserted at a 45- to 60-degree angle near the center of the transducer. The needle is advanced while aspirating the syringe, and visual confirmation of the needle tip within the vein is confirmed along with venous blood return. The transducer is then rotated to the longitudinal position so the guidewire is visualized within the lumen of the vein. The remainder of the procedure follows the guidelines of the Seldinger technique. Although a chest x-ray is still recommended for the confirmation of central line position, ultrasound offers an alternative method. The 3.5- to 5-MHz curvilinear transducer is oriented for the sagittal view and placed in either the apical or subcostal pericardial areas to obtain the four cardiac chambers view. The distal port of the central venous line is flushed rapidly with 10 mL of warm saline. A rapid atrial swirl is visualized on the ultrasound real-time image as a turbulence entering the right atrium from the superior vena cava immediately after the flush and then migrating into the right ventricle. The rapid atrial swirl indicates that the central venous line is in the correct position. Turbulence initially identified in the right ventricle is consistent with a central venous line that should be withdrawn into the atriocaval junction, and lack of turbulence indicates intraarterial placement and should be removed.

THE USE OF ULTRASOUND IN THE ASSESSMENT OF INTRAVASCULAR VOLUME AND CARDIAC FUNCTION

For several years, ultrasound has been used by specialists to assess a patient's intravascular volume status. An inferior vena cava that is easily compressible indicates that the patient is hypovolemic, whereas an inferior vena cava that is noncompressible or has a diameter greater than 2 cm indicates that the patient is euvolemic or hypervolemic (Fig. 13).

Assessment of Intravascular Volume Status Technique

This focused examination is performed with the same transducer as that used for the FAST examination. With the patient in the supine position, the transducer is oriented for sagittal sections and placed in the subxiphoid area. The inferior vena cava is identified, and then the transducer is rotated to obtain a long axis view. The width of the inferior vena cava is measured, and then the vessel is compressed. The transducer is once again rotated to obtain a transverse view of the vessel, and the diameter is measured and the vessel compressed.

In 2011, Ferrada and colleagues reported that the Focused Rapid Echocardiographic Examination (FREE) could estimate an ejection fraction, diagnose moderate to severe cardiac dysfunction, and identify inferior vena cava compressibility and diameter during respiratory variation. In this study, findings on the FREE changed the management of 54% of the patients, and the authors concluded that the FREE was a useful adjunct in determining the treatment plan for critically ill patients. Other studies have confirmed the usefulness of bedside ultrasound as a useful tool in determining the correct therapy for hypotensive patients during the early phases of resuscitation.

The FREE is a transthoracic examination that was developed to assess the critically ill patient's volume and cardiac status. This point-of-care ultrasound examination uses hemodynamic information to determine whether the patient needs volume, inotropes, or vasopressors.

FREE Technique

The patient is placed in the supine position for the four critical views of the FREE examination: (1) parasternal long axis, (2) parasternal short axis, (3) apical four-chamber view, and (4) subxiphoid view to examine for the diameter and compressibility of the vena cava (described earlier). Figure 14 indicates the transducer positions and the resultant images.

SUMMARY

Evidence-based guidelines for the appropriate uses of ultrasound are provided by the Society of Critical Care Medicine (*Guidelines for the Appropriate Use of Bedside General and Cardiac Ultrasonography in the Evaluation of Critically Ill Patients—Part 1: General Ultrasonography; Part II: Cardiac Ultrasonography*). A summary of key recommendations is provided in Tables 1 and 2.

As the role of the general surgeon continues to evolve, the surgeon's use of ultrasound will surely influence practice patterns, particularly for the evaluation of patients in the acute setting. With the use of real-time imaging, the surgeon receives "instantaneous" information to augment the physical examination, narrow the differential diagnosis, or initiate an intervention. Algorithms for the

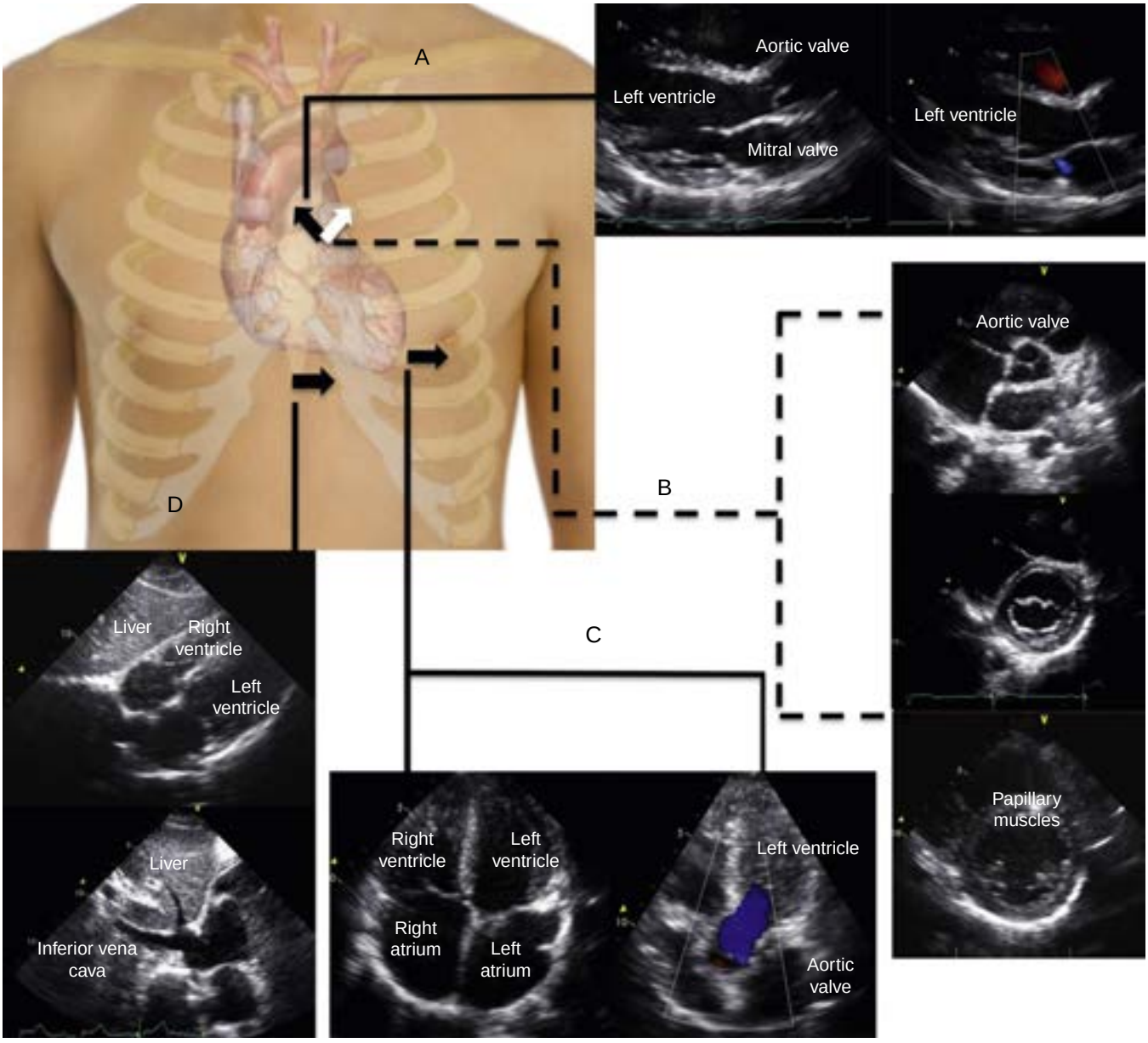


FIG. 14 Critical views of focused rapid echocardiographic examination.

suggested use of ultrasound in penetrating trauma and blunt abdominal trauma are provided in Figure 15.

The advantages of ultrasound are easily seen in each of the following clinical scenarios. As a noninvasive, non-ionizing radiation modality, ultrasound can be used to evaluate the injured pregnant patient and simultaneously identify the fetal heart so the heart rate can be recorded. For the patient with multiple fractures who is in traction, the portable machine is wheeled to the patient's bedside, and the FAST is performed without having to move the patient. If hypotension or an unexpected decrease in hematocrit occurs, an ultrasound examination can be easily repeated to exclude hemoperitoneum as the source of hypotension. When several patients with penetrating thoracoabdominal injuries present simultaneously to the emergency department, a rapid FAST examination with thoracic views can assess for pericardial effusion, massive hemothorax, or hemoperitoneum within seconds. This information helps the surgeon prioritize resources and triage patients. Finally, this painless noninvasive modality is well accepted, even by children, because it is performed at the bedside and is not intimidating.

TABLE 1 Summary of Recommendations

Topic	Overall Grade	Level of Training	Strength of Recommendation	Degree of Consensus	Level of Evidence
Preload responsiveness, ventilated	1B	Basic	Strong	Very good	B
Left ventricular systolic function	1C	Basic	Strong	Very good	C
Left ventricular diastolic dysfunction	2C	Advanced	Conditional	Good	C
Acute cor pulmonale	1C	Basic	Strong	Very good	C
Pulmonary hypertension	1B	Advanced	Strong	Very good	B
Symptomatic pulmonary embolism	1C	Basic	Strong	Very good	C
Right ventricular infarct	1C	Basic	Strong	Very good	C
Sepsis resuscitation	1C	Basic	Strong	Very good	C
Asystole	2C	Basic	Conditional	Good	C
Pulseless electrical activity	2C	Basic	Conditional	Good	C
Ventricular tachycardia/fibrillation	1B	Basic	Strong	Very good	B
Cardiac tamponade	1B	Basic	Strong	Very good	B
Pericardial effusion	1C	Basic	Strong	Very good	C
Native valvular dysfunction	1C	Basic	Strong	Very good	C
Mechanical valvular dysfunction	1C	Basic	Strong	Very good	C
Blunt chest trauma for pericardium	1B	Basic	Strong	Very good	B
Penetrating chest trauma	1C	Basic	Strong	Very good	C

TABLE 2 Summary of Key Recommendations*

Topic	Overall Grade of Recommendation	Strength of Recommendation	Level of Quality of Evidence
Diagnosis of pleural effusion (ruling-in)	1-A	Strong	A
Diagnosis of pneumothorax	1-A	Strong	A
Ascites (nontrauma setting)	1-B	Strong	B
DVT diagnosis	1-B	Strong	B
Central venous access			
General	1-A	Strong	A
Real time	1-B	Strong	B
Access location			
Internal jugular	1-A	Strong	A
Subclavian/axillary	2-C	Conditional	C
Femoral	1-A	Strong	A
Others venous	2-B	Conditional	B
Others arterial	2-B	Conditional	B

*Numbers indicate the strength of recommendation: 1 = strong and 2 = weak/conditional. Letters indicate the level of quality of evidence: A = high, B = moderate, and C = low.
DVT, Deep venous thrombosis.

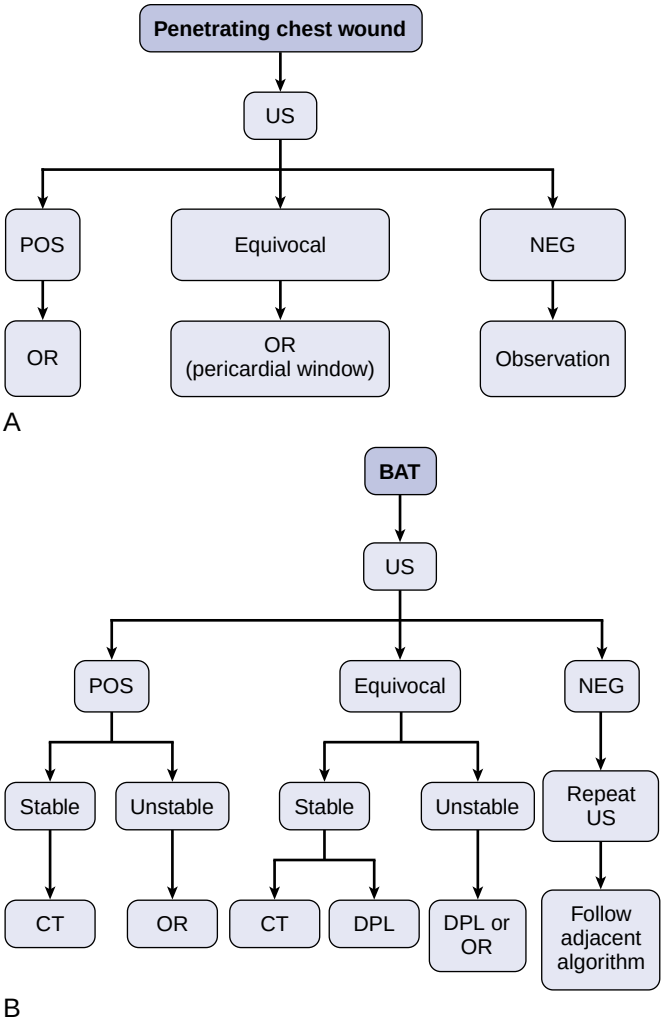


FIG. 15 **(A)** Algorithm for the use of ultrasound (US) use in patients with penetrating chest wounds. **(B)** Algorithm for US use in patients with blunt abdominal trauma *(BAT). CT,* Computed tomography; *DPL,* diagnostic peritoneal lavage; *NEG,* negative; *OR,* operating room; *POS,* positive.

Suggested Readings

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Emergency Department Resuscitative Thoracotomy

Ryan B. Fransman, MD, and David T. Efron, MD

OVERVIEW

Noncompressible thoracic trauma hemorrhage is the number one cause of death in organized trauma centers. The emergency department resuscitative thoracotomy (EDRT) originally described during the late 1800s remains one of the most debated procedures performed in the realm of trauma care. It is a heroic effort that has the potential to be lifesaving, if performed by an appropriately trained and skilled provider in the rapid fashion it is intended. Using minimal instrumentation, access to the thorax, pericardium, myocardium, and aorta can be achieved within minutes of patient arrival to the trauma bay.

The attraction to this procedure is the satisfaction of attempting drastic measures to save a life; however, identifying the appropriate patient is of utmost importance. Ideally, accessing the chest of those in extremis will hopefully relieve pericardial tamponade but may temporize exsanguination from either above or below the diaphragm and enhance cerebral and cardiac blood flow; even if successful, the patient may survive with unfavorable outcomes. This maximally invasive intervention, if performed by an untrained hand, is a futile effort at best and places involved personnel at risk for direct injury as well as exposure to copious amounts of body fluids. Iatrogenic injury to thoracic structures will lead to added insult including but not limited to potential further blood loss, lung parenchymal compromise,

nerve transection, and direct cardiac injury. Attention to technique is therefore also vitally important.

Over the years, multiple recommendations and guidelines have been proffered and revised to specify when it is appropriate to attempt undertaking this procedure (Tables 1 and 2). Although the supporting data are all retrospective in nature, the sheer number performed and reviewed by expert panels both nationally and internationally has allowed the creation of some guidance on suitable candidacy for effective intervention, defined not just as those likely to survive but those who have a chance at meaningful survival. It should be remembered that the thoracotomy is performed for two distinct reasons: (1) to access the chest for an injury that is surgically intervenable (i.e., release of tamponade and hemorrhage control) and (2) to optimize resuscitation (open cardiac massage, aortic cross-clamping, central drug administration, and internal defibrillation). Often both needs are present; however, outcomes are very different depending on the patient's mechanism of injury, physiologic state, and presenting characteristics (age and comorbidities).

Current guidelines rely on a few key factors to advise the practitioner on which patients would likely benefit from resuscitative thoracotomy. Type (penetrating versus blunt) and location of injury are two common starting points on various intervention models to risk stratify these patients. Time of last perfusing vital signs, electrical cardiac activity, pupillary response, and cardiac activity on bedside cardiac point of care ultrasonography can then further assist in guiding patient selection.

The patient in extremis with a single penetrating stab injury to the "cardiac box" (loosely defined as the anterior or posterior chest where a stab may penetrate the heart, confined within a rectangle with its superior border being the sternal notch, inferiorly the xyphoid process and laterally the nipples) with evidence of pericardial tamponade on bedside ultrasound and witnessed loss of vital signs in the emergency department (ED) is most likely to benefit from this intervention, with the highest proven survival rates approaching close to 35%. The chest is entered via a left anterolateral thoracotomy, the pericardium is opened and evacuated of pericardial clot, and direct repair of the cardiac injury is undertaken. In contrast, a patient who is in traumatic cardiac arrest status post blunt trauma with unwitnessed loss of vital signs in the prehospital setting have close to if not zero survival. Based on retrospective data, ED thoracotomy intervention for thoracic trauma secondary to stab injuries have improved outcomes when compared with gunshot wounds. Additionally, patients who have arrested from traumatic cardiac injuries have increased survivability as compared with those suffering noncardiac injuries.

There are "relative indications" allowing provider discretion in decision making. Penetrating abdominal, pelvic, and extremity as well as blunt thoracoabdominal trauma arrests with witnessed loss of vital signs in the field (with signs of life) or with arrest and loss of signs of life in the trauma bay are deemed appropriate candidates with survivability reaching up to 15%. ED thoracotomy performed for abdominal trauma is undertaken with the goals of cross-clamping the descending aorta, thereby prioritizing perfusion to the brain and coronary vasculature as well as proximally controlling intraabdominal arterial hemorrhage, ruling out intrathoracic pathology and allowing access to the heart for open massage and defibrillation.

Although absolute indications (and contraindications) are clear, there remains a wide swath of patients with relative indications. They are conditionally recommended for ED thoracotomy because of extremely low likelihood of survival, and for those who do survive, there is a high incidence of neurologic insult and disability. However, this is balanced against the chance for some to enjoy a meaningful survival.

It needs to be remembered that the resuscitative thoracotomy is just a beginning maneuver, and rapidly proceeding to definitive management of the "downstream" injuries is vital to the patient's survival. Additionally, the open chest introduces another large wound to these severely injured patients. Another very important concept is that the ED thoracotomy, unlike other invasive procedures, is truly an operation. Injuries found need to be addressed, and in those who survive, thoracic wall reconstruction needs to be undertaken.

ANTEROLATERAL THORACOTOMY

Adhering to the Advance Trauma Life Support (ATLS) algorithm approach to the trauma patient, a resuscitative thoracotomy would

TABLE 1 Summary of Eastern Association for the Surgery of Trauma Practice Management Guideline Recommendations for the Use of Emergency Department Thoracotomy

Signs of Life on Arrival to Emergency Department	Injury Mechanism	Location of Injury	Recommendation for Emergency Department Thoracotomy
Yes	Penetrating	Thoracic	Strongly yes
No	Penetrating	Thoracic	Conditional yes
Yes	Penetrating	Extrathoracic	Conditional yes*
No	Penetrating	Extrathoracic	Conditional yes*,†
Yes	Blunt		Conditional yes*,†
No	Blunt		Conditional no

*Does not pertain to isolated cranial injuries.
†Poor data and largely based on speculation of patient preference.

TABLE 2 Western Trauma Association Recommendations for Emergency Resuscitative Thoracotomy

	Blunt	Penetrating Torso	Penetrating Neck	Penetrating Extremity	Blunt/Penetrating
Recommends EDT	<10 min prehospital CPR	<15 min prehospital CPR	<5 min prehospital CPR	<5 min prehospital CPR	Active CPR and signs of life or profound shock with systolic blood pressure <60 mm Hg

systematically fall into the circulatory bucket succeeding airway intubation, chest decompression, blood pressure assessment with infusion/transfusion protocols, and pulse check. In reality, a patient in arrest often requires efforts in parallel (that is, when resources permit, intubation occurring simultaneous to the performance of the thoracotomy). While an anterolateral thoracotomy may be rapidly performed, it requires familiarity with anatomy and physiology, as well as an understanding and preparedness to tackle repairs to injuries sustained.

When the decision is made to make the incision, the site is identified at the anterolateral chest wall, on the male from the left parasternal main body (as should you extend through the sternum you desire body to body wire placement) on an imaginary line along the nipple, and female on the inframammary fold in the direction of the rib in the 4th/5th intercostal space, with the intention to target the inferior border of the pectoralis major muscle group on the chest wall. The left arm is raised above the patient's head while the patient is in the supine position, and the chest cage is rapidly painted with an antiseptic, usually betadine. If possible, placement of an orogastric tube may assist in differentiating the esophagus from the aorta. The anterior chest should be cleared of all equipment in preparation for clamshell extension should it be needed for further exposure.

Gaining access inferiorly along the pectoralis minimizes the amount of soft tissue incised, making it more efficient, allows for the best exposure of most areas of the thoracic cavity, and minimizes raw surface as a cause of intra- and postoperative bleeding should the thoracotomy be successful. When performing this procedure in a female with larger breasts, the mammary tissue should be retracted toward the ipsilateral shoulder and maintained in place to optimize exposure either by a colleague's hand or by taping. The incision follows the natural curvature of the rib down toward the stretcher (Fig. 1). This is carried out in a rapid fashion incising through the skin and subcutaneous tissue exposing serratus anterior musculature, which is transected as laterally as the latissimus dorsi allows when it is retracted laterally. This can be done to expose the underlying intercostal musculature to take in a separate incision; if you have managed to get into the chest safely medially, then it can be taken simultaneously with a heavy Mayo scissors. Special attention should be placed on maintaining the incision on the superior aspect of the inferior rib to avoid damage to the intercostal neurovascular bundle. With anatomic awareness, the internal mammary artery may be avoided when approaching the lateral sternum and, if transected, can be ligated when the patient gets a perfusing blood pressure and presents itself. Posterolaterally, the chest wall is opened well beyond the medial border of the latissimus dorsi; there is no need to divide the latissimus dorsi muscle, which again, if done, results in problematic bleeding if the thoracotomy is a success. Occasionally patients will have pleural adhesions, so attention should be paid to the lung parenchyma when entering the chest as to not cause avoidable parenchymal damage and can be bluntly dissected away from the thoracic wall and mobilized as needed for hilar, aortic, cardiac, or subclavian control.

A Finochietto retractor (rib spreader) is placed, and the ribs are spread. There is debate over the optimal orientation of the retractor. If a clamshell extension is possibly required, then the handle is placed closer to the stretcher (i.e., away from the sternum as to allow extension to the contralateral side). In the event of thoracotomy extension, the incision is taken across the sternal body down to the bone and extended in the same fashion down the right hemithorax. A heavy-set shears or a Lebsche knife can be utilized to transverse the distal sternum. Unfortunately, anatomically when extending the initial thoracotomy across the sternum, both internal mammary arteries will be transected and will require ligation once blood flow has been restored.

PERICARDIOTOMY AND CARDIORRHAPHY

Upon entering the chest, immediate inspection allows for assessment of pathology. The pericardium should be opened routinely to rule out cardiac injury, cardiac tamponade, and facilitate open cardiac massage. An incision on the pericardium should be made anterior to the phrenic nerve (usually well seen with its accompanying fat stripe) and extended parallel to the phrenic nerve as superiorly as possible and inferiorly to the cardiac apex (Fig. 2). The pericardium is tough and fibrous and is often difficult to grasp with forceps, especially if bulging with blood. A nick with a scalpel blade is often required. Inspection alone can give a great deal of information, which helps drive therapeutic intervention. Is there cardiac injury or pericardial blood? Is the heart empty and still moving (in which case, more effective intravascular repletion may be required)? Does the heart have effective electromechanical activity (does it need cardioversion)? The heart is then delivered from the pericardial sac (Fig. 3).

In the event of tamponade, cardiac delivery should precede clot evacuation and methodical examination of the myocardium. If cardiac injury with active extravasation is identified, prompt control with light digital pressure should be swiftly undertaken. Several options have been well described for temporary control of full thickness cardiac injuries and include Foley catheter placement (through the injury into the chamber) with balloon inflation and minimal traction, large staples, vascular clamps (may be effective on atrial injuries), or suture control until definitive cardiorrhaphy can be achieved in the operating room. One needs to remember that gunshot wounds to the heart most frequently have both entrance



FIG. 1 Line of the left anterolateral thoracotomy; note that it follows the curve of the rib. The inframammary fold (in a woman) or the lower border of the nipple is a key landmark for sighting the incision.



FIG. 2 The pericardiotomy is made anterior and parallel to the phrenic nerve. Note the clamp positioned across the thoracic aorta.



FIG. 3 Clamshell thoracotomy with the heart fully delivered from the pericardial sac. Note the pledgeted repair at the apex of the ventricle and the catheter placed in the atrium for resuscitation.

and exit wounds, so thorough inspection of the heart is imperative to management.

NONCARDIAC-RELATED THORACIC HEMORRHAGE

Access to the posterior thorax often requires division of the inferior pulmonary ligament. This is well identified by grasping the inferior lobe from below with one's left hand and slipping a finger posteromedially. It will fall into the groove between the lung and the medial thoracic border. Gentle lateral retraction demonstrates the thin ligamentous tissue for sharp division. Care must be taken to stop short of the hilar vessels. This releases the left lower lobe for easy superior traction and provides access to the inferior descending thoracic aorta. Intentional collapse of the left lung further aids visualization. With the assistance of the airway management team, the endotracheal tube can be advanced into the right main stem bronchus to collapse the left lung allowing optimum exposure of the left hemi thorax.

In the event of entering the chest and encountering a significant hemothorax without evidence of cardiac or descending aortic injury, blood should be evacuated, and immediate exploration should begin for identification of the source. When identified, temporizing measures with direct pressure should be attempted if control cannot be achieved in the ED until the patient gets to the operating theatre; most of the aortic branches and mediastinal vascular injuries are nearly impossible to achieve adequate exposure for repair in the ED. Pulmonary parenchymal injury as the source of hemorrhage is another potential source of major blood loss, and these injuries when encountered should be controlled with direct finger occlusion or noncrushing vascular clamp placement until the patient is transported to the OR for formal resection and/or repair. For uncontrollable vascular or larger parenchymal disruption, pulmonary hilar clamping or complete twisting of the lung about the pulmonary hilum once the inferior pulmonary ligament has been divided can be undertaken. This maneuver is effective in the way of completely occluding vascular inflow for hemorrhage control yet will also cease aeration in the lung. This "hilar twist" has a high morbidity and mortality rate with the physiologic stress it places on the already shocked myocardium by increasing pulmonary vascular resistance and immediate right heart stress with potential resultant right heart failure.

AORTIC CROSS-CLAMPING

Control of the aorta during an emergency thoracotomy is achieved by pressure at the distal descending thoracic aorta. The aorta runs anterior to the vertebral bodies and directly next to and to the left of the esophagus in this location. It is separated from the left hemithorax proper by the mediastinal pleural tissue, and posteriorly the prevertebral fascia is quite firm. The aorta is easily palpable when there is a pulse but may be difficult to feel as distinct from the esophagus in the arresting patient. As mentioned earlier in the chapter, a nasogastric verse orogastric tube helps to localize the esophagus when attempting to isolate the aorta away from it. However, when attempting to save a life with a noncrushing atraumatic aortic cross-clamp, the focus should be getting aortic control and not a meticulous dissection of the esophagus.

As with most necessary exposures for the left hemithorax, the inferior pulmonary ligament will need to be released, and lung collapse should be facilitated with main-stem endotracheal tube placement. Initial aortic control may be achieved with manual pressure of the aorta against the vertebral bodies. This has the disadvantage of blocking effective manual cardiac massage should that be required simultaneously (Fig. 4).

To expose the aorta for placement of a cross-clamp, the overlying mediastinal pleural needs to be opened over the aorta. This



FIG. 4 Active cardiac massage precludes manual pressure on the intrathoracic aorta. Note aortic cross-clamp in place.

is often difficult to initiate. We use a clamp with the tips pushed against vertebral column just posterior to the aorta in the groove created between the two, scratch through the pleural membrane, and spread parallel to both structures facilitating the dissection. Finger fracturing will allow exposure of the aorta and esophagus off their respective pleural covering anteriorly, the prevertebral fascial tissue posteriorly, and will also allow separation of the two structures from one another. Once this has been achieved, the aorta should be accessible and mobile enough to allow elevation for aortic clamp placement and successful cross-clamping. When placed for presumed distal hemorrhage control, once cardiac activity is ensured, the patient must proceed expeditiously to the operating room for other definitive management.

Although this maneuver allows for preferential blood shunting to the brain and myocardium, all distal structures will in turn be exposed to prolonged ischemia with simultaneous massive physiologic changes proximally. As with all arterial clamping, an effort needs to be made to minimize clamp time. Restoration of global perfusion can be challenging given the post-clamp physiologic stress of reperfusion and reperfusion injury. Acidosis, hyperkalemia, and shock all should be anticipated, but with prolonged continual aortic clamp times (>40 minutes), this is frequently fatal.

APPROACH TO OPEN CARDIAC MASSAGE

Effective internal cardiac massage should be undertaken as soon as cardiac arrest is identified and appropriate ED surgical intervention has completed. Bimanual approach is the preferred approach to effective cardiac massage in a "hinge clapping" motion. Using the entirety of the palms of the hands and fingers, commence the compression at the apex of the heart and complete the compression at the base. This maneuver can be further described by firmly adducting the fingers and cupping the anterior hand with the posterior base hand in a rigid flat supinated position, providing a flat surface for the heart to be compressed against. Appose both palmar aspects of the hands to firmly compress the myocardium (Fig. 5). This provides effective circulation and avoids direct cardiac injury.

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA

There continues to be a growing enthusiasm for the use of endovascular aortic occlusion in the management of a selected group of severely injured patients. Tried first in the early 1950s with the idea of an intraluminal rapid occlusion of the descending thoracic aorta/abdominal aorta without the morbidity of thoracotomy, there has been a resurgence of its use in the past several years primarily because of practical and specifically designed catheters (Fig. 6). Brand dependent, the technique is commenced percutaneously or via vascular cut down of the common femoral artery; an arterial micropuncture needle with wire guide and Seldinger technique allows for introducer catheter insertion followed by expeditious sheath upsize and with or without guidewire assistance balloon insertion into the desired anatomic zone.

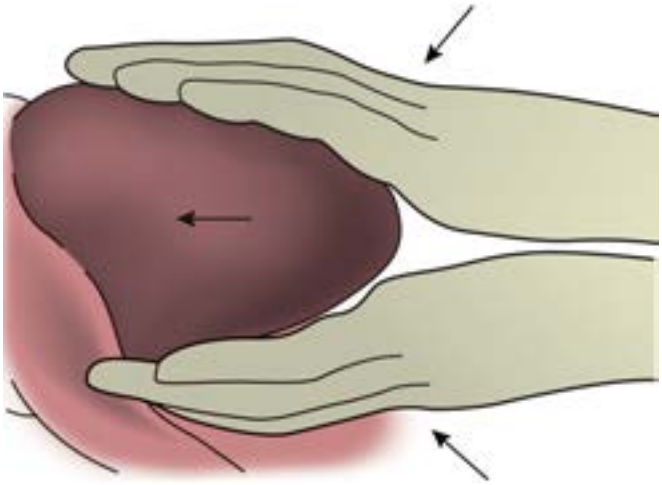


FIG. 5 Open cardiac massage is best achieved with a bimanual, open, flat-handed approach.

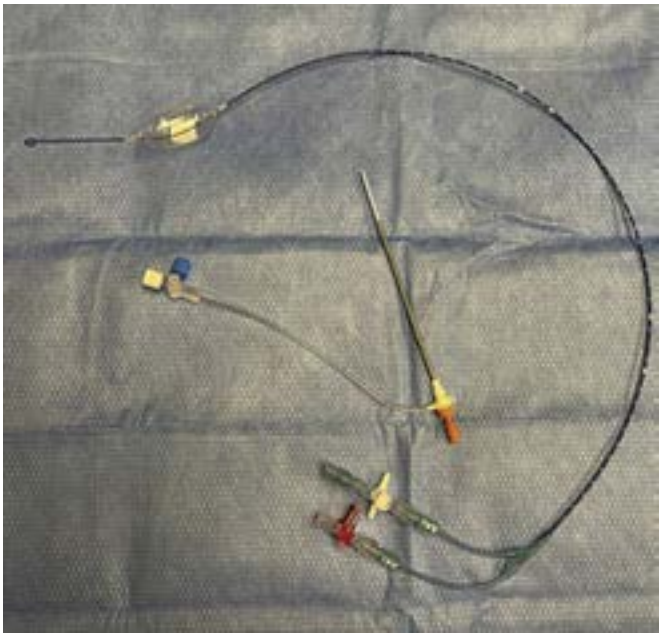


FIG. 6 REBOA catheter with introducer sheath.

Positioning of the balloon occlusion is determined by likely anatomic location of hemorrhage in either the thoracic aorta above the renal arteries (zone 1) for intraabdominal hemorrhage control or just above the aortic bifurcation (zone 3) for control of pelvic hemorrhage. Once again, depending on the brand, positioning can later be confirmed with fluoroscopic, x-ray, or CT imaging if the balloon is filled with dye mixed with saline in place of air. It is vital to understand that the EDRT and the REBOA are not interchangeable procedures. It is obvious that REBOA would have no use in a patient who arrives with penetrating thoracic trauma, neck trauma, and blunt thoracic trauma-related hemopericardium and/or hemothorax with arrest and is in fact contraindicated. However, for patients who require subdiaphragmatic hemorrhage control with aortic occlusion, the REBOA is a very attractive alternative to the maximally invasive traditional full thoracotomy.

Multiple algorithms are being used to ascertain the optimum scenario for ED-REBOA placement. The one most fitting with the best success data is in those patients arriving in extremis (i.e., unstable vital signs) with minimal or no response to volume resuscitation, no evidence of aortic trauma on simple chest films, and a likely cause of exsanguination, for example, severe pelvic fractures. As for the ideal positioning of the device, the Focused Assessment with Sonography for Trauma (FAST) exam is undertaken with a positive result requiring positioning of the balloon occlusion in zone 1 (above the celiac artery) and a negative result requiring a pelvic plain film. Should the pelvis show any signs of instability the balloon is deployed in zone 3 (below renal arteries and above the aortic bifurcation) and if the film proves to be unremarkable, the balloon is deployed in zone 1.

There is a growing body of evidence supporting the effectiveness of the ED-REBOA and in which patient population its purpose is served best. As with any intervention, it too is associated with

adverse outcomes, high mortality rates, and the potential for significant morbidity. It certainly has a place and role in acute care, being an effective tool to buy the trauma surgeon time for definitive operative intervention in a controlled setting.

Suggested Readings

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Joseph B, Khan M, Jehan F, Latifi R, Rhee P. Improving survival after an emergency resuscitative thoracotomy: a 5-year review of the Trauma Quality Improvement Program. *Trauma Surg Acute Care Open*. 2018;3(1):e000201 Published 2018 Oct 9.

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Management of Traumatic Brain Injury

Purvi P. Patel, MD, Patrick M. McCarthy, MD, and Matthew J. Martin, MD

Traumatic brain injury (TBI) is a leading cause of disability, healthcare resource expenditure, and death after injury. In the past year, there were over 2 million TBI-related emergency department visits, with 60,000 deaths attributable to the pathology in the United States alone. The major causes of TBI include falls, motor vehicle crashes, firearm-related suicide, and assaults. Groups more likely to be affected by TBI include military veterans, minorities, the homeless population, and those in correctional and detention facilities. The initial insult to the brain from the injury has a component that is irreversible because of neuronal cell death and a component that is potentially reversible with high-quality supportive care and interventions. Goal-directed therapies for TBI management aim to prevent progression of the initial injury by optimizing medical management and identifying select patients who will benefit from prompt surgical intervention.

INITIAL EVALUATION AND IMMEDIATE MANAGEMENT

The initial evaluation of all trauma patients starts with establishing an airway, confirming breathing, and optimizing circulation. For those with brain injuries, the disability step of the evaluation is essential. A focused neurologic exam centers on the patient's ability to follow basic commands, the pupillary response to light, and identifying lateralizing signs. A simple reproducible assessment that is widely used to evaluate a patient's global neurologic state is the Glasgow Coma Scale (GCS) shown in Table 1. A composite score can be generated by grading a patient's motor, verbal, and ocular response to stimuli, with scores ranging from 3 (no neurologic function/response) to 15 (normal mental status). TBI is commonly graded in severity as mild

TABLE 1 Glasgow Coma Scale

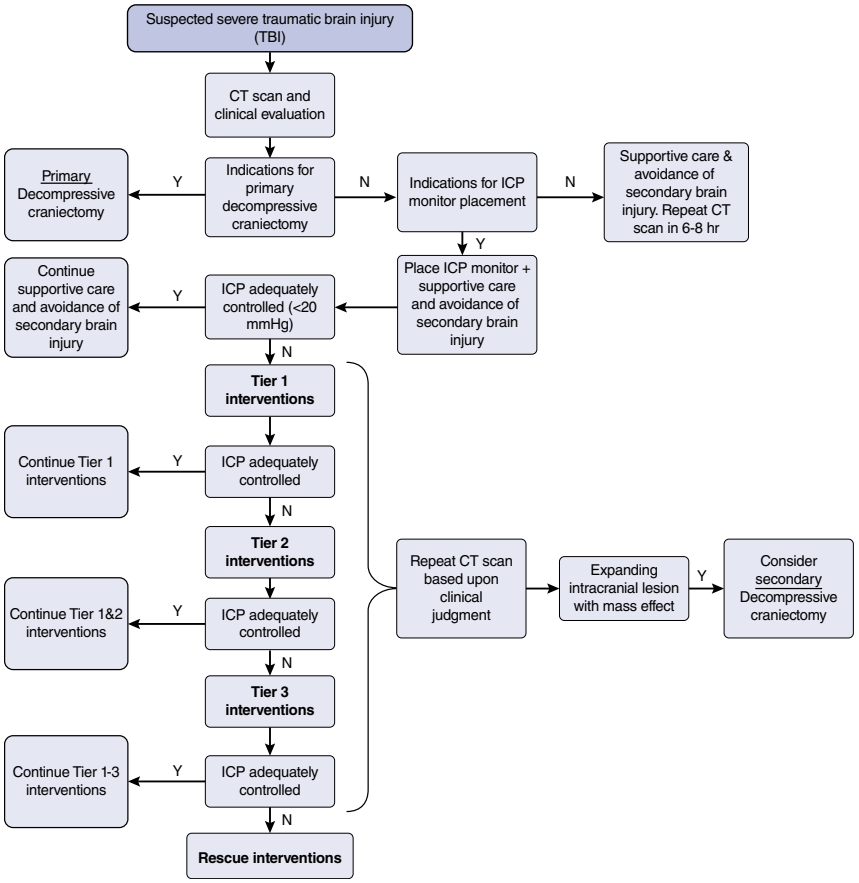
Subcategory	1974 Classification	2014 Classification	Points
Eye opening	Spontaneous	Spontaneous	4
	To speech (command)	To sound	3
	To pain	To pressure	2
	None	None	1
Verbal response	Orientation	Orientated	5
	Confused conversation	Confused	4
	Inappropriate speech	Words	3
	Incomprehensible speech	Sounds	2
	None	None	1
Motor response	Follows commands	Obey commands	6
	Localizes painful stimuli	Localizing	5
	Withdraws from pain (nonlocalizing)	Normal flexion	4
		Abnormal flexion	3
	Abnormal flexion (decorticate)	Extension	2
	Abnormal extension (decerebrate)	None	1
	Gives no motor response		

(GCS ≥13), moderate (GCS 9–12), or severe (GCS ≤8). The Western Trauma Association has provided an algorithm on how to evaluate and manage a patient with suspected TBI (Fig. 1). For patients who can safely tolerate imaging, a noncontrast head computed tomography (CT) scan should be completed as soon as possible. Imaging should be reviewed to identify the presence of intracranial blood, brain parenchymal injury, midline shift, mass effect, herniation, and skull fractures to help characterize the injury and guide further interventions.

TBI encompasses a variety of lesions with different underlying mechanisms. Epidural hematomas (EDHs) are associated with temporal bone fractures and bleeding from the middle meningeal artery. There is often a lucid interval after the initial injury followed by clinical deterioration. A "lenticular-shaped" lesion that does not cross suture lines is a pathognomonic finding for EDH (Fig. 2A). A subdural hematoma (SDH) results from a tear in a bridging vein that causes bleeding in the layer between the dura and the brain, resulting in a "crescent-shaped" mass on CT (Fig. 2B). Subarachnoid hemorrhage (SAH) can also arise after trauma and appear as diffuse bleeding along the subarachnoid membrane. Intraparenchymal hemorrhage (IPH) results from contusions in the brain tissue most often found in the frontal and temporal regions (Fig. 2C). Intraventricular hemorrhage (IVH) is blood within the ventricles of the brain and is often associated with other brain injuries. Diffuse axonal injury (DAI) results from an acute acceleration or deceleration force that causes shearing of axons and is better characterized on MRI with an assessment of the gray-white matter junction.

Once TBI is identified, immediate measures should be taken in the trauma bay to minimize progression of the injury or the development of secondary injuries. Maintaining oxygen delivery to the brain to minimize ischemia and additional neuronal cell injury or death is critical. Derangements in blood pressure, oxygenation, and ventilation are all independently associated with increased morbidity and mortality. Older adult patients are even more susceptible to derangements in these parameters and require higher systolic blood pressure (SBP) goals for improved outcomes. The Brain Trauma Foundation (BTF) TBI guidelines recommend an SBP ≥ 100 mm Hg for those 50 to 69 years of age and above 110 mm Hg for patients 70 years of age and older. Resuscitation with normal saline, hypertonic fluids, and blood along with early hemorrhage control is critical in preventing hypotension. Vasopressor therapy may be required to achieve and maintain these blood pressure goals and should be used liberally in conjunction with resuscitation to prevent any episodes of severe hypotension.

Hypoxemia (defined as SpO_2 less than 90%) for as little as 5 minutes can result in irreversible worsening of brain injury. All TBI patients should have continuous pulse oximetry and be provided supplemental oxygen to maintain adequate oxygen saturation. Many patients with severe TBI require intubation for airway protection, and a general rule is that intubation is mandatory if the GCS is less than 9. Target oxygen saturation should be 94% or higher with a partial pressure of oxygen in arterial blood level > 70 mm Hg. Ventilation is also critical to ensure eucapnia as both hypercapnia and hypocapnia can worsen TBI and neurologic outcomes. Hypercapnia causes vasodilation resulting in increased blood volume and intracranial pressure (ICP) elevation that can cause additional neuronal injury. Although hyperventilation to induce hypocapnia will effectively decrease ICP in most patients, this effect is secondary to cerebral vasoconstriction



Categories	Interventions
Supportive care and measures to avoid secondary brain injury	• Standard trauma care • Hemorrhage control • Adequate resuscitation and administration of blood products • Elevation of the head of bed • Analgesics/sedatives • Fluid and electrolyte management • Avoidance of hyponatremia
	• Prevention of hyperpyrexia • Treatment for hyper/hypoglycemia • Supplemental oxygen to maintain oxygen saturation >90% and pO_2> 60 mmHg • Normocarbic ventilation (pCO_2 35-40 mm Hg) • Correction of coagulopathy • Early delivery of nutrition (preferentially enteral) • Treatment of infections
Tier 1	• Additional analgesia/sedation • Cerebrospinal fluid drainage
Tier 2	• Hyperosmolar therapy • Neuromuscular paralysis
Tier 3	• High dose barbiturates • High dose propofol
Rescue strategies	• Decompressive craniectomy • Experimental therapies

FIG. 1 Western Trauma Association algorithm for the evaluation and management of severe traumatic brain injury (TBI). *(From Alam HB, Vercruysse G, Martin M, et al.; Western Trauma Association Critical Decisions in Trauma Committee. Western Trauma Association critical decisions in trauma: Management of intracranial hypertension in patients with severe traumatic brain injuries.* J Trauma Acute Care Surg. *2020;88:345–351.)*

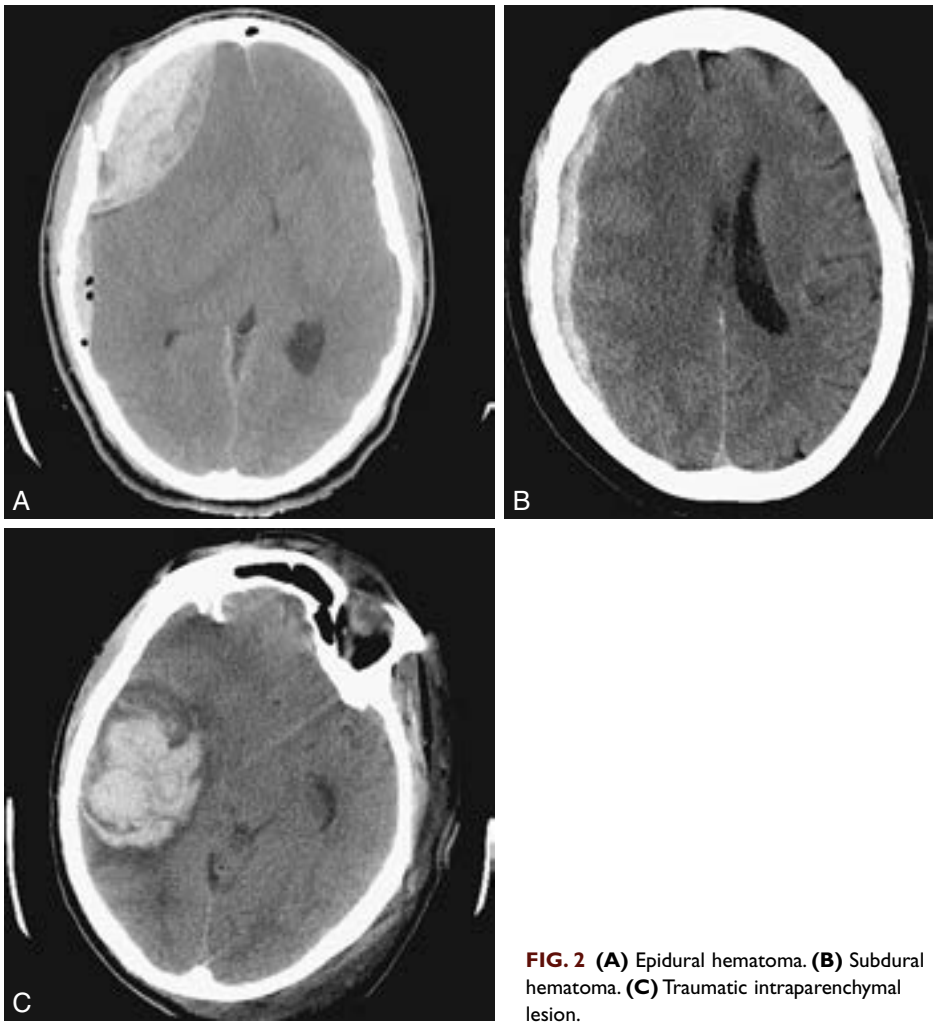


FIG. 2 **(A)** Epidural hematoma. **(B)** Subdural hematoma. **(C)** Traumatic intraparenchymal lesion.

and decreased cerebral blood flow (CBF), which can further exacerbate ischemic injury. Continuous end-tidal carbon dioxide (EtCO) monitoring can guide respiratory management with a recommended goal of mild hyperventilation to maintain a pCO_2 of 35 to 40 mm Hg. More significant degrees of hyperventilation have been found to be associated with poorer neurologic outcomes and should be avoided other than as a brief temporizing measure for patients with severe intracranial hypertension and impending herniation.

Use of anticoagulant and antiplatelet medications has increased over the past decade and should be addressed in the setting of intracranial injury. In 2016, the Neurocritical Care Society and the Society of Critical Care Medicine put forth recommendations on how to manage common agents in the setting of TBI with intracranial hemorrhage (ICH; Table 2). Since that time, the dosing to reverse direct factor Xa inhibitors with four-factor PCC has been updated to 25–50 U/kg IV. Laboratory testing should be completed on all trauma patients and should include measurement of prothrombin time, activated partial thromboplastin time, platelet count, and fibrinogen level. Viscoelastic coagulation testing may also be performed using thromboelastography or rotational thromboelastometry and can identify additional dysfunction within the coagulation pathway to help guide therapy.

Patients with severe TBI may present with clinical signs of intracranial hypertension with concern for impending herniation. The Cushing reflex or triad is a physiologic response to a sudden increase in ICP that manifests as a triad of increased blood pressure, bradycardia, and irregular respirations. Brainstem compression can present as posturing and Cheyne-Stokes ventilation (a cyclic breathing pattern marked by rapid deep breaths followed by a period of apnea). Unilateral pupil dilation and loss of light reactivity is concerning for uncal herniation on the ipsilateral side. In these cases, immediate measures must be taken to reduce ICP. In patients who do not require spinal protection precautions, the head of the bed should be elevated. If spine precautions remain, the patient can be placed into the steep reverse Trendelenburg position. Short periods of hyperventilation can be utilized to induce transient hypocarbia and cause cerebral vasoconstriction to reduce ICP. This should only be used as a temporizing measure, as prolonged hypocarbia and cerebral vasoconstriction can detrimentally reduce cerebral oxygen delivery. Hypertonic saline solutions or mannitol, an osmotic diuretic, can be used to shift fluid out of brain cells into the intravascular space and reduce cerebral edema. These measures will be discussed in further detail later in this chapter.

MEDICAL MANAGEMENT

TBI patients are classified using a combination of clinical and radiographic findings. Table 3 details the recently developed and validated Brain Injury Guidelines (BIG) which can assist trauma surgeons in determining the necessary level of care a patient may require based on his or her clinical history, neurologic exam, and CT imaging findings. Those with mild injury are categorized as BIG 1. A patient with a BIG 1 TBI and a normal neurologic exam after 6 hours can often be discharged home without repeat imaging. Those with the most

TABLE 2 Management Recommendations for Common Antiplatelet and Anticoagulation Agents in the Setting of Traumatic Brain Injury with Intracranial Hemorrhage

Antithrombotic	Reversal Agent
Vitamin K antagonists	If INR ≥1.4: Vitamin K 10 mg IV, plus three- or four-factor PCC IV (dosing based on weight, INR, and PCC type) or fresh-frozen plasma 10–15 mL/kg IV if PCC not available
Direct factor Xa inhibitors	Activated charcoal (50 g) within 2 hours of ingestion, activated PCC (FEIBA) 50 U/kg IV or four-factor PCC 50 U/kg IV
DTIs	For dabigatran reversal: Activated charcoal (50 g) within 2 hours of ingestion, and idarucizumab 5 g IV (in two 2.5-g/50-mL vials) Consider hemodialysis or idarucizumab redosing for refractory bleeding after initial administration For other DTIs: Activated PCC (FEIBA) 50 U/kg IV or four-factor PCC 50 U/kg IV
Unfractionated heparin	Protamine 1 mg IV for every 100 units of heparin administered in the previous 2–3 hours (up to 50 mg in a single dose)
LMWH	Enoxaparin Dosed within 8 hours: protamine 1 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose) Dosed within 8–12 hours: protamine 0.5 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose) Minimal utility in reversal > 12 hours from dosing Dalteparin, nadroparin, and tinzaparin: Doses within 3–5 half-lives of LMWH: protamine 1 mg IV per 100 anti-Xa units of LMHW (up to 50 mg in a single dose) or rFVIIa 90 μg/kg IV if protamine is contraindicated
Danaparoid	rFVIIa 90 μg/kg IV
Pentasaccharides	Activated PCC (FEIBA) 20 U/kg IV or rFVIIA 90 μg/kg IV
Thrombolytic agents (plasminogen activators)	Cryoprecipitate 10 units IV or antifibrinolytic (tranexamic acid 10–15 mg/kg IV over 20 min or ε-amino-caproic acid 4–5 g IV) if cryoprecipitate is contraindicated
Antiplatelet agents	Desmopressin 0.4 μg/kg IV × 1 If neurosurgical intervention: platelet transfusion (one apheresis unit)

From Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: Executive Summary. A Statement for Healthcare Professionals From the Neurocritical Care Society and the Society of Critical Care Medicine. Crit Care Med. 2016;44(12):2251–2257.
DTI, Direct thrombin inhibitor; *FEIBA*, factor eight inhibitor bypassing activity; *INR*, international normalized ratio; *LMWH*, low-molecular-weight heparin; *PCC*, prothrombin complex concentrates; *rFVIIa*, recombinant factor VIIa.

severe injury are categorized as BIG 3, and guidelines recommend ICU admission, frequent serial neurologic examinations, and immediate neurosurgical evaluation.

Monitoring is essential to providing timely care in TBI patients. ICP monitoring is indicated in severe TBI patients with ICH on CT scan. Additional criteria to consider placement of an ICP monitor include patients older than 40 years of age with hypotension and posturing on neurologic exam, although this is an area of significant debate. Commonly used invasive methods of ICP measurement include placement of an external ventricular drain (EVD) or "ventriculostomy" and intraparenchymal pressure monitors, often called *bolts*. EVDs are zeroed at the midbrain, and in addition to measuring ICP, they can also be used to drain cerebrospinal fluid (CSF) and thus lower ICP. Continuous CSF drainage can more effectively lower ICP than intermittent drainage, and the greatest benefits can be seen in patients with a GCS <6 who receive CSF drainage within 12 hours of their injury. Alternative noninvasive measures of ICP include transcranial Doppler and optic nerve sheath diameter monitors; however, these measurements are less precise and reliable. Arterial lines should be placed to obtain mean arterial pressure (MAP), which allows for calculation of cerebral perfusion pressure (CPP). Central lines can be placed for ongoing resuscitation, for delivery of vasopressor agents, and to provide hypertonic saline therapy.

Intracranial hypertension has traditionally been defined as an ICP ≥20 mm Hg. The recent update of the BTF guidelines supports interventions when ICP measures ≥22 mm Hg. CPP is calculated by subtracting the ICP from the MAP and should be maintained between 60 and 70 mm Hg to optimize CBF and oxygen delivery. In almost all cases, management of significantly elevated ICP in the ICU requires a multimodal strategy. Figure 3 shows an algorithmic approach for the management of elevated ICP using a series of tiered interventions. The key components of these include adequate sedation, analgesia, mild hyperventilation, and osmotic therapies.

Pain and agitation often result in elevations of ICP. Commonly used short-acting sedatives include benzodiazepines and propofol, both GABA agonists. These medications can be bolused and infused in higher doses as a first-line therapy for elevated ICP. When pain is likely the inciting factor, patients can also be given a dose of analgesic. Infusions of both sedatives and analgesics are preferred to

TABLE 3 Brain Injury Guidelines for Classification and Initial Management of Traumatic Brain Injury

Variables	BIG 1	BIG 2	BIG 3
LOC	Yes/No	Yes/No	Yes/No
Neurologic exam	Normal	Normal	Abnormal
Intoxication	No	No/Yes	No/Yes
CAMP	No	No	Yes
Skull fracture	No	Non-displaced	Displaced
SDH	≤4 mm	5–7 mm	≥8 mm
EDH	≤4 mm	5–7 mm	≥8 mm
IPH	≤4 mm, 1 location	3–7 mm, 2 locations	≥8 mm, multiple locations
SAH	Trace	Localized	Scattered
IVH	No	No	Yes
Therapeutic plan			
Hospitalization	No observation (6 hr)	Yes	Yes
RHCT	No	No	Yes
NSC	No	No	Yes

From Joseph B, Friese RS, Sadoun M, Aziz H, et al. The BIG (brain injury guidelines) project: defining the management of traumatic brain injury by acute care surgeons. *J Trauma Acute Care Surg*. 2014;76(4):965–969.
BIG, Brain injury guidelines; *CAMP*, coumadin, aspirin, Plavix; *EDH*, epidural hemorrhage; *IVH*, intraventricular hemorrhage; *IPH*, intraparenchymal hemorrhage; *LOC*, loss of consciousness; *NSC*, neurosurgical consultation; *RHCT*, repeat head computed tomography; *SAH*, subarachnoid hemorrhage; *SDH*, subdural hemorrhage.

boluses as these medications tend to cause hypotension, which could worsen brain injury by lowering the CPP. Chemical paralysis is a highly effective additional adjunct that can be utilized for elevated ICP despite adequate sedation and analgesia. Continuous infusion of paralytic agents is preferred over intermittent bolusing, with close monitoring to ensure both adequate paralysis and sedation. For situations in which maximal therapies have been given and ICP remains elevated, barbiturate coma accomplished with an infusion of phenobarbital can be considered. Sedation holds or holidays should occur frequently to assess the neurologic exam provided that the ICP is well controlled. For patients requiring active interventions for elevated ICP, adequate sedation and analgesia should be maintained without interruption.

Hyperosmolar therapy using either hypertonic saline or mannitol is utilized to shift free fluid into the intravascular space and improve blood viscosity, and it remains the cornerstone of pharmacologic treatment for intracranial hypertension. Commonly used concentrations of hypertonic saline solutions are 3%, 7.5%, and 23.4%. These can be given as a bolus or continuous infusions. Mannitol is a simple sugar that is dosed at 0.25 g/kg to 2 g/kg. It works as an osmotic diuretic by increasing the tonicity of plasma and drawing fluid from cells. This is used to decrease brain cell volume and reduce ICP. However, mannitol should be used with caution in polytrauma patients with tenuous hemodynamics, as the excess fluid excreted by the kidneys can result in hypovolemia and exacerbate or cause hypotension. In head-to-head comparisons, hypertonic saline has been shown to more rapidly lower ICP and to have a more sustained response, but there is no high-quality evidence supporting the use of one versus the other for ICP management.

Prophylaxis is provided to TBI patients to prevent common complications including seizures, venous thromboembolism (VTE), and fever. Postinjury seizures are most common in the first 7 days of injury. The damaged brain tissue and hematoma can be foci for epileptiform activity. Seizures cause a sharp major increase in neuronal activity that leads to locally decreased oxygen and glucose levels that can further worsen cerebral metabolic injury. Factors that increase the risk of seizures in TBI patients include initial GCS ≤10, loss of consciousness >30 minutes, immediate seizures, depressed skull fractures, penetrating injury, age 65 years or younger, and chronic alcoholism. Antiepileptics including phenytoin and levetiracetam are now commonly given for 7 days after a TBI with ICH. The use of seizure prophylaxis has been associated with a decrease in the incidence of early post-TBI seizures, but it has no effect on late seizures. Thus, the duration of administration is usually limited to 7 days, with longer administration reserved for patients who develop early seizures or who have some additional high-risk features.

Trauma patients, especially those with TBI, are at increased risk of venous thromboembolic events. This risk increases with the severity of the TBI but must also be weighed against the risk of additional ICH. Much research has been done to assess the best time to initiate therapy while minimizing the risk of bleeding and worsening of brain injury. Multiple studies have demonstrated that the risk of additional hemorrhage does not appear to be increased when early VTE prophylaxis is administered at 48 to 72 hours after injury providing there is no evidence of ongoing bleeding. We recommend the initiation of VTE prophylaxis to all patients with a stable TBI beginning at 48 to 72 hours from the time of injury and no other contraindication to prophylactic anticoagulation.

Euthermia is ideal for TBI patients. Hyperthermia is associated with increased cerebral metabolic demands resulting in increased CBF and elevated ICP, both of which may have a negative impact on outcomes. While hypothermia has traditionally been viewed as neuroprotective, the associated complications of coagulopathy, immunosuppression, and cardiac dysrhythmias currently outweigh

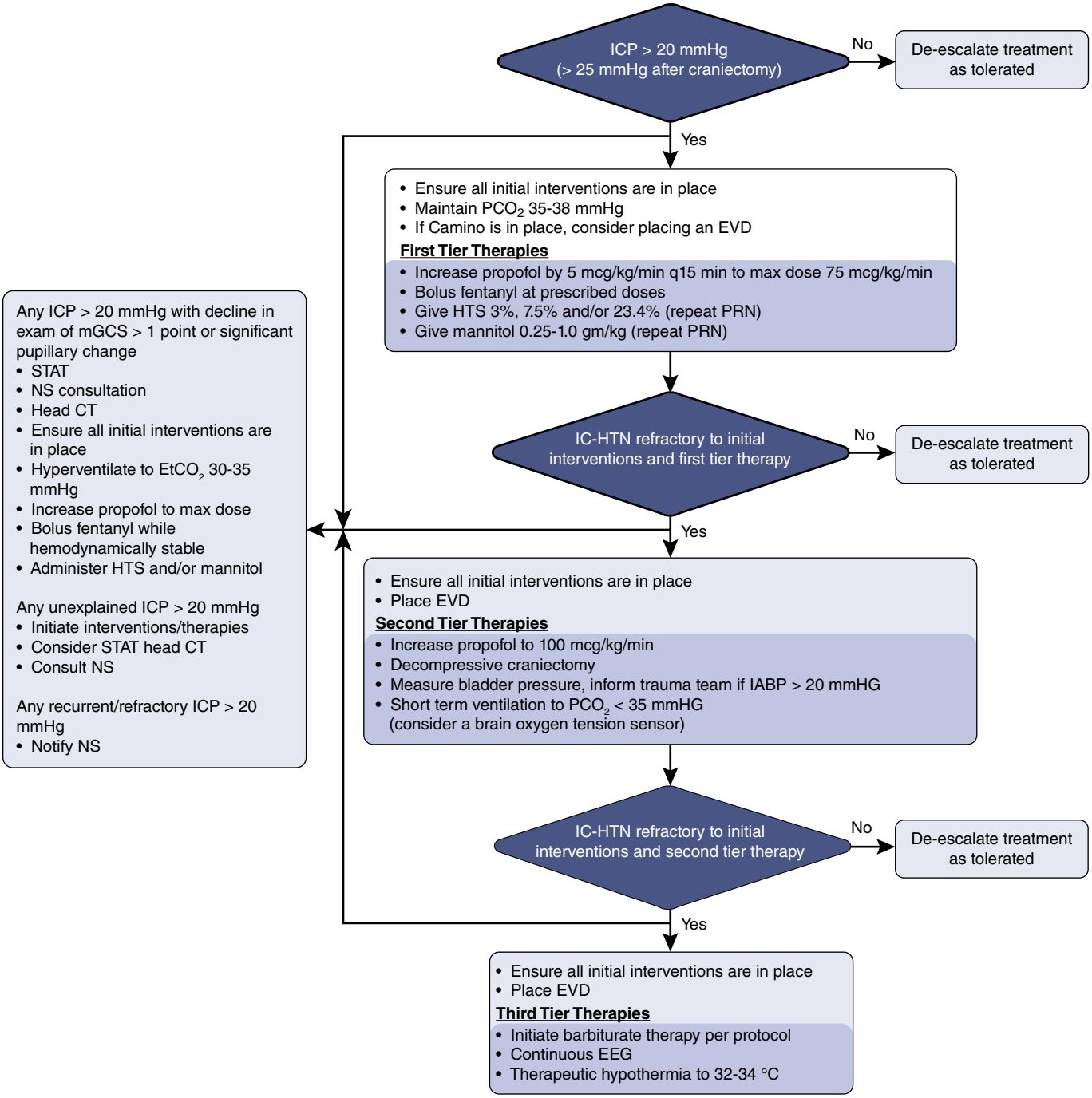


FIG. 3 Algorithm for evaluation and tiered management of elevated intracranial pressure in severe traumatic brain injury. *(From Hampton DA, Stein DM. Intracranial pressure. In: Salim A, Brown C, Inaba K, Martin M, eds.* Surgical Critical Care Therapy. *Springer, Cham; 2018.)*

the benefits of induced hypothermia in most TBI patients. Current recommendations support maintaining normal body temperature with acetaminophen, cooling and/or warming blankets, and warmed fluids. Therapeutic hypothermia is not currently recommended, although it remains an area of ongoing investigation.

Many patients experience dysregulation of their autonomic system after injury. This hypermetabolic state secondary to a catecholamine release or "storm" has been called many names: *neurostorming, hypothalamic dysregulation syndrome, paroxysmal sympathetic hyperactivity syndrome,* and *paroxysmal sympathetic storm*. Associated symptoms include tachycardia, tachypnea, hypertension, fever, diaphoresis, and dystonic positioning. Recent studies indicate that the use of β-blockers, specifically propranolol, in this early period can reduce mortality and significantly improve functional outcomes.

SURGICAL MANAGEMENT

Surgical therapy is most commonly indicated when the mass effect from ICH or cerebral edema causes elevated ICP and brain-tissue displacement with neurologic symptoms or deficits, signs of cerebral ischemia, or evidence of brain herniation. These issues are commonly addressed surgically with either craniotomy or decompressive craniectomy. During a craniotomy, a skull flap is created and then replaced at the end of the case once the blood is evacuated.

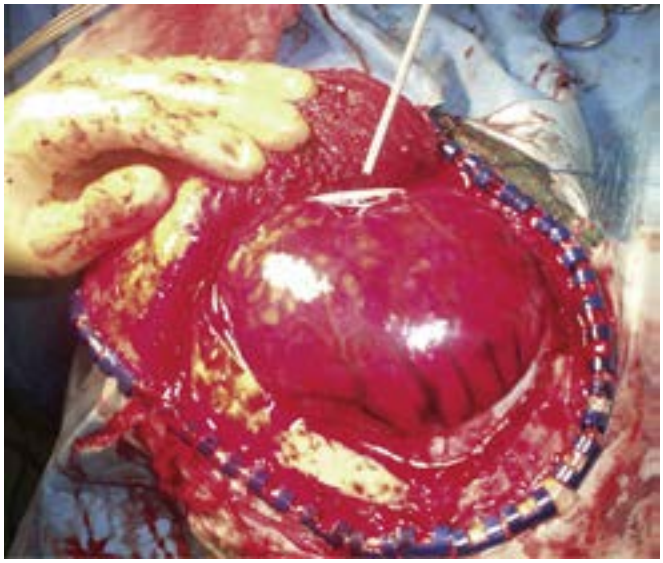


FIG. 4 Intraoperative image of a decompressive craniectomy with severely swollen and herniating brain parenchyma.

Craniectomy removes a large section of the skull to accommodate additional brain volume and swelling (Fig. 4), with a plan for later coverage of the bone defect. Urgent surgical intervention is indicated in patients with at least one of the following: midline shift greater than 5 mm, cisternal compression, elevated ICP refractory to medical management, low GCS score on presentation, and decline of clinical exam. Subdural hematomas thicker than 10 mm, epidural hematomas measuring 30 cm^3, and intraparenchymal lesions larger than 50 cm^3 should also undergo primary decompression.

The BTF released a 2020 update regarding secondary or delayed decompressive craniectomy recommendations for refractory ICP elevations based on results from RESCUEicp (Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension) and DECRA (Decompression Craniectomy in Patients with Severe Traumatic Brain Injury). The RESCUEicp focused on patients with elevated ICP for 1 to 12 hours within 10 days of admission (late), while DECRA looked at patients with elevated ICP for 15 minutes within 72 hours of presentation (early) despite maximal medical therapy. In both groups, patients who underwent craniectomy were noted to have decreased ICP and shorter ICU stays; however, favorable mortality outcomes were only seen in the late group. Both studies noted a higher proportion of patients with resultant severe neurologic deficits compared with medical management, thus highlighting the importance of strict patient selection criteria and realistic counseling of patients and/or their families.

Many cases of severe TBI have concomitant skull fractures. Although most skull fractures do not require intervention, fixation is indicated for open fractures, skull table displacement greater than 1 cm, gross deformity, or wound contamination. Broad-spectrum antibiotic prophylaxis is used for penetrating injuries or contaminated wounds until CSF leak has resolved. Complications of emergent or urgent craniectomy in trauma include CSF leak, hygroma, hydrocephalus, hematoma expansion, and infection including meningitis, encephalitis, and brain abscess.

OUTCOMES

TBI can result in a spectrum of disabilities. An analysis of 5-year outcomes for TBI patients shows that approximately 30% improved, 20% stayed the same, 30% became worse, and 20% died. Most moderate to severe TBI patients will have some types of cognitive disturbances including difficulties with attention, learning, and memory. They may also experience headaches, fatigue, sleep disturbances, and mood disorders. The National Institute of Neurological Disorders and Stroke (NINDS) has collaborated with other groups to create a Common Data Elements (CDE) Outcomes Workup group to establish domains that assess short- and long-term outcomes. A few included domains are global outcomes, recovery of consciousness, physical and behavioral function, and social role participation. Patients with higher functionality scores before injury and at time of hospital discharge benefit the most from TBI rehabilitation. TBI rehabilitation focuses on cognitive and physical activities to help patients regain their ability to complete activities of daily of living. TBI remains a large burden to society, with associated direct and indirect medical costs estimated at over $75 billion.

Severe TBI often causes irreversible damage to the brain and can result in brainstem herniation and brain death. The American Academy of Neurology guidelines for the determination of brain death include medical optimization, elimination of cofounding factors, a through neurologic examination, and apnea test. Prerequisites for declaring brain death include the presence of an irreversible coma from a known cause confirmed with neuroimaging, no spontaneous respirations, normothermia (core temperature ≥36°C), and hemodynamic stability (SBP ≥100 mm Hg). The effects of sedating drugs, paralytics, and electrolytes or acid-base derangements must be excluded. Examination maneuvers test for the absence of brainstem reflexes by examining pupillary light response; corneal, oculocephalic, and oculovestibular reflexes; no response to noxious stimuli; and the gag and cough reflexes induced with deep suctioning. To perform an apnea test, the patient should be preoxygenated and normocapnic. The patient is then disconnected from the ventilator but provided oxygen. The test is consistent with brain death if the final $PaCO_2$ measures ≥60 mm Hg or if there is an increase of 20 mm Hg from baseline without evidence of spontaneous respirations. Additional testing can include electroencephalogram, CT angiography of the head and neck, and nuclear CBF scans.

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Chest Wall Trauma, Hemothorax, and Pneumothorax

Raul Coimbra, MD, PhD, and David B. Hoyt, MD

Chest trauma is common. Data suggest that approximately 30% to 50% of all blunt trauma patients admitted to trauma centers have sustained chest trauma. Thoracic injuries account for 20% to 25% of all trauma-related deaths, and complications of chest trauma contribute to another 25% of all deaths. Early deaths in chest trauma patients are caused primarily by major respiratory problems, such as tension pneumothorax and massive hemothorax. These clinical situations must be recognized and managed promptly. The most common injury in thoracic trauma is chest wall trauma. Because of the high prevalence of rib fractures and associated pneumothorax and hemothorax, most thoracic injuries can be managed with simple procedures such as thoracentesis, respiratory support, and adequate analgesia. Only 15% of patients sustaining chest trauma will require a thoracotomy for definitive management of intrathoracic injuries.

This chapter reviews the most current concepts of diagnosis and management of chest wall injuries, pneumothorax, and hemothorax.

INITIAL EVALUATION

The physical examination of the chest is critical in identifying life-threatening situations that will require immediate attention. These include tension pneumothorax, massive hemothorax, open pneumothorax, flail chest, and cardiac tamponade.

The Advanced Trauma Life Support (ATLS) principles of primary assessment, resuscitation, secondary assessment, and definitive care should be followed. Pulse oximetry should be applied as soon as the patient arrives. A complete physical exam is helpful in identifying significant physiologic changes. Throughout the assessment, high-flow oxygen should be administered to the patient. A chest x-ray is usually performed as soon as is feasible to radiographically evaluate the soft tissues, bones, lung parenchyma, and thoracic cavities. The use of ultrasonography to assess the chest cavity, lung parenchyma, and the pericardium (Extended Focused Assessment with Sonography in Trauma [eFAST]) carries the potential to confirm diagnoses that sometimes are difficult to make based only on the clinical exam. The same is true with the use of chest CT with contrast (CT angiography) (Fig. 1), which is certainly more sensitive than conventional x-rays and the physical exam alone. However, it exposes patients to much higher levels of ionizing radiation, a significant problem in the pediatric population.

To help guide decision making for chest imaging, the National Emergency X-Ray Utilization Study (NEXUS Chest) screening tools have been developed and shown to have a sensitivity greater than 99% for thoracic injuries of major clinical significance (Boxes 1 and 2).

We still believe a chest x-ray is essential in evaluating thoracic trauma; however, tension pneumothorax or massive hemothorax should be diagnosed clinically.

SPECIFIC INJURIES

Rib Fractures

Blunt chest wall trauma varies from an isolated rib fracture to bilateral multiple rib fractures caused by crush mechanisms of injury, leading to significant respiratory distress resulting from pneumothorax, hemothorax, or marked pulmonary contusion. Mortality rates following blunt chest wall trauma range from 4% to 20%.

After blunt chest trauma, ribs fractures are the most common injuries, with an overall prevalence of 10% in trauma admissions. Ribs 4 to 10 are the most commonly fractured. These injuries are accompanied by high mortality rates, varying from 10% to 20%, usually resulting from the development of respiratory dysfunction and pneumonia.

An isolated single rib fracture without lung involvement, pneumothorax, or hemothorax is usually treated on an outpatient basis. However, the ideal management of patients with multiple rib fractures or significant chest wall trauma without life-threatening

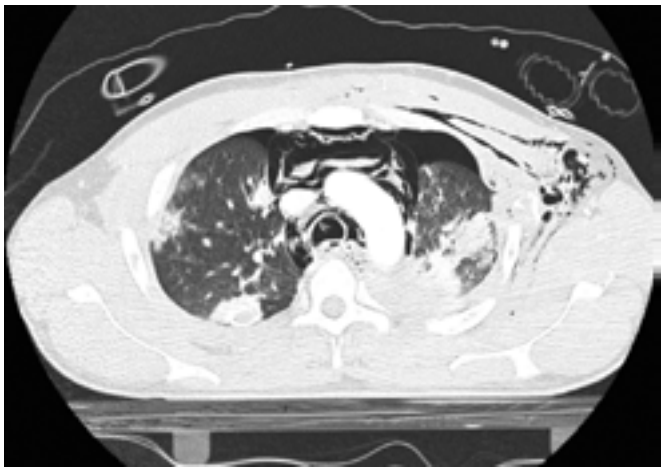


FIG. 1 CT scan of chest showing deformity of chest wall, rib fractures, bilateral pulmonary contusions, subcutaneous emphysema, and bilateral pneumothoraces.

BOX 1 NEXUS Chest: Indications for Chest X-Ray*

Age >60 years
Rapid deceleration mechanism
Fall >20 feet
Motor vehicle crash >40 mph
Chest pain
Intoxication
Abnormal alertness or mental status
Distracting injury
Chest wall tenderness

*All criteria absent: Very low risk for intrathoracic injury and chest imaging not indicated.

BOX 2 NEXUS Chest: Indications for Chest CT*

Abnormal chest x-ray
Distracting injury
Chest wall tenderness
Sternum tenderness
Thoracic spine tenderness
Scapula tenderness
Rapid deceleration injury

*All criteria absent: May forgo chest CT.

injuries is controversial. It is well known that elderly patients have a reduced ability to cough, reduced vital capacity, and increased incidence of infectious complications following rib fractures as a result of decreased bone density, reduced chest wall compliance, and increased incidence of underlying parenchymal disease.

The primary clinical manifestation of rib fractures is pain. Other clinical signs include tenderness to palpation and crepitus. Rib fractures are confirmed with a chest x-ray or by chest CT. Approximately 55% of rib fractures are missed on routine chest radiographs. Special views, including an oblique view, may increase sensitivity but are not commonly used during the initial evaluation of a trauma patient. CT scans are the most sensitive study to diagnose rib fractures.

Multiple rib fractures are the hallmark of severe trauma as a result of high-energy transfer. These patients should undergo a complete evaluation to rule out intrathoracic and abdominal injuries. Fractures of the lower ribs (9 to 12) are associated with an increased incidence of solid organ injuries (liver and spleen), and fractures of the upper ribs (1 to 3), clavicle, or scapula are associated with major thoracic vascular injuries as well as blunt cerebrovascular injuries.

In addition to rib number, the total number of fractures also dictates risk, with each additional rib fracture increasing the risk of pulmonary complications and death. Fracture location within the rib also affects patient outcome. In general, lateral and subscapular fracture lines produce the most pain, whereas posterior or anterior fracture lines are usually better tolerated. In addition, the degree of displacement, overlap, and angulation of the fracture all contribute to changes in pulmonary mechanics, pain, and injury to surrounding structures such as the intercostal bundle, lung, and diaphragm.

The patient's age also augments the increased risk of poor outcomes following chest wall trauma. Elderly trauma patients (>65 years of age) are particularly susceptible to deterioration after chest wall trauma. They have an overall mortality rate of 22% and a pneumonia rate of 33% compared with 10% and 17%, respectively, in younger patients.

In this particular patient population, pain control and aggressive pulmonary toilet should be implemented early, with a low threshold for intubation. Care should be taken to avoid fluid overload because it may further impair respiratory function. Pneumonia is the most frequent complication, particularly in the elderly, aggravating chronic lung diseases, increasing ventilator days, and significantly contributing to mortality.

Inadequate pain control significantly contributes to complications following rib fractures such as atelectasis and pneumonia. Pain control is attempted initially with oral or intravenous analgesics. Intercostal nerve blocks with bupivacaine are effective for pain control; however, they are not feasible for multiple fractures as they require frequent injections.

Epidural analgesia is adequate for patients with multiple or bilateral fractures, and it provides sufficient pain control and appropriate pulmonary toilet, decreasing the number of complications.

Flail Chest

A flail chest occurs when three or more contiguous ribs are broken in two places, creating a segment of bone and muscle that can move independently of the thoracic wall. It can also occur following costochondral separation. Fractures can be located in the anterior, lateral, or posterior chest wall. Flail chest occurs in 10% to 15% of patients sustaining major chest trauma, and the chance of having an intrathoracic injury increases several-fold. Flail chest represents the most severe form of chest wall injury after blunt trauma, with more than 80% of patients needing ICU admission, more than 50% requiring mechanical ventilation, and an overall mortality rate of 16%.

Closed traumatic brain injury is the most frequent associated extrathoracic injury, contributing to higher morbidity and mortality rates. Isolated flail chest carries a low mortality rate in younger patients.

The fractured segment of the chest wall moves paradoxically with spontaneous respirations, pulling inward with inspiration secondary to the negative intrathoracic pressure. The paradoxical respiratory movement can cause significant pain to the patient, leading to a respiratory pattern characterized by rapid shallow breaths and resulting in atelectasis and hypoxia caused by pain. Additionally, the force required to create a flail segment is excessive and usually results in significant underlying pulmonary contusion, further increasing hypoxia. Sequential measurements of forced vital capacity, tidal volume, and inspiratory force are helpful to predict which patients will require ventilatory support. The pathophysiologic effects may be present immediately or may progress over several hours and present as late respiratory decompensation. Lastly, the flail segment may be associated with hemothorax or pneumothorax, which is treated by tube thoracostomy in most instances.

Several scoring systems have been developed to quantify the severity of chest wall injury. The RibScore, which involves several detailed radiographic parameters related to rib fracture pattern, has been recently proposed (Box 3). This score is highly predictive of adverse pulmonary outcomes and is helpful in predicting which patients may benefit from surgical stabilization of rib fractures (SSRF).

Treatment of the flail segment and multiple rib fractures with similar physiologic impact as a flail chest varies according to the patient's clinical presentation. The great majority of patients will undergo conservative (nonsurgical) management. For simple unilateral fractures involving no more than three ribs, young patients with adequate pain control on oral analgesics and without comorbidities can be managed successfully as outpatients. All other patients should be considered for admission, and there should be a low threshold to admit patients with high-risk features to the ICU (Box 4). If stable from a respiratory standpoint, supplemental oxygen, aggressive pulmonary toilet, and adequate analgesia are enough. Pain can be controlled with oral or intravenous analgesics, patient-controlled analgesia (PCA), intercostal nerve blocks, paracostal catheters, which deliver a continuous stream of local anesthetic, or with epidural anesthesia. If a paracostal catheter is used, the anesthetic regimen is usually a bolus dose of 0.25% bupivacaine (20 mL) followed by a continuous infusion (0.125% at 12 mL/h) by either a pump or an elastomer reservoir. Because of the overuse of opioids and the risk of chemical dependency, a multimodal therapy approach has been proposed (Box 5).

Several studies have shown that epidural pain control is superior to other methods and have demonstrated that epidural analgesia after chest wall injuries is associated with decreased ventilator days, fewer pulmonary complications, and shortened ICU and hospital length of stay, primarily when used in older adult patients with multiple fractures. Current guidelines strongly recommend placing an epidural catheter for patients older than 65 years of age with four or more rib fractures. Most patients are eligible for epidural analgesia. Absolute contraindications include increased intracranial pressure, localized infection or rash, and inability to maintain the position for catheter placement, while relative contraindications include a history of spine surgery, spinal fracture, instability near the desired

BOX 3 RibScore*

≥6 rib fractures
≥3 bicortical displaced fractures
≥1 fracture in each anatomic area†
Flail chest
Bilateral fractures
First rib fracture

*1 point is assigned for each variable. RibScore ≥4 may benefit from surgical stabilization.
†Defined as anterior, lateral, and posterior.

BOX 4 Admission Criteria for Rib Fractures

Admission if ≥2 of the following are present after pain control with oral medication:
- Respiratory rate >18
- Incentive spirometry <75% predicted
- Numeric pain score ≥6
- Poor cough
- Age ≥65 years
- ≥3 fractures

If admission criteria are met, ICU admission if ≥1 of the following are present:
- Age ≥65 years
- ≥6 fractures
- Incentive spirometry <60% predicted
- Flail chest
- >4 L oxygen required to maintain SpO_2 >90%
- Associated injury requiring ICU admission

ICU, Intensive care unit.

BOX 5 Multimodal Pain Management of Rib Fractures

Outpatient

Incentive spirometry
Ibuprofen 800 mg PO q6h
Gabapentin 100 mg PO TID
Diazepam 5–10 mg PO QD
Oxycodone PRN

Inpatient

Incentive spirometry
Ambulation
Ibuprofen 800 mg PO q6h
Gabapentin 100 mg PO TID
Diazepam 5–10 mg PO QD
Oxycodone PRN
Intravenous narcotics PRN
Consider epidural or paravertebral catheter
Consider surgical stabilization of rib fractures

level of epidural placement, severe aortic stenosis, mitral stenosis, or pulmonary hypertension, uncorrectable coagulopathy, and ongoing vasopressor requirement.

In patients who develop respiratory distress, intubation and positive pressure ventilation are the treatment of choice. The intubation allows more aggressive pain management and sedation; the positive pressure ventilation can recruit an atelectatic lung and support the contused lung to improve oxygenation. Additionally, the positive pressure ventilation splints the flail segment so the paradoxical motion is halted and the entirety of the thoracic wall can move in synchrony, relieving pain and allowing healing of the soft tissue and bones.

Surgical Stabilization of Rib Fractures

SSRF has gained attention in recent years. The routine use of SSRF is still controversial, and the indications are being better defined as more studies are conducted. The absolute and relative indications for operative intervention in rib fractures are presented in Box 6. Over the past 15 years, several studies, including randomized controlled trials and meta-analyses, have documented the efficacy of SSRF, primarily in patients with flail chest. These studies have consistently reported shorter recovery time, shorter ICU and hospital length of stay, decreased incidence of pneumonia, and shorter duration of mechanical ventilation following the procedure. The timing of SSRF also remains controversial. Some have advocated SSRF after certain clinical variables become apparent (i.e., failed ventilator wean, intractable pain); however, earlier repair has definite advantages. Inflammation around the fractures peaks between 3 and 5 days postinjury, and pain from rib movement during respiration can cause progressive splinting, atelectasis, and potentially respiratory failure. It seems that SSRF within 72 hours of patient presentation provides the best window for technical success and prevention of complications.

BOX 6 Potential Indications for Surgical Stabilization of Rib Fractures

Crushed chest with marked chest wall deformity
Flail chest
Rib fracture nonunion with chest wall deformity
Open rib fracture
Intractable pain
Persistent paradoxical respiratory movement

In most cases, SSRF is accomplished by a muscle-sparing technique. Anterior fractures are approached via a submammary incision in the supine position, with the elevation of a pectoralis flap. For isolated lateral fractures of 3 to 5 contiguous ribs, an 8- to 10-cm longitudinal incision after the anterior border of the latissimus dorsi muscle and centered over the middle fracture usually provides adequate exposure. The serratus anterior muscle fibers are split, thereby exposing the fractures. Alternatively, extensive lateral and posterior fractures involving five or more contiguous ribs typically are best approached through a standard posterolateral thoracotomy incision. Details of the procedure are shown in Figure 2.



FIG. 2 Operative approach for surgical stabilization of rib fractures through a posterior thoracotomy.



FIG. 3 **(A)** Preoperative chest x-ray demonstrating multiple right-side rib fractures and a large hemothorax. **(B)** Preoperative chest CT scan with 3D reconstruction showing several displaced right rib fractures. **(C)** Postoperative chest x-ray showing appearance of the rib plates placed via thoracoscopy. Residual pulmonary contusion is observed.

One recent meta-analysis focused on the potential reduction of complications, hospital-related end points, pulmonary function, and pain scores following SSRF. The study showed that surgical fixation of fractured ribs leads to a shorter duration of mechanical ventilation, shorter ICU and hospital stay, lower incidence of pneumonia, lower mortality rate, less chest wall deformity, and less need for tracheostomy when compared with those treated conservatively. Interestingly, there was no difference in pulmonary function and pain scores between groups. Other meta-analyses have shown similar results, although the heterogeneity of the data is high, and better designed future studies focusing on indications, timing, and long-term follow-up are needed.

A systematic review of 48 studies focusing on complications and outcomes following rib fracture fixation was recently published. The authors reported that the overall risk of surgery- and implant-related complications was 10.3%, wound infection occurred in 2.2%, and fracture-related infection occurred in 1.3%. Pulmonary complications occurred in 31%. The overall mortality rate was 2.9%, with none directly related to SSRF. Studies reporting on long-term quality of life reported good quality of life after rib fracture fixation.

Although SSRF has been frequently studied in patients sustaining flail chest, its efficacy in patients with severe but non-flail chest has only been reported recently. In a multicenter, prospective, controlled clinical trial (12 centers) with 110 patients comparing SSRF within 72 hours to medical management, the authors reported outcomes in a 2-week follow-up. The surgical group had lower pain scores and higher quality of life scores as measured by the disability score. Narcotic consumption and pleural space complications were also lower in the operative group.

More recently, a thoracoscopic approach has been used for SSRF with the added advantages of being minimally invasive, allowing for extensive irrigation and complete evacuation/aspiration of retained pleural blood (Fig. 3).

Sternal Fractures

Although rare, sternal fractures may occur following blunt mechanisms, including motor vehicle accidents and falls. The presence of a fractured sternum suggests significant energy transfer to the anterior chest wall. Signs and symptoms include chest pain, particularly over the sternum and crepitus. A hematoma over the sternum or across the chest may be seen, and it is a common occurrence after frontal car crashes in patients wearing a three-point seatbelt. A lateral x-ray usually confirms the diagnosis, but more subtle fractures are only diagnosed by chest CT. Sternal fractures also constitute a marker for serious associated injuries, including myocardial contusion, myocardial rupture, esophageal perforation, airway injury, and thoracic aortic rupture.

Treatment of sternal fractures is usually conservative, although patients with significant chest wall instability may require open reduction and internal fixation.

Pneumothorax

A pneumothorax occurs when air from an injured lung or airway is trapped within the pleural cavity, increasing the normal negative intrapleural pressure. It may be caused by penetrating or blunt mechanisms. Following blunt trauma, pneumothorax is caused by rib fractures penetrating the lung parenchyma or by lung injuries without chest wall involvement. Deceleration injuries and sudden increases in intrathoracic pressure also may cause pneumothorax.

Clinical findings suggestive of a pneumothorax include decreased breath sounds, hyperresonance to percussion, and decreased expansion of the affected lung during inspiration. Pneumothoraces are classified according to the volume of lung loss or collapse identified on chest x-ray or by respiratory and systemic signs. In a small pneumothorax, the volume loss is one-third of the average lung volume. In a large pneumothorax, the lung is completely collapsed, but there is no mediastinal shift or associated hypotension.

Tension Pneumothorax

Tension pneumothorax is the most challenging and life-threatening of all breathing problems. It occurs when air continuously enters the thoracic cavity from the lung, airway, or atmosphere and cannot escape. The pressure causes collapse of the lungs preventing oxygenation and ventilation on the ipsilateral side, and it eventually causes deviation of the mediastinum to the opposite side. This causes compression of the superior and inferior vena cava, decreasing preload to the heart and resulting in hypotension. Tension pneumothorax should be recognized immediately by air hunger, hypoxia, tachypnea, hyperresonance, unilateral absence of breath sounds, deviation of the trachea away from the affected side, distended neck veins, hypotension, and tachycardia. The tracheal deviation may be challenging to visualize and may be prevented if the patient is intubated. Distended neck veins may not be present if the patient is hypovolemic.

Tension pneumothorax may be confused with pericardial tamponade as both result in distended neck veins, a feeling of impending doom or restlessness, and hypotension. However, tamponade will result in muffled heart sounds and does not cause tracheal deviation or asymmetric breath sounds.

Tension pneumothorax is diagnosed clinically, constituting a life-threatening emergency. Chest x-rays are not necessary to



FIG. 4 Needle decompression for tension pneumothorax.

confirm the diagnosis, and delays to definitive treatment significantly increase the risk of circulatory collapse and cardiorespiratory arrest.

If tension pneumothorax is suspected, emergent decompression must be performed. ATLS principles recommend needle decompression with large-bore needles or angiocatheters placed in the second intercostal space in the midclavicular line. In obese patients, the needle may be inserted in the fifth intercostal space in the anterior axillary line. If the needle is placed correctly, a rush of air should be observed with an immediate improvement in vital signs as the tension pneumothorax is converted to a simple pneumothorax (Fig. 4). This should then be followed by placing a chest tube for more permanent decompression of the affected hemithorax and draining any blood that may be associated with the tension pneumothorax. Reexpansion of the lung and reapproximation of the pleural surfaces usually seal the lung defect.

Open Pneumothorax

Open pneumothorax, also known as a *sucking chest wound,* occurs when there is a defect on the chest wall (e.g., large-caliber gunshot wounds, traumatic thoracotomy) large enough to exceed the laryngeal cross-sectional area, allowing the air to enter from the exterior into the pleural cavity and leading to lung collapse caused by rapid equilibration between the intrathoracic pressure and the atmospheric pressure. The increased intrathoracic pressure also causes mediastinal shift and decreased venous return. Signs and symptoms include hypoxia, hypercarbia, hypotension, and respiratory and circulatory failure.

Management of an open pneumothorax includes applying an occlusive dressing and placing a chest tube before closing the chest wall defect to avoid development of a tension pneumothorax. When the initial assessment is completed and the patient is stable, the wound should be cleansed, debrided, and closed in the operating room.

Occult Pneumothorax

Occult pneumothorax is defined by the presence of a pneumothorax seen on CT but not seen on conventional chest x-ray. The incidence of occult pneumothorax in trauma patients varies from 2% to 10%. The critical issues related to occult pneumothoraces are determining whether or not they have any clinical relevance and trying to identify those that have the potential to grow and cause problems, particularly in patients undergoing positive pressure ventilation, and determining whether or not they should be treated preemptively by tube thoracostomy. A recent multi-institutional prospective observational study sponsored by the American Association for the Surgery of Trauma (AAST) was carried out to elucidate these issues.

The authors analyzed 588 cases of occult pneumothoraces. Of these, 121 patients (21%) underwent immediate tube thoracostomy, and 448 (79%) were observed. Observation failure, defined by the need for tube thoracostomy after a period of observation, occurred in 27 (6%). The observation failure rate of patients undergoing positive pressure ventilation was 14% (10 of 73). Increased hospital and ICU length of stay and ventilator days were observed in the failure of observation group. Univariate analysis identified the size of the occult pneumothorax (7 mm), use of positive pressure ventilation, progression of the occult pneumothorax (seen on subsequent chest x-ray films), respiratory distress, and the presence of a hemothorax as independent factors associated with failure of observation. Multivariate regression analysis identified only the occult pneumothorax and respiratory distress progression as significant predictors of failed observation. Because no patients who failed observation developed a tension pneumothorax or experienced any adverse events, the authors concluded that patients with occult pneumothorax could be carefully monitored and observed without tube thoracostomy.

Hemothorax

Blood may accumulate in the pleural cavity following blunt or penetrating injuries. Depending on the nature of the injury, bleeding may vary from minor to massive. Symptoms depend on the amount of blood accumulated in the pleural space. On physical examination, breath sounds may be decreased on the side of the injury. A chest x-ray obtained in the supine position may reveal accumulations of blood greater than 200 cc; however, a supine film may demonstrate a diffuse haziness or none at all. The pleural space can accumulate up to 3 L of blood.

Hemothoraces are initially treated by chest tube placement. In approximately 85% of cases, the bleeding will stop as the lung is reexpanded as a result of the low pressure in the pulmonary circulation. A small number of patients will have continued bleeding and will require a thoracotomy. These are usually injuries in systemic arteries (intercostal or internal mammary artery) or veins, major pulmonary vessels, or the heart.

Massive hemothorax may present with tension physiology similar to tension pneumothorax. Hypotension may be a result of decreased preload from tension physiology as well as from massive blood loss (Fig. 5). Treatment includes immediate placement of a chest tube in the affected side. Blood loss of greater than 1500 mL defines a massive hemothorax and is an indication for operative exploration.

Additional indications for thoracotomy include massive continuous air leak, which may indicate massive parenchymal lung injury or



FIG. 5 Massive hemothorax with tension component. Note the tracheal deviation to the right side and marked opacification of the left hemithorax.

injury to a major airway, and blood loss of 200 mL/h for greater than 4 hours. Shed blood should be collected in a sterile fashion so it may be autotransfused.

Retained Hemothorax

Although common (approximately 10%–15% of hemothorax is treated by tube thoracostomy), the true incidence of retained hemothorax is unknown. Retained hemothorax is not only a complication of chest trauma and tube thoracentesis, but it is also recognized as a risk factor for the development of posttraumatic empyema and fibrothorax. A recent study revealed a 26.8% risk of empyema with retained hemothorax compared with only 2% of patients who had complete evacuation. Other independent risk factors for empyema included rib fractures, Injury Severity Score of 25 or more, and the need for additional procedures to treat the hemothorax.

In modern trauma centers, the diagnosis of retained hemothorax is based on CT images of the chest. It seems to be a reliable method to characterize and quantify the volume of a retained clot in the pleural cavity.

Treatment strategies include observation, image-guided drainage, thoracostomy, intrapleural fibrinolytics, video-assisted thoracoscopy (VATS), and thoracotomy. In recent years, trauma surgeons have preferred to use less-invasive modalities initially, leaving the open thoracotomy approach for cases that do not resolve by less-invasive methods.

A recent AAST multi-institutional prospective observational trial was carried out to determine current management strategies used in modern trauma centers in North America. The authors analyzed 328 cases of retained hemothorax over 2 years from 20 centers. Successful observation occurred in cases of hemothorax volume less than 300 cc. VATS was used in 33.5% of patients. Factors related to its success included hemothorax volume up to 900 cc, absence of a diaphragmatic injury, and use of periprocedural antibiotics for thoracostomy placement. Of note, several patients required more than one and sometimes more than two VATS procedures to completely evacuate the pleural cavity of retained blood. Thoracotomy was necessary in 20.4%. The overall incidence of empyema was 26.8%.

The timing of VATS to treat retained hemothorax is still controversial. However, in recent years it seems that consensus is building around the concept that early VATS (between 3 and 5 days post–chest tube placement) is accompanied by more favorable outcomes and less need for reintervention or thoracotomy and extensive decortication.

SPECIAL CONSIDERATIONS IN PEDIATRIC CHEST TRAUMA

In the pediatric age group, rib fractures are less common than in adults because of the compliant nature of the chest wall and the presence of more flexible ribs. Because of the increased flexibility of the ribs, which fracture less often, force is transmitted to the lung parenchyma, causing significant pulmonary contusion. It is essential to recognize that when rib fractures occur in the pediatric group, they are accompanied by a higher incidence of other internal associated injuries.

The presence of rib fractures in infants and toddlers should raise suspicion for nonaccidental trauma. Several studies have shown rates of child abuse varying from 56% to 82% when children 0 to 36 months of age present with posterior rib fractures.

As opposed to the current trend of adult patients receiving whole-body CT following blunt injury, in the pediatric age group, a chest x-ray is still valuable and sensitive as a screening test to aid in the diagnosis of significant chest injuries, limiting the exposure to radiation from unnecessary CT scans.

Unquestionably, the sensitivity of chest CT is higher than plain chest x-rays in diagnosing the so-called *occult pneumothorax and hemothorax* as well as rib fractures; however, the clinical relevance of occult hemothorax and pneumothorax in the pediatric population is still unclear as most patients do not require management changes.

The use of eFAST in the pediatric trauma population performs well in diagnosing pneumothorax and hemothorax, with sensitivity and specificity approaching 100% in the hands of experienced examiners. The absence of lung-sliding and comet tail artifacts are ultrasonographic signs suggestive of a pneumothorax. The diagnosis of rib fractures by ultrasound is possible but operator-dependent.

Clinical signs and symptoms of pneumothorax and hemothorax in children are similar to those found in the adult population. However, an astute clinician must recognize that right mainstem intubation, which occurs more often in young children, is a cause of decreased breath sounds without pneumothorax. In addition, severe gastric distention caused by bagging may also be a confounding factor when examining the chest of an injured child.

The management of pneumothorax and hemothorax in the pediatric age group is also no different than in adults. The great majority of cases will satisfactorily resolve after placing a chest tube (when indicated). An emergency thoracotomy for trauma is rarely needed in children. The indications include hemorrhage greater than 20% to 25% of blood volume or loss of 4% of blood volume per hour after chest tube placement. Rib fractures should be treated with aggressive pain management, and selected patients may require escalation to regional blocks or epidural analgesia.

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Management of Pulmonary Parenchymal Injury

Alison M. Bales, MD, and Mary C. McCarthy, MD

Trauma is the leading cause of death in those under age 40. In patients with multiple trauma, thoracic injuries have a mortality of 20% to 25%, second only to head trauma. Surgical intervention is required in only 10% to 15% of patients with thoracic trauma. Thoracic injuries include fractures of the sternum, ribs, or spine, and injuries to heart, lungs, great vessels, and diaphragm.

This chapter focuses on the anatomy, diagnosis, injury patterns, and treatment of pneumothorax, hemothorax, pulmonary contusion, pulmonary laceration, and pulmonary vascular injury.

INITIAL EVALUATION

Initial evaluation of trauma patients adheres to the Advanced Trauma Life Support algorithm, ensuring rapid treatment of life- and limb-threatening conditions. Assessments and interventions are done sequentially, or with a larger team, simultaneously following a prearrival briefing and assignment of roles. Unequal, absent, or diminished breath sounds, crepitus, or rib fractures should prompt the surgeon to consider pulmonary parenchymal injuries.

Radiologic studies completed during the secondary survey include chest and pelvis radiographs and an extended focused assessment with sonography in trauma (eFAST) exam, which includes thoracic examination for pneumothorax or hemothorax in addition to the traditional four views (cardiac, right upper abdomen, left upper abdomen, and suprapubic). In an unstable patient with high clinical concern for a pneumothorax or hemothorax, a tube thoracostomy should be performed immediately; confirmation imaging before placement is unnecessary.

Optimal visualization of the thoracic cavity during eFAST exam can be obtained by sliding the probe from the right or left upper quadrant views cranially and dorsally until the "spine sign" is seen (fluid present provides visualization of vertebral bodies above diaphragm) identifying hemothorax. The sensitivity for detection of hemothorax is 92% and specificity 100%. The probe should then be moved to the anterior thoracic view at the highest point of the chest wall (second intercostal space) to detect the presence or absence of pleural lung sliding. Pneumothorax is indicated by the absence of pleural lung sliding, the "marching ants" sign, or "seashore sign." A normal view will show a static parietal pleura overlying mobile, homogenous, granular pulmonary tissue. Lack of comet tail artifact or hyperechoic reverberation artifact extending upward from the pleural line represents alveolar or interstitial pulmonary edema. The size of a pneumothorax measured on ultrasound correlates well with CT. A chest radiograph can demonstrate the presence of a hemo- or pneumothorax. In a stable patient with blunt trauma, CT scans are the next step in evaluation (Fig. 1.)

ANATOMY

Lung parenchyma is covered by visceral pleura; the interior of the chest wall is covered by the parietal pleura. The left lung has upper and lower lobes divided by an oblique fissure, further subdivided into 10 segments, while the right lung has upper, middle, and lower lobes divided by oblique and horizontal fissures and includes eight or nine segments. Further divisions are based on segmental bronchi. The pulmonary vasculature and bronchi converge at the hilum, which is located at the medial aspect of both lungs and includes, from anterior to posterior, the vein, artery, and bronchi (one on the left, two on the right).

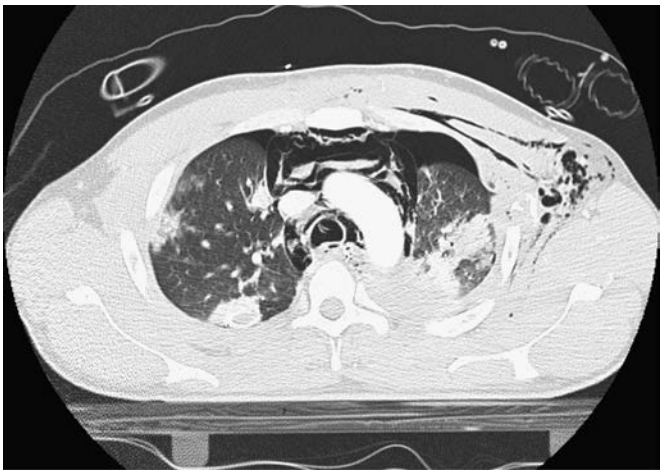


FIG. 1 CT scan of the chest showing rib fractures, bilateral pulmonary contusions, bilateral pneumothoraces, left hemothorax, and left subcutaneous emphysema.

SPECIFIC INJURIES

Pulmonary parenchymal injuries include contusions, lacerations, pulmonary vascular injury, and secondary pneumothorax and hemothorax. Cardiac, great vessel, and chest wall injuries will be discussed elsewhere. The American Association for the Surgery of Trauma (AAST) lung injury grading system is useful to describe injury severity (Table 1).

Pulmonary Contusion

Pulmonary contusions are due to direct or indirect damage of the pulmonary parenchyma, causing alveolar and capillary tears, and resulting in blood and interstitial fluid leakage into the alveoli and tissues. Initially there is hematoma formation, which leads to protein infiltration and edema and loss of physiologic structure. This leads to impaired function and reduced gas exchange and pulmonary compliance with increased vascular resistance. In severe cases, the pulmonary inflammatory response to injury can lead to acute respiratory distress syndrome (ARDS). The typical mechanism of injury is rapid deceleration of the body such as a motor vehicle collision (MVC) or fall from height. Severity of the lung injury is difficult to determine based on imaging alone, and the appearance of the contusion does not correlate well with the clinical impact on the patient. The exact mechanism is not well understood; however, several have hypothesized that molecular mechanisms of inflammatory response, immunologic status, and aspiration are contributing factors. The location of the contusion is usually directly at point of impact and often associated with rib fractures. Contrecoup contusions can be seen as well.

The Murray Lung Injury Score may be used to classify the clinical severity of acute lung injury (ALI) (Table 2). A chest radiograph, blood gas, and ventilator settings are collected to calculate the score.

Pulmonary contusions are diagnosed with a chest radiograph or a thoracic CT scan, which is highly accurate and able to detect even clinically insignificant contusions. Treatment is supportive and includes adequate oxygenation, euvolemia, pain management, and, in the most severe trauma patients, intubation with attention to ventilation parameters, reducing barotrauma by use of low tidal volumes

(6–8 mL/kg of ideal body weight) and PEEP. The prognosis is difficult to determine because imaging does not correlate well with the severity of contusions, nor are preexisting pulmonary comorbidities included in the available indices.

Pulmonary Laceration

Laceration to the parenchyma may be caused by blunt trauma with associated rib fractures or from penetrating trauma that can sever large vessels causing hemodynamically significant bleeding. This diagnosis is assumed if a pneumothorax or hemothorax is present on CT scan. If the lesion is small, observation alone is adequate; however, a chest tube should be placed if sizable or the patient is unstable. Rarely, operative intervention is required and is discussed later in this chapter.

Traumatic Pneumatoceles

Traumatic pneumatoceles (Fig. 2) develop after intraparenchymal laceration and air and fluid leak into the newly developed cavity. Typically management is nonoperative and involves pain control and pulmonary hygiene. Rarely, infection may develop in the cavity requiring antibiotics and/or drainage. Thoracotomy is rarely required and only after nonoperative minimally invasive methods have failed.

Pneumothorax

A pneumothorax occurs when air from a pulmonary injury is trapped in the pleural space between the lung and chest wall, increasing the normally negative intrapleural pressure. These may be due to rib fractures puncturing the lung or deceleration injuries. Diagnosis is made on physical examination (decreased breath sounds, crepitus, hyperresonance to percussion) and confirmed with ultrasound, chest radiograph, or CT scan. If a patient is unstable, prompt pleural drainage catheter or tube thoracostomy is indicated.

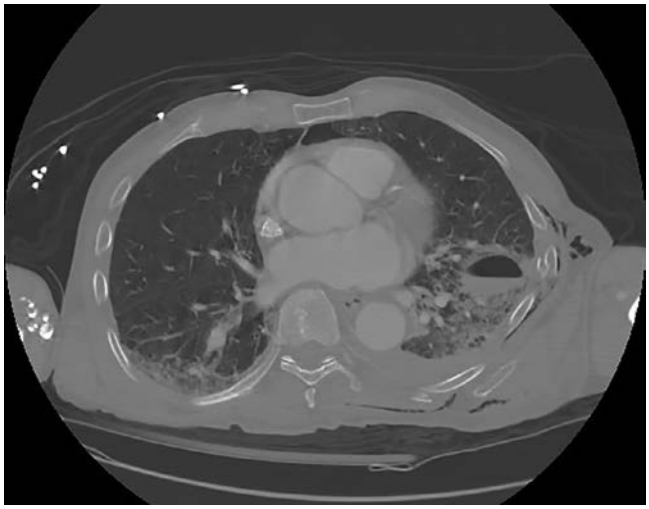


FIG. 2 Large left pneumatocele, hemothorax, subcutaneous emphysema, rib fractures, and pulmonary contusions after a blunt assault inflicted by beating with a golf club.

A pneumothorax that occupies less than 10% to 20% of the chest cavity or measures <2 cm in an asymptomatic patient does not require a chest tube. This patient can be observed for a few hours or overnight at the physician's discretion. A larger pneumothorax or any symptomatic patient (hypoxia, tachypnea, labored breathing, painful breathing, extensive subcutaneous emphysema), open pneumothorax, tension pneumothorax, or patients requiring mechanical ventilation should generally have a chest tube placed expeditiously.

Tension pneumothorax indicates that air is continuously released from the lung and is unable to escape the chest cavity, causing complete collapse and shift of the mediastinum toward the opposite side, kinking the vena cava and resulting in hypotension due to reduced cardiac preload. On physical examination, one finds tachycardia, hypotension, asymmetric breath sounds, and distended neck veins; chest radiograph will show tracheal deviation and lung collapse.

Open pneumothorax due to a sucking chest wound occurs when there is a large chest wall defect that allows air into the pleural cavity, causing the lung to collapse as it equalizes with atmospheric pressure. A dressing that is occlusive on three of four sides should be placed to act as a one-way valve. However, this can progress to tension physiology and requires immediate chest tube placement at a site

TABLE 1 The AAST Lung Injury Scale

Grade*	Injury Type	Description of Injury
I	Contusion	Unilateral, <1 lobe
II	Contusion	Unilateral single lobe
III	Laceration Contusion	Simple Pneumothorax Unilateral, >1 lobe
IV	Hematoma Laceration	Nonexpanding intraparenchymal Major (segmental/lobar) air leak
V	Vascular	Hilar vessel disruption
VI	Vascular	Total uncontained transection of pulmonary hilum

*Advance one grade for bilateral injuries up to grade III that hemothorax is scored under.

TABLE 2 The Murray Lung Injury Score*

Classification	0	1	2	3	4
Chest x-ray Infiltrates/quadrant	No	1 quadrant	2 quadrants	3 quadrants	4 quadrants
Hypoxemia PaO_2/FiO_2, mm Hg	≥300	225–299	175–224	100–174	≤100
PEEP Setting, cm H_20	≤5	6–8	9–11	12–14	≥15
Compliance Static, mL/cm H_20	≥80	60–79	40–59	30–39	≤29

*Classifies severity of acute respiratory distress syndrome and predicts need for extracorporeal membrane oxygenation in treatment.

away from the wound. An occlusive dressing should then be placed; eventually, operative debridement and closure of the wound should be performed.

Hemothorax

Hemothorax is the presence of blood in the thoracic cavity, varying from a minimal amount seen on CT scan to a massive hemothorax, filling the entire hemithorax (Fig. 3). Physical examination reveals decreased breath sounds and dullness to percussion. Often there is an associated pneumothorax. If hemothorax in a hemodynamically unstable or compromised patient is suspected, tube thoracostomy should be performed immediately. If the patient is stable, imaging should be pursued—chest radiograph, eFAST, or CT scan. Extended FAST exam has a sensitivity of 77% and a negative predictive factor close to 100%. Thoracic CT scan is the gold standard for detection of hemo- or pneumothorax; however, it is less than ideal in an unstable patient.

TREATMENT

The initial decision point in the treatment of pulmonary injury is whether intervention is required. The physician must assess the patient's clinical stability: vital signs, oxygen requirements, and other injuries. Some thoracic injuries such as tension pneumothorax can be fatal. However, lifesaving tube thoracostomy can be performed quickly when the appropriate supplies are available. More invasive interventions including thoracotomy and video-assisted thoracoscopic surgery have specific indications (Table 3).



FIG. 3 Chest radiograph demonstrating large left-sided tension hemothorax with complete opacification and tracheal deviation.

Emergent thoracotomy after chest tube placement for hemothorax is guided by initial output >1.5 L or >200 mL/h over 4 hours. Guidelines for urgent/delayed thoracotomy or video-assisted thoracoscopic surgery (VATS) for pulmonary injuries are continuous air leak, retained hemothorax, empyema, or trapped lung.

Nonoperative Treatment

Even if the patient does not require operative intervention, supportive measures are essential. Supplemental oxygen, appropriate multimodal pain control, nebulizer treatments, incentive spirometry, early ambulation, and maintenance of euvolemia are important steps in the treatment of pulmonary injuries.

Needle Decompression

In a patient with a pneumothorax requiring prompt intervention, needle decompression can be performed by inserting a large bore needle or angiocatheter in the second intercostal space at the midclavicular line (or laterally at the midaxillary line in the 4th or 5th intercostal space); this results in an immediate rush of air and symptomatic improvement. In obese patients or those with a thick pectoralis muscle, it can be difficult to reach the thoracic cavity with available needles. In a trauma center, an experienced physician can place a tube thoracostomy quickly.

Percutaneous Tube Thoracostomy

Position the patient supine with ipsilateral arm extended overhead for lateral placement (fourth or fifth intercostal space midaxillary line). There are many different kits produced for percutaneous chest tube insertion, but all include some variation of the Seldinger technique. The steps in insertion include prep and drape, infiltration of local anesthetic, 5 mm skin incision, insertion of needle, aspiration, wire placement, removal of needle, insertion of dilator, and finally, placement of pigtail or small-bore chest tube, with connection to Pleur-Evac on −20 cm H_2O suction, and suturing it in place.

These can be helpful for isolated pneumothoraces as there is a smaller incision and less pain, still providing effective drainage. Data are conflicting on the effectiveness of small-bore chest tubes for drainage of hemothorax. However, some have shown that 14 French (Fr) percutaneously placed chest tubes had comparable initial output and effectiveness in draining hemothorax.

Open Tube Thoracostomy

The patient is placed supine with the ipsilateral arm extended overhead for lateral placement (fourth or fifth intercostal space in the midaxillary line); it is helpful to place a soft restraint around the wrist to hold it in place. Prep and drape the patient's anterolateral chest. Landmarks to include in the sterile field are the nipple medially, axillary hairline superiorly, lower ribcage inferiorly, and the bed laterally. Identify the fourth or fifth intercostal space at the midaxillary line; this usually correlates to the nipple level in men or inframammary fold in women. Inject local anesthetic, making a wheal in the skin

TABLE 3 Timing, Settings, and Injury for Thoracotomy

Thoracotomy	Immediate	Urgent	Delayed
Setting	Emergency room: upon arrival and assessment	Operating room: within 1–4 hr	Operating room: >24 hr
Injury	Patients in extremis after penetrating chest injury	Cardiac, lung esophagus, tracheobronchial, great vessel injuries, aortic rupture	Retained hemothorax, posttraumatic empyema, delayed tracheobronchial injuries, intracardiac injuries

From Meredith JW, Hoth JJ. Thoracic trauma: when and how to intervene. *Surg Clin* 2007;87:95–118.

and injecting more in the pleura at the proposed entrance site. Local anesthetic blocking of a rib above and a rib below will provide a better field of anesthesia. Intravenous conscious sedation may facilitate placement.

Perform a 2 cm transverse incision with a scalpel through the skin, next using scissors or a hemostat to spread through subcutaneous tissue, creating a short tract superior, until able to palpate the chest wall. Use a hemostat to feel the rib and then slide it just above that rib, taking care to avoid the intercostal neurovascular bundle running inferior to the rib above. Push the hemostat through the intercostal muscle and into the chest. A pop is usually heard and felt; a rush of air or blood may occur. Insert a finger through the interspace into the chest, sweeping the lung away, checking for adhesions, and confirming chest entry. Spread with a hemostat and insert a chest tube through this hole, guiding it superior and posteriorly by holding the exterior portion of the tube anterior and inferiorly. Confirm that the last drain hole is securely inside the chest. Once satisfied with placement, attach to wall suction at −20 H_2O using a Pleur-Evac and suture the tube in place, with 0 or 2-0 silk. Before breaking down the sterile field, obtain a portable chest radiograph to ensure correct positioning of the tube. If the sterile field remains intact, the tube can be manipulated. Secure chest tube connections with tape or zip ties (i.e., a ratcheting cable tie). Remove the tube as soon as the air leak is resolved and drainage decreases (<200 cc serosanguineous drainage).

Previous recommendations advocated for a large bore chest tube (36–40 Fr) for hemo- or pneumothorax. However, more recent studies did not show a benefit to a larger tube, and a smaller 28Fr tube or even a 14Fr percutaneous catheter can be considered. Current Eastern Association for the Surgery of Trauma (EAST) guidelines for the prophylactic administration of antibiotics do not support routine administration.

The benefits of tube thoracostomy insertion usually far outweigh the risks for all patients. Surgeons must be aware of the potential for complications. Vascular injuries, most commonly the intercostal artery or vein, can require suture ligation, interventional radiographic embolization, or thoracotomy to resolve. More significant injuries are rare but include injuries to the heart, lung parenchyma, diaphragm, or intraabdominal organs (stomach, spleen, liver, colon, other). Also reported are pleural shock (exceedingly rare vagal reflex resulting in cardiac arrest after reexpansion that should be treated with cardiopulmonary resuscitation algorithms), expansion edema, wrong side placement, fistulas including bronchopleural/chyle, empyema, pneumonia, and pain.

Emergency Department Thoracotomy

Patients requiring emergency department (ED) thoracotomy arrive in extremis, and the decision to proceed is based on rapid decision making by the trauma team leader. Determination of survivability of the patient's injuries, ability to control hemorrhage, duration of time without a palpable pulse, and the presence of cardiac activity on ultrasound are factors that must be considered. A patient with penetrating chest trauma with minimal downtime has the greatest likelihood of survival after opening the chest in the ED.

Once the decision has been made, one person should continue cardiopulmonary resuscitation, and the patient should be positioned supine with the left arm extended overhead (Fig. 4). Using a No. 10 scalpel blade, perform a left anterolateral thoracotomy that extends from the sternum below the nipple to the midaxillary line through skin, soft tissue, and muscle. This should expose the intercostal space, which is opened along the upper margin of the rib into the axilla. Push the lung away, and use scissors to open the pleura along the length of the incision. Place a Finochietto self-retaining retractor with handle facing down toward the bed to spread the ribs. If necessary, a scalpel, Lebsche knife, or trauma shears can divide costochondral junctions or across the sternum. Evacuate blood from the chest and control identified injuries. Cardiac, major vessels, pulmonary, and chest wall injuries may be a source of hemorrhagic shock. Massive pulmonary hemorrhage may be controlled by freeing the inferior pulmonary ligament and twisting the lung at the hilum. Once these injuries have been identified and stabilized, cross-clamp the thoracic aorta by opening the posterior mediastinum, then proceed to the OR for definitive repair.

Video-Assisted Thoracoscopic Surgery

Indications for VATS include diagnostic evaluation of the diaphragm or other thoracic structures in a stable patient, empyema, persistent air leak, or retained hemothorax that has clotted and can no longer be drained by a chest tube. Suspicion may be raised by the appearance on chest radiograph; however, a noncontrast chest CT scan better quantifies the residual blood.

A dual-lumen endotracheal tube should be used to allow for single lung ventilation during the procedure. The patient should be placed in a lateral decubitus position with the operative side up, prepped, and draped. Typically, two or three 2-cm incisions are triangulated low on the chest. A 10-mm angled scope is inserted through a trocar in one incision while a combination of long-ringed forceps and suction are used to remove any remaining blood and strip off any

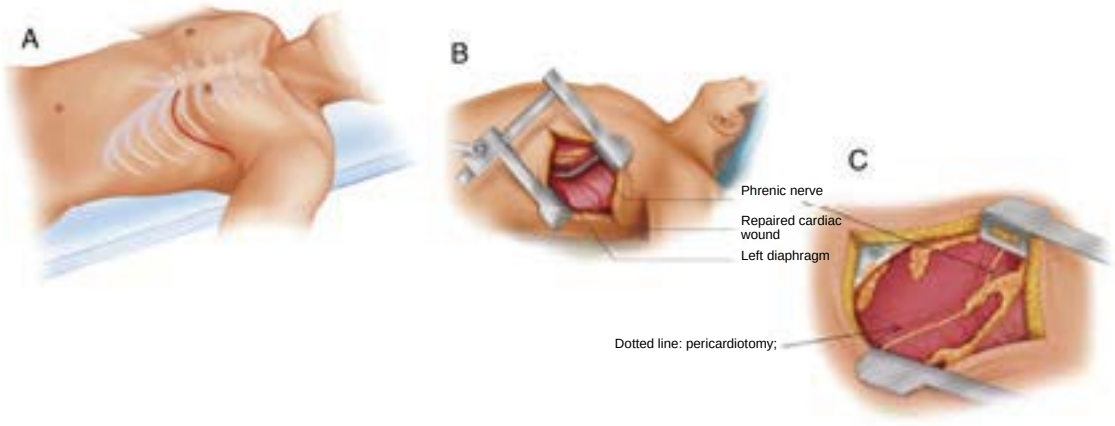


FIG. 4 Surgical approach for ED thoracotomy showing curvilinear initial incision **(A)**, placement of rib retractor **(B)**, and location for pericardotomy in relation to phrenic nerve **(C).** *(From Aseni P, Henry S, Scalea T. Emergency Resuscitation Procedures in Major Trauma: Operative Techniques. Chapter 11, p. 169. In Aseni et al.* Operative Techniques and Recent Advances in Acute Care and Emergency Surgery. *Springer Nature Ed, 2019).*

formed rind from the lung and chest wall. This will facilitate full lung expansion and prevent it from becoming trapped by adhesions. One or two chest tubes should be placed and secured after the conclusion of the case to allow continued drainage.

Urgent/Delayed Thoracotomy

For most patients, treatment with a well-placed chest tube will be adequate. However, for the few that do require thoracotomy, indications usually include either persistent air leak or hemorrhage. There are multiple less common indications for delayed thoracotomy such as chyle leak, trapped lung, or need for rib fixation.

In contrast to ED thoracotomy, an urgent or delayed thoracotomy is typically through a posterolateral incision on the injured side. This will give better exposure for pulmonary injuries. First, anesthesia should intubate with a dual-lumen tube, and then the patient should be positioned with a bean bag in lateral decubitus with arms extended anteriorly and supported 90 degrees at the shoulder on a Mayo table with pillows. A posterolateral thoracotomy at the fifth intercostal space should be made and a rib spreader placed. If better exposure is required, the fifth rib may be resected. Initially, evacuate fluid and clot to improve visibility, divide the inferior pulmonary ligament to provide better exposure and mobility of the lung, and repair identified injuries.

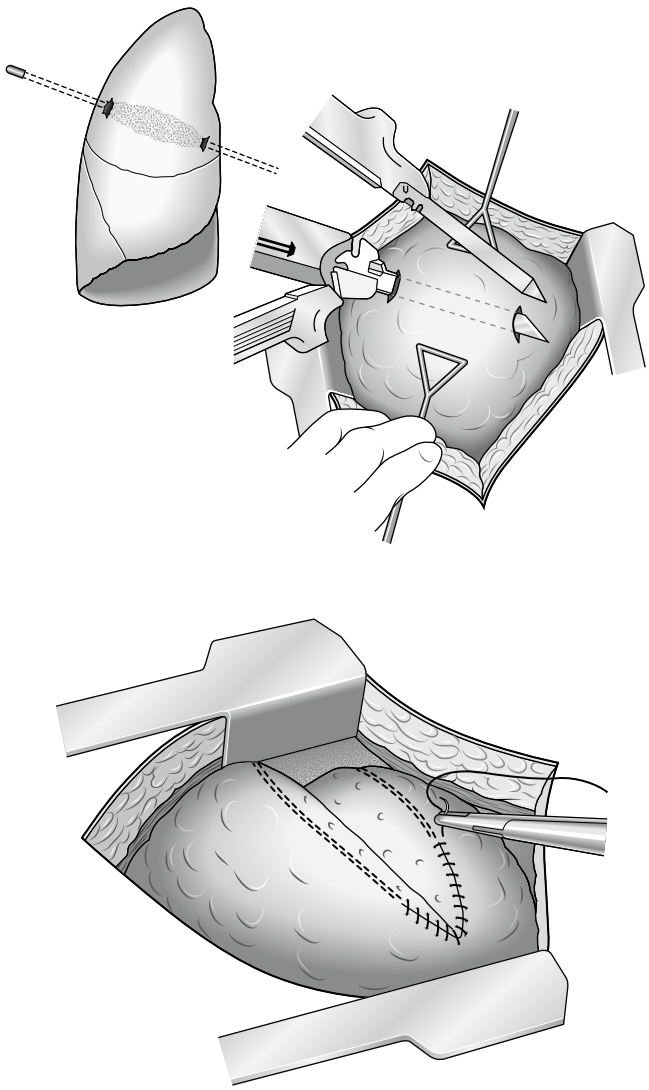


FIG. 5 Tractotomy. *(From Novell, et al.* Kirk's General Surgical Operations, *6th edition. Churchill Livingstone, 2013.)*

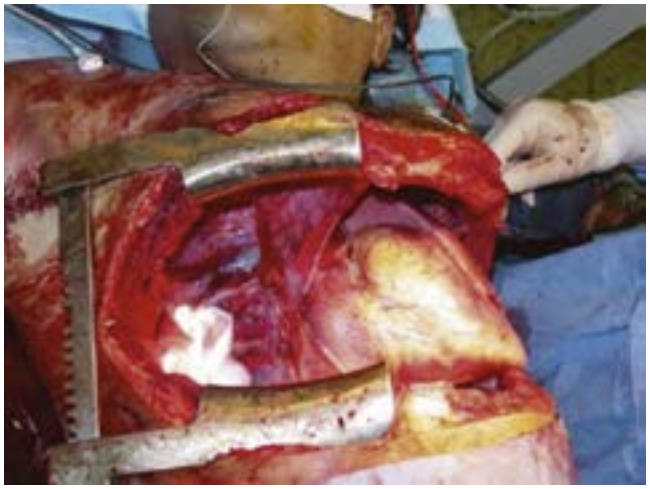


FIG. 6 Operative photo after clamshell thoracotomy and right pneumonectomy. *(From Koganti D, Beekley AC. Fundamentals of Exploratory Thoracotomy for Trauma.* In Fundamentals of General Surgery. *Springer, Cham, 2018. pp. 275–288.)*

Thoracotomy: Specific Operative Strategies

Thoracic trauma can be managed nonoperatively with supportive measures and a chest tube in 90% of patients. For the remaining 10%, anatomic lung resection is rarely needed; in fact, less than 1% of patients will require it. More common techniques include simple suture repair, nonanatomic wedge resection, or tractotomy (Fig. 5). Penetrating injury to the pulmonary hilum is likely to be associated with other fatal mediastinal injuries, reducing the frequency of formal lobectomy or pneumonectomy (Fig. 6).

In a patient with a persistent air leak and an injury amenable to suture repair, large horizontal mattress and pledgeted sutures can be used to approximate the tissue. A stapled wedge resection may be performed by grasping the tissue to be resected with Allis clamps, elevating it, and firing a stapling device below the grasper. Multiple staple loads can be used to complete the resection if necessary. It can be tempting to just oversew lung tissue for bleeding; however, this does not resolve the issue but traps the hemorrhagic source deep in the lung, forcing the blood into the parenchyma or tracheobronchial tree leading to hemoptysis, aspiration, pneumonia, and ARDS. In this scenario, a tractotomy should be undertaken. Tractotomy opens the lung parenchyma along the tract of the injury to allow for better exposure of the bleeding vessel, which can then be directly oversewn with a 3-0 polypropylene suture; a second suture can be used to close the tractotomy after bleeding has been controlled.

If hilar bleeding is encountered after entering the chest, hilar control should be obtained expeditiously by placing a large clamp across the hilum or dividing the pulmonary ligament up to the pulmonary vein and then twisting the lung. If both lung and artery are injured, pneumonectomy may be indicated; however, the mortality after this operation in the emergent setting is extremely high at 50% to 100%. Death occurs due to acute right heart failure. Extracorporeal membrane oxygenation (ECMO) may be considered, however. If heart failure develops over several days after surgery, then medical management can be attempted, and the prognosis is slightly better.

Delayed thoracotomy for incompletely drained hemothorax will result in either resolution, infection (posttraumatic empyema), or trapped lung; therefore, VATS or thoracotomy should be considered if the patient fails chest tube drainage. Operation should include

irrigation and decortication, removing all blood, fluid, and clot from the pleural space as well as peeling all fibrinous exudate off the lung and inner chest wall. Before closing, after placement of chest tubes, anesthesia should inflate the lung under direct visualization to confirm full expansion.

CONCLUSION

Management of patients who have sustained traumatic injuries, whether blunt or penetrating, isolated or multisystem, requires a team-based approach and systematic evaluation. This chapter provides an overview of managing pulmonary injuries, including pulmonary contusion, laceration, pneumatocele, pneumothorax, and hemothorax. These injuries are often associated with each other, as well as with rib fractures, cardiac injuries, and, more commonly, with blunt mechanisms, and other nonthoracic injury patterns. Discussions on incidence, anatomy, injuries, and both nonoperative and operative management strategies are included.

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Blunt Abdominal Trauma

L.D. Britt, MD, MPH, and Michael Martyak, MD

The abdomen remains one of the most critical and vulnerable anatomic regions in blunt trauma. Before focusing on any specific management strategy for a patient who has sustained blunt abdominal trauma, an initial assessment of the entire patient is imperative. The concept of initial assessment includes four essential components: a rapid primary survey, resuscitation, a detailed secondary survey (evaluation), and reevaluation. Integrated into primary and secondary surveys are often necessary adjunct interventions, such as electrocardiographic monitoring, arterial blood gas determination, pulse oximetry, insertion of a urinary and/or gastric catheter, and obtaining necessary x-rays and other diagnostic studies, when applicable. The management of blunt abdominal trauma continues to evolve more in the nonoperative arena. The workup has shifted largely from the use of a physical examination, plain x-rays, laboratory findings, and diagnostic peritoneal lavage to physical examination and liberal the use of computed tomography (CT) and ultrasonography. Treatment for visceral injury has traditionally been surgical. However, many forms of solid organ injury can now be successfully managed nonoperatively or with minimally invasive and interventional radiology techniques. Nonoperative management of the multiple injured trauma patient at level 1 trauma centers, with state-of-the-art techniques, has conclusively shown significantly improved patient outcomes and survival.

DIAGNOSTIC AND IMAGING ADJUNCTS

Diagnostic Peritoneal Lavage

Diagnostic peritoneal lavage has now been essentially supplanted by the adoption of focused assessment with sonography in trauma (FAST). The utilization of diagnostic peritoneal lavage has diminished substantially. Originally described by Root in 1965, diagnostic peritoneal lavage (DPL) was once a mainstay in the management of blunt abdominal trauma for over four decades. Before the era of routine CT scanning, it was used as a screening tool to evaluate patients having blunt or penetrating abdominal trauma with an accuracy rate reported between 92% and 98%. CT and FAST are now the diagnostic modalities of choice assessment of the injured patient. However, DPL remains an excellent tool for further workup of occult bowel injury or when FAST is not available or has questionable findings. In the workup for occult bowel injury, traditional parameters (Table 1) should be used to guide therapy. When FAST is not an option, a diagnostic tap is usually all that is necessary, and exploration is indicated when there is aspiration of greater than 10 mL of gross blood.

The pitfalls of DPL are a relatively high false-positive rate, risk of creating visceral injury, and poor sensitivity for detecting injury to retroperitoneal structures such as the pancreas and duodenum. Iatrogenic events are minimized if a Foley catheter and nasogastric tube are placed before the procedure. Patients with pelvic fractures and suspected retroperitoneal hematoma or pregnant females should undergo a supra-umbilical approach.

Focused Abdominal Sonography for Trauma

In the diagnostic assessment of the acutely injured patient, the bedside ultrasonography for detection of cardiac and intra-abdominal injury is considered the standard of care. Because focused abdominal sonography for trauma is noninvasive, this diagnostic modality allows the operator to perform an examination simultaneously during the initial resuscitation and stabilization of a multiple injured trauma patient. Due to the relative insensitivity of the abdominal

TABLE 1 Diagnostic Criteria for a Positive Diagnostic Peritoneal Lavage

Any Viscus	Bowel
10 mL gross blood	Bacteria
>100,000 red blood cell/mm^3	Bile
>500 white blood cell/mm^3	Food particles
>75 IU/L amylase	

examination in the severely injured patient, this technique may provide evidence of significant hemorrhage early in the course of an evaluation. An ultrasound probe is used to examine four key windows for fluid; the subxiphoid area permits visualization of the pericardium, the left subcostal area permits visualization of the splenorenal recess, the right subcostal area permits visualization of Morison's pouch, and the suprapubic area permits visualization of the pelvic cul de sac (Fig. 1). The presence of fluid may indicate cardiac tamponade, hollow viscus perforation, hemoperitoneum, or ascites. False-positive results secondary to preexisting ascites or false-negative results caused by operator error and/or body habitus are the main limitations. Scanning the suprapubic area with distension of the urinary bladder will enhance the sensitivity of the exam for the detection of pelvic fluid.

A threshold of at least 200 mL of fluid in the abdominal cavity is necessary for detection, and intraabdominal injuries must be associated with the presence of this much free fluid for a positive finding. Reported sensitivities range between 73% and 88%, and specificities range between 98% and 100%. Accuracy rates range from 96% to 98%. FAST is an inexpensive, rapid, portable, noninvasive technique that can be performed in serial fashion if there is a change in patient stability. Additionally, it obviates the risk of exposing pregnant female patients to radiation. Positive findings in stable patients can be further evaluated with CT, while unstable patients with a positive finding should prompt emergent exploration in the operating room.

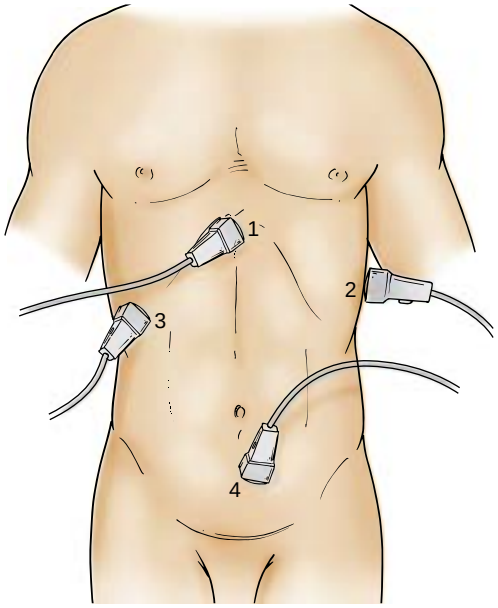


FIG. 1 Sonographic windows for *(1)* subxyphoid, *(2)* left subcostal, *(3)* right subcostal, and *(4)* suprapubic areas. Distension of the urinary bladder either before Foley catheter placement or by installation of 150 to 200 mL normal saline enhances sensitivity. *(From Rozycki GS, Ochsner MG, Schmidt JA, et al. A prospective study of surgeon-performed ultrasound as the primary adjuvant modality for injured patient assessment.* J Trauma. *1995;39:492–500.)*

Computed Tomography

Steady advances in the technology and speed of CT have continued to be an intergral part of the diagnostic management of trauma patients. Multidetector scanners have drastically improved resolution and accuracy of these imaging studies. Negative predictive values as high as 99.63% have been reported for patients sustaining significant mechanisms of blunt trauma, allowing the use of CT as a reliable and noninvasive screening tool for patients with blunt abdominal trauma. In light of modern-day CT capabilities, prospective data have demonstrated that patients with a signinficant mechanism and a benign abdomen can be released from the emergency department if a CT scan of the abdomen shows no evidence of visceral injury, provided that there are no other reasons for hospitalization.

CT reliably identifies injuries in solid organs such as the spleen, liver, and kidney because of the associated vascular nature demonstrating disruption of normal architecture, associated free fluid, and the so-called *vascular blush.* Established grading scales continue to be used for accurate classification and determination of management (Tables 2–4).

Detection of bowel injury via CT in patients who are intoxicated, are intubated, or have associated closed head injury or other distracting injuries can present a diagnostic challenge in the absence of a reliable abdominal exam. The incidence of blunt bowel injury varies from series to series but is generally reported in the 1% to 5% range in all blunt trauma patients admitted to level 1 trauma centers. A high index of suspicion is predicated on mechanism of injury and physical exam findings, such as abdominal wall ecchymosis, tattooing, and/or seat belt sign. CT findings may be overt, such as extravasation of oral contrast or pneumoperitoneum, or more commonly subtle, such as bowel wall thickening, stranding of the mesentery, or free fluid in the absence of solid organ injury. Indirect findings may be fairly nonspecific and secondary to bowel edema from resuscitation or preexisting ascites. Reproductive-age females may have a small amount of normal or "physiologic" pelvic fluid present, sometimes adding to the complexity of the evaluation. Patients on positive

TABLE 2 Spleen Injury Scale of the American Association for the Surgery of Trauma

	Grade*	Injury Description
I	Hematoma	Subcapsular, <10% surface area
	Laceration	Capsular tear, <1 cm parenchymal depth
II	Hematoma	Subcapsular, 10%–50% surface area; intraparenchymal, <5 cm in diameter
	Laceration	1–3 cm parenchymal depth that does not involve a trabecular vessel
III	Hematoma	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma
	Laceration	Intraparenchymal hematoma >5 cm or expanding >3 cm parenchymal depth or involving trabecular vessels
IV	Laceration	Laceration involving segmental or hilar vessels producing major devascularization (>25% of spleen)
V	Laceration	Completely shattered spleen
	Vascular	Hilar vascular injury that devascularizes spleen

*Advance one grade for multiple injuries, up to grade III.

TABLE 3 Liver Injury Scale of the American Association for the Surgery of Trauma

	Grade*	Injury Description
I	Hematoma	Subcapsular, <10% surface area
	Laceration	Capsular tear, <1 cm parenchymal depth
II	Hematoma	Subcapsular, 10%–50% surface area; intraparenchymal, <10 cm in diameter
	Laceration	1–3 cm parenchymal depth, <10 cm in length
III	Hematoma	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma
	Laceration	Intraparenchymal hematoma >10 cm or expanding >3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25%–75% of hepatic lobe or 1–3 Couinaud segments within a single lobe
V	Laceration	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud segments within a single lobe
	Vascular	Juxtahepatic venous injuries (i.e., retrohepatic vena cava/central major hepatic veins)
VI	Vascular	Hepatic avulsion

*Advance one grade for multiple injuries, up to grade III.

TABLE 4 Kidney Injury Scale of the American Association for the Surgery of Trauma

	Grade*	Injury Description
I	Contusion	Microscopic or gross hematuria, urologic studies normal
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma	Nonexpanding perirenal hematoma confined to renal retroperitoneum
	Laceration	Parenchymal depth of renal cortex (>1.0 cm) without urinary extravasation
III	Laceration	Parenchymal depth of renal cortex (>1.0 cm) without collecting system rupture or urinary extravasation
IV	Laceration	Parenchymal laceration extending through the renal cortex, medulla, and collecting system
	Vascular	Main renal artery or vein injury with contained hemorrhage
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of renal hilum that devascularizes kidney

*Advance one grade for bilateral injuries, up to grade III. Modified from Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. *J Trauma*. 1989;29:1664.

pressure ventilation or with significant barotrauma may develop mediastinal or subcutaneous emphysema that can track through the peritoneum or retroperitoneum and give the appearance of free air. Great care in the radiologic interpretation and close clinical correlation are necessary in such cases. The liberal use of diagnostic modalities (e.g., abdominal CT) in the hemodynamically normal injured patient may prevent nontherapeutic laparotomies. Obviously, when significant doubt remains, abdominal exploration may be required to confirm an injury.

The role of oral contrast in the evaluation of the acutely injured patient has recently come into question. Little time is usually available in the emergency setting to permit adequate opacification of the small bowel. Patients are further at risk for aspiration of the contrast media, and administration often requires placement of a nasogastric tube. There have been several reports that have shown that elimination of oral contrast media does not lead to an increased incident of missed bowel injury. Many centers have now safely eliminated the use of oral contrast media from their routine trauma protocols, expediting management and ease of patient care. Resuscitation edema may cause a hazy appearance around the head of the pancreas and duodenal c-loop, raising the question of a pancreas or duodenal injury. Further clarification in this situation can be obtained when it occasionally occurs via repeat CT scan with the administration of oral contrast and the injection of 300 to 500 mL bolus of air down the nasogastric tube to make pneumoperitoneum obvious.

CT may also be of great importance in identifying patients with arterial hemorrhage related to pelvic fracture. CT imaging may demonstrate an arterial blush or large hematoma in the vicinity of a pelvic fracture, indicating the need for pelvic arteriography, pelvic packing, or pelvic external fixation. A "CT cystogram" may also be helpful and eliminate redundancy of x-ray evaluation. The Foley catheter is clamped after placement in the trauma bay. Real-time interpretation of the CT scan is performed by the evaluating physician, which may dictate further delayed images or a formal cystogram.

Although CT can be an important diagnostic modality in the assessment of the trauma patient, it is contraindicated in the hemodynamically unstable patient who is in shock.

SPECIFIC CONSIDERATION FOR BLUNT TRAUMA

The Bowel

There is no place for nonoperative management of hollow viscus injury, and the nemesis of nonoperative management of blunt abdominal trauma is therefore the missed bowel injury and all of its catastrophic consequences. Otherwise, most management is straightforward and involves debridement and primary repair for nondestructive injuries and resection with primary repair versus stomal formation for destructive injuries.

Radiographic Findings of Blunt Bowel Injury

There are two basic types of findings of bowel injury on CT scan: direct and indirect. Direct findings are usually straightforward *if* present and amount to extravasation of oral contrast (if administered) and free air, which have been reported to occur 4% and 28% of the time, respectively. Indirect findings include mesenteric hematoma or contrast blush, bowel wall edema, unexplained free fluid, "fat streaking," and bowel loops that do not opacify with intravenous contrast.

Mesenteric hematoma is nonspecific and can occur from associated injuries, such as pelvic fractures or renal injuries, with hematomas from these structures expanding into the bowel mesentery. However, a vascular blush in the leaves of the mesentery is indicative of active hemorrhage until proven otherwise and is a general determinant for immediate operative exploration. Bowel wall edema and ascites are common in blunt trauma patients, can occur from resuscitation of other injuries, and do not necessarily connote bowel injury. Free fluid in the absence of solid organ injury can be further evaluated with DPL or diagnostic peritoneal aspiration (DPA) if the abdominal exam is unreliable. Fat stranding can occur with mesenteric contusion and does not necessarily portend an operative indication. Unopacified bowel loops can indicate vascular disruption of the mesentery or simply result from poor contrast timing in an underresuscitated patient. These findings increase the likelihood of finding an injury at exploration, and multiple findings enhance the evidence of identifying a bowel injury.

Operative Management

Appreciation of the American Association for the Surgery of Trauma (AAST) organ injury grading scale is helpful in describing wounds of the bowel. Grade I injuries are contusions and partial-thickness lacerations of the bowel wall without perforation. Grade II injuries are full-thickness wounds involving less than 50% of the bowel wall circumference. Grade III injuries are lacerations involving greater than 50% of the bowel wall circumference without complete transection. Grades IV and V injuries represent complete transection of the bowel wall and transection with segmental tissue loss and/or devascularization of the mesentery, respectively. The terms *destructive* and *nondestructive* simplify the terminology; nondestructive wounds are injuries that can be managed with debridement and primary-suture enterorrhaphy and are classified as grades I and II. Destructive wounds require resection of an entire segment of the bowel as a result of loss of bowel integrity or devascularization of the mesentery and are classified as grades III to V (Tables 5 and 6).

TABLE 5 American Association for the Surgery of Trauma Small Bowel Injury Scale

Grade*	Type of Injury	Description of Injury
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration ≥50% of circumference without transection
IV	Laceration	Transection of the small bowel
V	Laceration	Transection of the small bowel with segmental tissue loss
	Vascular	Devascularized segment

*Advance one grade for multiple injuries, up to grade III.

TABLE 6 American Association for the Surgery of Trauma Colon Injury Scale

Grade*	Type of Injury	Description of Injury
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration ≤50% of circumference
III	Laceration	Laceration >50% of circumference
IV	Laceration	Transection of the colon
V	Laceration	Transection of the colon with segmental tissue loss

*Advance one grade for multiple injuries, up to grade III.

The distinction between destructive and nondestructive wounds is important in terms of the prescribed management. Nondestructive wounds of the large or small bowel can generally be repaired without further consideration. Most small bowel destructive injuries should be resected and reconstituted unless damage control conditions prevail. In contrast with the small bowel, the management of colon injuries has received great scrutiny. Ushering in the dawn of modern day trauma surgery, the World War II military experience dictated that *all* colon wounds, destructive or not, be managed by colostomy. This philosophy remained surgical dogma until the 1980s. In a comprehensive review of the literature since 1979, primary repair of the colon for nondestructive wounds was shown to have a leak rate of 1.6%. Compared with patients receiving colostomy for similar types of wounds, the incidence of intraabdominal abscess was 4.9% for primary repair and 12% for colostomy, and the overall complication rate was 14% for primary repair and 30% for colostomy. Mortality rates were similar, at 0.11% for primary repair and 0.14% for colostomy. These findings clearly show the superiority of primary repair for nondestructive wounds of the colon.

Several risk factors for anastomotic failure pertaining to destructive colon injury have been addressed in the literature: hypotension, shock, interval from injury to operation, amount of fecal contamination, associated organ injury, transfusion requirement, and comorbid disease. No data have conclusively shown that any of these risk factors increase the likelihood of anastomotic failure. Patients with massive blood loss or shock may be better served by undergoing a damage control procedure, with delay of definitive repair. An interval from injury to repair greater than 12 hours can be a relative contraindication to definitive repair if there is widespread (greater than one quadrant) fecal contamination. Greater than one or two organ system injuries has been a concern, but this may just be a marker for degree of shock and overall physiologic derangement. Comorbidities, such as AIDS and cirrhosis, deserve special consideration, and these patients may be better off with the establishment of an ostomy. Patients with any of these risk factors have a higher incidence of intraabdominal abscess and overall complication rates.

Notwithstanding the caveats of the previously mentioned comorbidities, colonic resection and primary anastomosis for destructive wounds would be permissible in most trauma settings. In a collective review of 207 patients reported in the literature, management of destructive bowel injury with resection and primary anastomosis had a reported leak rate of 7.2%, with a mortality rate of 1.7% attributable to the colon wound. In the largest single-institution experience, Murray showed a leak rate of 11% in 112 patients undergoing resection and primary anastomosis for destructive colon wounds, with two deaths related to leaks. However, the ultimate decision for the choice

of operation should be up to the discretion of the surgeon, at the time of operation, and on a case-by-case basis.

At laparotomy, the bowel should be examined in its entirety after all other sources of major bleeding are controlled. Small injuries should be noted and tagged with an identifiable suture for easy reference. Larger wounds contributing to ongoing soiling can be temporarily controlled with a "whip stitch" (quick running suture) or Babcock clamps. Mesenteric injuries are identified, and active bleeding is controlled appropriately. Attention should be directed to the location of the superior mesenteric artery for injuries encroaching on the root of the mesentery. Mesenteric hematomas should be explored with ligation of injured vessels and mesenteric defects closed by careful reapproximation of the peritoneal edges so as not to compromise any associated vasculature. Bowel viability should be noted in relation to any mesenteric injury. Clusters of grade I and II injuries may be resected or individually repaired depending on the particular injury pattern. In blunt trauma, there is usually only one or two grade I or II wounds that can be repaired primarily or one or more devitalized segments that require resection.

Small, superficial grade I injuries can be left alone while deeper, longer grade I injuries can be closed with a simple running suture or interrupted Lembert sutures. Grade II wounds should be debrided back to healthy, viable bowel and closed transversely to prevent narrowing of the lumen of the bowel. Single-layer running or interrupted closure is generally sufficient for repair of the small bowel. When there is significant bowel wall edema, peritonitis, or soiling, a two-layer closure with a running inner layer and interrupted Lembert outer layer may be preferential. Grade I colon wounds may be managed with single-layer closure. However, grade II colon wounds should be closed in two layers for added protection.

The leak rate associated with stapled versus hand-sewn anastomosis for destructive wounds of the bowel has been an area of ongoing controversy. In two retrospective studies totaling 284 patients undergoing stapled versus hand-sewn anastomosis, Brundage showed that hand-sewn procedures had lower leak rates. Two other retrospective studies totaling 484 patients showed no difference in the leak rate of stapled versus hand-sewn procedures. Brundage's two studies included 78 colon wounds, while the other studies were confined only to the small bowel. Stapled procedures may be a little quicker, particularly if there is more than one anastomosis. In general, the technique chosen according to the literature can be a matter of surgeon preference. However, with edematous bowel, the hand-sewn technique is a more prudent approach.

The Spleen

The spleen is the most commonly injured intraabdominal organ, followed by the liver and small bowel in blunt trauma patients. The spleen's location in the left upper quadrant lends susceptibility to injury from broken ribs, deceleration, and blunt percussion forces. Clinically, patients with splenic injury may present with hypotension, left upper quadrant pain or tenderness to palpation, or diffuse peritonitis from extravasated blood. Referred pain to the left shoulder on deep inspiration in face of splenic hematoma is known as *Kehr's sign.*

Nonoperative Management

Most series indicate that approximately 60% to 80% of patients presenting with blunt splenic injury can be managed nonoperatively at level 1 or 2 trauma centers. Facilities without the resources and experience of a bona fide trauma team may not safely meet the demands of nonoperative management and should consider patient transfer. Patients selected for nonoperative management must have normal vital signs, be free from peritoneal signs or other concern for hollow viscus injury, and have no evidence of free extravasation of intravenous contrast from the splenic parenchyma (Fig. 2).

Considerable debate remains regarding risk factors for failure of nonoperative management. Higher AAST splenic injury grade, age greater than 55 years, moderate to large hemoperitoneum, subcapsular hematoma, and portal hypertension have all been suggested to increase the risk of failure. Early reports in the evolution of nonoperative management regarding AAST grade did not demonstrate higher failure rates for higher grade injury. More recent reports using high resolution multidetector CT scanners allow better assessment of injury grade. The data from these studies show that patients with injury grades III to V are at increased risk for nonoperative failure. Age continues to be a controversial subject matter in the literature, with numerous reports claiming that age greater than 55 years *is* or *is not* a risk factor for failure. Documentation of a moderate or large hemoperitoneum is suggestive of a major injury and should be considered a significant factor in individual patient assessment.

Patients with a splenic subcapsular hematoma or a history of portal hypertension are specific subgroups of patients that deserve special consideration. These patients are at increased risk for delayed rupture 6 to 8 days following injury and may already be discharged from the hospital if they have isolated injury. Furthermore, splenic embolization is not a very effective treatment of this condition because it usually necessitates coiling of the main splenic artery, which can lead to significant pain and abscess formation. History of portal hypertension or cirrhosis, while not absolute contraindications to nonoperative management, certainly should serve as a caveat. The general risks of laparotomy in Child-Pugh B or C cirrhosis must be carefully weighed against the risk of ensuing and worsening coagulopathy. This scenario may, indeed, dictate the need for splenic artery embolization. None of these risk factors alone should dictate the decision to proceed immediately to operative intervention. Nonoperative management does reduce hospital length of stay and transfusion requirement; however, the morbidity of splenectomy should remain low in any surgeon's hands. Overall, the patient's condition, including comorbidities, coagulopathy, and other problems (such as traumatic brain injury, aortic injury, and suspicion for concomitant hollow viscus injury) factor into the decision-making process. Patients undergoing nonoperative management should never succumb to splenic hemorrhage.

Approximately 20% of patients initially undergoing nonoperative management of blunt splenic injury require further intervention. Failure has been associated with the presence of a contrast blush in up to two-thirds of these patients. The presence of a contained contrast blush within the parenchyma of the spleen represents pseudoaneurysm formation of a branch of the splenic artery. Angioembolization is now commonly used to selectively occlude the arterial branches containing these injuries. Implementation of this salvage technique at centers that routinely screen for the presence of pseudoaneurysm has increased the success of nonoperative management to 90% or greater. Pseudoaneurysm formation has been observed in even grade I and II injuries and may not be present on initial imaging.

Long-term data are unavailable concerning the risk of outpatient or delayed rupture, but the incidence is low and has been reported to be about 1.4%. The average date to readmission for delayed splenectomy after discharge was 8 days in this study. Lower-grade (I, II) injuries tend to heal more quickly, and almost all injuries are healed by 5 to 6 weeks. However, approximately 20% of blunt splenic injuries will not show complete healing and may be at risk for pseudocyst formation. A CT scan should be repeated in 6 weeks for grades I and II injuries and 10 to 12 weeks for grades III to V injuries before allowing patients to return to normal activity.

Splenectomy

Patients requiring urgent or emergent intervention for splenic hemorrhage may develop hypothermia, coagulopathy, and visceral edema. The most expeditious and safest course of action under these conditions is removal of the spleen. The general assumption of abdominal exploration for trauma is that there are known and, possibly, unknown injuries. The operative approach is via a midline vertical incision that allows the best exposure and facilitates

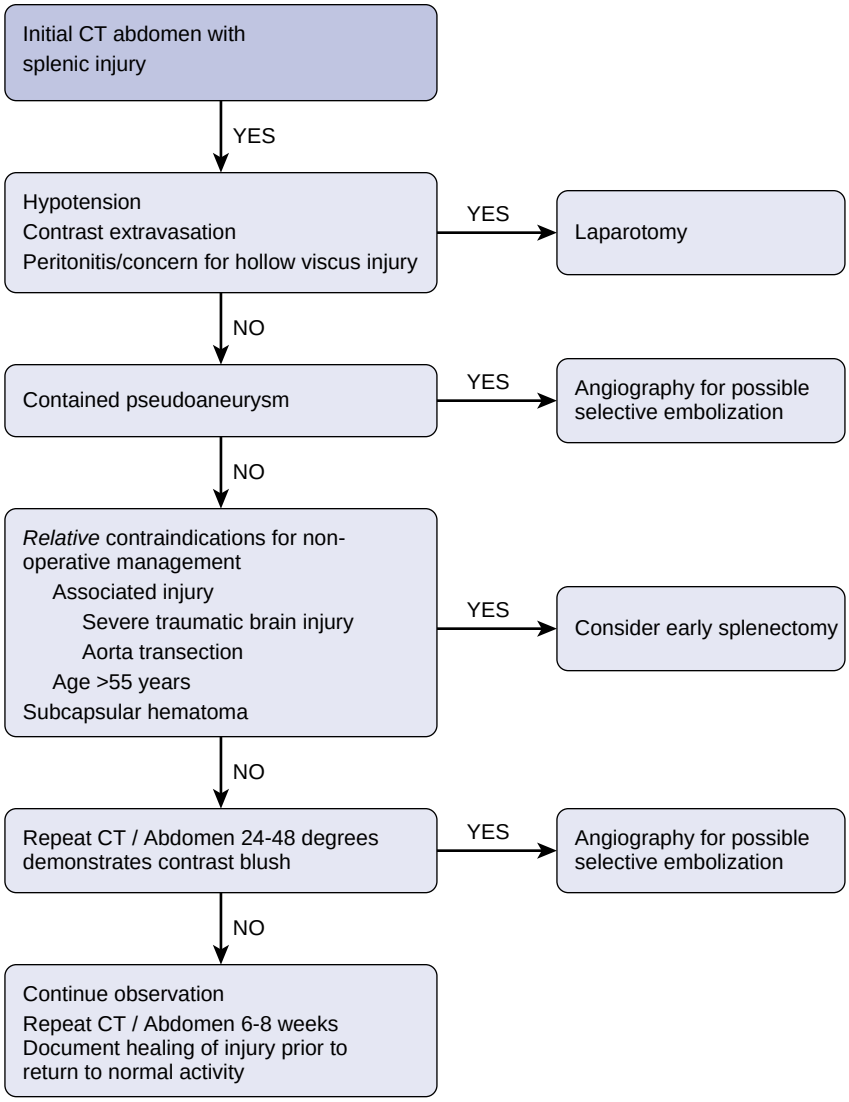


FIG. 2 Management of blunt splenic injury. *CT,* Computed tomography.

temporary abdominal closure should visceral edema or damage control measures be necessary.

With respect to performing a splenectomy, an OMNI retractor can be used to expose the left upper quadrant. The spleen is retracted medially, with some downward compression, while taking down the posterior attachments with the cautery. Once these attachments are freed, the spleen can be mobilized medially for optimal exposure. The assistant stands on the left side of the table and supports the spleen while the surgeon ligates short gastric and hilar vessels. Being careful to avoid the tail of the pancreas, a large clip, placed on the specimen side of the splenic hilum, will reduce back-bleeding and expedite the procedure. Once the spleen has been removed, the splenic fossa is meticulously inspected for further bleeding with a rolled laparotomy pad.

Splenorrhaphy

Hemodynamically stable patients found to have small to moderate amounts of parenchymal hemorrhage, at laparotomy, may be candidates for splenic preservation. The spleen is mobilized into the wound using the same technique as for splenectomy. The injury to the spleen is assessed, and a decision is made whether to resect a portion if the parenchymal injury extends into the hilum or if arterial bleeding is coming from within the splenic laceration itself. If the decision is made to resect the upper or lower pole, the parenchyma is divided with the cautery, and the associated hilar vessels are taken with clamps and ties. Any arterial bleeding from the parenchyma is controlled with suture ligature, and the cautery is used to control oozing from the parenchyma. A tongue of omentum is then sutured into the laceration or to the raw surface of the remaining spleen in the case of a partial splenic resection. Approximately 50% of the spleen is required to preserve adequate phagocytic and immunologic function. If this cannot be achieved, a splenectomy is probably the best option.

Overwhelming Post-Splenectomy Infection

The incidence of overwhelming post-splenectomy infection (OPSI) following trauma is not well understood because it may not be appreciated when it occurs, along with the fact that it is not routinely reported. However, the reported incidence of OPSI in adult patients undergoing splenectomy for all causes is 0.9% with a mortality of 0.8%. The risk of OPSI in adults following trauma is felt to be lower than the incidence seen after splenectomy for hematologic disorders such as immune thrombocytopenia, lymphoma, and thalassemia. Children are at greater risk for OPSI and should receive prophylactic penicillin V 125 mg twice daily until 3 years of age and then 250 mg twice daily until 5 years of age. Currently, anyone older than 2 years of age should receive the 23-valent pneumococcal vaccine and a one-time dose of the *H. influenza* and meningococcal vaccine. A

one-time booster dose of the pneumococcal vaccine is recommended 5 years after the original vaccine.

Hepatobiliary System

Blunt trauma contributes over 75% of the mechanisms of injury for most trauma centers in the United States. The liver, the largest solid organ in the body, is one of the most frequently injured abdominal organs by either blunt or penetrating mechanisms. Fortunately, the majority of hepatic injuries are low-grade injuries and require no surgical repair (Table 7). Suspicion of liver injury is predicated on several factors including clinical suspicion derived from the mechanics of the crash, hemodynamic state of the patient, and findings obtained during abdominal examination (Fig. 3). High-energy crashes involving application of force to the upper abdomen or to the right thoracoabdominal area should arouse immediate suspicion of a possible hepatic injury. Hemodynamic lability, although not an exclusive feature of liver injury, mandates evaluation to exclude it as the source of the hemorrhage. Tenderness in the right upper quadrant, in the absence of other signs, can be suggestive of subcapsular hematoma requiring attention and further evaluation. Unfortunately, the physical examination is not perfect and has a false-positive rate of approximately 50% and a false-negative rate of 40%.

The additional methods available to evaluate the abdomen include FAST, CT, and diagnostic peritoneal lavage. FAST has become a highly reliable test used when seeking to determine whether there is blood in the abdomen in a patient who is hemodynamically labile. In the stable patient in whom liver injury is suspected, the use of CT has become widespread. Several classification schemes have been described for liver injuries, but the grading scheme proposed by the AAST is now in wide use (see Table 7).

Approach to the Injured Liver

With hepatic injuries, the paramount decision is to determine if and what intervention is needed to control hemorrhage. Hemodynamic instability mandates expeditious operative management or angiography/embolization (if the patient can be stabilized with volume

TABLE 7 The American Association for the Surgery of Trauma Liver Injury Scale (1994 Revision)

Grade	Type of Injury	Description of Injury
I	Hematoma Laceration	Subcapsular, <10% surface area Capsular tear, <1 cm parenchymal depth
II	Hematoma Laceration	Subcapsular, 10%–50% surface area Intraparenchymal <10 cm in diameter Capsular tear 1–3 parenchymal depth, <10 cm in length
III	Hematoma Laceration	Subcapsular, >50% surface area of ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma >10 cm or expanding >3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25%–75% hepatic lobe or 1–3 Couinaud segments
V	Laceration Vascular	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud segments within a single lobe Juxtahepatic venous injuries, (i.e., retrohepatic vena cava/central major hepatic veins)
VI	Vascular	Hepatic avulsion

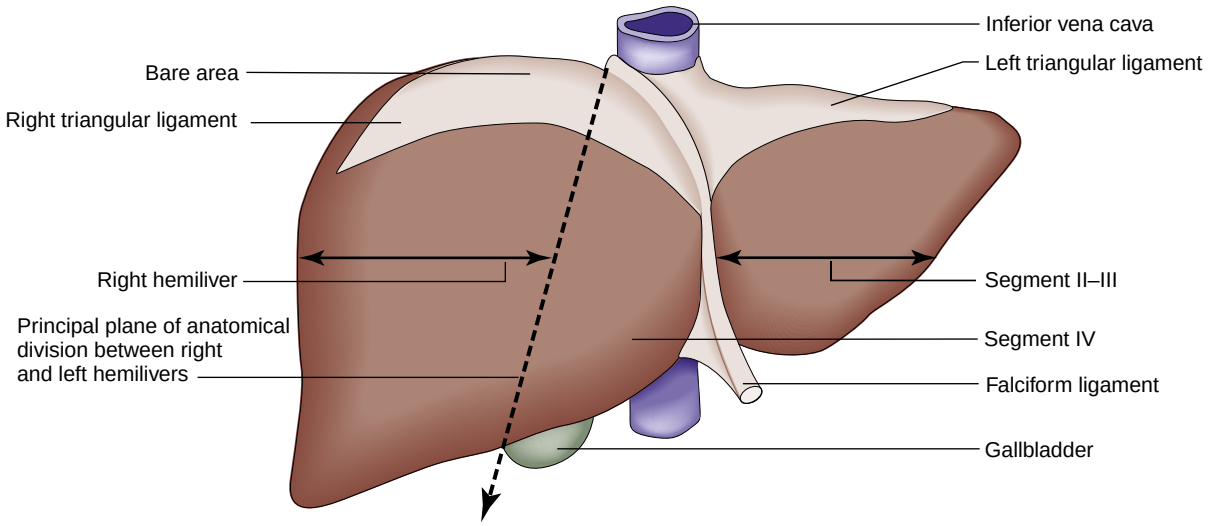


FIG. 3 Juxtahepatic (or retrohepatic) vena cava is in direct contact with the posterior aspect of the liver. *(From Garden OJ, Parks RW.* Principles and Practice of Surgery. *7th ed. Philadelphia: Elsevier; 2018.).*

resuscitation to make transportation to the radiographic suite less risky for the patient). The hemodynamically stable patient may be evaluated by any of the methods noted earlier. Minor grade I or II injuries frequently require no operative intervention. When diagnosing by CT scan, the surgeon must be cognizant of the magnitude and anatomy of the liver injury. Contusion contained within the liver capsule or minor laceration, such as in grade I or II injuries, may be observed. These diagnoses together constitute most liver injury cases, accounting for 60% to 70%. Grade III injuries (deeper, larger wounds with more tissue destruction) occur in approximately 25% of cases. Grade IV and V injuries, involving large amounts of tissue destruction, have an incidence of 7% and 3%, respectively, and they are highly lethal. It should be emphasized that evidence of blood in the peritoneal paracolic gutters, in the pelvis, or tracking along the periportal triads is suggestive of a more significant injury than the liver anatomy may indicate. Also, the concomitant existence of hollow viscous injury occurs in 5% to 20% of major hepatic injuries, which mandates exploration.

In addition, it is important to realize that massive parenchymal injuries can occur with surprisingly little bleeding and that minor lacerations may bleed profusely. An understanding of the tissue architecture of the liver is a prerequisite to successful management. Most blunt lacerations may occur along segmental fissures because the vascular and biliary duct structures are moderately shear resistant. This explains why a large stellate or "bear claw" laceration may be seen, with little or no intraperitoneal blood in a hemodynamically stable patient. This can be managed nonoperatively with observation. Nonoperative treatment of the stable patient sustaining a blunt liver injury is the management approach of choice today. Table 8 highlights the reported failure rates for nonoperative management of hepatic trauma.

Conversely, the deceleration forces are responsible for a shear effect that can result in avulsion of the hepatic veins from the vena cava or major branches of the portal venous or hepatic venous systems. Hemorrhage is devastating, difficult to control, and responsible for the high mortality rate seen with such injuries.

Intraoperative Decisions: General Principles

Once the decision to operate has been made, the surgeon must proceed in an orderly fashion to a fully equipped operative theater that includes the capabilities of invasive monitoring. Before opening the abdomen, the surgeon must ensure that there is optimal venous access. Large-bore central access is essential. The prudent, historic dictum is that access should be from the upper torso in the event there is a retrohepatic caval injury. The blood bank must be notified of the potential for massive transfusion of packed cells and blood components to treat the often associated coagulopathy. The development of blood salvage systems has greatly improved the care of these patients; shed blood from the operative field can be washed and reinfused, provided there is no evidence of gastrointestinal contamination. Infusion systems are available that allow rapid delivery of large volumes of warmed fluid to help minimize hypothermia and hypovolemia. Hypothermia is a common cause of coagulopathy and must be aggressively defended against. Invasive monitoring capabilities are essential in the management of these critically injured patients.

Optimal surgical exposure is essential and starts with performing a midline vertical incision for expedient entry into the abdominal cavity. The incision should extend from the xiphoid process to the symphysis pubis. Such an approach allows, if necessary, relatively easy extension into the thorax through either a median sternotomy or a lateral thoracotomy.

Performing a celiotomy could potentially decompress the tamponade, thereby necessitating expeditious vascular control. The need to perform an emergency thoracotomy for vascular control of the aorta before opening the abdomen is rarely indicated. Such control of the bleeding can usually be obtained with the assistant's manual compression of the liver.

Once the abdomen is open, a rapid assessment of the injury is made and priority management begun. All clots are evacuated, and the four quadrants are packed to control bleeding. A sequential examination is then carried out with priority given to control of blood loss followed by control of any enteric content spillage.

The general approach to the liver injury requires adequate visualization of the anatomic features of the injury. This may require mobilization of the liver along the falciform and triangular ligaments. Full mobilization of the liver allows delivery onto the abdominal wall that can often facilitate suture repair of a hepatic wound in a difficult area. When mobilizing the liver, care must be taken that the hepatic veins are not injured. The coronary ligaments are in close proximity to the hepatic veins. Also, the surgeon must be cautious during the mobilization of the liver that venous return through the vena cava is not obstructed for a prolonged period. Hemorrhage control during mobilization can often be done by the assistant's applying direct pressure with laparotomy packs, compressing the liver between the hands.

As noted previously, most of the injuries encountered are grade I or II and require little more than simple suture repair. Grades III, IV, and V injuries require an organized approach for successful control of hemorrhage, which includes manual compression, direct ligation, or clipping of lacerated vessels, along with sophisticated techniques for more complex wounds.

Vascular occlusion of the portal triad (performing the Pringle maneuver) is a useful method of controlling hepatic arterial and portal venous inflow to the liver. A noncrushing or vascular clamp can be applied to the porta hepatis and safely left in place for approximately 45 minutes, although the specific duration threshold is not known for the hemodynamically labile patient. Also, an umbilical

TABLE 8 Failure Rates for Nonoperative Management of Liver Trauma

Study (Yr)	Number of Patients	Immediate Surgery (%)	Overall Failure Rate (%)	Liver Failure Rate (%)	Other Failure Rate (%)
Meredith (1994)	116	48	3	3	0
Croce (1995)	136	18	11	5	6
Pachter (1996)	404	53	1.2	0.7	0.5
Malhotra (2000)	661	15	7	3	4
Velmahos (2003)	78	29*	15	0	15
Christmas (2005)	561	32†	1.8	0.4	1.4

Other Failure refers failure caused by injuries from other intraabdominal organs such as the spleen, kidney, pancreas, or bowel.
*15% for liver bleeding.
†13% for liver bleeding.

tape placed around the porta hepatis structures can be used for such control. If this maneuver markedly reduces the liver's bleeding, the parenchymal injury can be assessed and a method of repair decided on. However, if hemorrhage persists, then an intrahepatic portal vein injury or a major hepatic vein injury must be suspected.

Proceeding with hepatotomy for localization and control of hemorrhage requires fastidious cooperation between the surgeon and the first assistant. With the depth of the hepatic wound exposed, it is usually the first assistant who controls the bleeding. The finger-fracture technique for hepatotomy, with the first assistant compressing the liver, is very effective. The operating surgeon using the fingertips or the handle of a scalpel to separate the liver parenchyma and the assistant using a multiple loaded clip applier, made popular for laparoscopic cholecystectomy, ligate severed vessels. Nonabsorbable suture ligation can also be performed to control vessels as each is encountered. Knowledge of the anatomy of the liver (along with reported anatomic variants) is a prerequisite to this approach. The confluence of the left and middle hepatic veins must be kept in mind to avoid overzealous ligation (Fig. 4). Likewise, the position of the inferior vena cava and the hepatic veins to the caudate lobe should be noted to avoid unnecessary injury that may complicate the surgical management. The placement of random deep sutures is fraught with difficulty. Failure of the above-mentioned maneuvers to control hepatic bleeding means that the surgeon either has not adequately identified the source or is dealing with coagulopathic bleeding (or both).

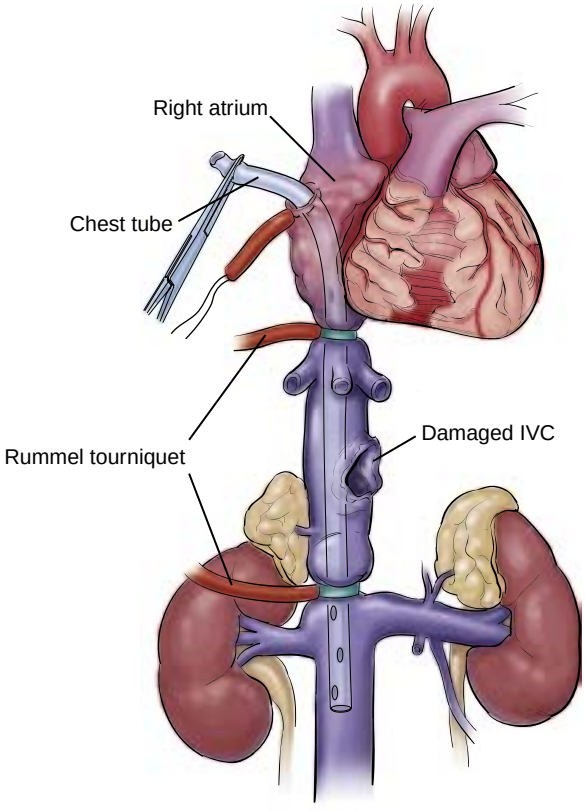


FIG. 4 After obtaining the necessary exposure (thoracotomy, mediastenotomy), an opening—along with a 2.0 Prolene pursestring suture—is created in the right atrial appendage to provide the access needed for insertion of the atriocaval shunt, which is usually a No. 36 chest tube. An extra hole must be made at the level of the right atrium. With the chest tube holes being outside of the umbilical tape occlusion, blood is directed from the lower half of the body and the kidney through the atriocaval shunt. *IVC,* Inferior vena cava. *(From Rasmussen TE, Tai NRM.* Rich's Vascular Trauma. *3rd ed. Philadelphia: Elsevier; 2016.)*

Although specific ligation of the hepatic artery or portal vein branch supplying a specific portion of the liver is rarely needed, the suspected branch should be isolated, and its occlusion should control hemorrhage while the Pringle maneuver is released. If such is the case, then the identified branch should be ligated.

Being able to perform a tractotomy of a missile wound should be in a surgeon's armamentarium when dealing with penetrating hepatic injury. In addition, a variety of methods designed for tamponade of the bleeding missile tract have been described, using various materials. Bluett et al. described a tamponade device with multiple Penrose drains dragged through the liver tract. However, it is more preferable to open the liver and suture or clip-control the bleeding site directly, if possible.

Liver injury infrequently follows the anatomic lines of demarcation delineating the right and left lobes, much less the segments. Anatomic resection, a once popular approach, is associated with high mortality rates. This technique has been essentially abandoned. Resectional debridement of a devitalized liver is not a formal lobectomy but rather a completion of the injury to remove nonviable hepatic tissue and to facilitate vascular control. This usually entails a degree of finger fracture through uninjured liver, which allows visualization of the bleeding raw surface and more direct control. Application of specific liver clamps designed to aid in lobectomy, such as the Lin clamp, is difficult because of positioning of the injury laceration and maneuvering around the clamp.

Once the bleeding has been controlled, the large, raw surface of the liver can be problematic, as persistent oozing of bile or blood continues. A viable omental patch sutured to the liver bed is an excellent homeostatic agent and internal drain. Stone and Lamb popularized the omental pack in their initial report. Fabian and Stone reported 90% successful hemostatic control with this procedure. For large, raw liver surfaces resulting from debridement or tractotomy, the omental patch held in place with several liver sutures is an excellent hemostatic agent. Also, utilization of the argon beam coagulator is another option in addressing bleeding of raw liver surfaces. The argon gas removes the blood from the hepatic tissue, and ionizing energy is transmitted. A maximum of 110°C is achieved, and an eschar is formed.

An alternative to surgical repair of the injured liver is a mesh wrap intended to provide compression, to control bleeding, and to close parenchymal defects. Delaney et al. reported success in six liver injuries controlled in this manner. Brunet et al. reported 35 liver injuries wrapped for control. Sequential CT examination of the patients demonstrated progressive restoration of normal liver architecture.

The premise underlying much of the preceding discussion is that liver bleeding can be controlled. However, even when advanced techniques of liver control are used, hemorrhage control can be precarious, at best. A critical error that can be made when dealing with major liver injury is to continue operative intervention in the face of a hypothermic (less than 32°C), acidotic patient who has developed coagulopathy. Although the specific time to make a decision to pack the liver and restore normothermia and coagulation factors is not always clear, the operating surgeon should always have a low threshold to incorporate packing and prepare the patient to be expeditiously transferred to the intensive care unit for aggressive resuscitation and monitoring or to the angiography suite for angioembolization. Once a patient has required a 10-U transfusion, packing should be seriously considered. Patients with severe injuries, hypothermia, refractory hypertension, coagulopathy, and acidosis need early packing. It must be emphasized that large-vessel bleeding must be controlled before packing can be effective.

Perihepatic packing was popularized during World War II. The high incidence of complications plus the advent of more sophisticated techniques for control of liver bleeding led to the demise of packing until its revival in the 1970s. The major indications for perihepatic packing were postrepair coagulopathy that developed or an

extensive subcapsular hematoma or capsular avulsion. They reported a 57% survival rate in their series. It is also a valuable adjunct to resectional debridement and tractotomy. The use of a folded, disposable plastic drape is helpful. It is placed against the liver, and the packs are placed on it to prevent the laparotomy pads from adhering to the liver and possibly minimize the recurrent bleeding on removal of the packs. Gauze packs are then placed to compress the liver. The packs should be placed at both the superior and inferior surfaces of the liver. The packing should be tight enough to control the bleeding but not so tight that it unnecessarily compresses the renal vessels and possibly the inferior vena cava, resulting in intraabdominal hypertension. Patients who have undergone packing will require continued sedation with mechanical ventilation until pack removal because of the interference of optimal diaphragmatic movement. Abdominal wall closure is rapid and is performed by towel clips or by running a nylon suture in the skin. Utilization of silo-like closures with sterile towels and plastic drapes should be used to minimize fluid loss and to maintain abdominal pressure. In addition, there should always be a high index of suspicion for the development of intraabdominal compartment syndrome.

Pack removal can be planned when the patient has regained normothermia and coagulation parameters have been normalized. This usually occurs within 24 to 72 hours. Packs are then removed during a second operation, and the surgical team again must be prepared to manage bleeding. Repacking at the second operation might be indicated. The complication rate of packing is appreciable. There is an increased incidence of sepsis in a group of patients subjected to liver packing. An additional benefit of liver packing is that it may allow transport of a critically ill patient to the angiography suite for angioembolization or from one center to a definitive treatment center where the liver injury can be treated.

Juxtahepatic Venous Injuries

The lethality of juxtahepatic venous injuries in blunt hepatic trauma and the management challenges of definitively addressing such injuries have been well chronicled. Fortunately, such liver wounds are seen infrequently. However, the downside is that very few acute care surgeons are familiar with and comfortable operating in this specific setting. Depending on the specific series, the mortality ranges from 50% to 80%, with massive hemorrhage being the overwhelming cause of death.

The deadly nature of this injury is a result of the difficulty in expeditiously getting access to the injury site. The retrohepatic vena cava and major hepatic veins are within the depth of the least mobile area of the liver, making exposure and direct control of bleeding very challenging. Attempting to rotate the liver in an effort to access the injury can actually extend the wound and cause increased bleeding. Also, such a misguided effort could result in a fatal air embolus.

Detailed knowledge of the pertinent anatomy is imperative for any surgeon attempting an operative management strategy. The juxtahepatic vena cava, which is within the "bare area" of the liver, extends for approximately 7 cm and is bordered by the phrenic veins and the right adrenal vein, cephalad and caudad, respectively. Approximately 3 cm above the most superior aspect of the retrohepatic vena cava, the inferior vena cava enters the right atrium. The retrohepatic cava is an extraparenchymal structure. The three major hepatic veins, along with their tributaries, enter directly into the anterior aspect of the retrohepatic vena cava. This anatomy is relatively constant, with major anomalies being uncommon. Although the course of the extraparenchymal hepatic veins is short, the intraparenchymal veins have a long course. Substantial blunt trauma can lacerate/avulse either or both.

Probably because of its highly lethal nature, juxtahepatic venous injuries are infrequently managed. Surrounding structures can provide a tamponade effect and contain juxtahepatic venous hemorrhage. Such structures include the liver, the diaphragm, and the suspensory ligaments of the liver. Adequate containment of hemorrhage by these structures might allow an attempt at expectant or nonoperative management. However, if these supporting structures are disrupted, substantial bleeding will ensue. As a consequence, overly aggressive or injudicious hepatic mobilization can result in uncontrollable hemorrhage.

Juxtahepatic injuries, which can be caused by blunt or penetrating injuries, are often classified as type A or B, with the former being hepatic venous wounds that are intraparenchymal and the latter being extraparenchymal venous wounds. Both type A and B injuries can occur together. In addition, there can be associated injuries to the portal vein and its tributaries, which occur more frequently with type A wounds. Fortunately, the extraparenchymal hepatic venous or the associated retrohepatic caval injuries are infrequent. Penetrating wounds to this anatomic region or the sheer forces from blunt injury are the predominant mechanisms of injury. Irrespective of the reported series on the management of juxtahepatic venous injuries, the mortality rates are overwhelmingly high.

There are, basically, three operative approaches in the management of juxtahepatic venous injuries: (1) direct repair of the venous wound(s), (2) surgical resection, and (3) pressure application (containment/tamponade measures) with reinforcement of the natural containment structures that have been disrupted. Although there have been several reports of the specific strategy and efficacy of operative exposure and direct repair of juxtahepatic venous injuries, the success is sporadic and overall outcomes dismal. In 1966, Feldman was credited with reporting the first successful application of direct suture repair of a juxtahepatic venous injury. In 1968, Schrock introduced the concept of vascular insolation with the utilization of an atriocaval shunt (see Fig. 4). However, the majority of surgeons have abandoned atriocaval shunting because of the challenges related to the technique and the overall dismal outcomes. The paramount principle in establishing vascular isolation is obtaining proximal and distal control of all vessels to totally isolate the liver. The Heaney maneuver advocates a more expedient approach to achieve vascular isolation (Fig. 5) to surgically address juxtahepatic venous injuries and other complex liver wounds. At all times, it is imperative that the patient is optimally resuscitated and closely monitored. Another alternative, with respect to achieving vascular isolation in an effort to access retrohepatic wounds, is the establishment of a venovenous bypass (Fig. 6). This approach necessitates cannulation of the femoral vein and the axillary vein in the upper arm. The cannulas are connected by a heparin-coated tubing, with a flow assisted by a centrifugal pump. Both suprahepatic and intrahepatic clamps are required for the venovenous bypass. Along with inexperience in the

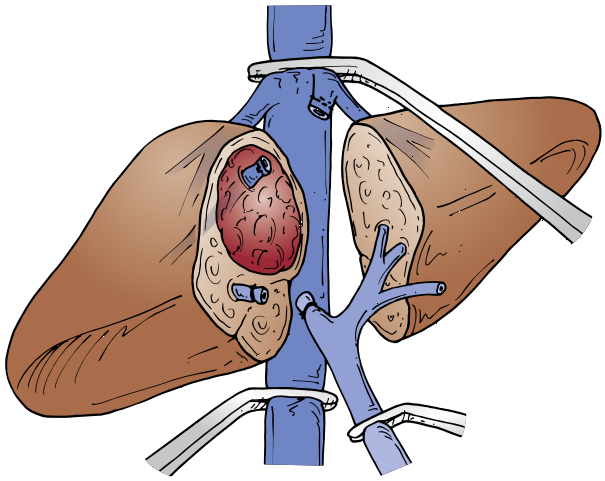


FIG. 5 The Heaney maneuver. Vascular isolation of the injured liver by applying vascular clamps to the suprahepatic and infrahepatic inferior vena cava, in addition to a Pringle maneuver. *(From* Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. *6th ed. Philadelphia: Elsevier; 2017.)*

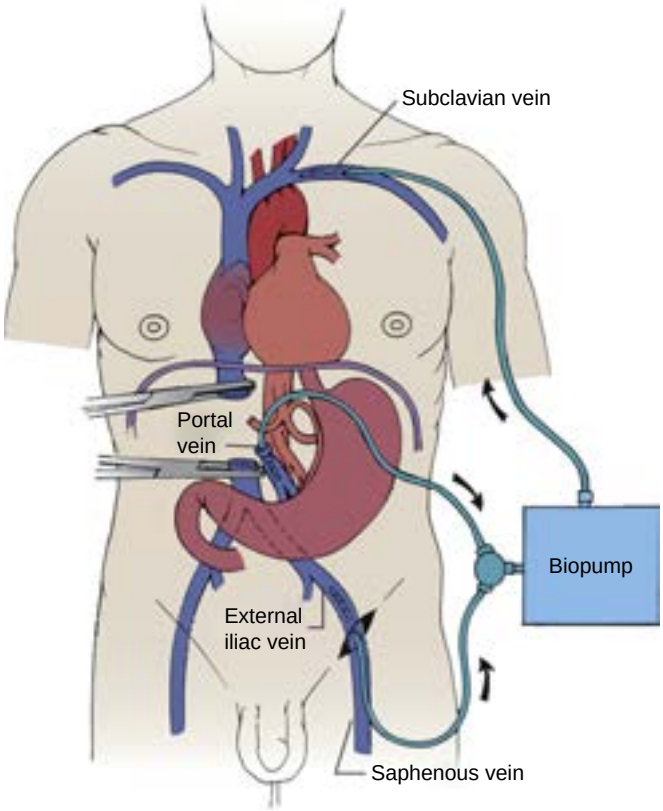


FIG. 6 The venovenous bypass requires cannulation of both the femoral vein and the axillary vein. A heparin-coated tubing connects the two cannulas. Flow is assisted by a centrifugal pump. *(From Urden LD, et al.* Critical Care Nursing. *8th ed. Philadelphia: Elsevier; 2018.)*

above techniques, major blood loss with associated coagulopathy precludes successful utilization of any of the shunting interventions. Operative hepatic resection, in an effort to access these retrohepatic wounds, is associated with a high mortality rate and should not be attempted.

Because of the inherent and overwhelming risks of surgical management of these complex injuries, tamponade with containment followed by angiography and possible embolization has become a viable option (when possible) in the management of juxtahepatic venous injuries. Such an approach often requires temporarily leaving the abdomen open. Although omentum has been proposed to create the tamponade effect, gauze packing is more expedient and effective. Pachter et al. described a "nonshunting approach" that consists of four components: (1) manual compression and aggressive fluid resuscitation; (2) prolonged portal triad occlusion (mean occlusion time, 46 minutes); (3) rapid and extensive finger fracture for vascular control, almost always through normal hepatic parenchyma to the site of injury; and (4) wide mobilization of the hepatic attachments with medial rotation of the liver to provide access to both the retrohepatic cava and the hepatic vein. In their series, six of the nine "nonshunted" patients survived.

Porta Hepatis

Injuries to the porta hepatis are rare, usually complex, and highly lethal. Review of the recent literature showed three large series that cumulatively report 180 patients treated between 1965 and 1994. These injuries are usually penetrating, occurring in 50% to 100% of the populations reported. Isolated injuries to the portal structures occur and are far more survivable than are multiple injuries. Overwhelming hemorrhage is the usual cause of death in all reported series.

The porta hepatis is composed of the hepatic artery, extrahepatic bile duct system, and portal vein. The proximity of these structures to other major structures and their relatively difficult exposure explains their high lethality. In the multi-institutional survey compiled by the Western Trauma Association and reported by Jurkovich et al., an overall 51% mortality rate was recorded. When broken down, the morality rate in single-structure injuries is still 45%, whereas the mortality rate in multiple-structure injuries increases to 80%. This is in line with results in other reports in the literature.

Portal Vein

Injuries to the portal vein are responsible for most deaths ascribed to trauma to the portal structures. Once identified and the bleeding controlled, the question of repair versus ligation must be addressed. Ligation of the portal vein can be tolerated in that there will be decompression of the portal hypertension by collateral vessels. Unfortunately, in patients subjected to ligation of the portal vein, the mortality rate is as high as 90%. This is in disagreement with survival rates of 50% to 80% reported previously by Pachter et al. and Stone et al. Patients treated by ligation of the portal vein have greater circumferential disruption of the vein and overwhelming hemorrhage, and ligation is used as a rapid method of bleeding control. Repair of the portal vein is used with lesser degrees of injury (less than 25% in circumferential injury) and is reported to have increased survivability. Many of the deaths occur because of massive hemorrhage before a repair can be accomplished. When confronted with a portal venous injury, repair is preferable to ligation, although ligation is an acceptable option. Second-look laparotomy to check for bowel viability has been advocated when the portal vein has been ligated.

Hepatic Artery

The liver receives a dual blood supply from the hepatic artery and the portal vein, allowing ligation of the hepatic artery without absolutely compromising hepatic blood supply. Lobar artery ligation is well tolerated, but the overall mortality rate remains in excess of 40%.

Extrahepatic Biliary Ducts

Bile duct injuries are uncommon, even in this relatively uncommon injury cluster. Partial circumferential disruption can be treated by primary repair as well as demonstrated from the experience with iatrogenic bile duct injury at the time of cholecystectomy. Complex or complete disruption of the ductal tree is best managed by biliary-enteric anastomosis. End-to-end anastomosis has an excessive stenosis rate. Adequate drainage of the area is essential because bile leaks can occur. On rare occasion, stenting and external drainage have been used in an unstable patient, with biliary reconstruction accomplished at a later date.

The key to the diagnosis of bile duct injury is suspicion that the injury has occurred. Evidence of bile staining and the presence of a duodenal injury should prompt investigation that is best done by an intraoperative cholangiogram. Small injuries may be missed at initial exploration. Endoscopic retrograde cholangiopancreatogram with stenting may provide diagnostic therapeutic answers if a patient develops a biloma subsequent to a missed injury.

ADVANCEMENTS AND ONGOING CONTROVERSY IN BLUNT ABDOMINAL TRAUMA MANAGEMENT

Resuscitative Endovascular Balloon Occlusion of the Aorta

Bleeding remains the leading cause of preventable death in trauma patients who reach the hospital. Both penetrating and blunt trauma can lead to life-threatening injury of the abdominal vasculature.

Traumatic injury to vessels may occur via direct laceration and transection or blunt injury resulting in dissection or thrombosis. Although endovascular treatment of abdominal vascular injuries has become increasingly utilized, the unstable patient with active hemorrhage will still require open surgical intervention. Appropriate management of these patients centers on prompt recognition of the injury, rapid exposure, and control of hemorrhage. Despite advances in technology, mortality from abdominal vascular injury remains high, and survival of these patients hinges on rapid exposure and control of the hemorrhage. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is gaining popularity as an adjunct for controlling major intraabdominal hemorrhage. The technique was first described in 1953 during the Korean War by Dr. Lt. Colonel Hughes on three soldiers in hemorrhagic shock. The surgeon placed a Foley catheter through the femoral artery to provide proximal vascular control. Although none of the three patients survived, Lt Colonel Hughes noted temporary improvement with inflation of the balloon. However, the procedure was not widely adopted during this time, likely because of concerns regarding the technical difficulty of the procedure and availability of the equipment needed. In 2000, Greenberg and colleagues described the use of an aortic balloon occlusion device to control hemorrhage before endovascular repair for ruptured abdominal aortic aneurysms in three patients. As the use of aortic balloon occlusion has continued to increase in the field of vascular surgery, it has also recently gained momentum as an effective method of obtaining proximal control in the setting of life-threatening abdominal or pelvic trauma.

The goal of REBOA is to provide proximal control of abdominal vascular hemorrhage before transport to the operating room or angiography suite (Fig. 7). After the groin has been prepped, the common femoral artery is accessed with a standard hollow 18-gauge vascular access needle. It is important that incorrect placement, either too proximally into the iliac artery or too distally into the superficial femoral artery, be avoided. As many of these patients may not have a readily palpable femoral pulse, the artery can be accessed using standard anatomic landmarks, using ultrasound guidance, or via direct exposure through an open cutdown. Once the artery is accessed, a 0.035-inch wire is fed through the needle in standard Seldinger fashion. Traditionally, a 6Fr vascular sheath and dilator are placed and then upsized to an 11Fr to 14Fr sheath depending on the size of the balloon being used; however, newer "one-pass" sheaths and dilators are currently available for the trauma setting. Once the appropriate size sheath is in place, a stiff Amplatz guidewire is placed through the sheath. The balloon device is then fed over the guidewire to the correct position.

The location of the balloon in the aorta is determined by the presumed location of the trauma, divided into three distinct zones (see Fig. 7). Zone I is the proximal zone of the descending aorta between the left subclavian and celiac trunk. Placement of the balloon in this zone is recommended for abdominal and visceral trauma. Zone II encompasses the abdominal vasculature from the celiac artery to the lowest renal artery. Placement of the balloon in Zone II is contraindicated as it is possible to directly occlude the celiac artery, superior mesenteric artery, or renal arteries resulting in organ ischemia. Zone III extends from the lowest renal artery to the aortic bifurcation. Positioning of the balloon in this zone provides proximal control for pelvic hemorrhage while still maintaining perfusion to the abdominal organs. Correct positioning of the balloon can be accomplished with either fluoroscopy, plain film x-ray in the trauma bay, or by physical landmarks.

Once positioned, the balloon is then inflated with either saline or a 1:1 mixture of saline and contrast if fluoroscopy is being utilized. Appropriate filling of the balloon can be confirmed by either visualization of the balloon flattening against the wall of the aorta if using fluoroscopy or loss of a pulse in the contralateral femoral artery. Several animal studies have demonstrated that aortic occlusion times greater than 60 minutes may result in severe physiologic derangement and irreversible organ failure; thus, it is imperative that the surgeon be mindful of the duration of balloon inflation and should limit this to less than 60 minutes. After hemorrhage has been controlled,

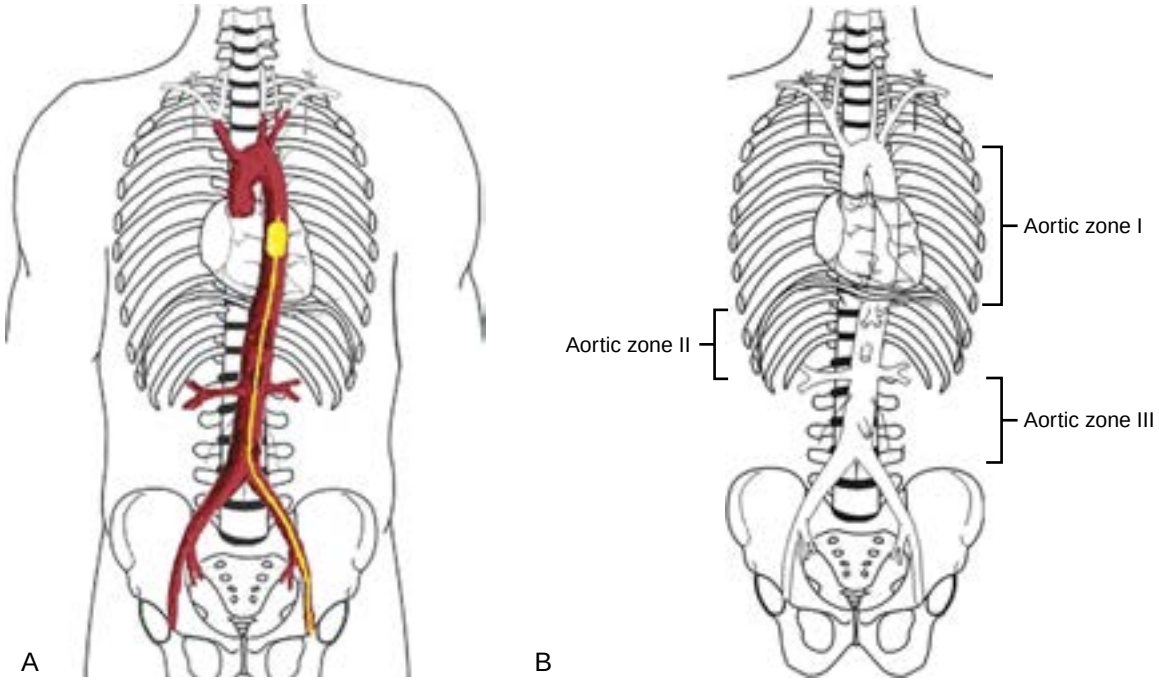


FIG. 7 **(A)** Aortic balloon occlusion device. **(B)** Aortic zones for positioning of resuscitative endovascular balloon occlusion of the aorta device. Zone I is between the subclavian artery and celiac artery, zone II is between the celiac artery and the lowest renal artery, and zone III is between the lowest renal artery and the aortic bifurcation. *(From Stannard A, Eliason JE, Rasmussen TE. Resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct for hemorrhagic shock.* J Trauma. *2011;71:1869–1872.)*

the balloon should be slowly deflated with ongoing communication between the surgeon and the anesthesiologist as there may be abrupt periods of hypotension as the balloon is deflated.

Concerns regarding the use of REBOA focus on incorrect placement of the device, effectiveness in controlling hemorrhage, and potential for organ ischemia. One of the initial case series in 1989 documented the use of REBOA in trauma patients and found that trauma surgeons were able to appropriately position and deploy the balloon, and the balloon was able to control hemorrhage in 11 of 21 patients with refractory hemorrhagic shock. Brenner and colleagues published a recent case series of six trauma patients with severe hemorrhagic shock in whom REBOA was utilized before angiographic or surgical control of the hemorrhage. REBOA resulted in an average increase in systolic blood pressure of 55 mm Hg, and none of the patients died as a result of hemorrhage. Additional studies have shown similar rates of successful placement and control of hemorrhage in patients with both blunt and penetrating abdominal trauma.

Although in many situations, the most effective method to control hemorrhage will be direct control via laparotomy or embolization, REBOA is a technically feasible and potentially life saving adjunct in the patient with refractory and end-stage hemorrhagic shock. As the technology for REBOA devices improves and more clinical research is performed, REBOA will likely become more widespread as a rapid and effective method of hemorrhage control before definitive surgical repair for life-threatening abdominal and pelvic trauma.

Laparoscopy in Blunt Abdominal Trauma

Although laparotomy is the standard of care for abdominal exploration in hemodynamically unstable trauma patients, there are roles for the use of laparoscopy for diagnostic and therapeutic approaches to intraperitoneal injuries in the hemodynamically stable trauma patient. The enhancements of diagnostic tools such as ultrasound and CT have certainly advanced noninvasive diagnostic capabilities, but limitations remain in the diagnostic accuracy for certain injuries. The identification of blunt traumatic bowel injuries, mesenteric injuries, and diaphragmatic injuries can be a diagnostic dilemma with modern imaging techniques. Laparoscopy can be a very useful diagnostic adjunct. Laparoscopy should be considered in patients who do not have an indication for trauma laparotomy but for whom there is concern for unidentified bowel, mesenteric, or diaphragmatic injury based on initial evaluation and imaging. Diagnostic laparoscopy has been reported to reduce nontherapeutic laparotomy rates up 73% in select trauma patients.

Evidence of intraperitoneal free fluid without detectable solid organ injury, while certainly not diagnostic, is concerning for possible hollow viscous injury or mesenteric injury. Although diagnostic peritoneal lavage can be employed, the relatively high false-positive rate and risk for creating visceral injury may portend a risk for unnecessary laparotomy. An early randomized controlled study comparing diagnostic laparoscopy to DPL found higher diagnostic specificity in the diagnostic laparoscopy group. Serial abdominal examinations and monitoring for the development of peritonitis is also a well-adopted diagnostic maneuver for the identification of occult bowel injury in blunt trauma. However, in a series of blunt bowel and mesenteric injuries, Ekeh et al. identified a 19.3% delay in recognition of bowel or mesenteric injury when utilizing a diagnostic armamentarium of physical examination, CT, DPL, and FAST examination. Laparoscopy can also be a useful diagnostic adjunct for identification of occult bowel injury in the patient with discordant imaging and clinical findings, or the so-called *unclear abdomen*. If an injury is identified, the case can then be converted to a laparotomy, or, depending on the skill set of the surgeon, the injury may be amenable to repair with minimally invasive techniques.

Acceleration and sudden deceleration injury mechanisms can result in mesenteric lacerations. Mesenteric injuries, including mesenteric bucket-handle injuries, are not always easily detected with CT imaging. Frick et al. reported that 29.7% of mesenteric lacerations lead to small bowel devascularization and subsequent complications in their series. Potentially devastating consequences associated with missed mesenteric lacerations with resulting bowel ischemia and perforation make prompt diagnosis of these injuries essential. Early diagnostic laparoscopy can be a useful tool to identify these injuries in patients with high suspicion for the injury pattern. Further investigation with laparoscopy may be warranted in patients with a "seat belt sign," imaging that detects free fluid without detectable solid organ injury, imaging that demonstrates evidence of mesenteric injury, or a discrepancy between imaging studies and clinical presentation.

Once a mesenteric injury is identified, the perfusion of the bowel must be assessed. With large tears in the mesentery, it is fairly obvious that the perfusion to the bowel has been sufficiently compromised to warrant bowel resection. For smaller lacerations, perfusion of the bowel can be assessed with indocyanine green (ICG)-enhanced fluorescence screening. Once ICG is injected into the vascular system via the intravenous route, it binds to plasma proteins. Based on the ability of ICG to become fluorescent when excited by near-infrared light, real-time intraoperative organ perfusion can be assessed. This technology is utilized by multiple disciplines including plastic surgeons to assess flap perfusion and colorectal surgeons to assess perfusion of colorectal anastomosis. This technology has been adapted to minimally invasive surgery, and the ability to laparoscopically perform ICG perfusion assessment is available and may be a useful aid in assessing bowel perfusion in mesenteric injuries.

CT has limited sensitivity in identifying diaphragmatic injuries; however, diagnostic laparoscopy is a superior technique to fill this diagnostic void. Furthermore, many diaphragmatic injuries are amenable to laparoscopic repair, as the most common therapeutic minimally invasive procedure in trauma identified in a large trauma database was repair of the diaphragm (19.2%). Diaphragm injuries amenable to laparoscopic repair are more common with penetrating injuries, as blunt diaphragmatic injuries are relatively rarer and are often associated with more significant concomitant injuries because of the substantial applied force to generate the injury. However, in the correctly selected patient without indication for laparotomy, laparoscopy remains a viable option for the diagnosis and treatment of diaphragmatic injuries in blunt abdominal trauma.

The technical approaches to diagnostic laparoscopy can vary, but the principles remain constant. Initial access for insufflation can be achieved with a variety of maneuvers including the open Hasson method, Veress needle technique, and direct optical trocar insertion. The surgeon's experience as well as the clinical variables may dictate the optimal method for initial peritoneal access. The open Hasson technique at the umbilicus can be a safe modality for peritoneal entry but can be very challenging in the obese patient. A history of various prior abdominal operations may also dictate the chosen technique for initial entrance.

Once access is obtained, pneumoperitoneum should be slowly established with close monitoring for any physiologic alterations. Insulation pressure should not exceed 15 mm Hg, and sometimes lower pressures are sufficient for adequate visualization and exploration. Pneumoperitoneum should be released if ventilatory difficulties are encountered or hemodynamic compromise develops. A 0-degree or 30-degree laparoscope can be utilized for exploration. Additional trocar placement location is often dictated by the suspected injured region. However, when suspicion for injury remains uncertain, beginning with two paramedian trocars on either side of the umbilicus at about the midclavicular line in addition to a trocar at the umbilicus is an adequate arrangement to achieve sufficient exploration. Additional trocars can be placed under direct visualization as needed to achieve further diagnostic or therapeutic maneuvers.

After establishing operative access with the trocars, the peritoneal cavity is explored in a systematic manner similar to an open exploration with visualization of all four quadrants. Operating table position manipulation can assist in fully evaluating for injuries in all four quadrants. Tilting the table in the reverse Trendelenburg

position can facilitate exploration of bilateral upper quadrant structures including the liver, spleen, diaphragm, and stomach, while positioning the table in the Trendelenburg position can assist in visualization of the pelvic viscera. After lifting the omentum cranially, the small bowel can be run from the ileocecal valve to the ligament of Treitz utilizing atraumatic graspers. Care should be taken to ensure that the bowel is completely evaluated during this exercise including the mesenteric and antimesenteric borders, and the mesentery should be thoroughly examined as well at this time. If there is concern for a posterior gastric or pancreatic injury, the lesser sac can also be explored laparoscopically. Significant hemoperitoneum, dilated bowel limiting the working space, or the surgeon's technical limitations can all be a hindrance to satisfactory exploration. A low threshold should be had for conversion to laparotomy if the surgeon is not confident in the laparoscopic exploration or missed injuries are suspected.

Complications from laparoscopy can result from access-related injuries, insufflation-related issues, iatrogenic injury during exploration, and inadequate visualization of injuries. Initial access can be achieved via a variety of techniques as described, but all of these maneuvers have the inherent risk of injury to structures along the path of entry including vascular, hollow viscous, and solid organ injury. Gas insufflation can lead to decreased cardiac output from decreased venous return causing hypotension and bradycardia. Capnothorax can also result if there is any violation of the diaphragm and can lead to tension pneumothorax physiology. Issues related to insufflation can generally be resolved with desufflation but may prohibit the utility of laparoscopy. Because of the associated increase in intracerebral pressure with pneumoperitoneum, laparoscopy is contraindicated in severe traumatic brain injury patients. Venous gas embolism is a very rare complication of laparoscopic surgery that infrequently results in a clinically significant event. Iatrogenic visceral injuries are most commonly associated with trocar insertion, direct mechanical instrumentation, and inadvertent electrocautery thermal injury. Missed hollow viscous injury was a significant dilemma in the infancy of laparoscopy in trauma; however, more recent, albeit small, studies have reported a 0% to 0.5% missed injury rate in laparoscopic evaluation of blunt trauma cohorts.

Laparoscopy is a safe and effective diagnostic tool in select trauma patients and can have therapeutic capabilities in the hands of the surgeon with advanced laparoscopic skills. The widespread adoption and progression of minimally invasive surgical techniques certainly adds to the diagnostic and therapeutic armamentarium of the trauma surgeon, but careful patient selection must be judiciously exercised when employing these techniques.

CONCLUSION

In addition to the management of abdominal trauma that has been underscored throughout the chapter for blunt trauma, there are several proposed treatment paradigms for many of the injuries sustained in trauma. However, the standard-of-care management for an individual is heavily dependent on the resources and personnel available along with transport options, if any. There are resource-rich trauma systems throughout the country, with highly qualified personnel. However, these systems are not uniform throughout the nation, and the concept of regionalization has not been perfected for all regions in the country. The overarching goal remains the same: optimal management for everyone, irrespective of where the patient receives trauma care.

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PENETRATING ABDOMINAL TRAUMA

David V. Feliciano

TRANSPORT

Interventions in the field or emergency department do not control intraabdominal bleeding or gastrointestinal contamination in the patient with a penetrating abdominal wound that causes injury. Therefore, transport and resuscitation in such patients is different from methods used in patients with blunt multisystem trauma. For example, the application of a cervical collar or spinal immobilization in the field is unnecessary unless the patient has a specific complaint at the scene. Rapid transport takes precedence over insertion of intravenous catheters at the scene in urban areas, where a trauma center is only 15 to 25 minutes away. Even with longer transport times to the trauma center, the military concept of hypotensive resuscitation *(limited or no resuscitation before operation)* is now applied by many civilian emergency medical services during transport. Obviously, this would be inappropriate in a patient with an associated traumatic brain injury. The ideal perioperative systolic or mean arterial blood pressure during hypotensive resuscitation in the symptomatic patient with a penetrating abdominal wound is unknown.

MANAGEMENT IN THE EMERGENCY DEPARTMENT

In the emergency department, emergency intubation is indicated in patients with the following:

- Profound hypotension (Advanced Trauma Life Support [ATLS] class III or IV shock) or recent cardiopulmonary arrest
- Associated wounds to the neck or chest affecting the airway or breathing
- Depressed neurologic state secondary to shock, acute alcoholism, or illicit drugs
- Extreme agitation preventing evaluation and resuscitation

An identification bracelet is applied to the patient; intravenous lines are inserted into the upper extremities, subclavian veins, or jugular veins; and venous blood is withdrawn for type and crossmatch and routine laboratory testing ("three *C*s" including *c*omplete blood count, *c*hemistry, and *c*oagulation studies). In the patient with ATLS class III or IV shock, most level I trauma centers will initiate a massive transfusion protocol (MTP) and administer packed red blood cells immediately. Smaller centers or those without an MTP often still administer a crystalloid solution initially and then transfuse when type-specific blood is available. Many centers have moved from *damage-control resuscitation* with administration of fixed ratios of packed red blood cells, plasma, and platelets to *goal-directed hemostatic resuscitation*. The latter is based on thromboelastography (TEG) or rotational thromboelastometry.

As resuscitation is ongoing, a surgeon-performed ultrasound examination of the pericardium, peritoneal cavity, and pleural cavities (expanded focused assessment with sonography in trauma [eFAST]) is performed with a 3.5-MHz ultrasound probe in *patients with wounds in the abdomen,* especially when there are other wounds, such as to the thorax or thoracoabdomen. Although this examination is primarily indicated in patients with blunt multisystem trauma, it also has diagnostic advantages in patients with possible penetrating abdominal trauma. For example, the presence of fluid (blood) in the pericardial sac might prompt a median sternotomy or anterolateral thoracotomy, even before a needed laparotomy, or rapid diagnosis of a hemothorax or pneumothorax (without the need for emergency chest radiography) would prompt insertion of a thoracostomy tube before a needed laparotomy. Finally, the presence of fluid (blood) in the peritoneal cavity confirms that the knife or gunshot wound has penetrated through the abdominal wall.

A patient with one or more classical indications for an emergency laparotomy (Box 1) should be moved to the operating room within 10 minutes of arrival in the emergency department or trauma center. Before this time, an intravenous dose of a second- or third-generation cephalosporin antibiotic is administered.

TIMING OF LAPAROTOMY IN BUSY TRAUMA CENTERS

The timing of operation in such patients in a busy trauma center will depend on the patient's hemodynamic status and associated injuries as well as the hemodynamic status of other patients with penetrating or blunt trauma who are being evaluated simultaneously.

BOX 1 Indications for Laparotomy After Penetrating Abdominal Trauma

Hypotension in absence of other site of potential hemorrhage (i.e., penetrating cervical, thoracic, or peripheral vascular wound with active hemorrhage)
Peritonitis on initial or subsequent physical examination
Evisceration of bowel and, in some centers, omentum (controversial)
Bleeding from stomach (hematemesis or bloody return from nasogastric tube) or rectum (bright red blood or hematochezia on finger examination or proctoscopy)
Bleeding from genitourinary tract (exception would be flank wound in stable patient and CT evidence of isolated nonhilar renal injury amenable to observation or angioembolization)
Contrast-enhanced CT demonstrates perforation of gastrointestinal tract, intraperitoneal bladder, or severe (AAST OIS* grade V) solid organ injury.

*American Association for the Surgery of Trauma (AAST) Organ Injury Scale (OIS).

Modified from Feliciano DV. Abdominal trauma revisited. *Am Surg.* 2017;83:1193–1202.

PATIENTS WITHOUT CLEAR-CUT INDICATIONS FOR LAPAROTOMY

The historic "aggressive" operative approach to abdominal trauma resulted from a concern about missed injuries should a nonoperative approach be chosen. This changed gradually when data on unnecessary or nontherapeutic laparotomies for all mechanisms of abdominal trauma became available through trauma registries. For example, historic nontherapeutic laparotomy rates for penetrating (through the peritoneum) anterior abdominal stab wounds, penetrating wounds of the flank and back, and gunshot wounds in proximity to the abdomen were 25% to 40%, 70% to 85%, and 15% to 27%, respectively.

Just as in patients with blunt abdominal trauma, the diagnosis of peritonitis on a physical examination after a penetrating abdominal wound, particularly a stab wound, may be difficult. This is particularly true in patients who are intoxicated, have ingested illicit drugs, have associated injuries to the brain or spinal cord, or have multiple penetrating wounds in areas adjacent to the abdomen (thoracoabdomen, pelvis, flank, back). When serial physical examinations may not be helpful in hemodynamically stable patients, standard diagnostic adjuncts are used, preferably in a sequence agreed up on by staff trauma surgeons (Box 2).

In patients in whom contrast-enhanced computed tomography (CT) will be part of the diagnostic workup, a 128-slice scanner should be used. This will allow scanning of the trunk to be completed with a limited number of revolutions in a short period of time.

Dual-energy CT in which images are acquired at two different energy levels simultaneously is now available in some hospitals, and attenuation differences allow for suppression of artifacts and enhanced images. This technology is now being used to image the brain and aorta and will soon have an impact on truncal imaging in injured patients.

The obvious goal of further diagnostic evaluation in patients without clear-cut indications for an emergency or urgent laparotomy is to avoid an unnecessary or nontherapeutic laparotomy. Patients undergoing such procedures have a fixed rate of postoperative complications and an extended length of stay as compared with those managed with observation or further diagnostic testing.

SELECTIVE MANAGEMENT OF PATIENTS WITH PENETRATING ABDOMINAL TRAUMA

Possible Penetrating Abdominal Trauma/ Multiple Truncal and Extremity Wounds (Hemodynamically Unstable)

One of the common-sense observations about patients with multiple gunshot wounds is that associated hypotension is likely related to one wound ("one bad bullet"). When there is no external bleeding from an injured neck or extremity to explain the hypotension, surgeon-performed ultrasonography is the diagnostic test of choice. As previously noted, an eFAST examination will document whether the hypotension is from pericardial tamponade, intrapleural hemorrhage, or intraperitoneal hemorrhage. An equivocal eFAST examination or lack of availability of an ultrasound machine should prompt

BOX 2 Diagnostic Adjuncts in Evaluating Patients with Possible Penetrating Abdominal Trauma

Local exploration of anterior stab wounds
Diagnostic peritoneal tap/lavage
Surgeon-performed ultrasound examination (FAST)
Contrast-enhanced CT of the abdomen and pelvis
Diagnostic laparoscopy

an open diagnostic peritoneal tap/lavage in the hypotensive patient, a rarely performed diagnostic test in the modern era.

Possible Penetrating Thoracoabdominal Trauma (Hemodynamically Stable)

The thoracoabdomen is defined as the nipple-to-costal margin from the midline to the anterior axillary line. Penetration through the diaphragm into the peritoneal cavity from a wound in the thoracoabdomen will occur in approximately 15% of stab wounds and more than 45% of gunshot wounds (Fig. 1).

Once again, surgeon-performed ultrasonography is the initial diagnostic test of choice in the patient without an obvious indication for a laparotomy. An ipsilateral pneumothorax or hemothorax can be confirmed, whereas the presence of intraperitoneal fluid (blood) documents that the hemidiaphragm and, possibly, intraabdominal viscera have been injured. An eFAST examination in which no intraperitoneal fluid is visualized is not helpful because only modest bleeding may result from a penetrating wound of the hemidiaphragm alone.

In the modern era, documentation of intraperitoneal fluid (blood) in the asymptomatic or mildly symptomatic patient after a thoracoabdominal wound does not prompt an immediate laparotomy. With a wound in the *right thoracoabdomen*, triple-contrast (intravenous, oral, rectal) CT is performed to evaluated the liver, right kidney, duodenum, and colon. This is a labor-intensive study for the radiology technician because all three contrast agents are administered simultaneously. In addition, metallic fragments from a bullet may create enough "scatter" to compromise the accuracy of one of the contrast studies. A patient with a wound to the liver or right kidney only without extravasation of contrast (no active bleeding) is managed nonoperatively with serial physical examinations for 24 to 36 hours. If desired, healing of the injury to the liver or right kidney can be evaluated on a follow-up CT examination in 5 to 7 days. In such a patient, the small penetrating wound in the right hemidiaphragm is not fixed. This is because omental herniation through the right-sided defect essentially never occurs, and the complication of a bronchobiliary fistula is so rare. A triple-contrast CT is performed after a penetrating wound to the *left thoracoabdomen* as well, with the goal of evaluating the liver, spleen, left kidney, stomach, and colon. Even if a patient has a nonbleeding wound to the left lobe of the liver, spleen, or left kidney and no extravasation of gastrointestinal contrast, the wound to the left hemidiaphragm must be repaired. This will prevent herniation of the omentum into the left hemithorax secondary to the negative intrapleural pressure of respiration. This can be accomplished via a laparoscopic approach depending on the surgeon's expertise.

Because of the labor-intensive nature of triple-contrast CT, some centers choose to perform diagnostic laparoscopy instead after a wound to the left thoracoabdomen. An equivocal triple contrast CT after a wound to either the right or left thoracoabdomen should be followed by diagnostic laparoscopy as well. Using a 30-degree laparoscope with the patient under general anesthesia in the operating room will allow for a careful inspection of the ipsilateral hemidiaphragm and intraabdominal viscera.

Penetrating Anterior Abdominal Stab Wound (Hemodynamically Stable)

The anterior abdomen is defined as the area from the costal margins to the inguinal ligaments between the anterior axillary lines. Historic data have documented that stab wounds in this location penetrate the peritoneal cavity only 25% to 33% of the time. Even in patients with documented peritoneal penetration, only 50% to 55% will present with overt indications for a laparotomy. In the remaining 45% to 50% who undergo serial physical examinations, only half will eventually become symptomatic and require laparotomy.

A local wound exploration under semisterile conditions and local anesthesia in the trauma room is the first diagnostic maneuver. Contraindications would include the agitated or uncooperative patient or one who is morbidly obese. A very localized layer-by-layer exploration will, at the least, document whether the anterior aponeurosis of the muscular abdominal wall has been penetrated. In many centers, the local wound exploration is terminated at this point and the patient admitted for serial physical examinations or further diagnostic testing. Other centers will continue the exploration through the muscular layers of the abdominal wall to determine whether the posterior aponeurosis, peritoneum, or both have been perforated (Fig. 2). If it can be confirmed that this has not occurred, the wound is irrigated and closed in layers, a tetanus immunization shot is administered, and the patient is discharged.

In most centers, an asymptomatic or mildly symptomatic patient with penetration of the anterior aponeurosis or peritoneum will then undergo serial physical examinations every 6 to 8 hours for 24 hours. Almost all patients with continued bleeding from a solid organ, the mesentery, or omentum or peritonitis from a gastrointestinal wound will become symptomatic within 6 to 16 hours. Despite the delay in operative management that inevitably occurs in this small subset of



FIG. 1 This patient with a left thoracoabdominal gunshot wound had a 3-day delay before wounds to the left hemidiaphragm and stomach were diagnosed.

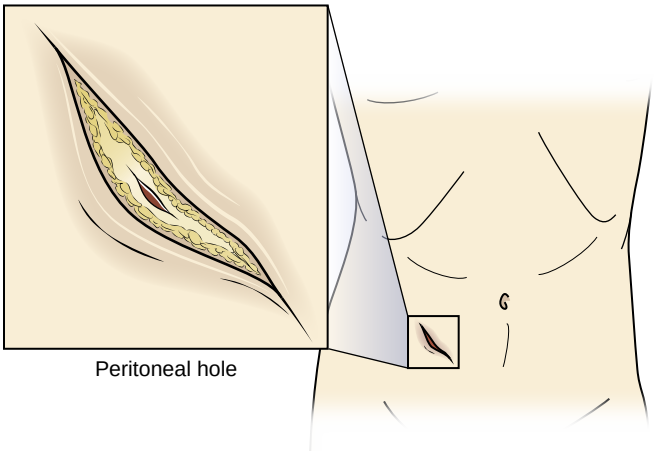


FIG. 2 Peritoneal perforation on a local wound exploration after a stab wound to the anterior abdominal wall mandates admission and serial physical examinations.

patients, postoperative morbidity is surprisingly low. Another option is to perform a triple-contrast helical CT examination, which has been implemented to assess flank and back wounds for the past 35 years. In one older study of patients with penetrating injury to the torso from the Shock Trauma Center at the University of Maryland, CT accurately predicted the need for laparotomy in 95% of patients.

A historic option in the asymptomatic or mildly symptomatic patient is to perform an immediate diagnostic peritoneal tap/lavage after a "positive" local wound exploration. This option has become less popular over time because of false-positive examinations resulting from intraperitoneal blood related to the injury to the abdominal wall. Also, there has been continuing controversy about whether a red blood cell count of 100,000/mm^3 (as in patients with blunt trauma) or 5000/mm^3 (to pick up a small wound in the hemidiaphragm) should be used to mandate a laparotomy. The accuracy of this approach using a cell count of 100,000 red blood cells/mm^3 or 500 white blood cells/mm^3 ranges from 88% to 92%.

Penetrating Anterior Stab Wound Away from Left Hemidiaphragm/Omental Evisceration (Hemodynamically Stable)

Evisceration of a large piece of omentum (or any piece of bowel) should prompt an emergency laparotomy. This allows for replacement of the omentum into the peritoneal cavity, a complete exploration for associated injuries (theoretically, a higher incidence than if a smaller defect in the abdominal wall), and repair of the abdominal wall. Controversy exists, however, when a small piece of omentum is eviscerated. In such patients, an emergency laparotomy will be nontherapeutic in 20% to 60% of patients. Therefore, some centers will ligate the base of the eviscerated omentum, excise it, return the remainder to the peritoneal cavity, close the defect in the abdominal wall, and perform serial physical examinations for 24 hours. This option is safe and has a delay to operative management essentially the same as if an omental evisceration had not occurred.

Penetrating Stab or Gunshot Wound to the Flank or Back (Hemodynamically Stable)

The *flank* is defined as the sixth intercostal space to the iliac crest between the anterior and posterior axillary lines, whereas the *back* is the tips of the scapulae to the iliac crests posterior to the posterior axillary lines. Wounds in these areas may penetrate the peritoneal cavity or the visceral-vascular area of the retroperitoneum. A historic policy of mandatory laparotomy for penetrating wounds to the flank or back in symptom-free patients has been abandoned over the past 30 years because the aforementioned negative/nontherapeutic rate was 70% to 85%. This was partially related to the often-forgotten thickness of the muscles in young men in these areas.

The two diagnostic options in these patients are serial physical examinations and triple-contrast CT. The concern with serial physical examinations is that perforation of the retroperitoneal duodenum, ascending colon, or descending colon will cause retroperitonitis or a delayed onset of symptoms. One large study of flank wounds in 2007, however, documented that 91% of patients who developed symptoms of an occult injury did so within 6 hours of admission. In addition, no patient observed for 18 hours developed symptoms from an occult injury after this time. Therefore, the 24-hour recommended period for serial physical examinations after presumed or documented anterior stab wounds can be applied to patients with flank or back wounds as well. Should the data described not be convincing for the trauma surgeons in a given center, extending the period for serial physical examinations to 36 hours is certainly appropriate.

As previously noted, triple contrast-enhanced CT examinations to evaluate patients with penetrating wounds to the flank or back were first reported in 1986. Along with the 35 years of experience with this diagnostic approach, the evolution to 128-slice scanners minimizes the risk of missing an occult retroperitoneal visceral or vascular injury (Fig. 3).

In summary, either serial physical examinations (labor-intensive for surgical team) or triple-contrast CT (labor-intensive for radiology

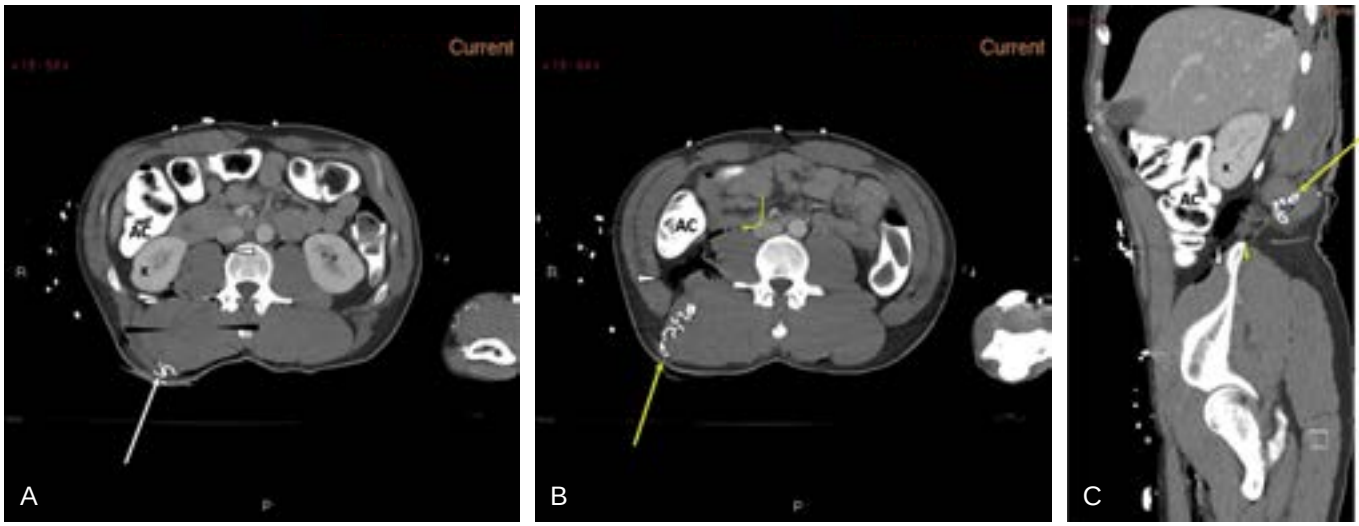


FIG. 3 Axial **(A, B)** and sagittal **(C)** images from an abdominopelvic CT scan obtained with both oral and intravenous contrast. **(A)** Combat gauze *(arrow)* is packed into the wound track that extends into an ill-defined posterior paraspinal hematoma *(black arrowheads)*. Pneumoretroperitoneum *(white arrowheads in* **A** *and* **C***)* suggest the track extending to either the right psoas or the right kidney *(K)* is normal in **A** *and* **C** as well as multiple other images *(not shown)*. **(B, C)** Combat gauze *(yellow arrow)* is packed into the second wound track that is directed toward a small retroperitoneal hematoma *(yellow arrowhead)*, pericolonic pneumoretroperitoneum *(AC)*, and pneumoperitoneum in the region of the right ureter *(curved yellow arrow)*. The ascending colon *(AC)* is normal in **A** *and* **C** as well as multiple other images *(not shown)*. Based on orientation of wound tracks extending to the regions of the ascending colon and right ureter as well as volume of pneumoretroperitoneum, the patient underwent laparotomy that revealed no injury to the colon, kidney, or ureter.

technician) are acceptable diagnostic options, with a delayed diagnosis and laparotomy rate of less than 5%.

Gunshot Wound from Flank-to-Anterior/Anterior-to-Flank Abdominal Wall *or* Possibly Through-and-Through Anterior Abdominal Wall Only (Hemodynamically Stable)

In the modern era, there is a tendency for victims facing an assailant holding a handgun to turn away. Also, obesity is present in more than 40% of adults in some states in the United States. This results in numerous patients having oblique missile tracks in proximity to the abdominal contents from the flank to the anterior abdominal wall, from the anterior abdominal wall to the flank, and from one location in the anterior abdominal wall to another.

When physical examination cannot rule out peritonitis, the diagnostic test of choice is abdominal CT with intravenous contrast. A preliminary film will often confirm that the gunshot wound is extraperitoneal. Because the kinetic (muzzle) energy of missiles from handguns is less than 1000 ft lbs (with the exception of a .44 caliber), a shock wave injury to an intraabdominal viscus would be highly unlikely in such a patient. Confirmation of an intraperitoneal track in the patient with a persistent equivocal physical examination should be followed by a triple-contrast CT or a diagnostic laparoscopy in the operating room because 78% to 98% of such patients will have an intraabdominal injury.

Selective Nonoperative Management of Gunshot Wounds in Proximity to the Abdomen/Unknown if Penetrating (Hemodynamically Stable)

Suggestions to choose nonoperative management in asymptomatic patients (e.g., no peritonitis, no hypotension) with gunshot wounds in proximity to the abdomen are now 60 years old. Significant enthusiasm for this approach and large studies on the topic have come from the group at the University of Southern California/Los Angeles County Hospital over the past 25 years. A recent systematic review and meta-analysis of 41 cohort studies with 22,847 patients with abdominal gunshot wounds included 6777 undergoing selective nonoperative management. The pooled estimate of the risk of failure of this approach in 28 studies was 7.0%. Delayed laparotomy was usually precipitated by the development of peritonitis or worsening abdominal tenderness, but the operation turned out to be unnecessary in 28% of these patients. Finally, mandatory use of abdominopelvic CT had a failure rate of approximately one-half that when used selectively.

Therefore, modern selective nonoperative management of gunshot wounds in proximity to the abdomen includes the following: (1) examination of the patient's abdomen at admission by a senior surgeon, (2) mandatory contrast CT to document whether or not peritoneal or visceral-vascular retroperitoneal penetration has occurred *and* whether an isolated nonbleeding injury to the liver or kidney is present, (3) "serial" physical examinations for 24 to 48 hours in patients with penetration of the peritoneal cavity or visceral-vascular retroperitoneum. In patients who remain asymptomatic after 24 to 48 hours of observation, specific written instructions are handed to the patient. These state that a new onset of an elevated body temperature, abdominal pain, lightheadedness, hematemesis, rectal bleeding, hematochezia, or hematuria should prompt immediate return to the trauma center. The phone number of the trauma service is included as well.

GENERAL PRINCIPLES OF TRAUMA LAPAROTOMY

The patient is placed in the supine position with the upper extremities at the sides. Placing the upper extremities at the patient's sides allows for easy insertion of self-retaining abdominal retractors and ready access for a median sternotomy. On occasion, there is a high likelihood of the need for a left anterolateral thoracotomy also being performed for an extraabdominal injury (e.g., massive left hemothorax or proximity of missile track to the thoracic esophagus or descending thoracic aorta). In such a patient, the left chest is elevated 30 degrees, and the left upper extremity is rotated superior to the patient. Skin preparation and draping extends from the chin to the knees and encompasses the anterior and lateral trunk. This allows for ready access for retrieval of the greater saphenous vein from the groin and thigh, if needed. Throughout the trauma laparotomy, all of the standard warming maneuvers are used to reverse or prevent hypothermia (increase room temperature, turn up the heating cascade on the anesthesia machine, cover the patient's head and extremities with a warming device, infuse blood and fluids through a warming device, irrigate tubes [nasogastric, thoracostomy] and open body cavities with warm saline solution if hypothermia is persistent).

In patients with profound preoperative hypotension or a cardiac arrest resulting from presumed intraabdominal hemorrhage, management in the trauma room or operating room has changed over the past 5 years. The addition of a left anterolateral resuscitative thoracotomy with cross-clamping of the descending thoracic aorta is being replaced rapidly by resuscitative endovascular balloon occlusion of the aorta (REBOA). A REBOA device with the balloon inflated at aortic zone I (xiphoid) may restore central blood pressure, slow intraabdominal arterial hemorrhage, and possibly slow intraabdominal venous hemorrhage. Of course, it avoids the extra loss of blood and heat associated with the left anterolateral thoracotomy.

Depending on the patient's hemodynamic status, the midline incision is not opened until type-specific blood is available in the operating room. Once the peritoneal cavity is opened, blood, clots, and gastrointestinal contents are evacuated using laparotomy pads and a Poole suction device. Sites of hemorrhage in the mesentery, bowel, retroperitoneum, or solid viscera are exposed and controlled with clamps or packing. Then all perforations in the gastrointestinal tract are controlled with bowel, vascular, Babcock, or Allis clamps or a stapling device. Depending on the patient's hemodynamic status, number and magnitude of gastrointestinal perforations, and associated injuries, the perforations are repaired and the peritoneal cavity is irrigated with a saline-antibiotic solution. Then treatment of injuries to solid organs or to retroperitoneal blood vessels is performed. This sequence is reversed in patients with active visceral or vascular hemorrhage.

As a general rule, the track of a knife or missile wound is followed first, with repair or resection of injuries as needed. Then a formal exploration of every intraabdominal organ including retroperitoneal viscera and vessels, especially those in proximity to the track, is performed. The organs most commonly injured in patients with stab wounds to the abdomen are the liver, small bowel, diaphragm, colon, and stomach. In patients with gunshot wounds, injuries to the diaphragm fall by one-half as compared with stab wounds, and injuries to named abdominal vessels are present in 20% to 25% of patients in large reviews. In any patient with multiple abdominal injuries from a penetrating wound, not just those undergoing a damage-control laparotomy, rapid operative techniques are performed (Box 3).

A *damage-control laparotomy* is indicated in patients with profound hypothermia (temperature <32°–34°C), metabolic acidosis (pH <7.2), signs of an intraoperative coagulopathy, or some combination of these. This limited laparotomy controls hemorrhage and gastrointestinal contamination only, and it should be completed within 60 to 90 minutes. Leaving the abdominal wall open under a vacuum-assist device or a plastic silo is appropriate after a damage-control laparotomy, when distension of the midgut precludes safe closure or when intraabdominal packs have been inserted. An early reoperation after a damage-control laparotomy is occasionally necessary. This is indicated when there is a continuing need for hourly transfusion of two units of red blood cells after a coagulopathy has been mostly corrected based on monitoring with TEG. Otherwise, a reoperation after an original damage-control procedure is performed when the patient is normothermic, no longer acidotic,

BOX 3 Rapid Operative Techniques After Penetrating Abdominal Trauma

Gastrointestinal Tract

Single-layer closure of gastrointestinal perforations
Single-layer technique of end-to-end anastomosis
Colon repair instead of colostomy
Delay gastrointestinal reconstruction

Solid Viscera

Hepatorrhaphy, hepatotomy, resectional debridement, or perihepatic packing instead of formal hepatic resection
Topical agent, suture, or absorbable mesh splenorrhaphy for AASTOIS* grade I to III injury instead of splenectomy
Avoiding placement of drains after visualization or repair of grade I and II hepatic or pancreatic injuries, splenorrhaphy, splenectomy

Diaphragm

Single-layer permanent suture repair

Named Arteries

Temporary intraluminal shunt instead of complex repair of proximal superior mesenteric artery, common iliac artery, or external iliac artery (same vessels are *never* ligated without bypass)

Named Veins

Ligation major injury to portal vein, superior mesenteric vein, splenic vein, left renal vein at midline, infrarenal inferior vena cava, common iliac vein, or external iliac vein

*American Association for the Surgery of Trauma (AAST) Organ Injury Scale (OIS).

BOX 4 Goals at a First Reoperation After Damage-Control Laparotomy

Remove and count packs, and confirm the absence of continued bleeding from the liver and retroperitoneum
Inspect all repairs and search for missed injuries
Complete gastrointestinal anastomoses, and/or create a stoma
Insert a nasojejunal feeding tube (avoids gastrostomy or jejunostomy)
Irrigate the abdominal cavity with saline solution containing an antibiotic
Decide if formal suture closure of the linea alba is safe

not coagulopathic, and has reasonable respiratory and cardiovascular function—usually at 48 to 72 hours. The goals of the first reoperation after a damage-control laparotomy are listed in Box 4.

SUMMARY

In patients undergoing laparotomy after abdominal stab wounds, the survival rate is 98%, and only 27% of patients required a blood transfusion in one large review. The most common postoperative complication was an infection in the incision (1.0%).

In patients undergoing laparotomy after abdominal gunshot wounds, the survival rate was 88% (97% in those without an abdominal vascular injury; 61% in those with an abdominal vascular injury) in one large review. The most common postoperative complications were intraabdominal abscess (3.0%), infection in the incision (2.6%), and reoperation for persistent bleeding (2.2%).

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Management of Diaphragmatic Injuries

Kazuhide Matsushima, MD, and Kenji Inaba, MD

INTRODUCTION

Injuries to the diaphragm are relatively uncommon in both blunt and penetrating trauma patients. However, failure to appropriately identify and manage traumatic diaphragmatic injuries (TDI) can lead to serious consequences including compromise of the gastrointestinal tract. With recent advances in imaging modalities and operative techniques, diagnostic and therapeutic approaches to TDI have evolved significantly over the past few decades. The objectives of this chapter are to review the epidemiology, anatomy, and pathophysiology of TDI and discuss current recommendations for evaluation and management of TDI.

EPIDEMIOLOGY

A recent study from the National Trauma Data Bank demonstrated that the overall incidence of TDI in trauma patients is 0.46%. Of

those, 67% were caused by a penetrating mechanism. A large single-center study including 773 TDI patients over 15 years reported a 40% incidence of right-sided TDI, 57% of left-sided TDI, and 3% bilateral. A higher incidence of left-sided TDI is likely due to the presence of a congenital weakness along the costal and lumber portions of the left hemidiaphragm, and the liver likely provides some degree of protection for the right hemidiaphragm.

The true incidence of TDI, however, is unknown as not all of these injuries are diagnosed during the index presentation. Blunt TDI is typically seen in patients after a motor vehicle collision or pedestrians or bicyclists hit by a vehicle. As blunt TDI is usually caused by high-energy trauma to the thoracoabdominal region, it is a marker for severe associated injuries, and the diaphragm is rarely injured in isolation. Pulmonary injury is the most commonly associated injury, followed by splenic and liver injuries. For penetrating trauma, most TDI are diagnosed in patients with thoracoabdominal gunshot wounds (GSW) or stab wounds (SW). The incidence of TDI following thoracoabdominal GSW is 61%. In a single-center study from a level 1 trauma center in Los Angeles, 37.8% of patients with thoracoabdominal SW were found to have TDI. Similar to blunt TDI, associated intrathoracic and abdominal organ injuries are relatively common in penetrating TDI. In addition to the lung and intraabdominal solid organs, hollow viscus injuries are more commonly seen in penetrating TDI compared with blunt TDI.

TDI left undiagnosed or untreated during the acute phase of treatment can progress to a larger defect size and ultimately chronic traumatic diaphragmatic herniation (TDH) due to radial forces placed on the diaphragm by respiration and the pressure gradient between the thoracic and abdominal cavity. In this latent phase, patients with chronic TDH may not be symptomatic, even with abdominal viscera herniated into the thoracic cavity. If the herniated viscus becomes incarcerated then strangulated, patients can develop symptoms related to mechanical obstruction, ischemia, perforation, and sepsis.

ANATOMY

The diaphragm is a dome-shaped musculoaponeurotic barrier that separates the thoracic cavity from the abdominal cavity. It is the main respiratory muscle of the body with expiratory and inspiratory functions. The diaphragm consists of peripheral muscular segments and a central aponeurosis. Muscle fibers originate anteriorly from the xyphoid process of the sternum and laterally, inferiorly, and posteriorly from the costal cartilages and osseous portion of the lower six ribs and the lumber spines (Fig. 1). These fibers insert into the aponeurotic segment known as the central tendon, which underlies the pericardium. There are three openings in the diaphragm. The caval hiatus (T8 level) contains the inferior vena cava and right phrenic nerve; the esophageal hiatus (T10 level) contains the esophagus and bilateral vagus nerves; and the aortic hiatus (T12 level) contains the aorta, thoracic duct and azygous vein. The right dome of the diaphragm is 2 cm higher than the left, accommodating the underlying liver. The arterial supply of the diaphragm comes from superior and inferior phrenic arteries that are direct branches off the thoracoabdominal aorta. Phrenic veins provide venous drainage directly into the inferior vena cava. The diaphragm is innervated by the right and left phrenic nerves that originate from the

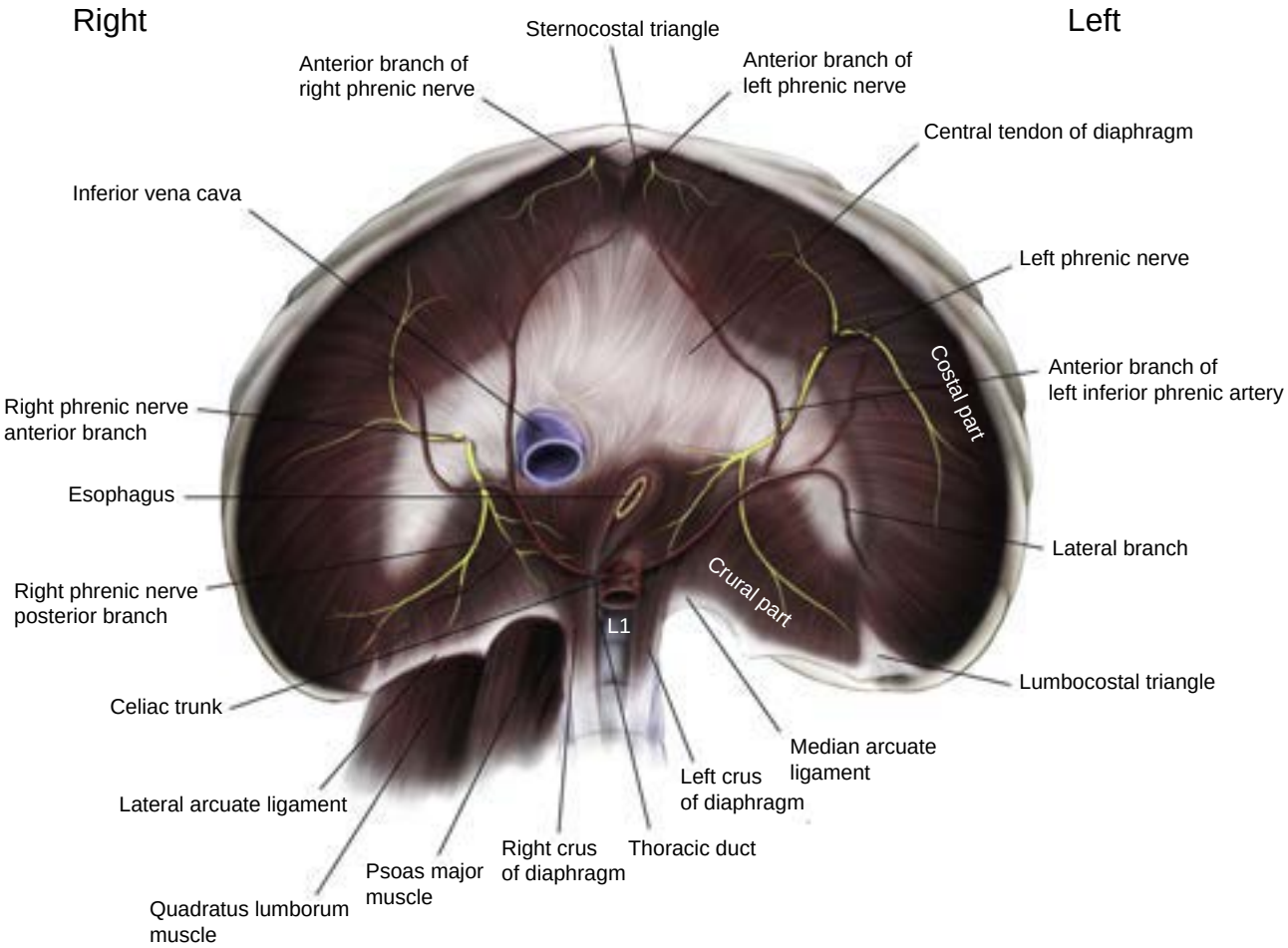


FIG. 1 Anatomy of the diaphragm (abdominal view).

TABLE 1 American Association for the Surgery of Trauma Diaphragmatic Injury Grading Scale

Grade*	Injury Description
I	Contusion
II	Laceration ≤2 cm
III	Laceration 2–10 cm
IV	Laceration >10 cm with tissue loss ≤25 cm^2
V	Laceration with tissue loss >25 cm^2

*Advance one grade for bilateral injuries.
From Moore EE, Malangoni MA, Cogbill TH, et al. Organ injury scaling. IV: thoracic, vascular, lung, cardiac, diaphragm. *J Trauma*. 1994;36:299–300.

C3–5 nerve roots. Both nerves pass over the anterior scalene muscle, run along the pericardium, and then terminate on the inferior surface of the diaphragm. Table 1 shows the American Association for the Surgery of Trauma Organ Injury Scale for TDI. Higher-grade injuries are more commonly seen in blunt trauma. Penetrating TDI are often less than 2 cm in size.

DIAGNOSTIC WORKUP: BLUNT TRAUMA

For patients undergoing laparotomy after blunt trauma, the diaphragm must be inspected for injury. Practically, because it is unusual to have an isolated TDI, the majority are diagnosed intraoperatively during laparotomy performed for other indications. For the rare patient with TDI who does not undergo operative intervention, the diagnosis can be challenging. Patients with TDI are often asymptomatic, particularly those with a small defect, especially on the right side. During the initial trauma assessment, there are no adequately sensitive clinical signs to ensure the definitive diagnosis of an underlying TDI. Although "classic" physical findings such as unilateral decreased breath sounds or bowel sounds heard in the chest have been described as alarming signs of TDI, these are neither sensitive nor specific. Therefore, it is important to have a high index of suspicion for TDI in all patients with evidence of severe thoracoabdominal force application.

The chest radiograph (CXR) obtained during the initial workup is rarely diagnostic of TDI, unless the diaphragm defect is large and intraabdominal contents have herniated into the chest. These classic radiographic signs more common in patients with chronic TDH (Fig. 2A, B). Most patients with acute TDI have a normal CXR or nonspecific signs such as an obscured diaphragmatic contour or elevation of the left hemidiaphragm (Fig. 3A, B). Historically, the sensitivity of CXR is poor, ranging from 27% to 68% and 17% to 33% for left- and right-sided TDI, respectively. In a recent multicenter study, the diagnosis of TDI was suspected on CXR in only 11% of patients.

With the increasing use of newer generation multidetector computed tomography (MDCT) as a mainstay of the diagnostic workup in trauma, the diagnosis of TDI is now more frequently made preoperatively. The diagnostic accuracy of MDCT is significantly better than CXR due to advances in data acquisition and multiplanar reformatting. Segmental defects in the diaphragm are the most common and sensitive sign of TDI in blunt trauma (Fig. 4). In addition, several CT findings of TDI and associated visceral herniation have been described (Fig. 5A, B). Recent studies have shown MDCT sensitivities upward of 61% to 87% and specificities of 72% to 100% for detecting blunt TDI.

It should be noted that there is no definitive screening modality that is perfectly sensitive for TDI. The gold standard for those with suspicious imaging is direct operative visualization.

DIAGNOSTIC WORKUP: PENETRATING TRAUMA

For patients who have sustained penetrating thoracoabdominal trauma, the approach is very different from blunt injury. Many of these patients who have been shot or stabbed will undergo urgent laparotomy, and the diaphragm should be visually inspected at this time. For those patients who meet criteria for a trial of nonoperative management, however, reliance on imaging for definitive diagnosis of TDI is even more difficult than in blunt trauma, as the defects are generally very small. Often, the best that can be expected from CT is collateral evidence of injury, for example, with an entrance wound in the chest wall, a visible bullet tract through the lung, a spleen injury on the other side of the diaphragm, or a retained bullet in the abdominal wall. Therefore, our recommendation for patients who have sustained a thoracoabdominal penetrating injury undergoing nonoperative management is to utilize diagnostic laparoscopy for definitive diagnosis. This is a high-yield process; a prospective study performed at our center found an occult TDI rate of 26% in SW and 13% in GSW patients at laparoscopy.

Right-sided injuries are unlikely to result in a clinically significant complication, but for left-sided injuries in the region bounded by the

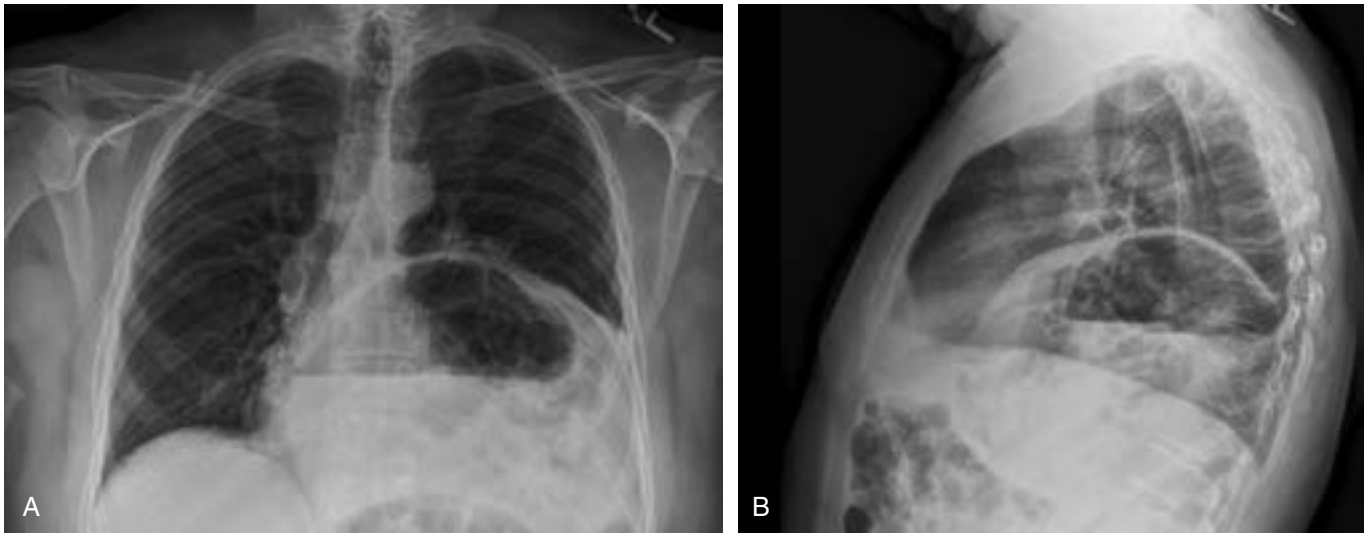


FIG. 2 Anteroposterior **(A)** and lateral **(B)** chest x-rays showing traumatic diaphragmatic injury with herniation of the stomach into the left chest.

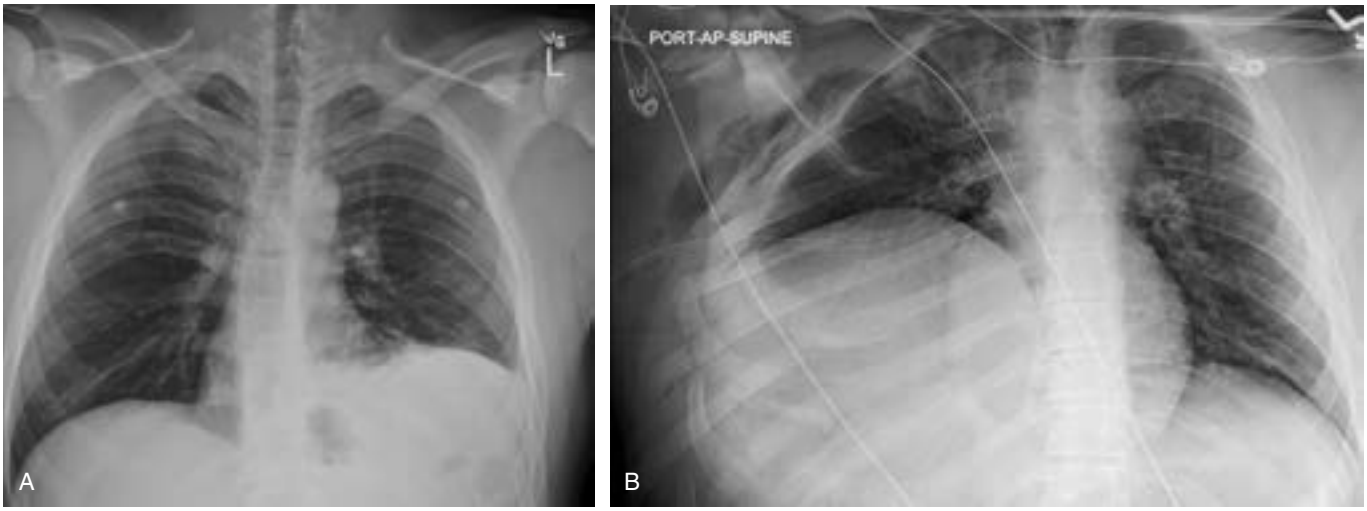


FIG. 3 **(A)** Chest x-ray of a patient with acute left-sided diaphragmatic injury. Elevation of the left hemidiaphragm with blunting of the costophrenic angle is noted. **(B)** Acute right-sided diaphragmatic injuries. In addition to significantly elevated right hemidiaphragm, there are multiple findings suggestive of associated thoracic injuries (subcutaneous emphysema, multiple rib fractures).



FIG. 4 Dangling diaphragm sign. A large defect in the left diaphragm with defect edges retracted and curled *(arrows)*.

nipple to scapular tip superiorly and costal margin inferiorly (Fig. 6), we start with a 24-hour observation period. If the patient develops peritonitis or any other indications for laparotomy, the diaphragm can usually be inspected at that time. If, however, the patient passes this period of observation, diagnostic laparoscopy is then performed specifically to visualize the left diaphragm, as injuries to the remainder of the hollow viscus have already been excluded (Fig. 7). It is critical that insufflation be performed cautiously. Any evidence of building tension physiology from the TDI, with increasing peak inspiratory or plateau pressures, hypoxia, or hypotension, will require immediate release of pressure and tube thoracostomy. If an injury is found, it can then be repaired laparoscopically. Because the defects in these cases are usually very small, primary repair with a nonabsorbable suture should always be attempted (Fig. 8). Alternatively, if after the period of observation the patient requires a concurrent thoracic procedure, for example, to wash out a retained hemothorax, a video-assisted thoracoscopic approach may be utilized.

SURGICAL MANAGEMENT

As discussed earlier, due to the high incidence of associated intraabdominal injuries, the majority of blunt diaphragmatic injuries are diagnosed and repaired acutely through a laparotomy performed for other indications. If, however, the diagnosis of TDI is made preoperatively on imaging, the diaphragm can be repaired via laparotomy or thoracotomy. For acute injuries, it is strongly recommended that an abdominal approach using a midline laparotomy rather than a thoracic approach be utilized due to the high incidence of associated intraabdominal organ injuries (Fig. 9A).

In general, the intraoperative management of TDI includes reduction of any herniated intraabdominal organs followed by repair of the diaphragmatic defect. The left upper quadrant organs such as the stomach, spleen, or colon can be herniated through the diaphragmatic defect. In the acute setting, it is usually easy to reduce these organs back into the abdominal cavity. Positioning the patient in reverse Trendelenburg with the right side down may help with this maneuver. An inspection of the herniated organs is then performed for any associated injuries (Fig. 9B). After the reduction of any herniated contents, the diaphragm can be fully evaluated for the defect size and presence of any tissue loss. Allis or Kocher clamps are applied to the wound edges, bringing the defect into the wound for better exposure of the injury (Fig. 10A). This maneuver is particularly useful for large defects or those involving the posterior portion of the diaphragm. Intrathoracic injuries can also be evaluated through the diaphragmatic defect and treated at this time if necessary. Any retained hemothorax should be evacuated through the defect and lavage of the thoracic cavity should be performed, especially if there is any significant contamination due to associated hollow viscus injuries. A thoracostomy tube is normally placed at this time.

Before surgical repair of the diaphragm defect, debridement of devitalized edges is usually required. As the diaphragm is very redundant, in the vast majority of cases, even high-grade injuries can be repaired primarily without any negative physiologic effect on pulmonary function. Size 0 or 1 nonabsorbable monofilament sutures are often used for the primary repair of TDI. The type of repair has not been shown to have any association with the incidence of postoperative complications or recurrence rate. Both interrupted figure-of-8, mattress, or simple sutures and running repairs can be performed (Fig. 10B). Although it is extremely rare, the use of prosthetic or biologic mesh products may be required for a very large size

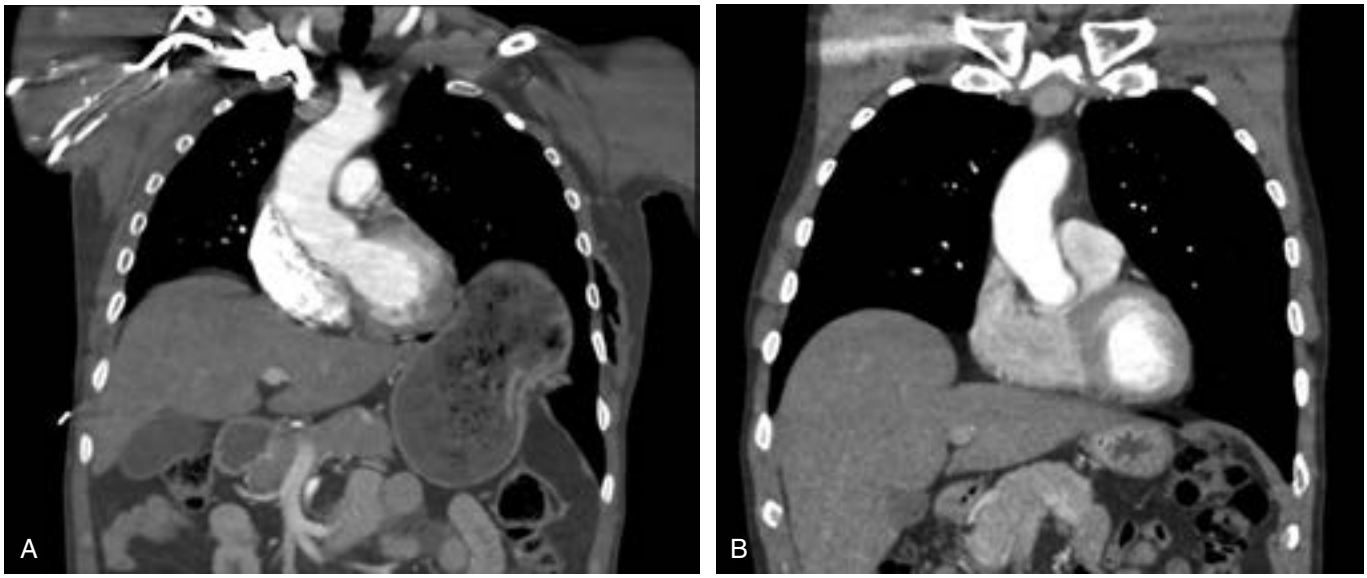


FIG. 5 **(A)** Collar sign. A waistlike constriction of the stomach herniated through a defect in the left hemidiaphragm is seen on a coronal reconstruction image. **(B)** Hump sign. Focal bulging of the right hemidiaphragm due to herniation of the liver parenchyma.



FIG. 6 Penetrating wounds to the left thoracoabdominal area bordered by the nipple to scapula tip superiorly and the costal margin inferiorly are high risk and should be evaluated for underlying diaphragmatic injuries.

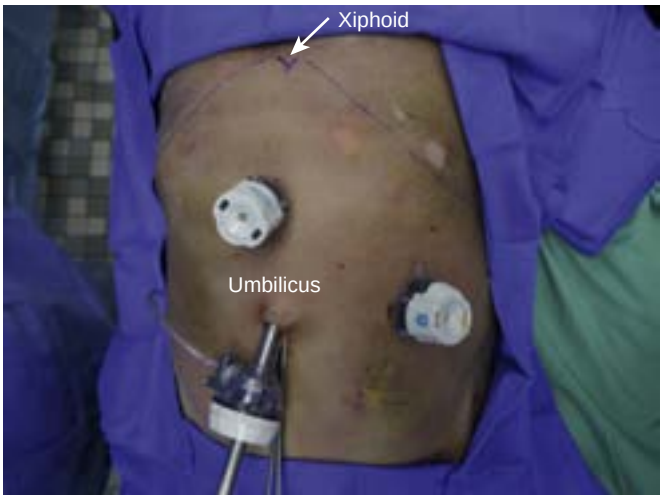


FIG. 7 Port placement for diagnostic laparoscopy for left-sided thoracoabdominal penetrating injuries.

defect associated with tissue loss. This is extremely rare, and there is insufficient data in the trauma patient population to recommend a specific mesh type. Based on the congenital diaphragmatic hernia evidence and our experience, the use of a tension-free polytetrafluoroethylene (PTFE) mesh is a practical option.

For diaphragmatic injuries that have been avulsed off the chest wall, in most cases, the remnant cuff of diaphragm can be used as a guide to reattachment, as well as an anchor for the sutures. There is a natural redundancy in the diaphragm that will compensate for any tissue loss and allow reconstruction. If, however, the defect is large and it is not possible to reattach the diaphragm to its original location, the natural curvature of the diaphragm facilitates repositioning of the attachment point higher up on the chest wall. By moving the attachment point several rib spaces up, a tension-free repair can usually be achieved. Failing this, prosthetic material can be used to bridge the gap.

For chronic TDH, surgical intervention is usually indicated. For patients in the latent phase, preoperative workup including cardiopulmonary function may be followed by semi-elective repair. In contrast, patients who present with evidence of obstruction or strangulation should be taken for emergent repair, as high morbidity and mortality rates have been documented with any delay. There are two operative approaches for chronic TDH repair, transthoracic and transabdominal. Furthermore, minimally invasive techniques can be considered if tolerated by the patient. There should not be any hesitation converting to an open procedure or opening the cavity on the other side of the diaphragm to facilitate access, content



FIG. 8 A small diaphragmatic defect seen during diagnostic laparoscopy following left-sided thoracoabdominal gunshot wound *(arrow)*.

reduction, and reconstruction in cases with severe adhesions or unclear anatomy.

PROGNOSIS

Patient outcomes following TDI are dependent primarily on the burden of associated injuries and physiologic status of the patient. Specific known clinical predictors for mortality following TDI include advanced age, higher injury severity score (ISS), and associated cardiac injury. The mortality rate documented in previous case series ranges from 0% to 35%. Among patients with TDI submitted to the National Trauma Data Bank in 2012, in-hospital mortality was significantly higher in patients who sustained blunt TDI (19.8% vs. 8.8%) with a higher mean ISS (33 vs. 24) compared with penetrating TDI. In addition, the length of hospital and intensive care unit (ICU) stay and ventilator days were longer in the blunt TDI group.

The complications reported in patients with TDI are most often related to their associated injuries. Postoperative complications following diaphragm repair can include a disruption of the repair site, phrenic nerve injury, and surgical site infections. Failure of the diaphragm repair is more commonly seen with large defect size or avulsion injuries following blunt trauma. Paralysis of the hemidiaphragm

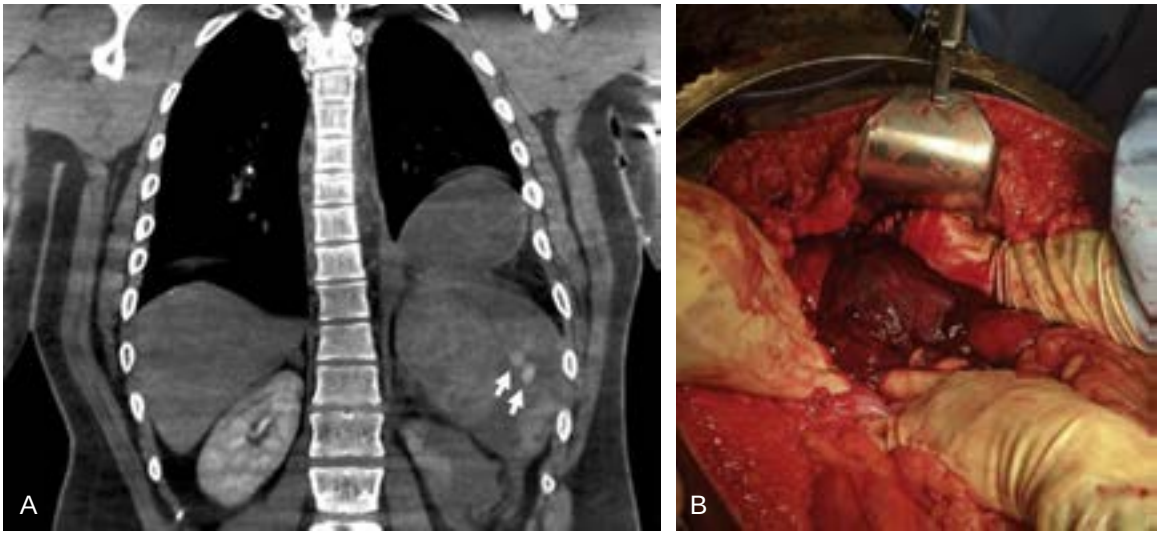


FIG. 9 **(A)** CT scan shows left-sided diaphragm injury associated with high-grade splenic injury with active contrast extravasation *(arrows)*. **(B)** Intraoperative view of the herniated spleen after reduction. Splenectomy was required for active hemorrhage.

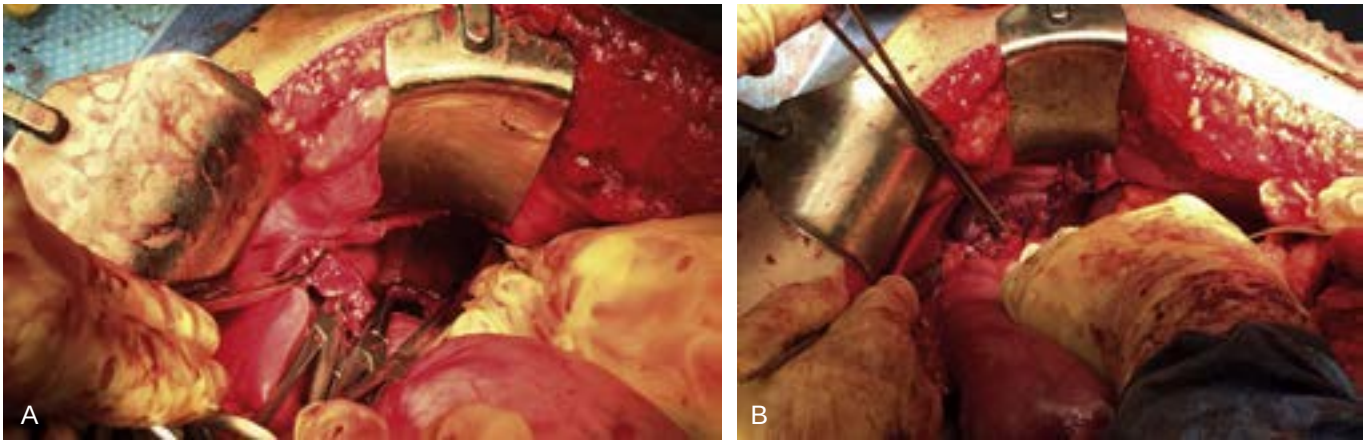


FIG. 10 **(A)** Exposure of the entire diaphragm defect and assessment of associated intrathoracic injuries through the defect should be performed before surgical repair. **(B)** Primary repair of the large diaphragm defect was performed with interrupted sutures.

secondary to phrenic nerve injury may be caused by the traumatic injury itself or can occur during the repair. For diaphragm injuries just lateral to the esophageal or caval hiatus, care must be taken to look for the phrenic nerves to prevent iatrogenic injury. Postoperative infectious complications following the diaphragm repair include subdiaphragmatic abscess and empyema. Although the incidence of empyema is very rare, in patients with TDI who survived more than 48 hours after admission, postoperative empyema was associated with prolonged hospital and ICU stay.

SUMMARY

Diaphragmatic injuries are often diagnosed and repaired at the time of laparotomy performed for other associated injuries. For isolated blunt TDI, as the sensitivity of CT is not perfect, a high index of suspicion is required. Acute injuries should be repaired through an abdominal approach. For penetrating left thoracoabdominal injuries in patients undergoing nonoperative management, diagnostic laparoscopy is the mainstay of diagnosis and, if required, treatment. The majority of diaphragmatic injuries can be repaired primarily. For large defects that cannot, a prosthetic bridge can be utilized.

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Management of Traumatic Liver Injury

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INTRODUCTION

Given its large size and location, the liver is a commonly injured organ in both blunt and penetrating trauma. Although mortality rates from high-grade liver trauma remain significant, evolving management of these injuries has led to improved outcomes. Traditionally, operative intervention alone was considered the standard of care. However, with the introduction of damage-control laparotomy, selective nonoperative management (SNOM), and endovascular intervention, a multi-pronged approach is now crucial in decreasing mortality in these potentially fatal injuries. Although an understanding of liver anatomy is important, liver trauma and the operations to address traumatic injury rarely follow the rules of elective surgery. Operative liver trauma is governed by the principles of rapid hemorrhage control and preservation of maximal parenchymal tissue, particularly at the index operation. Because these patients often present in extremis, the surgeon must have an algorithm and a mental tool kit readily available to act expeditiously in these high-acuity situations.

INITIAL EVALUATION

The initial evaluation of all trauma patients should follow standard Advanced Trauma Life Support (ATLS) principles. The initial hemodynamic status and stability of the patient must be assessed immediately as it will dictate further management. Intravenous access should be obtained on the patient's arrival. A rapid but comprehensive primary and secondary survey should be done to assess for other injuries along with appropriate x-rays and focused assessment with sonography in trauma (FAST). The FAST examination, although useful in detecting hemoperitoneum, is not specific in identifying the source of intraabdominal bleeding. A positive FAST in the setting of hypotension is typically an indication for operative intervention; however, a positive FAST in and of itself does not require operative intervention.

Once the initial evaluation is complete and appropriate resuscitation initiated, the next phase of management in patients with suspected abdominal trauma is guided by the hemodynamic status and the physical examination. Early blood product resuscitation should be considered in patients with suspected ongoing hemorrhage or hemodynamic instability. Patients with peritonitis belong in the operating room. Patients with ongoing hypotension with a suspected abdominal hemorrhagic source also belong in the operating room, irrespective of peritonitis.

For the hemodynamically unstable patient with suspected ongoing abdominal hemorrhage, a resuscitative endovascular balloon occlusion of the aorta (REBOA) may be considered as a bridge to definitive hemorrhage control. If the source of bleeding is below the level of the diaphragm, a REBOA may be inflated in zone I (between the left subclavian artery and celiac trunk). A chest x-ray is performed to evaluate for thoracic hemorrhagic source or aortic injury. If neither is suspected, a sheath may be placed in the common femoral artery and a REBOA inserted to support hemodynamics en route to the operating room or hybrid suite. The REBOA should be deflated and removed expeditiously along with the sheath to avoid distal ischemia. Placement of a REBOA or other endovascular balloon should not delay transport to definitive hemorrhage control.

If the patient responds to resuscitation or is hemodynamically normal, a CT scan with intravenous contrast may provide additional key clinical information. Cross-sectional imaging allows for further evaluation, not only of hepatic injury but also of the associated injuries that are common in the setting of high-grade liver injury (Fig. 1). The American Association for the Surgery of Trauma (AAST) liver injury grading scale is a standardized way to categorize severity of liver injuries based on imaging (Table 1). Based on the overall clinical picture and the imaging findings, the decision for operative or angiographic intervention can be determined.

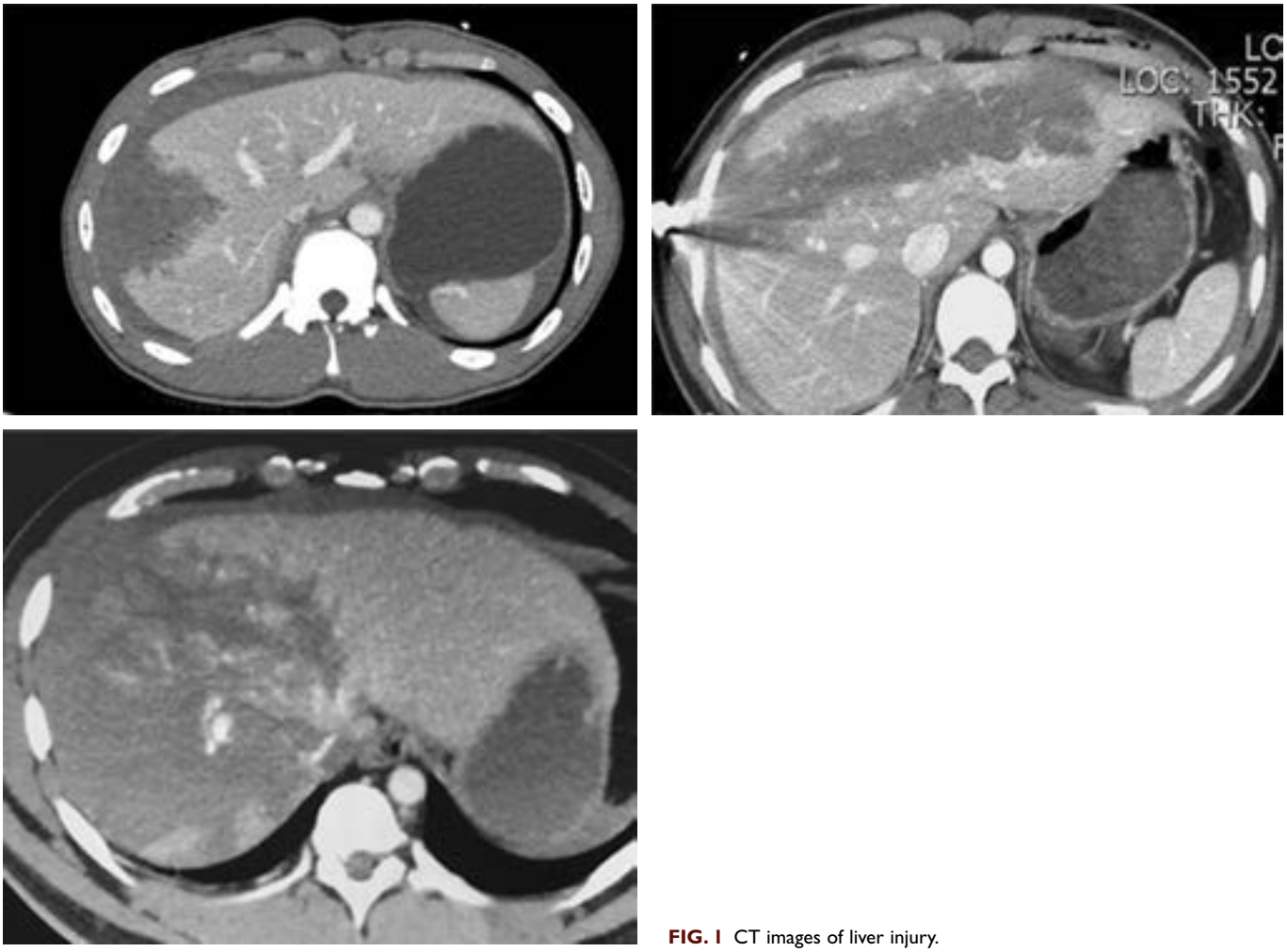


FIG. 1 CT images of liver injury.

TABLE 1 American Association for the Surgery of Trauma Liver Injury Scale

Grade	Injury	Description
I	Hematoma Laceration	Subcapsular, 10% surface area Capsular tear, <1 cm parenchymal depth
II	Hematoma Laceration	Subcapsular, 10%–50% surface area Intraparenchymal, <10 cm diameter 1–3 cm parenchymal depth, <10 cm length
III	Hematoma Laceration	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma >3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25%–75% of hepatic lobe or 1–3 Couinaud segments in a single lobe
V	Laceration Vascular	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud segments within a single lobe Juxtahepatic venous injuries (i.e., retrohepatic vena cava/central major hepatic veins)
VI	Vascular	Hepatic avulsion

From Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling: spleen and liver (1994 revision). *J Trauma*. 1995;38:323–324.

NONOPERATIVE MANAGEMENT

For trauma patients who remain hemodynamically normal and do not have peritonitis, SNOM for both blunt and penetrating hepatic injuries has become the standard of care. Fundamental to this concept is the use of cross-sectional imaging and reliable serial abdominal examinations to thoroughly evaluate for associated intraabdominal injuries, which can be common in the setting of high-grade liver injury. Although SNOM has long been the standard for blunt abdominal injury, this algorithm in the setting of penetrating trauma

has gained recent support. Contemporary studies have shown that isolated penetrating liver injuries managed nonoperatively result in shorter hospital length of stay and fewer complications.

Whether the liver injury is caused by blunt trauma or penetrating trauma, the principles of SNOM are similar and consist of close monitoring to rule out ongoing hemorrhage as well as associated hollow viscus injury. Patients are admitted to a monitored setting with serial laboratory tests and abdominal examinations, ideally by the same provider team. The provider team should consider that an increasing grade of hepatic injury is associated with an increased risk of failing SNOM. Hemodynamic instability or worsening abdominal examination are indicators that the patient is failing SNOM and requires operative intervention. If the patient fails SNOM, expeditious exploration is imperative. Therefore, SNOM might not be possible in rural or austere environments or in the setting of minimal providers, and a lower threshold for operative exploration after initial assessment is prudent.

Endovascular techniques have become a critical component in the management of liver trauma. Patients who are hemodynamically stable or transient responders may be candidates for angioembolization. Typically, a CT scan with intravenous contrast will identify embolization targets based on contrast extravasation or the presence of a pseudoaneurysm or arteriovenous fistula (Fig. 2). Although angioembolization may also be used as an adjunct to operative intervention, many injuries are managed with endovascular techniques alone with high success rates and improvement in overall outcome. Despite the success of endovascular techniques, it is important to remember that some patients will require operative intervention despite successful angioembolization, either for ongoing hemorrhage or for associated hollow viscus injury. In addition, patients who undergo angioembolization must be carefully selected, as liver necrosis is a common complication following embolization.

OPERATIVE MANAGEMENT

Although SNOM has transformed the algorithms used to manage both blunt and penetrating hepatic injury, a solid understanding of operative technique in tackling these difficult cases is paramount. In patients who require operative intervention for their liver injury, hemorrhage can be brisk, and the operative strategies can be challenging for even the experienced trauma surgeon. For these reasons, massive transfusion protocols should be considered early, and balanced resuscitation with adjuncts such as thromboelastography (TEG) are considered critical. In addition, clear and ongoing communication with the anesthesia team is crucial.

The patient should be prepped from the neck to the knees to obtain adequate exposure and also to have access to vascular structures for hemorrhage control or venous conduit if needed. Adequate central access, preferably above the diaphragm, should be obtained immediately if not done before the patient is brought to the operating room. A midline laparotomy from the xiphoid process down to the pubis symphysis is the initial incision of choice. If additional exposure is needed, particularly for access to the retrohepatic vena cava, a right subcostal extension may be included. Additional access to the dome of the liver and the suprahepatic vena cava can be obtained via a right thoracotomy or a median sternotomy.

Upon entry into the abdomen, a rapid evaluation for hemorrhagic source should be conducted in the standard fashion and sources of gross enteric spillage controlled using temporary techniques. In the setting of liver trauma, the first step is to divide the falciform ligament along the anterior surface of the liver, taking care not to disturb the hepatic veins at the level of the diaphragm. This allows for more effective packing and minimizes traction injury to the liver. The liver is then packed with laparotomy pads, medializing the parenchyma starting from the dome of the liver and placing pads between the diaphragm and the liver posteriorly (Fig. 3). To be successful, the liver

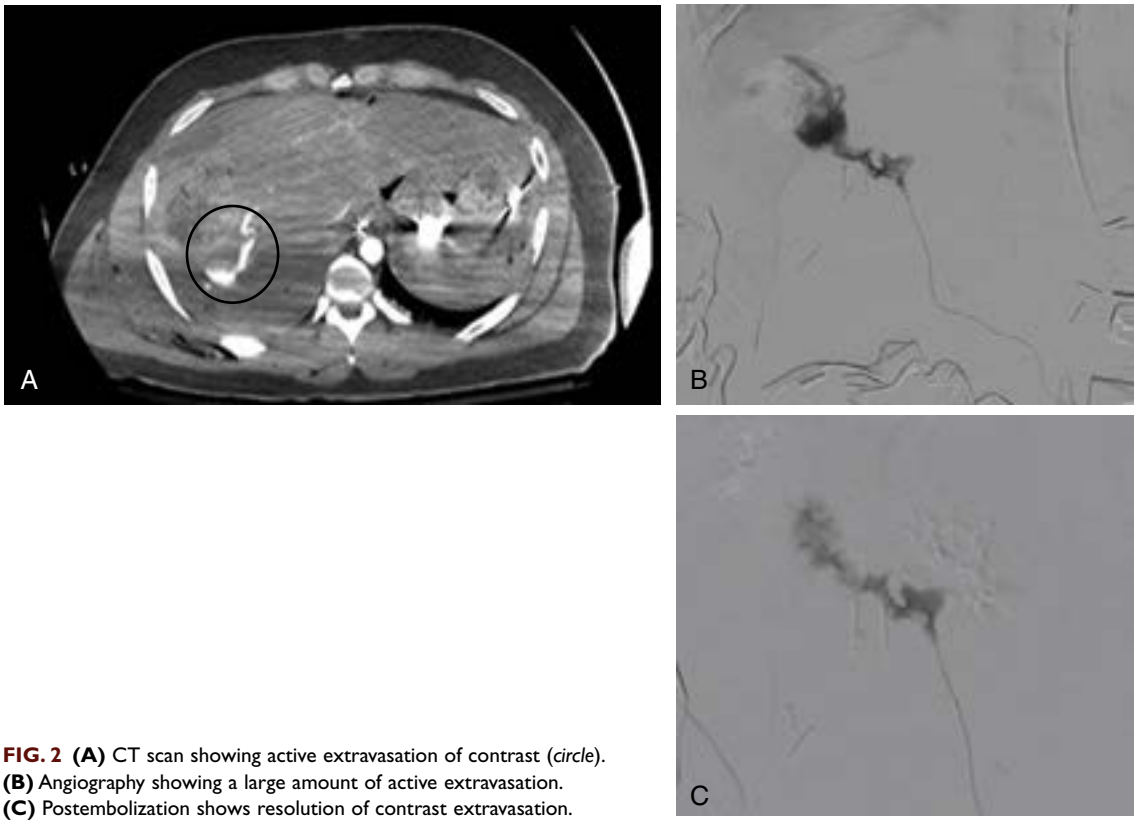


FIG. 2 **(A)** CT scan showing active extravasation of contrast (*circle*). **(B)** Angiography showing a large amount of active extravasation. **(C)** Postembolization shows resolution of contrast extravasation.

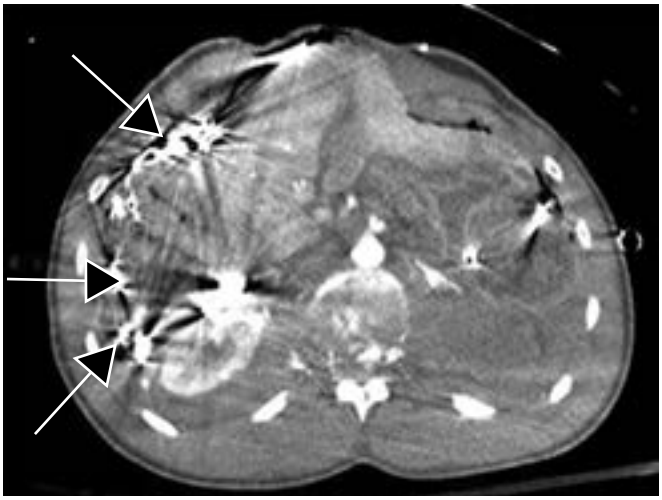


FIG. 3 CT scan of anterior and posterior hepatic packing *(arrows)* in grade V liver injury.

should effectively be sandwiched between anterior and posterior laparotomy pads that are tightly packed, taking care not to occlude flow through the inferior vena cava (IVC). This allows for time to inspect the remainder of the abdomen and for anesthesia to progress with their resuscitation. If packing provides hemorrhage control, do not continue with dissection of the liver attachments as doing so can often release the natural tamponade that the attachments provide. Instead, consider the option of damage-control laparotomy with delayed reoperation after taking the patient to the intensive care unit (ICU) for further resuscitation or for angioembolization. If packing is ineffective or if there is increased hemorrhage with anterior displacement of the liver, strongly suspect a retrohepatic vena cava or hepatic vein injury, and begin early preparations for repair.

A combination of techniques may be required in the severely damaged liver with the primary goal of rapid hemorrhage control to prevent coagulopathy and further physiologic derangements. For minor lacerations, hemostasis can often be achieved with electrocautery or argon beam coagulation. Topical hemostatics are a useful adjunct, and hemostasis is often achieved with patience, tactical placement, and pressure. Several topical hemostatics are effective, and availability is based on each institution. In addition to topical hemostatics, a tongue of omentum can be used to provide hemostasis in a liver laceration.

Simple sutures with a large, blunt-tipped absorbable suture such as 0 chromic or 0 PDS can be used to reapproximate parenchyma. The liver parenchyma is very fragile, so great care must be taken to incorporate intact liver capsule in the repair to avoid further damaging the parenchyma. Simple interrupted sutures or horizontal mattress sutures allow for adequate approximation of the parenchyma. The sutures must be secured gently to avoid further fracturing of the liver parenchyma.

In the setting of penetrating trauma, placement of a balloon catheter through the tract with gentle inflation of the balloon can aid in immediate hemorrhage control. A Foley catheter, Blakemore tube, or Penrose drain on a red rubber catheter can be used for this purpose. The catheter is inserted and the balloon or lumen inflated until resistance is felt. An occluding clamp is placed on gentle traction at the capsule surface or at the skin to affix the catheter in place. This catheter can be left in place during a damage-control operation and removed at the return operation 24 to 48 hours later.

If local techniques and attempts at topical hemostasis are not successful, this may be indicative of a more severe injury (Fig. 4). Several techniques can help identify and address these injuries. In a complex laceration with devitalized hepatic tissue, finger fracture techniques can delineate the remaining viable tissue. Hemostasis on the exposed edge can be obtained with a combination of the above techniques and direct ligation with suture or surgical clips of bleeding vessels and transected or damaged biliary ducts. For more peripheral injuries, a vessel-sealing device or GIA stapler can be used to perform a tractotomy or to remove nonviable tissue.

Formal hepatectomies can be considered if there is significant bleeding refractory to all other maneuvers but is avoided if possible. In the setting of trauma, with hemorrhage control as the primary goal, the liver parenchyma is highly forgiving to non-anatomic resection (Fig. 5). Intraoperative consultation for angiography and possible embolization is a valuable adjunct to control intraparenchymal bleeding that is difficult to access surgically and should be considered early based on the injury complex and surgeon's discretion.

In uncontrolled hemorrhage, another useful adjunct is the Pringle maneuver, or compression of the portal triad, which includes the hepatic artery and portal vein (Fig. 6). The portal triad can be

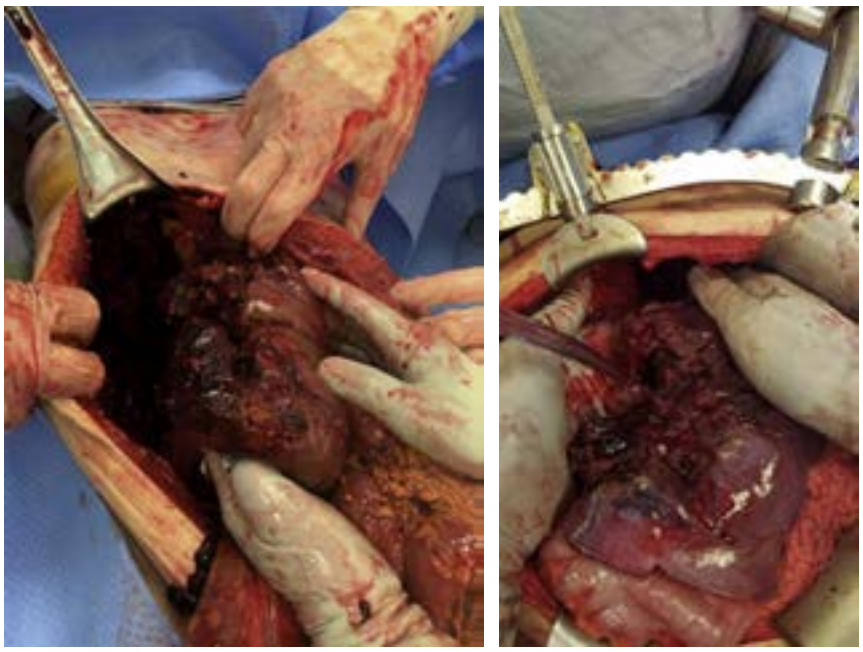


FIG. 4 Intraoperative images showing significant parenchymal destruction.



FIG. 5 Intraoperative image of nonanatomic hepatic resection.

encircled by entering the pars flaccida, or avascular caudal portion of the gastrohepatic ligament, followed by placement of a Rummel tourniquet or vascular clamp around the porta. The Pringle maneuver interrupts hepatic artery and portal vein flow to the liver. Cessation or slowing of ongoing hemorrhage using this maneuver can help identify the specific source of hemorrhage to allow a more controlled repair. The Pringle maneuver can result in significant ischemia to the liver, however, and interruption of flow should be minimized with a maximum occlusion time of 30 minutes.

If the patient continues to bleed despite packing and a Pringle maneuver and significantly worsens with anterior mobilization of the liver, a retrohepatic vena cava injury is likely. These injuries are hard to identify and rapidly lethal so the surgeon's index of suspicion must be high. To access these injuries, the liver must be freely mobilized, a dissection that will release any natural tamponade that existed with the liver attachments. After the falciform is divided, the left triangular ligament is divided to the anterior and posterior coronary ligaments with care to avoid the left hepatic vein. This mobilizes the left lobe of the liver and provides access to the supraceliac aorta. The right triangular ligament is then divided with the goal to medialize the whole right lobe of the liver. Freeing of these attachments should allow for significantly increased exposure and mobility of the liver. Care should be taken when mobilizing the liver as the accessory veins on the posterior surface of the liver are easily avulsed from the retrohepatic vena cava, resulting in prodigious bleeding.

To repair injuries to the retrohepatic IVC or the hepatic veins, additional interruption of blood flow is often required. Consideration of these approaches should occur before mobilization of the ligamentous attachments of the liver. Two options exist for this injury: total hepatic isolation or an atriocaval shunt. Although total hepatic vascular isolation is typically performed using traditional open techniques, endovascular approaches for several of the steps have been well described and should be considered if within the surgeon's skillset. Total hepatic vascular isolation requires four sites of occlusion. First, the supraceliac aorta is occluded by mobilizing the left lobe of the liver and entering the retroperitoneum at the diaphragmatic hiatus. The esophagus is retracted to the patient's left, and the aorta is identified on top of the vertebral body between the diaphragmatic crux. A vascular clamp can be used for interruption of the aorta. The second step is occlusion of the porta hepatis, described earlier as the Pringle maneuver. Finally, control of the infrahepatic and suprahepatic IVC is required. The suprarenal infrahepatic IVC is accessed via the Kocher maneuver. The suprahepatic IVC can be accessed by inferior retraction of the dome of the liver above the hepatic veins. In most patients, there is a 1- to 2-cm length of suprahepatic IVC that can be accessed from the intraabdominal approach. However, if the anatomy is not amenable or if there is significant ongoing bleeding obscuring visualization, the suprahepatic vena cava can be accessed via a right thoracotomy or a median sternotomy. If there is consideration for progressing to an atriocaval shunt, a median sternotomy should be considered early in the approach. Early and frequent communication with the anesthesiologist is imperative. Occluding blood flow return to the right atrium typically results in hemodynamic collapse, and ongoing aggressive resuscitation is needed.

To perform an atriocaval shunt, a 28Fr chest tube is prepared by cutting a side hole in the body of the tube at the level of the atrium (Fig. 7). A clamp is placed above and below the newly placed hole. A purse-string suture is placed in the right atrial appendage, an incision is made, and the tube is passed through the atrium and fed down into the IVC. The first clamp is removed, and once the hole is at the level of the atrium and positioned for blood return, the purse-string suture is tightened. A Rummel tourniquet or vessel loop is used to secure the tube at the level of the supra and infrahepatic IVC, creating a shunt across the retrohepatic IVC and an opportunity for injury repair. The shunt should be removed as expeditiously as possible and blood flow restored.

A final option in uncontrollable hemorrhage with complete destruction of the liver parenchyma is to perform a total hepatectomy with portocaval shunt and consider liver transplantation. This

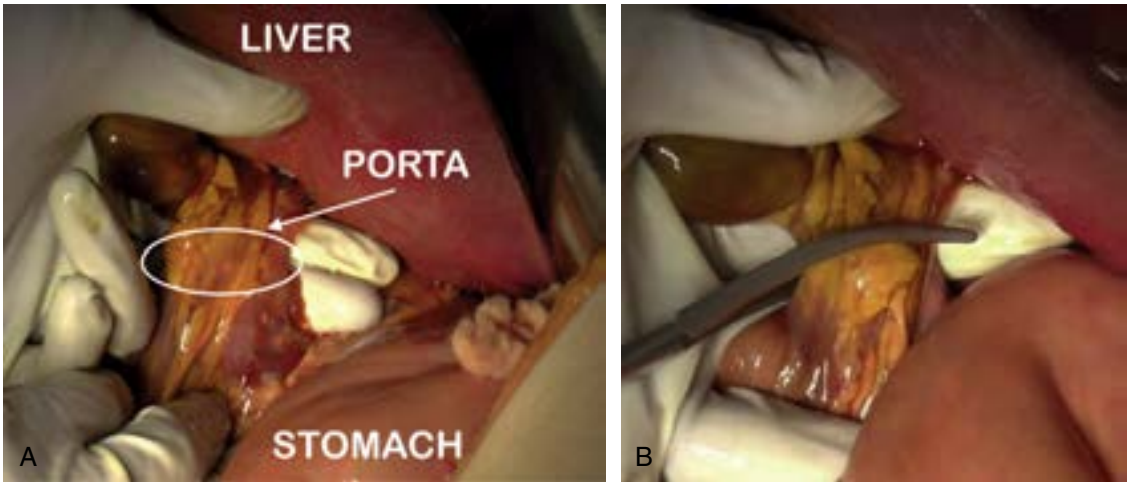


FIG. 6 Intraoperative images showing Pringle maneuver with a vascular clamp.

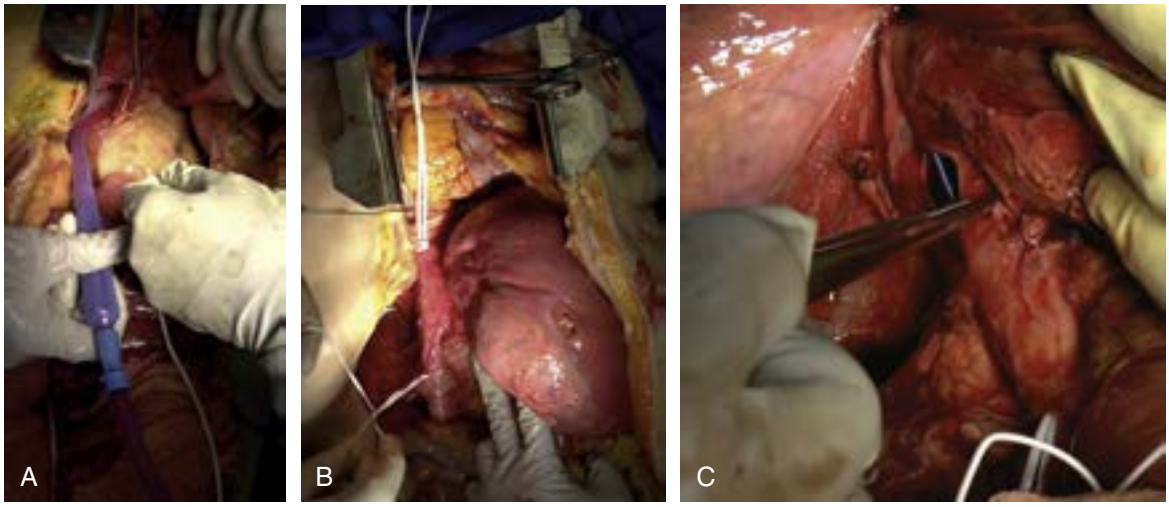


FIG. 7 Atriocaval shunt. **(A)** A chest tube is placed in right atrial appendage and secured with a purse-string suture. **(B)** The chest tube is secured at the suprahepatic and infrahepatic inferior vena cava. **(C)** Isolation of the retrohepatic injury.

is rarely indicated and should only be considered at select centers with the expertise and immediate availability of transplant services.

In the setting of massive hemorrhage and severe liver trauma, damage-control techniques should be prioritized followed by continued resuscitation and warming in the ICU. Prolonged operative time is associated with poor outcomes as a result of irreversible coagulopathy and physiologic derangements.

Postoperatively, patients with significant liver injury should be taken to the ICU for further resuscitation. Monitoring of coagulopathy is crucial, and serial TEG is recommended for guidance of resuscitation. Patients who underwent damage-control laparotomy with temporary abdominal closure should plan to return to the operating room for reexploration in 24 to 48 hours. Any signs of ongoing hemorrhage in the ICU should prompt an earlier return to the operating room.

MANAGEMENT AND COMPLICATIONS

Severe liver injuries are associated with a high level of postinjury and postoperative complications. In the acute setting, profound coagulopathy from massive blood loss, resuscitation, as well as acute liver damage including ischemia reperfusion injury can occur. Patients require close monitoring with care placed on balanced resuscitation, attention to volume overload and underresuscitation, and appropriate hemodynamic control to maintain perfusion while avoiding vast swings in hemodynamics that might disturb the tenuous balance of hemostasis. Given the high incidence of biliary leaks, wide drainage is recommended after operative exploration before abdominal closure. In the setting of high-volume biliary leaks, early endoscopic retrograde cholangiopancreatography (ERCP) with possible stent placement should be considered. Other potential complications, particularly after high-grade injury, include pseudoaneurysm or hepatic arteriovenous fistulae formation. A CT angiogram is routinely performed 72 hours to 1 week after high-grade injuries to screen for this class of complications. Hepatic necrosis also occurs with high rates after angioembolization or surgical repair of high-grade liver injuries (Fig. 8). Necrosis may manifest as high fevers, tachycardia, and/or leukocytosis and should be evaluated with cross-sectional imaging. Even severe necrosis can often be managed with percutaneous drainage; however, remnant necrotic tissue can lead to abdominal sepsis, and operative intervention may be required.

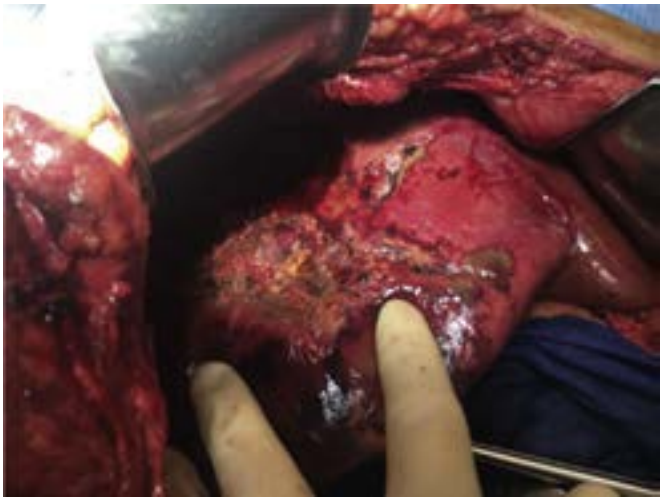


FIG. 8 Hepatic necrosis seen after angioembolization.

CONCLUSION

Management of traumatic liver injury encompasses a wide breadth of treatment modalities. The algorithm continues to evolve, with decision making based on the patient's clinical status. In hemodynamically normal patients or transient responders with no other injuries requiring exploration, SNOM including evaluation with CT and possible angioembolization is now the standard of care. For hemodynamically unstable patients, surgery remains the gold standard. It is imperative that the surgeon has a depth of knowledge regarding hemostatic maneuvers and potential interventions as hepatic injuries can be rapidly lethal.

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Pancreatic and Duodenal Injuries

Madhu Subramanian, MD, and Elliott R. Haut, MD, PhD

Trauma to the pancreas and duodenum remain some of the most challenging injuries to diagnose and manage in trauma. The advent of new imaging technologies such as magnetic resonance cholangiopancreatography (MRCP) and therapeutic options including endoscopic retrograde cholangiopancreatography (ERCP) have improved diagnosis and created minimally invasive techniques for management. Still, without a high index of suspicion for injury, delays occur and are common, which result in significant morbidity and mortality within this trauma population.

DUODENAL INJURIES

Outcomes related to duodenal injuries are largely influenced by timing of identification. Delays in diagnosis can have catastrophic effects. Because the duodenum is "protected" by its largely retroperitoneal position, injuries are relatively rare and encompass less than 2% of abdominal injuries. As such, delays in diagnosis remain high, with up to 28% of diagnoses occurring after 24 hours. The effects of delays are real; operative mortality nearly quadruples from 11% to 40% after 24 hours. Injuries to the duodenum are further complicated by their proximity to major vascular structures and their intimate relationship with the pancreas, which often leads to complex combined injuries.

A high index of suspicion should exist based on the mechanism of injury. Classic blunt trauma mechanisms associated with duodenal injury include any significant direct force to the epigastrium, such as bicycle handlebars in children, steering wheel impacts, and seatbelt injuries. Diagnosis remains most challenging in blunt injury in which the duodenum's retroperitoneal position can make classic findings of bowel perforation, such as peritonitis, absent. X-ray imaging may initially look "normal" as duodenal perforation may not have evidence of free air. The most expeditious manner of diagnosis is via CT scan, although the missed injury rate remains high at 27%. This is because early evidence of injury such as inflammation and perforation may not be present at the time of imaging. If stable with evidence or concern for duodenal injury, repeat imaging either as CT with enteral contrast or fluoroscopic evaluation (with contrast) should be performed to evaluate for extravasation or obstruction, which may assist in operative planning.

Duodenal repairs are associated with high rates of failure. As such, surgical management has evolved over the past several decades from complex repairs to more simple repairs because no single technique provides consistent results, and complex repairs may cause more problems than create solutions. The type of repair is largely based on the patient's hemodynamic status, associated injuries, and the timing of diagnosis. If the patient has evidence of peritonitis, hemodynamic compromise with concern for hemorrhage, or CT evidence of free air, surgery is indicated. If the patient is stable with evidence of periduodenal air with inflammatory changes, surgical exploration with either laparoscopy or laparotomy is indicated as delays can be catastrophic. In all other scenarios, attempts at nonoperative management can be attempted with close monitoring.

Management of Duodenal Injury

Initial surgical versus selective nonoperative management is dependent on the patient's hemodynamic status at presentation. If the patient is hemodynamically unstable, immediate laparotomy is recommended, and management should be based on intraoperative findings. If duodenal injury is identified based on imaging (i.e., CT), some cases of injury can be managed nonoperatively. If the patient has evidence of periduodenal air with inflammatory changes, surgical exploration with either laparoscopy or laparotomy is indicated, as delays can be catastrophic. Most management plans are based on the grade of duodenal injury as assessed by the American Association for the Surgery of Trauma (AAST) grading system (Table 1).

Grade I

In a grade I injury, a hematoma involves one portion of the duodenum or laceration (partial thickness) with no transmural perforation. If a grade I injury is identified on CT imaging without indications for operation, an attempt at nonoperative management with nasogastric decompression is recommended for up to 2 weeks as progressive obstruction may occur. Lack of resolution warrants operative intervention with drainage of the hematoma and simple repair (ideally transversely). If identified in the operating room, lacerations should be closed transversely. Hematomas <50% warrant no further intervention, although nasogastric decompression and distal feeding tube placement should be considered. Injuries with >50% circumferential involvement warrant hematoma evacuation, taking care to avoid mucosal disruption, and simple closure; if larger (e.g., 75%), reconstruction with gastrojejunostomy should be considered.

Grade II

In a grade II injury, a hematoma involves more than one portion of the duodenum or full-thickness laceration <50% circumference without evidence of duct disruption or ampulla involvement. Management is similar to grade I injuries. The majority can be managed by simple, tension-free repair if identified early (Fig. 1). If unable to sufficiently mobilize for simple transverse repair or if there is concern for significant contamination/delayed identification, there are several options. For mobilization/narrowing issues, debridement

TABLE 1 American Association for the Surgery of Trauma (AAST) Grading System for Duodenal and Pancreatic Injury

Grade	Duodenum	Pancreas
I	Hematoma: involving single portion of duodenum Laceration: partial thickness, no perforation	Hematoma: minor contusion without duct injury Laceration: superficial laceration without duct injury
II	Hematoma: involving more than one portion Laceration: disruption <50% of circumference	Hematoma: major contusion without duct injury or tissue loss Laceration: major laceration without duct injury or tissue loss
III	Laceration: disruption 50%–75% of circumference of D2 Laceration: disruption 50%–100% of circumference of D1, D3, D4	Laceration: distal transection or parenchymal injury with duct injury
IV	Laceration: disruption >75% of circumference of D2 Laceration: involving ampulla or distal common bile duct	Laceration: proximal transection or parenchymal injury involving ampulla
V	Laceration: massive disruption of duodenopancreatic complex Vascular: devascularization of duodenum	Laceration: massive disruption of the pancreatic head

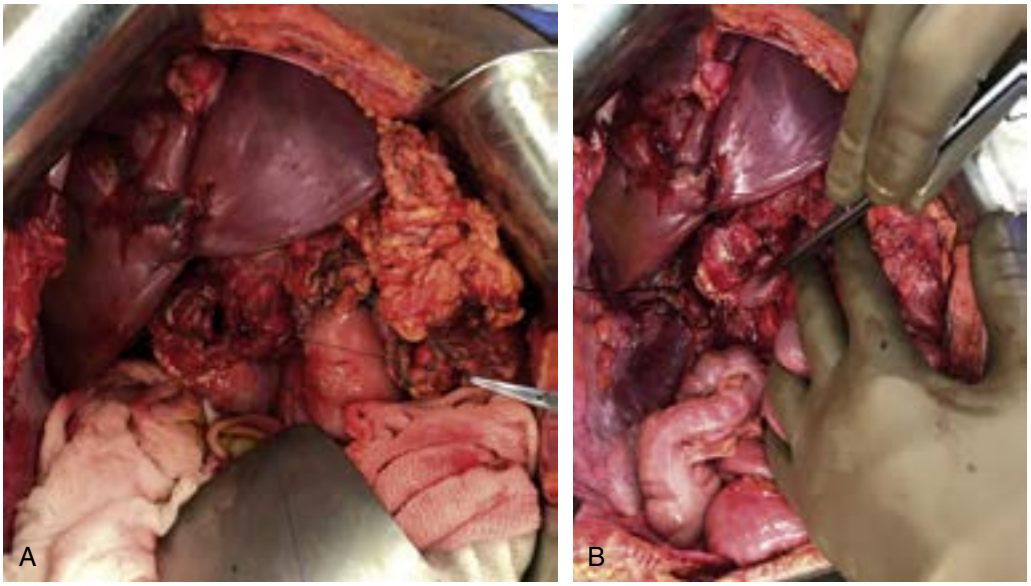


FIG. 1 Simple, tension-free primary repair of duodenal trauma. **(A)** Injury before repair. **(B)** Injury after repair. *(Courtesy Stefan W. Leichtle, MD)*

with duodenoduodenostomy or laceration repair with gastrojejunostomy are viable options. In the setting of delayed repair or significant contamination, the safest option is often debridement to healthy edges with a Roux-en-Y duodenojejunostomy sewn to the duodenal defect.

Grade III

In grade III injuries, a laceration involves 50% to 75% the circumference of D2 (without duct or ampulla involvement) or 50% to 100% circumference of D1, D3, or D4. In patients with grade III injuries, attempt at simple closure can be performed. Other options include duodenoduodenostomy or Roux-en-Y duodenojejunostomy to the defect, after debridement to healthy tissue. If the injury is proximal to the ampulla with a D1 injury, an antrectomy with gastrojejunostomy (Billroth II) may be a viable option.

Grade IV

Grade IV injuries involve 75% to 100% circumference of D2 with intact ampulla/bile duct or 75% to 100% circumference of D2. Grade IV injuries are distinguished from higher-grade injuries by whether there is involvement of the ampulla and/or common bile duct (CBD). If neither the ampulla or CBD are involved, management may be similar to other lower-grade injuries. However, most grade IV and grade V injuries are managed similarly.

Grade V

Grade V injuries involve complete destruction of the duodenum and pancreatic head complex. Management of grade IV and grade V injuries usually require complex reconstruction with either a Roux-en-Y duodenojejunostomy or pancreatoduodectomy (Whipple procedure). The timing of reconstruction is dependent on clinical stability of the patient. In general, if the patient is clinically unstable, the focus should be on hemorrhage control followed by contamination control. Because of the proximity to major abdominal vessels (i.e., the portal vein, inferior vena cava [IVC], superior mesenteric artery [SMA], superior mesenteric vein [SMV]), all attempts should be made to ensure adequate vascular control first. Once vascular control is obtained, attempts at limiting enteric spillage can be addressed. This usually involves damage control surgery consisting of temporary control of holes in the gastrointestinal tract, wide drainage, temporary abdominal closure, and further resuscitation in the intensive care unit. In grade IV injuries in which duodenal reconstruction

is possible, the CBD can occasionally be reimplanted into the duodenum away from the injury or more often reconstructed with a Roux-en-Y loop that can also accommodate the duodenal repair. If irreparable or there is involvement of the pancreatic head, a Whipple procedure may be necessary. If considering a Whipple procedure while still unstable, resection should focus on removal of devitalized tissue and possible closure of the defect with definitive reconstruction at a later date. This may include resection and/or ligation of the CBD. If time permits, cannulation and externalization of the CBD and pancreatic duct can be performed to assist with reconstructive measures at the takeback operation when the patient is adequately resuscitated. This temporary drainage can minimize spillage and the associated early complications.

Operative Techniques for Repair of Duodenal Injury

Exposure begins with a standard midline trauma laparotomy. Due to the central location of the duodenum in the abdomen, duodenal injury is often associated with injuries to surrounding structures. Of greatest concern are injuries to the intraabdominal vascular structures. Before evaluating for duodenal injury, life-threatening sources of bleeding must be controlled. Hirschberg and Mattox divided the vascular structures into three layers: deep, middle, and superficial. The deep layer contains the IVC and right renal pedicle. These generally present as contained retroperitoneal hematomas (sometimes with active bleeding from the renal hilum). Initial management consists of direct compression with packing until other areas of concern have been addressed. The middle layer contains the SMA, SMV, and portal vein. Exposure is achieved using the Kocher maneuver (dissection of the lateral peritoneal attachments and achieving rotation of the duodenal C-loop and pancreatic head from right to left). Hemorrhage control is first achieved by manual compression, followed by proximal and distal vascular control, and then eventual ligation, repair, or more complex vascular reconstruction. The superficial layer consists of bleeding from the pancreaticoduodenal vessels, which is initially managed with Kocherization and manual compression. Once bleeding has been addressed and managed, evaluation of duodenal injury can progress. Concern for duodenal injury should be considered at exploratory laparotomy if any retroperitoneal bile staining, hematoma, or bubbles are encountered.

The Kocher maneuver (Fig. 2A) begins by identifying the C-loop of the duodenum and dissecting the lateral attachments of the duodenum from the retroperitoneum. The surgeon's hand can then be placed behind the duodenum and head of the pancreas and retracted superomedially to expose the retroperitoneum. The dissection margins are the CBD cranially and the SMV caudally. Because these injuries are often associated with injuries to nearby structures, the Kocher maneuver is often performed in conjunction with mobilization of the right colon including the hepatic flexure, which covers the lower part of the duodenum.

If exposure of the IVC and right renal hilum is necessary, the incision can be continued inferiorly toward the white line of Toldt. Once the right colon is fully mobilized, it can be reflected medially to expose the infrahepatic IVC, right renal hilar structures, and the right iliac vessels. Figure 3 provides an example of a repair of combined penetrating injury to the duodenum and IVC.

Description of Cattell-Braasch Maneuver

The final extension of the right medial visceral rotation is the Cattell-Braasch maneuver (Fig. 2B). This maneuver allows complete mobilization of the small bowel from its posterior attachments. By doing so, the third and fourth portions of the duodenum are exposed; the underside of the pancreas can be seen; and the entire infrarenal IVC and aorta, bilateral iliac vessels, and the bilateral renal vessels become accessible. To accomplish this, after the white line of Toldt is incised and the right colon is reflected medially, the cecum is elevated and the small bowel is retracted to the patient's left and cranially. This gives exposure to the attachment of the small

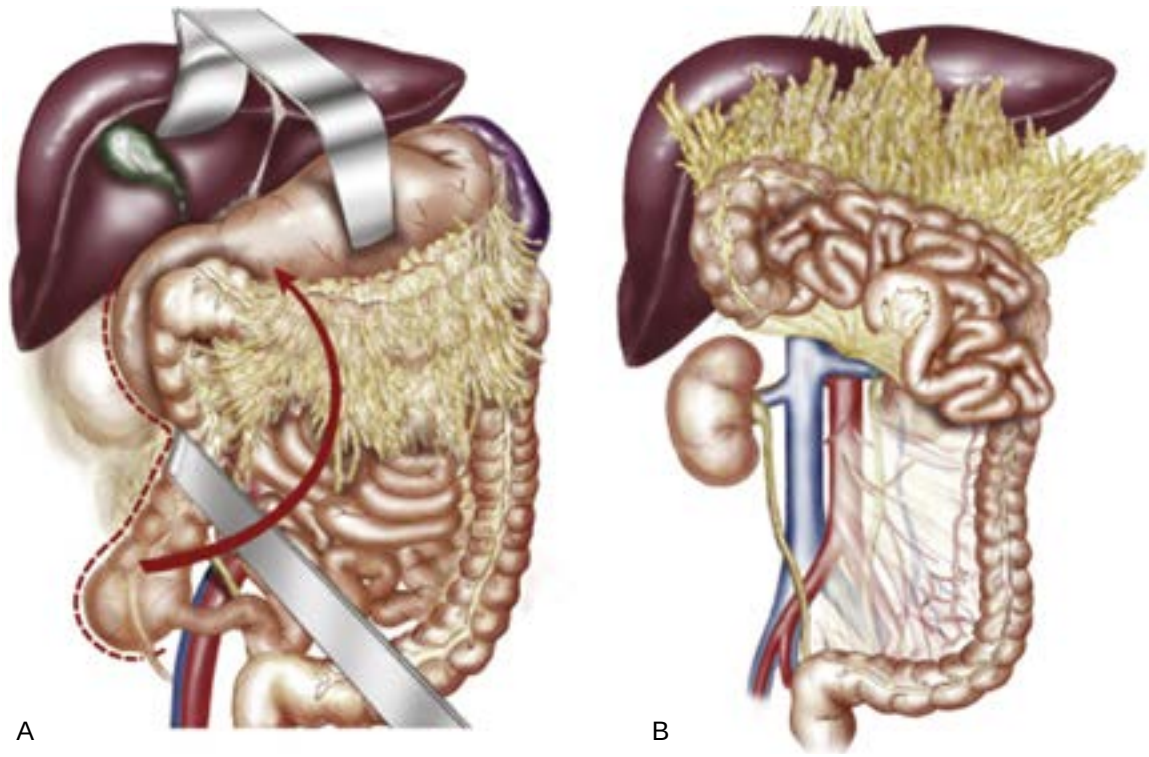


FIG. 2 **(A)** Cattell-Braasch maneuver for exposure of the entire right retroperitoneum starts with taking down the white line of Toldt and then mobilizing the C-loop of the duodenum (Kocher maneuver). **(B)** This uncovers the inferior vena cava, right kidney, right renal vessels, and the root of small bowel mesentery. *(From Voiglio EJ, Dubuisson V, Massalou D, et al. Abbreviated laparotomy or damage control laparotomy: why, when, and how to do it? J Vasc Surg. 2016;153:13–24.)*

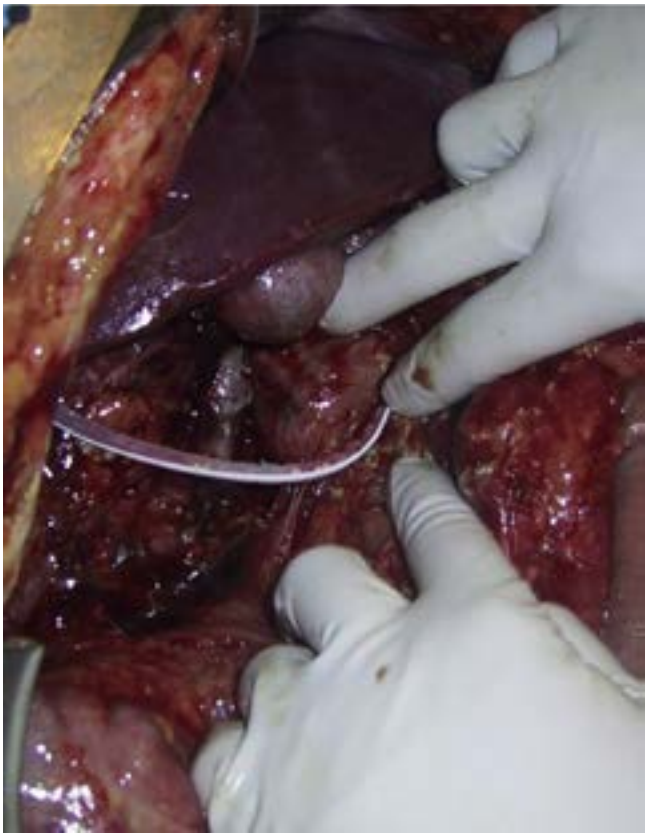


FIG. 3 Image of primary repair of the duodenum and inferior vena cava in a patient with combined penetrating duodenal and vascular penetrating injury. *(Courtesy Elliott R. Haut, MD, PhD)*

bowel mesentery to the posterior abdomen, which is incised from the cecum to the ligament of Treitz. It is important to take care while retracting because once these posterior attachments are incised, the right colon is affixed by its mesentery alone and can result in avulsion of the right colic vein of the SMV.

Surgical Techniques for Duodenal Repair

For historical perspective, the "classic" repair technique for complex duodenal injuries was the Berne duodenal diverticulization. The goal of this procedure was to turn a "lateral" fistula into a more manageable "end" fistula by primarily closing the duodenal defect, performing an antrectomy and vagotomy, and performing reconstruction with a gastrojejunostomy similar to a Billroth II procedure. To manage the biliary system, a silastic T-tube was inserted into the bile duct and externalized. To protect the duodenal stump, another tube was inserted at a separate incision and also externalized. This technique has largely been abandoned because of the difficulty in construction and lack of evidence for benefit.

In the majority of duodenal injuries that are identified early, attempt should be made to perform a primary repair (see Figs. 1 and 3). The goal should be to create a closure/anastomosis that is tension-free and widely patent, which is best accomplished by transverse closure. First, the duodenum should be mobilized (as noted earlier) to remove any undue tension. The edges of the defect then should be sharply debrided to healthy tissue, and then a primary repair can be performed. One option is a two-layer, full-thickness running absorbable suture (i.e., 3-0 PDS) followed by a second layer of permanent interrupted silk suture in a Lembert fashion; however, a single-layer closure is also reasonable.

If the injury is significant enough that transverse primary closure is not possible, the duodenum can be mobilized to allow full circumferential resection and primary duodenoduodenostomy. The duodenum should be sharply debrided back to healthy tissue, and then an end-to-end anastomosis is performed (as there should not be much of a size discrepancy). We prefer a two-layer closure with a posterior wall of permanent silk Lembert sutures, followed by a running absorbable (3-0 PDS) inner layer, followed by a row of Lembert sutures for the anterior wall. If mobilization is an issue and a two-layer approach is not possible, a single-layer full-thickness running closure can be performed, beginning on the inside along the pancreas side and working circumferentially.

Pyloric Exclusion or Antrectomy with Gastrojejunostomy

As discussed earlier, attempts should be made at primary repair of duodenal injuries as complex reconstructions have not produced more favorable outcomes. Pyloric exclusion was a technique developed to protect a duodenal repair by diverting gastric contents away from a fresh repair. This was accomplished by either using a purse-string closure (from inside the stomach) or a noncutting transverse stapler and creating a gastrojejunostomy. Most studies have not shown any benefit to this technique over simple repair. The pyloric closure is not permanent; it opens after several weeks. However, the creation of a gastrojejunostomy is not without long-term risk. There is debate over whether a gastrojejunostomy alone is ulcerogenic, and some surgeons place patients on lifelong acid suppression.

For injuries of D1 that are not amenable to primary repair or duodenoduodenostomy, an antrectomy or proximal duodenal resection may be necessary with creation of a gastrojejunostomy to return gastrointestinal continuity. Again, this should be reserved for patients in whom simple repair cannot be accomplished. This anastomosis can be performed via stapler or a two-layer, hand-sewn, side-to-side anastomosis. We prefer a retrocolic approach, bringing the small bowel through the colonic mesentery to the left of the middle colic artery.

Roux-en-Y Duodenojejunostomy

In the setting of severe duodenal injuries without evidence of ampulla or CBD involvement that are not amenable to primary repair, we believe the safest and simplest reconstructive technique is a Roux-en-Y duodenojejunostomy. If a destructive injury occurs near D2, the ampulla must be identified before reconstruction to ensure that obstruction does not occur, which could have devastating consequences. We recommend an end-to-side duodenojejunostomy in two layers with closure of the distal duodenum. If the injury is not complete, a side-to-side anastomosis can also be performed. It is worth mentioning that reconstruction such as this should only be attempted when the patient is hemodynamically stable as it is a time-consuming procedure. If available, calling for help from an experienced hepatobiliary surgeon is useful as these are uncommon injuries for trauma, but are more commonly done for other indications.

Abdominal Drains and Intraluminal Drain Placement

Duodenal leak after repair is the most feared complication because of the high morbidity and mortality associated with leakage. Patients at high risk for leak include those with high-grade injuries, shock on presentation, or associated vascular or pancreatic injuries. As such, many surgeons have advocated for intraluminal drainage. The classic intraluminal drainage technique is the *triple-tube technique.* This approach involved the placement of a gastric tube for proximal drainage and decompression of the duodenum. It also includes two jejunal tubes: a retrograde jejunostomy tube to evacuate biliary and pancreatic fluids (to decompress the bowel and lower pressure on the anastomosis) and a distal jejunostomy tube for feeding access. We no longer use the retrograde tube as it is prone to dislodgment because of its antiperistaltic placement and can be the nidus for obstruction or intussusception. An alternative, simplified drainage technique has been recommended and is derived from diverticulization techniques. This involves direct drainage of the duodenum via a lateral

duodenostomy tube either through the suture line or adjacent to it. We feel this should be avoided completely as these types of drainage are associated with high rates of fistula formation and associated morbidity. Other options for intraluminal drainage include using a gastrojejunostomy tube placed percutaneously through the stomach (see later) or simply advancing a nasogastric tube into the duodenum for temporary decompression.

Intraluminal drainage is unnecessary in the majority of scenarios and is associated with a risk for further complications; therefore, its use should be limited to selected cases. We do suggest that any repair should be followed by external drainage (i.e., Jackson-Pratt, Blake) as this is simple and usually sufficient to control leaks.

Jejunostomy Tube or Gastrojejunostomy Tube

Regardless of the type of repair, nutrition (ideally enteral nutrition) is of utmost importance for recovery. Even after simple repair, patients are at high risk for edema at the repair site (and associated partial obstruction) or ileus, which limits their ability to tolerate oral enteral nutrition. Most patients benefit from a temporary nasojejunal tube, but a distal jejunostomy tube may be considered.

In the case of patients who are at high risk for leak, the use of gastrojejunostomy (i.e., Moss) tubes may solve internal drainage as well as allow for enteral nutrition without the associated risks of multiple enterostomies (Fig. 4). This device also has the added benefit of being easily removed once oral intake is possible. The Moss gastrojejunostomy tube has multiple lumens to allow simultaneous gastric/duodenal decompression and distal feeding. When there is high concern for risk of leak from any duodenal repair, this is our recommendation for management.

Techniques for Identification of Ampulla

If possible, identification of the injury via imaging such as MRCP is a safe option but is rarely used in the acute trauma setting. If unable to obtain preoperative imaging before reconstruction, the safest method involves performing a cholecystectomy. We recommend cannulating the cystic duct and passing a Fogarty balloon through the cystic duct, which is manually guided down the CBD through the ampulla into the duodenum (Fig. 5). Another option is to perform intraoperative cholangiography via a similar method. After identification of the ampulla, a completion cholecystectomy can be performed.

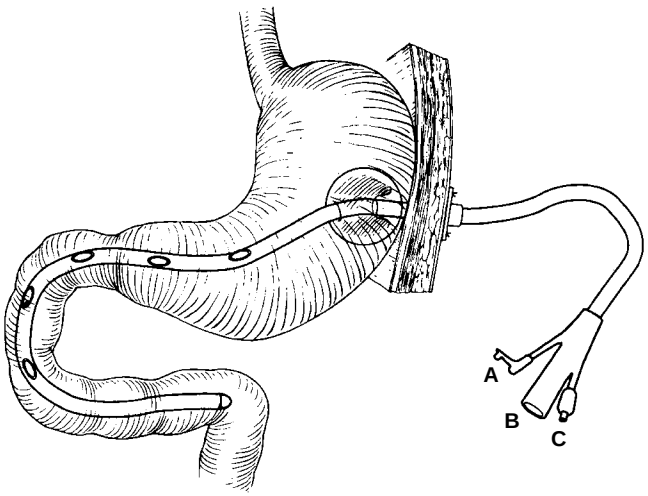


FIG. 4 Moss gastrojejunostomy tube may help with internal drainage and allow for distal enteral nutrition without the associated risks of multiple enterostomies. *(From Bland MD, Kirby I, Copeland EM.* Atlas of Surgical Oncology. *Philadelphia: WB Saunders; 1995.)*

Pancreatic Injury

Pancreatic injuries, like duodenal injuries, are associated with high morbidity and mortality. This is because of the close proximity to major vasculature and other vital structures. Mortality often results from massive exsanguination because the proximity of the aorta and its branches, the portal vein, the SMV, and the IVC lead to a high likelihood of bleeding from numerous sources.

Diagnosis

Early diagnosis and management is critical as delays in diagnosis are associated with high rates of morbidity and mortality. A high clinical suspicion should be present based on mechanism, such as decelerating injuries involving handlebars or steering wheels and associated injuries such as Chance fractures (unstable spine fracture typically at the thoracolumbar junction) or hollow viscus injuries to the stomach or duodenum. The physical examination may have findings such as pain out of proportion to the examination, the seatbelt sign, bruising at the umbilicus (Cullen's sign) or flanks (Grey Turner's sign); however, bruising may not present until hours to days after injury, making it less useful for diagnosis in real time.

Workup is largely dependent upon the physical examination and hemodynamic stability of the patient. As with most abdominal trauma, diffuse peritonitis and/or hemodynamic compromise warrant operative exploration. In the setting of a stable patient, elevated amylase and lipase can assist with recognition, although they are nonspecific and not sensitive early after injury (within the first 6 hours). CT imaging is the test of choice, although it is not perfect; rates of missed injury remain as high as 13% to 40%. CT findings may be subtle such as fluid in the lesser sac, retroperitoneal fluid, intrapancreatic/peripancreatic hematoma, pancreatic disruption, or injuries to nearby structures such as the duodenum, jejunum, thoracic spine, or vascular injuries near the celiac or SMA (Fig. 6). The Western Trauma Association algorithm and Eastern Association for the Surgery of Trauma guidelines for pancreatic trauma suggest that patients with evidence of parenchymal laceration with concern for major duct injury should undergo MRCP to evaluate the integrity of the duct, and surgical management should be reserved only for those with evidence of ductal injury on MRCP. However, we do not always use MRI in the acute setting and will often operate based on CT alone because of the high likelihood of other injuries and the plan for pancreatic drainage.

Management

Management is largely dependent on the clinical stability of the patient and whether there is evidence of major pancreatic duct involvement. In the setting of a hemodynamically stable patient with pancreas injury without duct involvement or transection and no other concerns that warrant operative exploration, a trial of selective nonoperative management can be attempted with nothing per mouth, total parenteral nutrition, and occasionally use of somatostatin analogues. In the setting of operative management, management is largely driven by the AAST grade of injury.

Grade I and II Injuries

Grade I and II injuries are summarized as contusions or lacerations of the pancreatic parenchyma without evidence of ductal injury or tissue loss. If identified on CT scan, per the Eastern Association for the Surgery of Trauma practice management guidelines, nonoperative management is appropriate. In the setting of injury identified at surgery, we suggest an attempt at nonresectional management. Some argue that capsular tears should not be repaired as these increase the risk for pseudocyst formation. Instead, wide external drainage is preferred. If possible, a nasoduodenal/nasojejunal tube can be placed at the time of surgery to allow for early enteral nutrition and theoretical avoidance of stimulation of the pancreas. Regardless of placement, without contraindications, an attempt at early enteral nutrition should occur. Pancreatic enzymes can be measured in the drain effluent to determine if a pancreatic leak is present.

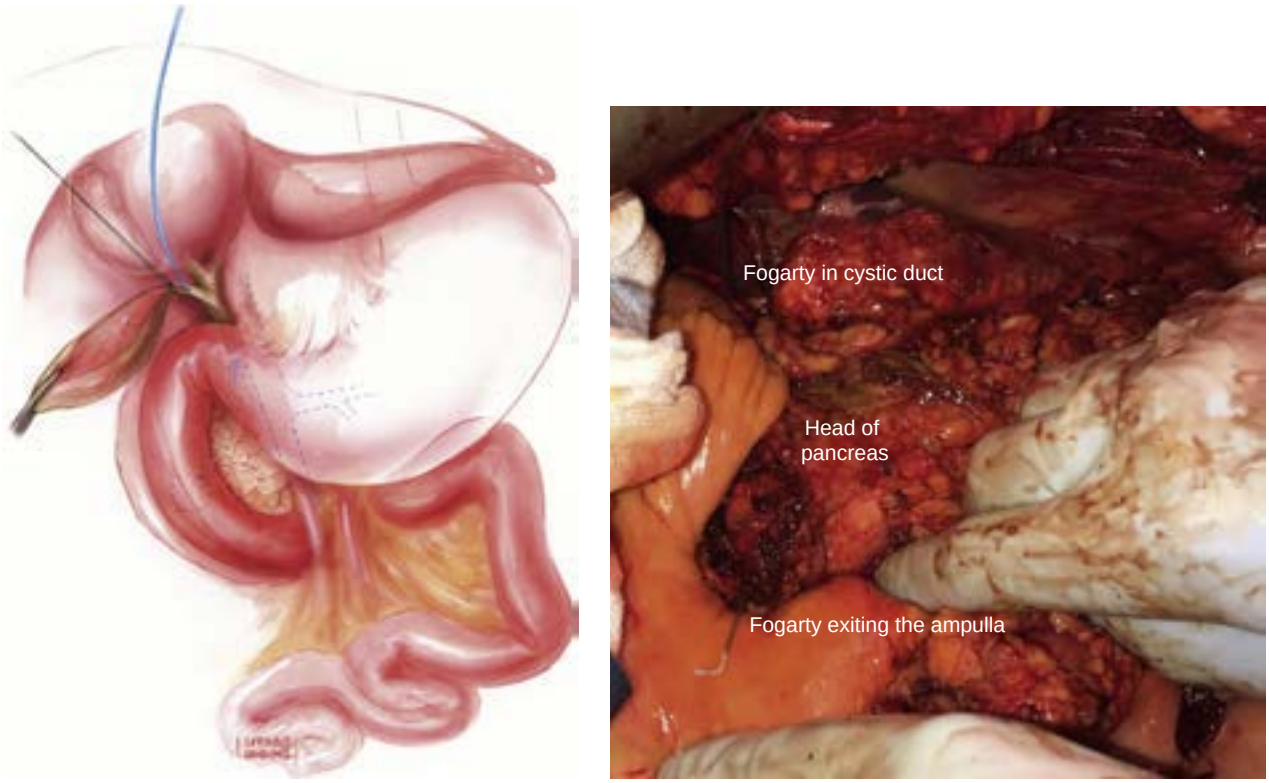


FIG. 5 Surgical approach to identify the ampulla of Vater starts with cannulation of the cystic duct and passage of a Fogarty balloon, manually guiding it down to the common bile duct and into the duodenum to ensure that the ampulla is intact and not injured when repairing the duodenum. *(Courtesy Corrine Sandone. From Cameron J, Sandone C.* Atlas of Gastrointestinal Surgery. *Vol. 2. 2nd ed. Shelton, CT: People's Medical Publishing; 2014.)*



FIG. 6 CT scan of complete transection through the distal body of the pancreas. *(Courtesy Stefan W. Leichtle, MD)*

Grade III Injuries

Grade III injuries involve distal pancreatic ductal transection or injury. A distal pancreatectomy combined with wide drainage is the procedure of choice in this setting as rates of pancreatic leak are high without resection. Some surgeons suggest central pancreatectomy with reconstruction in blunt trauma, although the complications related to leak remain high; we suggest against this approach except in rare cases and at an institution with expertise in central pancreatectomy in the elective setting.

Grade IV and V Injuries

Injuries involving proximal pancreatic transection or parenchymal injury involving the ampulla are classified as grade IV injuries. These injuries generally also involve combined injury to the duodenum. An attempt at wide drainage may be considered. In the setting of grade V injuries, where there is massive disruption of the pancreatic head, a Whipple procedure should be considered as a last resort. Some small cases series have demonstrated that in isolated pancreas injury involving the proximal main duct, transpapillary stenting (via ERCP) or nasopancreatic drain insertion can successfully bridge the disruption or reduce leakage, allowing for successful nonoperative management. However, this is less successful in complete transection of the duct. The majority of these patients have evidence of combined injuries, and most will likely undergo a damage-control operation with reexploration after further resuscitation. On reexploration, a decision can be made regarding wide drainage versus performing a Whipple procedure.

SURGICAL EXPOSURE OF THE PANCREAS

Anterior Exposure

To gain anterior exposure to the pancreas, the stomach is elevated, and the transverse colon is retracted caudally (Fig. 7). On the left side of the omentum, there is typically an avascular plane that can be entered bluntly to gain access to the lesser sac. Next, the gastrocolic ligament can be divided along this plane using an energy device (i.e., LigaSure, Harmonic Scalpel) or via the clamp-tie method. This allows retraction of the transverse colon and omentum inferiorly and the stomach superiorly. If further exposure is necessary, the right colon can be mobilized inferiorly, and the transverse mesocolon

is dissected free from the head of the pancreas. The SMV can be identified by following venous tributaries as it crosses over the third portion of the duodenum.

Posterior Exposure

The posterior exposure of the pancreatic head is performed via the Kocher maneuver (as described earlier). The posterior aspect of the pancreatic body and tail can be exposed by medial rotation of the spleen (Fig. 8). This involves mobilizing the white line of Toldt along the left colon at the splenic flexure and dividing the attachments of the spleen from its ligaments to the diaphragm and colon and short gastric arteries. This allows medial rotation of the spleen to visualize the posterior aspect of the pancreas.



FIG. 7 The anterior portion of the body of the pancreas can be exposed by first entering the lesser sac and retracting the stomach superiorly and then separating the pancreas from its attachments to the retroperitoneum. *(Courtesy Corrine Sandone. From Cameron J, Sandone C.* Atlas of Gastrointestinal Surgery. *Vol. 1. 2nd ed. Shelton, CT: People's Medical Publishing; 2007.)*

Identification of the Pancreatic Duct

The pancreas should be inspected for ductal injury. Historically some advocated for interrogation of the pancreatic duct by direct cannulation via a duodenotomy or even performing a distal pancreatectomy. These procedures should be avoided as they result in additional sources for enteric leak or pancreatic fistula formation and may convert a possible pancreatic injury into a combined pancreato-duodenal injury. Direct cannulation can be performed if a duodenal injury already exists; this can be done with a 5Fr catheter with saline or water-soluble contrast or a lacrimal/blunt probe. MRCP is an accurate means to assess ductal integrity without the morbidity associated with cannulation. Other authors suggest intraoperative ERCP, although this is rarely performed because of technical and logistic reasons in the acute trauma setting.

For distal duct injuries, methods to identify injury include direct visualization of ductal disruption. The use of lacrimal probes may assist, but in the setting of trauma, identification can be difficult. Findings that suggest ductal disruption include complete transection of the pancreas, laceration of more than one-half the diameter of the pancreas, and severe maceration of the gland. In these scenarios, we strongly recommend distal pancreatectomy as the consequences of a missed injury can be extremely morbid. At the least, wide external drainage should be performed if there is any suspicion of ductal injury.

In cases in which proximal ductal injury is unclear, we suggest MRCP (often after temporary closure for damage control). Intraoperatively, water-soluble contrast with fluoroscopy or methylene blue dye can be used to look for pancreatic ductal injury. Assessment can be performed in a similar manner to assessment of the ampulla. Instead of a Fogarty catheter, a cholangiocatheter is passed through the duct with injection of water-soluble contrast or directly looking for ductal disruption. If a cholangiocatheter is not available, a large-bore intravenous line with a butterfly catheter can be inserted directly into the gallbladder with injection for fluoroscopy. Of note, these techniques can be time-consuming and are only sometimes helpful in diagnosing a ductal injury. If proximal disruption is not obvious



FIG. 8 Aird maneuver for exposure of the posterior aspect of the pancreatic body and tail is performed by medial rotation of the spleen. *(Courtesy Corrine Sandone. From Cameron J, Sandone C.* Atlas of Gastrointestinal Surgery. *Vol 1. 2nd ed. Shelton, CT: People's Medical Publishing; 2007.)*

but suspicion still exists, wide external drainage is a safe temporary option, followed by MRCP.

Distal Pancreatectomy

Intraoperatively, the posterior exposure of the pancreas is performed via mobilizing the spleen from its retroperitoneal attachments. The spleen is mobilized in a manner that the posterior aspect of the pancreas can be visualized and the splenic vessels can be reflected medially. Ideally, this allows for the splenic artery and vein to be isolated and individually ligated. If this is not possible because of hemodynamic instability, a linear cutting stapler can be fired across the splenic vessels followed by a second fire across the pancreas. The inferior mesenteric vein should be identified before division as it drains into the splenic vein.

After division of the pancreas, we oversew the transected pancreas with overlapping 3-0 absorbable U-stitch sutures. The rate of pancreatic leak is high in these dissections as the gland is generally soft. To aid with minimization of leakage, if the duct is visualized, it should be oversewn. After resection, the pancreatic bed should be widely drained with external drainage.

For most patients undergoing distal pancreatectomy, we routinely also perform splenectomy. We generally do not perform splenic preservation as this surgical technique adds significant time to the procedure, with little potential benefit. The rates of infectious complications after splenectomy are quite low with appropriate vaccination. Splenic preservation may lead to increased operative morbidity as meticulous dissection must be performed to ligate all of the small venous tributaries of the splenic vein to the splenic hilum. Preservation should only be attempted in a stable patient with no other associated injuries by a surgeon experienced in the technique.

Combined Duodenal and Pancreatic Injuries

Combined injuries to the duodenum and head of the pancreas or proximity to the ampulla are extremely rare. Pancreatoduodenectomy (Whipple) maybe warranted in cases of near-complete destruction of the duodenum or pancreatic head, proximal pancreatic main duct injury combined with CBD injury and duodenal injury, injury to the ampulla of Vater, or uncontrolled bleeding from unrecognized vessels of the head of the pancreas or from the retropancreatic portion of the portal vein or SMV.

Whipple Procedure

Pancreatoduodenectomy is a time-consuming, complex operation. In the setting of trauma, this should largely be considered after adequate resuscitation. The goals of the initial operation should be hemorrhage control and control of gastrointestinal spillage. After adequate resuscitation, the patient can return for thorough examination of the pancreatic head/duodenum, ampulla, CBD, and pancreatic duct. Often, the resection has been nearly completed already by the initial trauma and just needs the final steps performed (Fig. 9). In almost all Whipple procedures for trauma, reconstruction should be performed in a delayed fashion using the techniques of damage-control surgery. Ideally, the bile duct is identified and cannulated for direct drainage. This is also theoretically possible for the pancreatic duct, although in practice it is much more difficult. The exact surgical reconstruction of the Whipple procedure is well described elsewhere in this textbook, and if available, we routinely ask our hepatobiliary colleagues for assistance at the takeback operation with this rare operation for trauma.

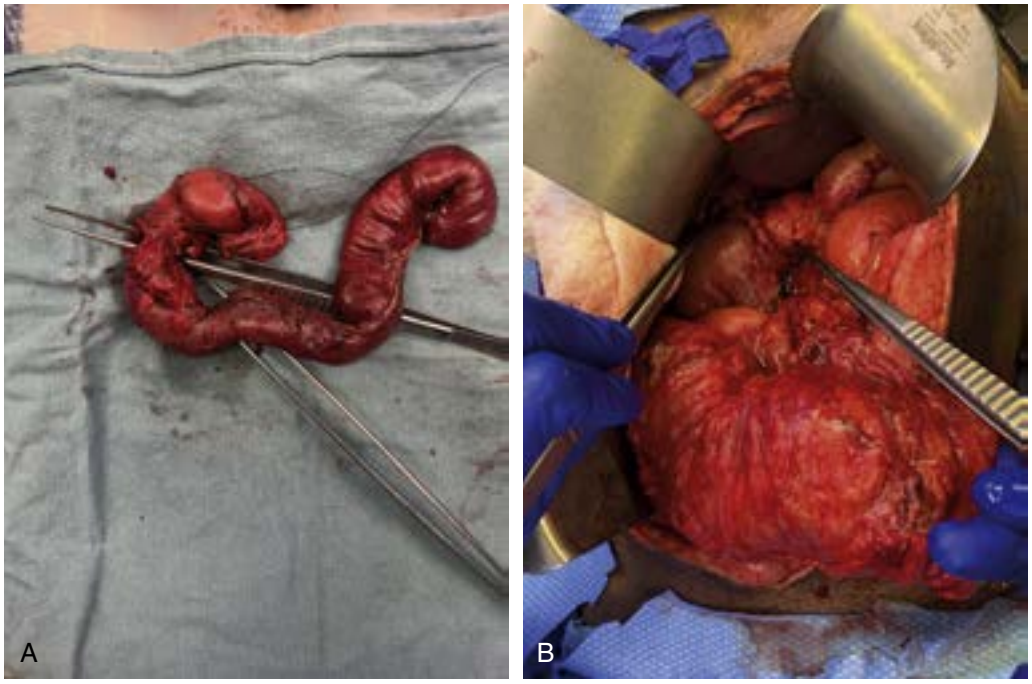


FIG. 9 Trauma Whipple procedure for penetrating trauma to the pancreatic head and duodenal *C*-loop. The resected specimen **(A)** and the reconstruction **(B)** are shown. *(Courtesy Scott C. Brakenridge, MD)*

OUTCOMES AND COMPLICATIONS

Pancreatic and duodenal surgery in the setting of trauma has a higher rate of complications than in the elective population. This is largely because these patients likely are under severe physiologic duress and have significant associated injuries. It is common that patients undergoing surgery in these scenarios will experience a complication; the focus should be on techniques that minimize complications and maximize success.

Duodenal Leak

Duodenal leak can be largely managed with drainage, either from surgically placed drains or from newly placed drains by interventional radiology. The patient should be maintained NPO and started on nutrition. Enteral nutrition is preferred if a tube has been placed at the time of surgery. If no tube is available, parenteral nutrition is an alternate option. Follow-up imaging with a contrast study should be performed before resumption of enteral nutrition.

Biliary Leak

The first step in biliary leak is wide drainage. This can be accomplished via surgical drains placed at the final operation or via percutaneous placement by interventional radiology. In the setting of dilated intrahepatic ducts caused by stricture/obstruction, percutaneous transhepatic drainage through the choledochojejunostomy can be performed. Endoscopy should be avoided early in the postoperative period because of the risk of anastomotic disruption, but it can be considered in the subacute phase (6 weeks postprocedure).

Pancreatic Fistula

Pancreatic fistula is a common complication of pancreas and combined pancreatico-duodenal injuries. It is higher in distal pancreatectomy than in Whipple procedures. In both scenarios, drainage is usually sufficient. Most pancreatic fistulas are identified by a high amylase drain level on resumption of a diet. In the setting of significant leaks, treatment by making the patient NPO and adding parenteral nutrition can be attempted to promote closure. Although we recommend against the routine use of somatostatin analogue in all patients after distal pancreatectomy, we do routinely use it in patients with proven pancreatic leak. In the setting of distal leaks, endoscopic procedures (ERCP) to proximally stent the main pancreatic duct has proven useful if medical management has not been successful (Fig. 10).

Delayed Gastric Emptying

Delayed gastric emptying is a poorly understood phenomenon but is common after an elective Whipple procedure. It can be managed with prokinetic agents such as erythromycin. Resolution generally occurs within 3 weeks. If the patient fails to improve by that time, one should consider placement of a percutaneous gastrojejunostomy.

Hemorrhagic Complications

Postoperative hemorrhage can have devastating consequences, and a heightened sense of awareness should always be present. Drains should be monitored closely for bleeding. Early evidence of bleeding is generally surgical in nature and warrants reexploration, whereas delayed bleeds are usually the result of a pseudoaneurysm in the setting of pancreatic leak. A change in drain appearance to sanguineous should be assumed to be a sentinel bleed with arterial spasm and should be followed by prompt action with immediate interventional radiology consultation for diagnostic angiography and therapeutic angioembolization. The source is usually dependent on the original operation performed. The gastroduodenal artery stump tends to be the source after a Whipple procedure, whereas the splenic artery is the more common source after distal pancreatectomy. Hemodynamic instability or inability to control via angiography warrants surgery.



FIG. 10 Endoscopic retrograde cholangiopancreatography (ERCP) demonstrating a main pancreatic duct leak that healed without surgical intervention after pancreatic duct stent placement. *(Courtesy Elliott R. Haut, MD, PhD)*

CONCLUSION

Duodenal and pancreatic injuries are rarer and more difficult to diagnose than other types of intraabdominal injury. Trauma surgeons must maintain a high suspicion of injury to diagnose and treat them to avoid morbidity and mortality. A thorough understanding of presentation, diagnostic workup, surgical anatomy, and methods of repair are necessary to evaluate and treat these injuries. Techniques of repair should be as simple as possible to achieve adequate control and drainage to optimize outcomes for injured patients.

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Injuries to the Small and Large Bowel

Crisanto M. Torres, MD, Amanda Radisic, MD, and Joseph V. Sakran, MD, MPH, MPA

INTRODUCTION

Injuries to the small bowel, colon, and associated mesentery are commonly encountered in trauma, depending on the mechanism involved. For example, penetrating abdominal gunshot wounds are frequently associated with injury to the bowel, occurring in 80% of cases. The space-occupying attribute of the small and large bowel provides an easy target for direct projectile injury or indirect damage from the accompanying blast effect. In contrast, bowel injuries secondary to blunt mechanisms are relatively uncommon, with an overall incidence of around 1% to 5%. A significant amount of force is typically necessary to cause blunt hollow viscus injury. Proposed mechanisms of blunt injury are sudden elevations in intraluminal pressure leading to rupture, rapid deceleration causing mesenteric shearing at fixed points producing bowel devascularization, and bowel being crushed against the spine. Therefore, the nature and severity of trauma involved dictate the workup and management of hollow viscus injury. Navigating the complexities that encompass the diagnosis, management, and surgical decision making of small and large bowel injuries is essential to ensure the most favorable patient outcome.

DIAGNOSTIC WORKUP

Blunt Injury

Despite advancements in diagnostic imaging modalities, there remains no clear-cut, definitive examination to diagnose blunt intestinal or mesenteric injury outside of operative exploration. The focused assessment with sonography in trauma (FAST) is typically the first radiologic examination performed on patients presenting with trauma. This rapid diagnostic examination should be employed during the initial workup of abdominal injury in the trauma bay. Patients presenting with hemodynamic instability in the setting of free fluid is a positive finding most suggestive of bleeding. However, the FAST examination is suboptimal for excluding hollow viscus injury. A negative examination in a stable patient suspected of having intestinal injury prompts additional workup. The Eastern Association for the Surgery of Trauma (EAST) provides a useful algorithmic workup in patients presenting with blunt abdominal trauma (Fig. 1). Regarding imaging choice, computed tomography (CT) is currently the best available radiographic modality to evaluate for blunt hollow viscus and mesenteric injury. However, missed intestinal and mesenteric injuries remain a constant obstacle, even with modern-day CT scanners, with a sensitivity of around 80%.

There are several nonspecific findings on CT imaging that may characterize blunt hollow viscus or mesenteric injury. For example, the presence of free air, bowel wall thickening, mesenteric stranding, or mesenteric hematoma are findings suggestive of injury but are infrequent on imaging. However, free fluid is by far the most common finding on CT imaging that is associated with blunt intestinal injury. In a recent retrospective study, the presence of free fluid in the absence of solid organ injury was present in over 80% of patients

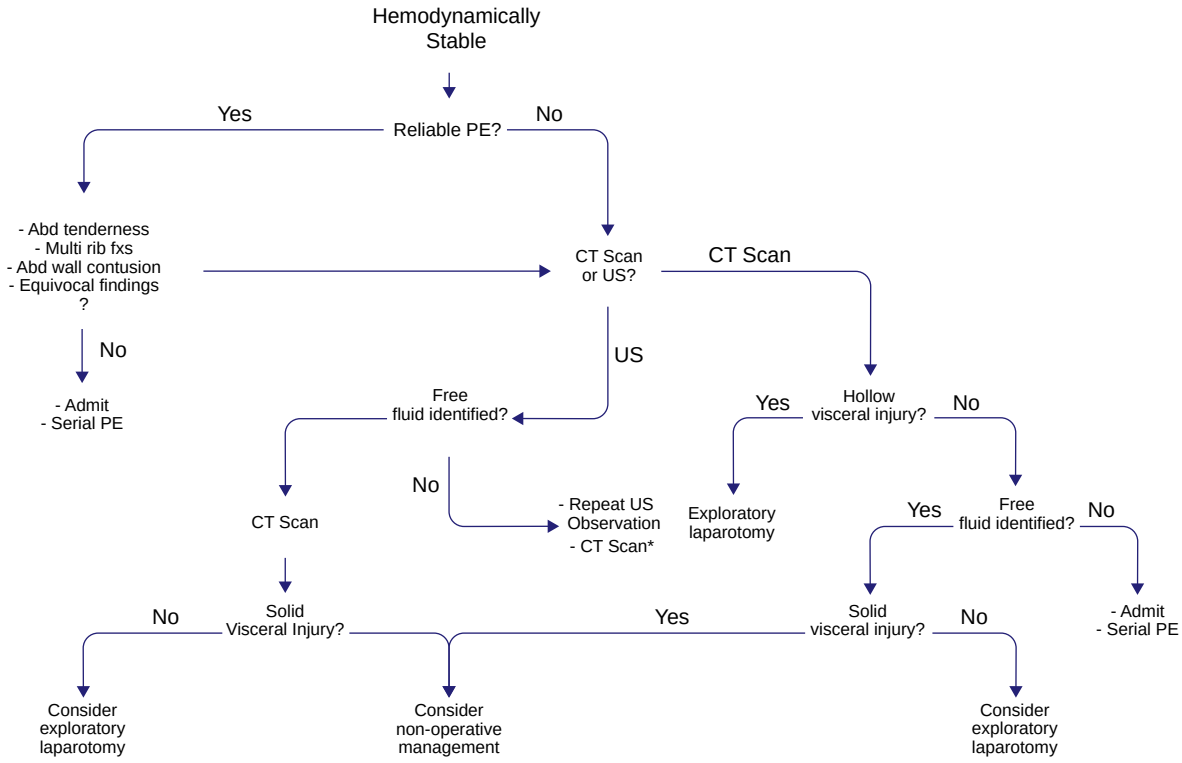


FIG. 1 **Algorithm for treatment of blunt abdominal trauma.** *(From Hoff WS, Holevar M, Nagy KK, et al. Practice management guidelines for the evaluation of blunt abdominal trauma: the East practice management guidelines work group. J Trauma. 2002;53:602–615.)*

with blunt intestinal injury, with a sensitivity and specificity just shy of 90%.

"Bucket handle" injuries of the mesentery are commonly missed on initial CT evaluation. This type of injury involves avulsion of the bowel mesentery caused by shear force seen with high-impact blunt trauma. Mesenteric avulsion can devascularize associated intestinal segments, leading to ischemia, frank necrosis, or delayed perforation.

Diagnostic peritoneal lavage (DPL) is a diagnostic procedure traditionally performed within the trauma bay that has largely fallen out of favor with the advent of diagnostic laparoscopy and improved CT imaging technology and availability. This procedure can be done via an open or closed Seldinger technique. Depending on the equipment and kits available, a small supraumbilical or infraumbilical incision is made. Upon access to the peritoneal cavity, if at least 10 mL of frank blood is initially aspirated, the patient is taken directly to the operating room. Gross fecal matter or succus would be another indication for immediate operative intervention. If the initial aspirate is grossly negative, 1 L of warm normal saline is infused into the abdomen through a catheter as rapidly as possible. After saline instillation, the IV bag attached to the catheter is lowered to the ground. The abdominal effluent is subsequently withdrawn into the bag via gravity. The collected peritoneal fluid is then analyzed by the laboratory and considered positive if at least one of the following criteria is met: red blood cells >100,000/mm^3, white blood cells >500/mm^3, elevated amylase, or elevated creatinine. This technique has a high sensitivity for blunt injuries at 99%, though a relatively low specificity (43%). When used as the sole diagnostic modality, a high number of nontherapeutic laparotomies were being performed as a result of a high false-positive rate. Therefore, in resource-limited areas, where CT imaging or laparoscopic capabilities are not readily available, DPL remains a suitable method for the evaluation of intraabdominal injury.

The physical examination may provide insight into the presence and severity of intraabdominal injury during the initial clinical evaluation, but overall findings remain nonspecific for bowel injury. The presence of a "seatbelt" sign, abdominal wall ecchymosis, abdominal distention, or diffuse abdominal tenderness are findings that raise clinical suspicion for bowel injury that warrants additional workup.

Penetrating Bowel Injuries

Similar to blunt injuries, the evaluation of penetrating bowel injuries starts with the initial trauma evaluation following the ATLS algorithm in the trauma bay. In addition to resuscitation as indicated for hemodynamically unstable patients, exposure is vital for the primary survey. Identifying the location and number of penetrating wounds on the abdomen are essential for determining trajectory and anticipating possible injuries. If patient stability permits, adjuncts to the initial assessment such as FAST and x-rays of the chest, abdomen, and pelvis, while not diagnostic, can provide helpful information. Although not specifically diagnostic for bowel injury, FAST can identify free fluid within the abdomen, and radiographs can help identify bullet trajectory and retained bullet fragments.

Patients presenting with abdominal gunshot wounds often proceed directly to the operating room without additional imaging beyond the FAST examination. Physical examination findings suggestive of overt bowel injury are commonly present and may include peritonitis, hematemesis, gross blood per rectum, and evisceration of abdominal contents. Not all patients with gunshot wounds to the abdomen present with peritoneal signs or clinical findings consistent with bowel injury; these individuals may simply have tangential subcutaneous wounds. A CT examination should be performed in stable patients with a benign abdominal examination to evaluate for tangential track wounds, potentially preventing unnecessary interventions.

Close to 20% of abdominal stab wounds result in injury to the bowel; in the stable patient, exposure is crucial and drives the next steps in the diagnostic workup. In addition, anterior abdominal stab wounds are more likely to violate the bowel than those in the thoracoabdominal or flank regions. Therefore, local wound exploration can be performed in stable patients without peritonitis to evaluate for peritoneal violation. The procedure can be safely done at the bedside with adequate analgesia and patient cooperation. An appropriate amount of local anesthesia, sometimes supplemented with sedation, is necessary to evaluate injury to the anterior fascia sufficiently. A full assessment of the wound to the most profound depth must be examined to ensure that injury is not missed.

MANAGEMENT

Management of patients with suspected bowel or mesenteric injury is frequently not straightforward; a comprehensive approach aims to mitigate missed or delayed injury (Fig. 2). The workup and initial direction of care in patients with blunt injury may differ from those with penetrating injury as the outcomes are not always similar.

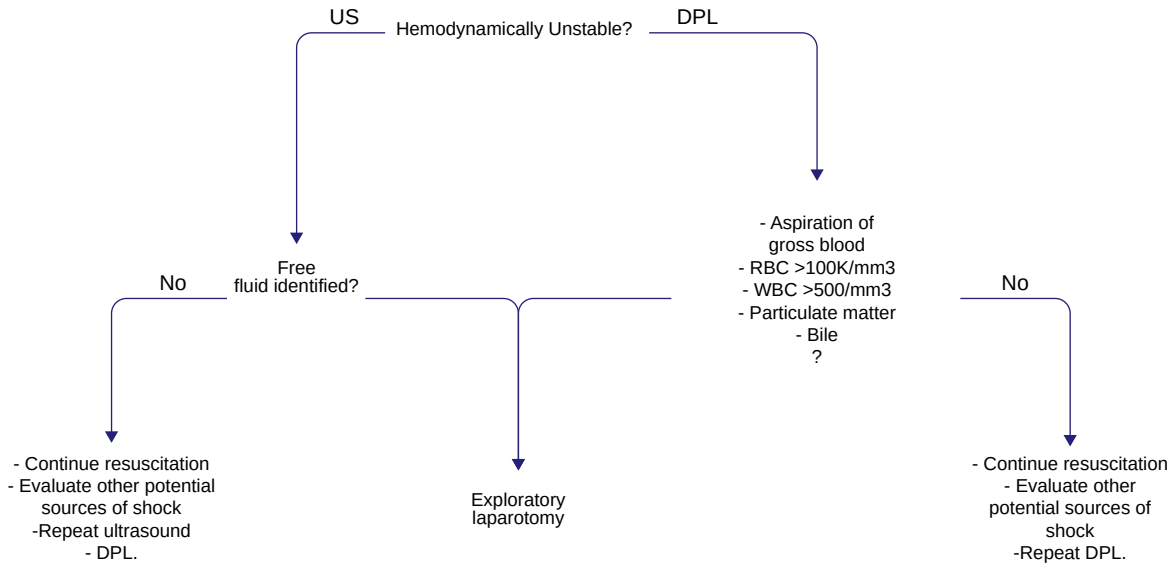


FIG. 2 **Algorithm for treatment of patients with missed or delayed blunt abdominal injury.** *(From Hoff WS, Holevar M, Nagy KK, et al. Practice management guidelines for the evaluation of blunt abdominal trauma: the East practice management guidelines work group. J Trauma. 2002;53:602–615.)*

Despite the observed differences in patients presenting with blunt versus penetrating injury, a common theme remains; a delay in operative intervention is associated with increased complications and mortality. A delay in surgery greater than 24 hours more than doubled the associated mortality from 13% to 31%. Therefore, it is ideal to operate within 8 hours of injury, as this time frame was not associated with an increase in complications or death.

Selective nonoperative management in stable patients with gunshot or stab wounds to the abdomen is a reasonable option if the wounds are tangential and there are no peritoneal signs. If possible, the same team should perform serial examinations during the observation period to ensure accuracy in clinical monitoring. Patients with a reliable examination may be discharged after 24 hours in the absence of diffuse abdominal tenderness or peritonitis. Alternatively, diagnostic laparoscopy could be considered in selected stable patients to more confidently rule out injury with equivocal clinical and radiographic findings.

Thoracoabdominal or upper abdominal stab wounds are likely to be associated with diaphragmatic injuries than bowel injuries. Therefore, patients with this injury pattern should undergo a CT examination to better evaluate for any intraabdominal injuries. Much of the expectant management of these injuries is mainly driven by suspicion of diaphragmatic injury.

The management of patients with blunt intestinal or mesenteric injury can be challenging as not all positive findings on radiographic studies warrant operative intervention. However, for patients with equivocal imaging who are stable and with minimal abdominal tenderness, serial abdominal examinations with repeat contrast imaging can be performed within 24 to 48 hours.

Blunt mesenteric hematomas can be safely observed in asymptomatic patients if CT findings are negative for bowel compromise, obstruction, or active arterial extravasation. However, these injuries are uniquely deceitful in that patients may present days later with delayed perforation secondary to devascularization. These patients typically require more than 24 hours of observation to remove any doubts of impending perforation.

Patients with hemodynamic instability, peritonitis, or worsening abdominal examinations should proceed to the operating room for exploration.

SURGICAL TECHNIQUE

Small Bowel and Mesenteric Injuries

The operative management of small bowel injury may differ depending on the mechanism and severity of injury, physiologic status, and other associated injuries present; however, the surgical approach for evaluating injury is largely invariable. Before incision, antibiotics should be given to cover typical intestinal flora. It is neither necessary nor recommended to continue surgical antibiotic prophylaxis beyond 24 hours postoperatively. Wide exposure of the abdominal cavity is facilitated by utilizing self-retaining retractors. A systematic inspection of the small bowel and associated mesentery should begin with identifying the ligament of Treitz proximally and "running the bowel" hand over hand, followed by an assistant to identify the ileocecal valve. Free perforations can be temporized with oversewing, noncrushing bowel clamps, or umbilical ties to control contamination during the initial inspection. Hematomas involving the bowel wall should always be opened and evaluated for an underlying injury; this is especially true for stab wounds.

The mesenteric border should be carefully inspected as injuries are often subtle and overlooked in this area. The associated mesentery should be assessed for full-thickness defects, active bleeding, hematomas, and regions with significant devascularization. Full-thickness mesenteric defects should be closed to avoid the risk of internal hernias. When suturing defects closed, care must be taken to abstain from taking excessive deep bites into the mesentery, which may compromise blood supply to the bowel. Large mesenteric defects are often associated with significant devascularization; the mesentery and its adjacent bowel segment should be resected. In the setting of active arterial bleeding within the mesentery, quick digital pressure can temporarily control bleeding. Simple suture ligation of mesenteric vessels will attain hemostasis without compromising perfusion to the small bowel because of the rich arterial collateralization within the mesentery. However, multiple ligations, proximal ligations, and ligations performed near the distal terminal ileum increase the risk of subsequent ischemia. Proximal or root of the mesentery arterial bleeding warrants precise evaluation for superior mesenteric arterial injury for which primary repair or revascularization may be needed. Small hematomas within the mesentery can be left alone. Expanding mesenteric hematomas, active arterial or pulsatile bleeding, hematomas along the mesenteric border, and large-size hematomas should be explored. If the decision is made not to explore moderate to large-size mesenteric hematomas, strong consideration for a second-look operation should be performed to assess intestinal viability.

Management for small-bowel injuries can be guided by assessing the severity of injury utilizing the American Association for the Surgery of Trauma (AAST) grading schema (Table 1). Serosal tears, contusions, and intramural hematomas (grade I) can be repaired with a single layer of seromuscular imbricating Lembert sutures. Full-thickness perforations or lacerations involving ≤50% wall circumference and without devascularization (grade II) should be repaired in a transverse orientation, avoiding luminal narrowing. Full-thickness absorbable sutures are used, followed by a seromuscular imbricating layer only after debridement of devitalized tissue edges. Multiple full-thickness injuries in close proximity should be resected and restored with a primary anastomosis; this may expedite operative time while possibly lowering the risk of stricture or leak. Adjacent

TABLE 1 Small Bowel Injury Scale

Grade*	Type of Injury	Description of Injury	ICD-9	AIS-90
I	Hematoma	Contusion or hematoma without devascularization	863.20	2
	Laceration	Partial thickness, no perforation	863.20	2
II	Laceration	Laceration <50% of circumference	863.30	3
III	Laceration	Laceration ≥50% of circumference without transection	863.30	3
IV	Laceration	Transection of the small bowel	863.30	4
V	Laceration	Transection of the small bowel with segmental tissue loss	863.30	4
	Vascular	Devascularized segment	863.30	4

*Advance one grade for multiple injuries, up to grade III.

From Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling. *Surg Clin North Am.* 1995;75:293–303.

perforations can be adjoined by excising the bridge of tissue separating the paired defects and repaired as a single defect. Perforations or lacerations that incorporate >50% circumference (grade III) are best managed with resection and anastomosis, with a few exceptions. For grade III injuries involving the proximal jejunum or patients at risk for short bowel syndrome, it is reasonable to repair these, primarily if significant luminal narrowing can be avoided. Grade IV and V injuries require resection and anastomosis. The decision and action to perform a repair should only be made after a full assessment of the bowel in its entirety. The length of available bowel, intestinal, and vascular characteristics and overall patient condition will dictate the most appropriate approach. For patients who are at the precipice of physiologic derangement leading to the well-known vicious cycle of coagulopathy, hypothermia, and acidosis, a damage-control laparotomy should be performed without hesitation. After prioritizing hemorrhage control, control of contamination while addressing bowel injury can be rapidly temporized with stapled resections and the bowel left in discontinuity. It is always ideal to leave a nasogastric tube and set to suction to allow for ongoing decompression of intestinal blind loops until continuity is restored.

Contention persists among trauma surgeons as to whether a hand-sewn versus stapled anastomosis should be the preferred technique for reestablishing intestinal continuity. To date, there have been several retrospective studies and one prospective observational study that attempt to clarify the technique associated with less anastomotic leak rate. However, the results are largely variable, with selection bias further complicating interpretation. Therefore, the premise to perform a hand-sewn versus stapled anastomosis should be based on the surgeon's experience and comfort level of either method. Of note, if there is significant bowel edema, a size mismatch, or friable tissue, a hand-sewn anastomosis may allow for a more customized effort along the bowel tissue than a fixed-staple height that limits the ability to conform in these unique conditions.

Large Bowel Injuries

The selection of broad-spectrum antibiotics to cover intestinal flora should be given before incision to reduce potential surgical site infections and should be given no more than 24 hours postoperatively. Inspection of the colon usually begins at the ileocecal valve and continues to the peritoneal reflection enveloping the intraperitoneal rectum. A rigid proctoscope should be utilized if there is a concern for an extraperitoneal rectal injury. For suspected posterior colonic injuries, it is necessary to excise the lateral peritoneal reflection, the white line of Toldt, to mobilize and inspect the colon in its entirety. The ureters should be identified and protected during colonic mobilization. A thorough and careful examination is achieved with complete flexure mobilization for suspected injuries encompassing the hepatic or splenic flexures, as these areas often obscure injuries. Like small bowel injuries, large bowel wall hematomas and paracolic hematomas should be opened and explored to evaluate for underlying bowel injury. Air tracking within the omentum, mesenteric planes, or bowel wall should be traced to identify occult perforations.

The operative management scheme of identified colonic injuries depends on the patient's stability and injury severity. The AAST Organ Injury Scale for colonic injury provides an injury classification system that groups injuries as destructive or nondestructive, which may assist in operative planning and approach (Table 2). Serosal tears or bowel wall contusions and hematomas (grade I) can be repaired with a single layer of imbricating Lembert sutures. For injuries involving lacerations ≤50% of wall circumference (grade II), sharp debridement of devitalized edges followed by a primary full-thickness repair reinforced with a seromuscular imbricating layer should be performed. High-energy injuries, such as high-velocity projectiles and blast injuries, leave a zone of nonviable tissue and capillary damage that may not be readily apparent on initial assessment, leading to potentially delayed perforation. Therefore, consideration for resection with primary anastomosis is a reasonable strategy for selected grade I and II injuries associated with high-energy injuries. Destructive colon wounds (grades III–V) require either resection with anastomosis or colostomy. The fundamental principles for resection and anastomosis follow in cadence with the tenets for small bowel anastomosis mentioned previously.

The decision to perform an ostomy should be considered in the presence of significant comorbidities, high blood transfusion requirements, hemodynamic instability, or compromised blood supply. In addition, following damage-control laparotomy, the presence of considerable bowel wall edema, mesenteric shortening, and tissue friability may be responsible for the increase in suture line dehiscence observed after delayed anastomosis. Therefore, the creation of an ostomy after abbreviated laparotomy should be contemplated after a comprehensive assessment of colonic integrity.

Frank fecal spillage or colonic contamination are known risk factors for clinically relevant postoperative surgical site infections and wound complications. In the presence of the aforementioned conditions, closure of the abdominal wall should include an attempt at primary fascia closure while mandating leaving the skin open or loosely approximated with staples. This aims to reduce the risk of fascia dehiscence or evisceration if an infection does ensue. The wound can be subsequently managed with negative-pressure vacuum-sponge therapy or dressing changes postoperatively to allow for secondary wound closure.

Laparoscopic Evaluation

The role of laparoscopy in trauma has steadily increased over time, likely related to the increase in operative experience and comfort level that has been achieved through surgical training. Successful

TABLE 2 Colon Injury Scale

Grade*	Type of Injury	Description of Injury	ICD-9†	AIS-90
I	Hematoma	Contusion or hematoma without devascularization	863.40–863.44	2
	Laceration	Partial thickness, no perforation	863.40–863.44	2
II	Laceration	Laceration <50% of circumference	863.50–863.54	3
III	Laceration	Laceration ≥50% of circumference without transection	863.50–863.54	3
IV	Laceration	Transection of the colon	863.50–863.54	4
V	Laceration	Transection of the colon with segmental tissue loss	863.50–863.54	4
	Vascular	Devascularized segment	863.50–863.54	4

*Advance one grade for multiple injuries, up to grade III.

†41, .51 = ascending; .42, .52 = transverse; .43, .53 = descending; .44, .54 = rectum.

From Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling. *Surg Clin North Am.* 1995;75:293–303.

laparoscopic management can be executed with appropriate patient selection. Penetrating abdominal stab wounds or blunt abdominal trauma with evidence of free fluid on imaging in a hemodynamically stable patient could be considered for laparoscopy. The benefits of laparoscopy are associated with less postoperative pain, less hospital length of stay, and fewer complications associated with a nontherapeutic laparotomy. A low threshold for laparotomy should be performed if the patient deteriorates or any doubt for missed injury remains.

CONCLUSION

The overall evaluation and management of small and large bowel injury can be quite complex. The critical decision that makes the most difference in the morbidity and mortality for these patients is the timing to operative intervention. Missed injuries lead to significantly increased morbidity and mortality. Therefore, understanding the relevant diagnostic tests to perform, choosing the most appropriate clinical pathway, and meticulous surgical prowess are essential to providing the most favorable possible outcome.

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CURRENT MANAGEMENT OF RECTAL INJURY

Katherine Albutt, MD, MPH, and Peter J. Fagenholz, MD

INTRODUCTION

Rectal injury is relatively uncommon in the civilian trauma population, seen in 1% to 3% of injuries, but more common in military trauma, seen in 5% of military casualties. Treatment of rectal injuries has evolved significantly over time, and civilian treatment strategies have mirrored what has been learned from wartime experiences. As new clinical approaches have been devised and as evidence-based medicine has come to the forefront, morbidity and mortality resulting from rectal injuries has improved dramatically. In this chapter, we present a workable management scheme for rectal trauma and touch briefly on the controversial issues of presacral drainage and distal rectal washout.

ANATOMIC CONSIDERATIONS

The rectum is the distal continuation of the colon, measuring 12 to 15 cm in length, and extending from the rectosigmoid junction to the dentate line. The rectum courses anterior to the three inferior sacral vertebrae, the coccyx, and sacral vessels, and is posterior to the bladder in men and the vagina in women. A well-vascularized structure, it is supplied by the superior, middle rectal, and inferior rectal arteries that branch off the inferior mesenteric artery, internal iliac arteries, and internal pudendal arteries, respectively. Venous drainage from the rectum is to both the portal and systemic circulation, with the superior rectal veins draining to the inferior mesenteric veins and the middle and inferior rectal veins draining to the internal iliac and pudendal veins, respectively. The anterior and lateral upper two-thirds of the rectum are located intraperitoneally and the remainder is extraperitoneal, made up of the posterior aspect of the rectum, which is adherent to the presacral soft tissues and the lower one-third of the anterior portion. Importantly, rectal injury is classified and managed based on the intraperitoneal or extraperitoneal location of the injury (Fig. 1).

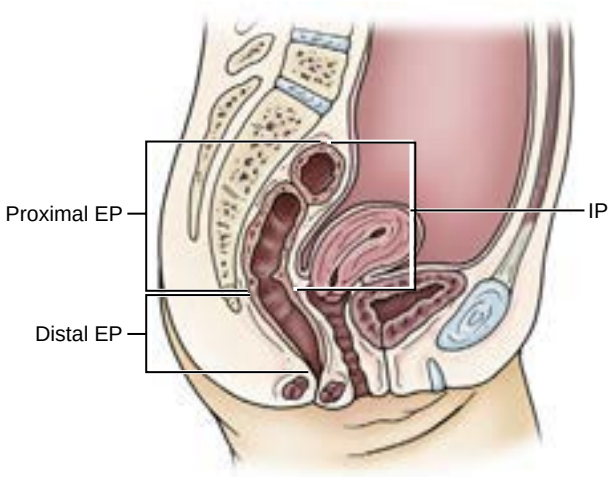


FIG. 1 The intraperitoneal *(IP)* and extraperitoneal *(EP)* divisions of the rectum. *(From Weinberg JA, Fabian TC, Magnotti LJ, et al. Penetrating rectal trauma: management by anatomic distinction improves outcome.* J Trauma Acute Care Surg. *2006;60:508–514.)*

DIAGNOSIS

Prompt recognition of rectal injuries requires a high index of suspicion with both penetrating and blunt trauma. Injuries range from minor bruising, to complete devascularization for blunt injuries and small perforations, to devascularization for penetrating injuries. Rectal injury can be easily missed and should be suspected with any penetrating wound to the lower abdomen, pelvis, perineum, buttocks, or upper thighs. Similarly, blunt trauma resulting in pelvic fractures and associated vascular or urologic injury should raise suspicion for possible rectal injury. Missed rectal injuries result in significant morbidity and mortality due to resultant pelvic sepsis. As with all trauma patients, initial resuscitation, diagnostic evaluation, and management should proceed per standard guidelines. During the secondary survey, attention should be paid to complete exposure and examination of the multiple folds and clefts in the perineal region. Digital rectal examination (DRE) is essential. Gross blood on DRE is a sign of possible rectal injury, present in 90% of rectal injuries, but its absence does not exclude rectal injury. Other information such as the presence of foreign bodies, bony fragments within the rectum, defects in the rectal wall, and position of the prostate gland are useful adjuncts. These findings should trigger further investigation with axial imaging, proctosigmoidoscopy, surgical exploration, or a combination of these. CT is typically the imaging modality of choice as it is rapidly available and excellent for evaluating associated bony, vascular, and visceral injuries. CT may reveal clear signs of rectal injury such as discontinuity of the rectal wall or extraluminal enteric contrast originating from the rectum, but signs may also be subtle and not clearly traceable to the rectum such as pneumoperitoneum, mesenteric air, free intraabdominal fluid, bowel wall thickening, or mesenteric hematoma. Rectal contrast should be considered and administered when possible if the index of suspicion for rectal injury is high or if a CT without rectal contrast is suspicious for rectal injury without showing clear signs. However, false negatives may result, particularly in the case of penetrating injury. If CT is insufficient to diagnose or rule out a rectal injury, then an anorectal exam under anesthesia with proctosigmoidoscopy should usually be the next maneuver. While blood or stool may obscure the exam, the use of a combination of CT and proctosigmoidoscopy has a reported sensitivity of over 95%. Importantly, laparotomy performed without preoperative imaging for other injuries or in the case of hemodynamic instability may fail to identify an extraperitoneal rectal injury unless such an injury is specifically sought. A complete surgical exploration should include evaluation of the extraperitoneal pelvis, and findings such as a transpelvic trajectory for penetrating wounds or a presacral hematoma should prompt further evaluation. This may include some combination of anorectal examination with proctosigmoidoscopy while in the operating room or direct exploration of the pelvis. When identified, injuries are graded by the American Association for Surgery in Trauma (AAST) rectum and rectosigmoid injury scales based on whether the injury is partial or full thickness, the percentage of rectal lumen compromised, and the extension into the perineum (Table 1).

TABLE 1 American Association for the Surgery of Trauma Rectal Injury Grading Scale

Grade*	Type of Injury	Description of Injury
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration >50% of circumference
IV	Laceration	Full-thickness laceration with extension into perineum
V	Vascular	Devascularized segment

*Advance one grade for multiple injuries, up to grade III.
Modified from Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling, II: pancreas, duodenum, small bowel, colon, and rectum. *J Trauma.* 1990;30:1427–1429.

MANAGEMENT

Four Ds in the management of rectal injury have historically been considered important: (1) diversion of the fecal stream, (2) distal washout, (3) presacral drainage, and (4) direct repair of the defect. Distal rectal washout can no longer be supported by contemporary data, and the remaining techniques are used selectively based on the anatomic classification of the injury: (1) intraperitoneal versus extraperitoneal and (2) proximal or distal location. The basic principles guiding all management approaches are control of bleeding and contamination, and restoration of continuity or diversion of the rectal stream.

Intraperitoneal Injury

Patients with intraperitoneal penetrating rectal injuries should be managed the same as those with colon injuries. Nondestructive injuries without devitalization of tissue can be repaired primarily in one or two layers. If there is significant tissue loss or vascular compromise, resection of the injured segment is appropriate. Primary anastomosis without diverting colostomy or ileostomy is preferred in the presence of hemodynamic stability and can be performed safely in most circumstances. If there is evidence of shock (prolonged hypotension, transfusion requirement greater than 6 units of packed red blood cells, delay in operation, heavy fecal contamination) or multiple associated injuries (such as pelvic fractures and complex perineal wounds), end colostomy with closure of the rectal stump is advised and is a safe option. A recent prospective multicenter trial undertaken by the AAST that included 297 patients found that restoration of continuity with primary anastomosis did not increase the rate of abdominal complications when compared with diversion, regardless of associated risk factors. During repair of intraperitoneal rectal injuries, a detailed assessment of the posterior wall of the rectum should be conducted surgically and/or endoscopically.

Extraperitoneal Injury

Extraperitoneal rectal injuries should be managed according to the anatomy of the injury (Fig. 2). Proximal extraperitoneal injuries (posterior aspect of the rectum above the peritoneal reflection) are more likely amenable to primary repair with limited mobilization of the mesorectum. If the injury is accessible, it may safely be repaired primarily with or without diversion. However, only an estimated 20% of extraperitoneal wounds are amenable to repair. Distal extraperitoneal injuries (below the peritoneal reflection) are technically challenging due to difficult exposure, limited space (especially in males), proximity of neurovascular and genitourinary structures, and anatomic distortion secondary to associated injuries. Extensive distal mobilization in search of a suspected wound is not indicated because of the risk for iatrogenic nerve, rectal, urologic, or vascular injury. Occasionally, transanal repair of very low rectal injuries may be possible without the morbidity of pelvic dissection, but we would never rely on this alone without proximal diversion. If a distal extraperitoneal rectal injury cannot be repaired or is inaccessible, then diversion is indicated. In 2016, the Eastern Association for the Surgery of Trauma published guidelines for management of penetrating nondestructive extraperitoneal rectal injury that recommended proximal diversion without routine presacral drainage or distal rectal washout. Current evidence does not support the practice of distal rectal washout and suggests that presacral drainage should be used very selectively if at all. We consider presacral drainage only for low posterior rectal injuries managed with diversion without

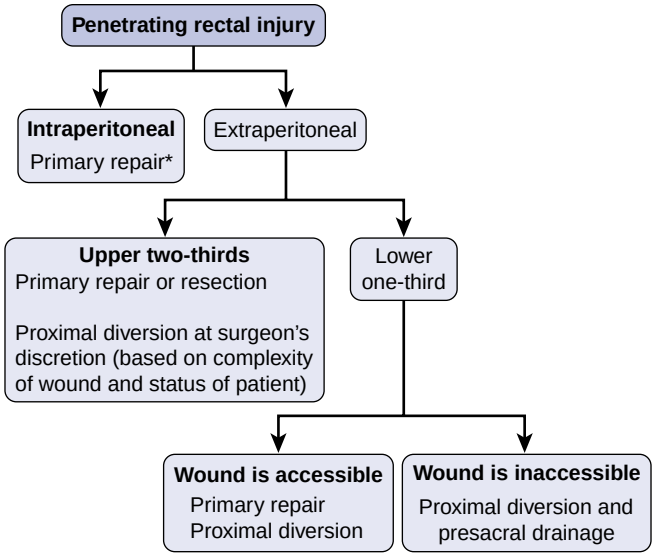


FIG. 2 Algorithm for the management of rectal injury. *DRE*, Digital rectal examination; *CT*, computed tomography. (From Clemens MS, Peace KM, Yi F. Rectal trauma: evidence-based practices. *Clin Colon Rectal Surg.* 2018;31:18.)

direct repair. Extraperitoneal wounds that are explored and repaired will effectively become intraperitoneal, thus precluding the need for presacral drainage. A recent multicenter AAST study identified presacral drainage and distal rectal washout as independent risk factors for abdominal complications, though this is somewhat subject to confounding as more severely injured patients may have undergone these interventions. Diversion can be accomplished via a loop sigmoid or transverse colostomy. If formed properly, loop colostomy is effective for diversion of the fecal stream, and outcomes are equivalent to those seen with end colostomy.

Anorectal Injuries

Traumatic injury to the anal sphincter complex is often secondary to obstetric injury, sexual assault, forceful introduction of a foreign body, or blunt injury due to complex pelvic fracture or "straddle"-type perineal injuries. A simple laceration to the anal mucosa can be repaired primarily, but complex lesions involving the distal perineum and rectum may require diverting colostomy. If extensive tissue debridement is required, referral to a colorectal specialist for consideration of overlapping sphincteroplasty, transposition of the gluteus or gracilis muscle with creation of a neosphincter, or abdominoperineal resection is advised. In the case of foreign body insertion, transanal extraction is successful in 70% of patients. The approach is with the patient in lithotomy, adequately sedated, and with adequate lubrication. A number of tricks can be used depending on the exact shape and consistency of the foreign body. Vacuum extraction devices, magnets for metal objects, penetrating clamps for rubber objects, and inflatable balloon catheters for jars or bottles have all been used as adjuncts to grasp or apply traction to foreign bodies. One or more rubber catheters (e.g., urinary catheters) can be passed around the object to break the vacuum seal that occasionally occurs. Even if transanal extraction fails and laparotomy is required, occasionally transabdominal assistance may make transanal extraction possible without opening the GI tract. If the colon or rectum must be opened, we usually try to open the sigmoid colon rather than the rectum. It is important to perform sigmoidoscopy after extraction to evaluate the patient for rectal injury. If the foreign body has caused perforation, then management is as for any other rectal injury.

COMPLICATIONS

Daily evaluation of the wound, perineum, ostomy (if present), and drains (if present) is essential. The primary concern with rectal injury is sepsis in the form of wound infections, abscesses, or anastomotic leak. Wound infections have been reported in up to 50% of patients with injuries to the rectum. Fevers, leukocytosis, and signs of infection should prompt axial imaging of the abdomen and pelvis to look for intraabdominal abscesses or anastomotic leak. These may be treated with a combination of broad-spectrum antibiotics, drainage, or reexploration. Fistulas are also potential complications, though distal colonic fistulas generally resolve with drainage and diversion.

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INJURED SPLEEN

Adil A. Shah, MD, Maaz K. Zuberi, MD, and Edward E. Cornwell III, MD

Splenic injury remains the most common solid organ injury after blunt abdominal trauma in adults. With the advent of computed tomography (CT) and early recognition of splenic injury, nonoperative management has become the appropriate modality with high success rates. This widespread acceptance of splenic salvage grows from concerns for the physiologic risk of the asplenic state, which includes possible susceptibility to nonfatal infections, as well as overwhelming postsplenectomy sepsis (OPSI), which is rare but lethal in adults. Asplenism has been shown to increase susceptibility to nonencapsulated organisms, increase the risk of hematologic events

such as myocardial infarctions, deep vein thrombosis, strokes, and pulmonary hypertension, and increase the risk of malignancy.

Some guidance regarding nonoperative management (NOM) of splenic trauma is obtained from evidence-based medicine guidelines generated by the Eastern Association for the Surgery of Trauma (EAST) in 2012. In describing two methods of splenic salvage, (1) NOM and (2) techniques in operative splenorrhaphy, it must be emphasized that some patients are best served with splenectomy. A patient's life should never be jeopardized to preserve the spleen.

NONOPERATIVE MANAGEMENT

Although selective nonoperative management of blunt splenic injuries in children has been accepted for decades, considerable evolution of thought has occurred regarding its efficacy in adults. Currently, the proportion of patients with splenic injuries managed nonoperatively has grown to more than 85%, due to improvements in CT scanning technology and advancement in angioembolization techniques of the spleen. Many patients whose minor splenic lacerations would have previously gone undetected are now being nonoperatively managed. This change in management is associated with a decrease in mortality rates. The development of the field has also been enhanced by the utility of the American Association for the Surgery of Trauma (AAST) Organ Injury Scale. The scale enables researchers and clinicians to make comparisons according to a standard approach, aiding in therapeutic and research decisions (Table 1). The AAST grades were revised in 2018 to include the presence of an arterial blush, pseudoaneurysm, and hemoperitoneum to aid in the selection of patients who would benefit from early angioembolization. Grades I and II injuries have a high rate of nonoperative management success, whereas grade III and higher more frequently require angiographic intervention or splenectomy.

Criteria of Patient Inclusion

Patients with blunt splenic injuries must meet the following criteria to be considered safe candidates for NOM (Box 1): (1) hemodynamic stability (SBP >90, HR <130), (2) CT documentation and classification of the injury, (3) absence on CT scan of intraabdominal (hollow viscus) or retroperitoneal (duodenum, pancreas, kidney) injuries mandating operative intervention, and (4) transfusion of fewer than 2 units of packed red blood cells (PRBCs) in a 24-hour period. Restricting transfusions to fewer than 2 units of PRBCs is extremely important in adults because, along with the known infectious risks associated with blood transfusions, compelling evidence now identifies blood product transfusion as an independent risk factor for complications in the injured patient. Portal hypertension is now classified as a relative contraindication to NOM due to increased splenic parenchymal pressures. Other exclusion criteria for NOM are patients with whom coagulopathy cannot be reversed and those who must urgently receive anticoagulation therapy (e.g., patient with an artificial heart valve or a trauma victim with blunt carotid injury requiring anticoagulation).

Particulars of Nonoperative Management

In 2012, the EAST published practice management guidelines for patients with blunt liver or spleen injuries derived from the best available evidence. Their level 2 recommendations suggest that age, neurologic status, or associated injuries do not preclude NOM in a hemodynamically stable patient, although age above 55 is linked to higher failure rates. An abdominal CT scan is the most reliable method to assess the severity of organ injury. Level 3 evidence suggests that this initial CT scan be obtained with intravenous and oral contrast to enhance its ability to delineate associated injuries.

The optimal success rate with NOM is obtained when CT scanning is combined with careful serial clinical examinations. Patients should be observed in a setting in which serial physical examinations, vital sign readings, and hematocrit determinations can be performed, and there should be immediate operating room availability in case of acute change in clinical examination. Although measuring hemoglobins every 6 hours for 48 hours while in the ICU setting is recommended by the Western Trauma Association (WTA), recent literature calls into question frequent serial hemoglobins, because most clinical decisions for intervention are based on hemodynamics and clinical examinations alone. A suggested NOM scheme for blunt splenic injury is depicted in Figure 1.

BOX 1 Criteria for Nonoperative Management of Blunt Splenic Injury

1. Hemodynamic stability
2. Documented computed tomography classification of injury
3. Absence of additional injuries requiring operative intervention
4. Transfusion of fewer than 2 of units packed red blood cells

TABLE 1 American Association for the Surgery of Trauma (AAST) Organ Injury Scale for the Spleen (2018 Update)

Classification	Description
Grade I	• Subcapsular hematoma <10% surface area • Parenchymal laceration <1 cm depth • Capsular tear
Grade II	• Hematoma: Subcapsular, 10%–50% surface area • Subcapsular hematoma 10%–50% surface area; intraparenchymal hematoma <5 cm • Parenchymal laceration 1–3 cm
Grade III	• Subcapsular hematoma >50% surface area; ruptured subcapsular or intraparenchymal hematoma ≥5 cm • Parenchymal laceration >3 cm depth
Grade IV	• Any injury in the presence of a splenic vascular injury or active bleeding confined within splenic capsule • Parenchymal laceration involving segmental or hilar vessels producing >25% devascularization
Grade V	• Any injury in the presence of splenic vascular injury with active bleeding extending beyond the spleen into the peritoneum

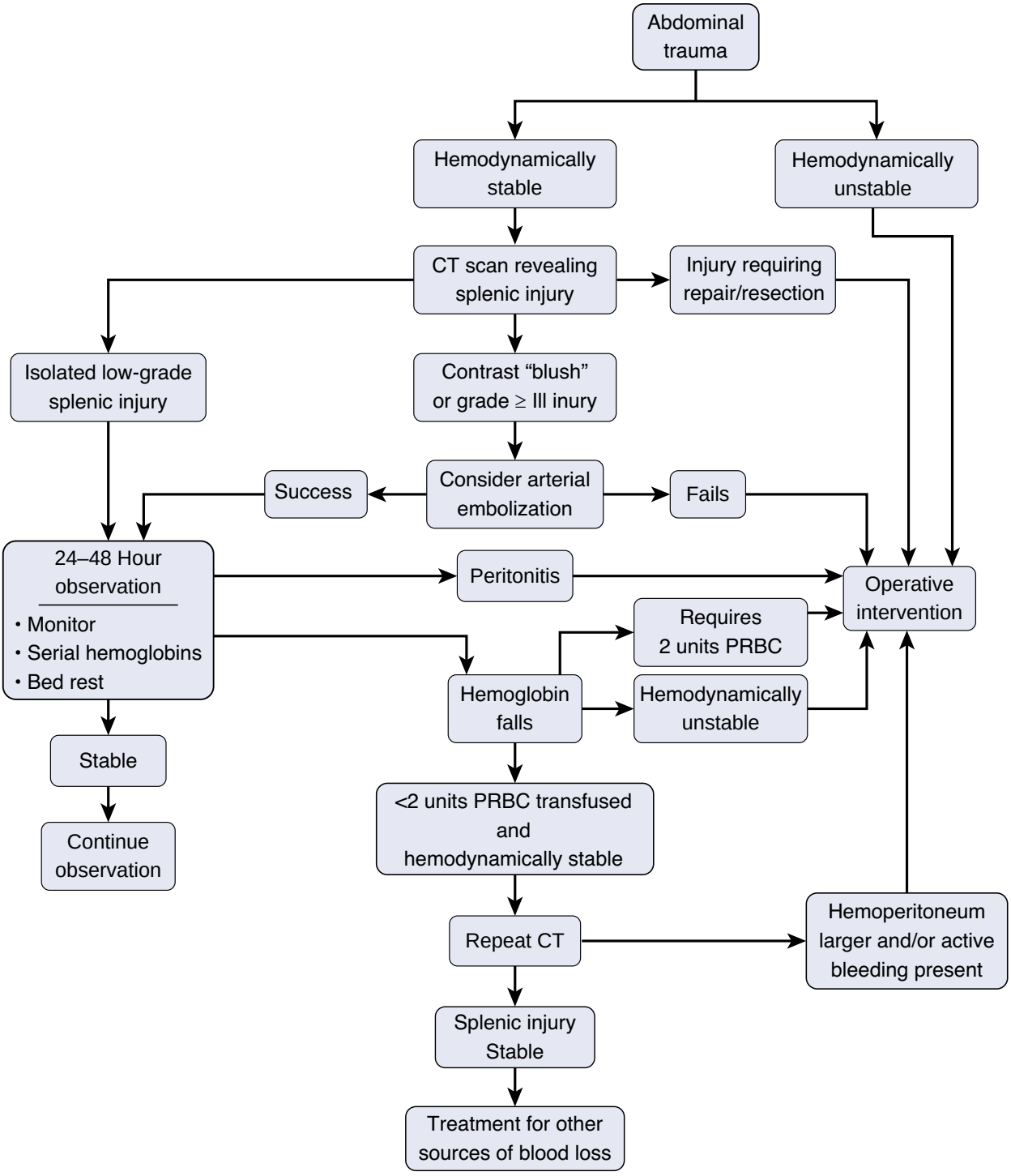


FIG. 1 Algorithm for nonoperative management of blunt splenic injuries

Angioembolization of the Splenic Artery

Angiography and embolization of the splenic artery have become mainstay adjuncts for NOM in patients with blunt splenic injury. Routine performance of an angiogram on all patients with splenic injury is unnecessary because few patients with grade I or grade II splenic injury require an interventional procedure. Angiography of the splenic artery should be considered in patients with grade III and higher splenic injuries and in patients with branch splenic artery hemorrhage delineated on the initial CT scan. In a multicenter study performed under the auspices of the WTA, hemorrhagic control was

achieved in up to 90% of patients who receive embolization, without any discernable loss of splenic function.

Embolization is either performed by using metal coils or gel foam (Pfizer). Although initial data were conflicting regarding the superiority of embolization material, a recent meta-analysis shows lower complication rates related to the use of coils, whereas gel foam has shown slightly better overall success rates of nonoperative intervention. The preference, however, is predicated on the interventional radiologist and their experience.

The splenic artery embolization can be performed distally, proximally, or in combination. Proximal embolization is favored in settings where a localized lesion is not identified as it reduces overall parenchymal flow. It is faster to perform and is associated with fewer complications. A disadvantage is the inability to reintervene intravascularly in case of a rebleed. Distal embolization is favored when a lesion is localized since it is a more targeted therapy. It carries a higher risk of postprocedure complications including splenic infarct and abscess formation but has a higher hemorrhage control success rate compared with proximal embolization. A combined embolization procedure has fallen out of favor due to high complications.

Splenic function tends to be relatively preserved postembolization; however, a definitive comment cannot be made due to small study sizes and inadequate parameters that can be studied to measure splenic function. The authors recommend vaccination for all patients who undergo embolization.

The WTA recommends considering a second CT scan in 48 to 72 hours to rule out a persistent or new pseudoaneurysm development. If found, additional endovascular or operative intervention should be pursued.

Progression of Care

There is still a paucity of data to determine the optimal time a patient receiving nonoperative therapy should be kept NPO (nothing by mouth) and on bed rest, and when they should be initiated on deep venous thromboembolism prophylaxis. Two recent studies have suggested that chemical DVT prophylaxis can be initiated within 48 hours in patients undergoing NOM; however, the number of patients with high-grade splenic injuries was low in these studies. Most experts, including the authors, prefer early enteral feeding within 24 to 48 hours. Other questions under study are when such patients can be safely discharged home and resume normal activity and whether they require follow-up radiographic imaging for their splenic injury. A recent study followed pediatric splenic injury patients with serial CT scans and showed complete resolution of low-grade injuries by 8 weeks. Ten percent of patients showed progression of splenic injury. Based on this, the WTA recommends a repeat CT scan in 48 to 72 hours to evaluate for progression of splenic injury before discharge, whereas EAST does not make any recommendations on routine repeat CT scans due to lack of definitive data. However, EAST recommendations favor repeating a CT scan in patients with high-grade splenic injuries, in patients with high-risk occupations (e.g., athletes, construction workers), or those that will be traveling before granting them medical clearance for normal activity.

Currently, there is no evidence to demonstrate a benefit to a specific period of bed rest in NOM splenic injury. The American Pediatric Surgical Association (APSA) does recommend bed rest of 1 day plus the grade of injury; however, physician practice has always been more liberal compared with the pediatric guidelines. The WTA and World Society of Emergency Surgery (WSES) recommend no bed rest for patients with grade I splenic injuries and bed rest for 24 hours with bathroom privileges for patients with splenic injury grades II to V. As part of an EAST multicenter trial studying the failure of observation for blunt splenic injury, Peitzman and colleagues found that 75% of patients who failed NOM did so within 48 hours, 88% within 5 days, and 93% of patients within 1 week of the injury.

The Success of Nonoperative Management

The practice management guidelines sponsored by EAST and published in 2012 revealed variable nonoperative management success rates ranging from 62% to 92% based on the grade of splenic injury. In 2015, the AAST Splenic Injury Outcomes Trial study group reported a 97% success rate with NOM (383 patients with nonoperative management of splenic trauma). If the patient becomes hemodynamically unstable, emergent exploration is indicated. If a stable patient demonstrates a downward drift in their hemoglobin, a repeat CT scan may be performed with intravenous contrast. On occasion, the initial CT may not reveal the true grade of splenic injury or an injured vessel that was previously in spasm may start to hemorrhage. Patients with such findings may benefit from angioembolization. However, if the patient has required 2 or more units of blood or has undergone prior angioembolization, operative intervention is indicated. Other causes for NOM failure include late bleeding (before or after discharge) and abscess formation.

SPLENORRHAPHY AND SPLENIC PRESERVATION

By the early 1980s, techniques of splenorrhaphy were fairly well standardized, including adequate exposure and splenic mobilization by division of avascular ligaments; facilitated organ repair, which was usually achieved by topical hemostatic agents; suture repair; partial splenectomy; or a combination of these. Three major adjuncts to operative splenic repair were introduced by the late 1980s: argon beam coagulation (ABC), fibrin glue, and polyglycolic mesh wrap.

The decision to save rather than remove an injured spleen requires consideration of the total complex of the patient's injuries. Splenic salvage should not be attempted in unstable patients undergoing damage-control surgery. Similarly, a patient with a severe head injury requiring intracranial pressure monitoring or a widened mediastinum that must be worked up deserves expeditious splenectomy so that other diagnostic and therapeutic maneuvers may be pursued. Likewise, a patient should not be subjected to multiple transfusions because of excessive surgical persistence at repairing a nonsalvageable spleen.

After the decision to attempt splenorrhaphy has been made, adequate exposure and mobilization are mandatory. Attempting to repair an incompletely mobilized spleen is a frustrating exercise in futility for both the surgeon and assistant. Division of avascular ligaments (splenophrenic, splenorenal, and splenocolic) is essential to mobilize the spleen medially out of its bed and up into the operative field close to the midline position of its embryologic origin (Fig. 2). After the spleen has been mobilized and placed on a bed of dry lap pads, assessed, and debrided of frankly devitalized fragments, hemostasis may be achieved by a combination of topical hemostatic agents such as microfibrillar collagen (e.g., Avitene; Davol, Cranston, RI), methylcellulose (e.g., Surgicel; Johnson & Johnson, New Brunswick, NJ), or mattress sutures (e.g., 3-0 Prolene; Ethicon, Piscataway, NJ) placed either directly or over Teflon pledgets.

Partial splenectomy may be selected when early ligation of a branch of the splenic artery to a segment of the spleen results in major progress toward hemostasis (Fig. 3). Provided that 50% of the splenic parenchyma attached to an identifiable vessel is viable, partial splenectomy may be performed, and splenic immune function can be expected to be maintained. Once the splenic hilum is dissected, the injured vessel or the feeding vessel to the area of the injury is clamped. The splenic parenchyma is observed to demarcate the area of ischemia after vessel clamp. Early demarcation of the segment of the spleen to be removed with the electrocautery device

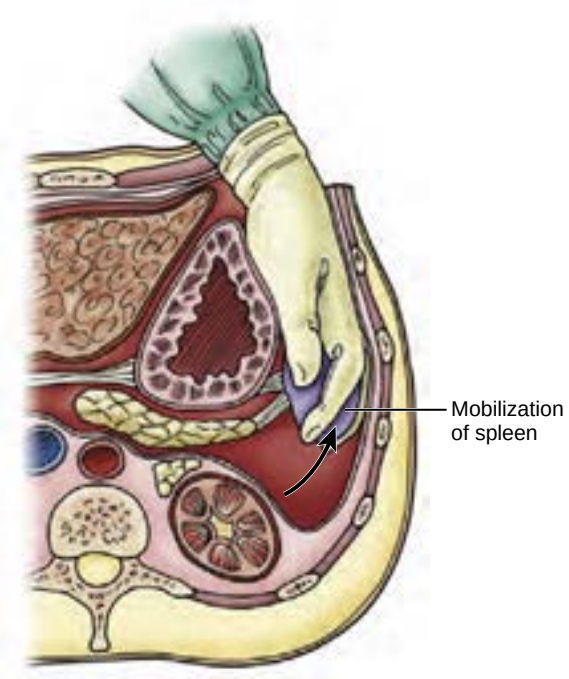


FIG. 2 After division of avascular ligaments, the spleen can be mobilized medially, up to the operative field, close to the midline position. *(From Trunkey DD. Spleen. In Blaisdell FW, Trunkey DD, eds.* Trauma management, Vol I: Abdominal Trauma. *New York, 1982, Thieme.)*

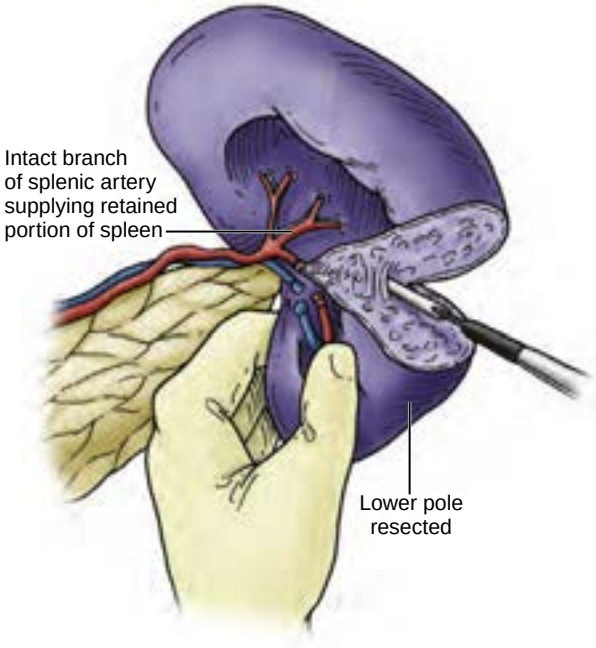


FIG. 3 To achieve hemostasis, the splenic artery branch to the lower pole of the spleen is ligated. Subsequently, an anatomic resection of the lower pole of the spleen is performed. *(Courtesy C. Sandone, Johns Hopkins School of Medicine, Baltimore, MD.)*

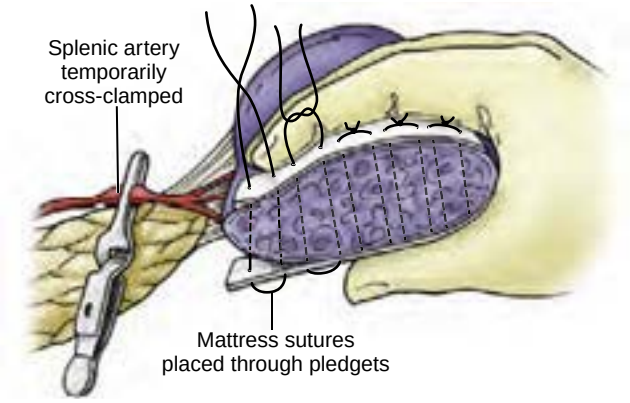


FIG. 4 Manual compression and, if necessary, clamping of the splenic artery provide necessary hemostasis required to oversew the margin of the retained spleen. Teflon pledgets are employed to prevent a suture from cutting through the otherwise friable tissue. *(Courtesy C. Sandone, Johns Hopkins School of Medicine, Baltimore, MD)*

facilitates exposing intrasplenic vessels for individual suture ligation, which should proceed meticulously. Occasionally, cross-clamping the splenic hilum may be temporarily required if manual compression does not produce adequate hemostasis. The resected margin of the spleen is then oversewn with mattress sutures with or without pledgets (Fig. 4). If necessary, a blunt liver needle may be used to place such mattress sutures. In certain circumstances, the upper pole of the spleen can be preserved if it has a short gastric pedicle; similarly, the lower pole of the spleen can be preserved as long as one major branch from the splenic hilum is preserved.

Argon Beam Coagulator

ABC is an electrocoagulation system that should not be confused with the argon laser. No eyewear is required. The instrument achieves hemostasis by using inert gas as a medium to conduct radiofrequency energy (Fig. 5). The gas is emitted as a constant flow at room temperature from a handpiece and nozzle that blows away blood and debris to optimize visualization. The first large clinical series using the ABC for splenic salvage was published in 1991. This report concluded that most spleens with superficial lacerations are easily salvaged with standard topical maneuvers and that the ABC offers a technical advantage in patients with deep parenchymal injuries. In the ensuing decade, the ABC has achieved wide acceptance in the management of both spleen and other solid organ injuries.

Absorbable Mesh Wrap

Polyglycolic mesh wrap is another modality reported to be useful for splenic salvage. The injured spleen is passed through an enlarged hole in the mesh fashioned for this purpose. The mesh is then wrapped around the spleen and sutured to itself to provide tamponade (Figs. 6 and 7). Recent reports have also suggested incorporating methylcellulose into the mesh to help "bulk it up." In this technique, multiple layers of methylcellulose are placed directly onto the injured surfaces, after which the mesh is secured around the spleen, enhancing the tamponade effect. Previous concerns of possible mesh infection, especially in the setting of hollow viscus injury, have proved to be unfounded based on large series of patients. We have not routinely used this described method due to the relative time required for completion in the setting of an unstable patient.

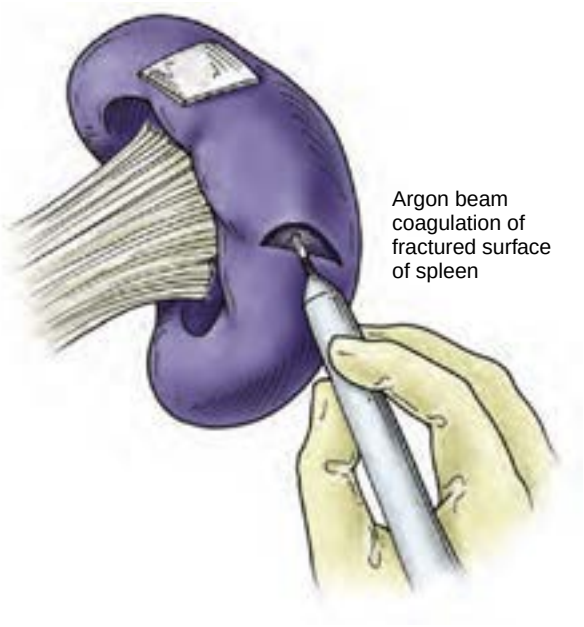


FIG. 5 Argon beam coagulator. *(Courtesy C. Sandone, Johns Hopkins School of Medicine, Baltimore, MD)*

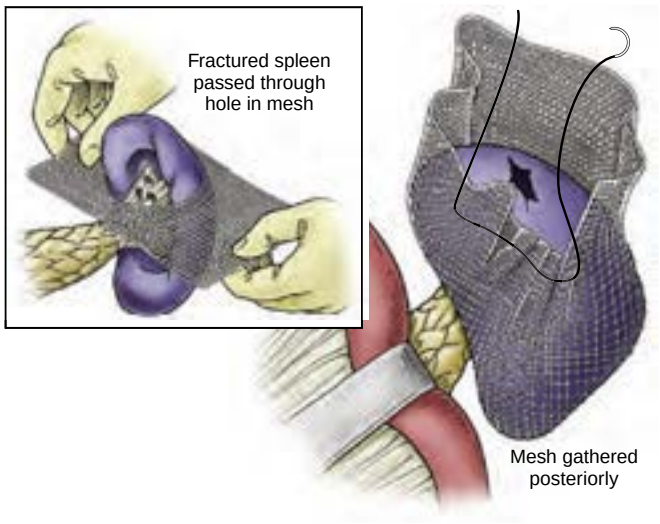


FIG. 6 Mesh splenorrhaphy: injured spleen is passed through an enlarged hole in the mesh. The mesh is then wrapped around the spleen and sutured to itself. *(Courtesy C. Sandone, Johns Hopkins School of Medicine, Baltimore, MD.)*

Fibrin Glue

Early impressive laboratory experience with fibrin glue, which consists of fibrinogen, dried thrombin, and calcium chloride, prompted its emergence in the clinical arena. Commonly available fibrin sealants such as Tisseal (Immuno, Vienna, Austria) and Crosseal (Omrix Pharmaceuticals, Brussels, Belgium) may be applied directly to the injured surface of the spleen to achieve immediate hemostasis, especially on linear tears and cracks.



FIG. 7 Mesh splenorrhaphy in situ with Surgicel placed directly over the injured portion of the spleen, before suturing to secure the mesh. *(Courtesy Horacio A. Massotto, MD, Costa Rica)*

Laparoscopy

The role of minimally invasive surgery in isolated splenic injury appears to be limited. Hemodynamically unstable patients warrant a laparotomy, and most hemodynamically stable patients can undergo nonoperative management successfully. Laparoscopy may play a role in patients who undergo laparoscopy to rule out diaphragm injuries in patients with left thoracoabdominal stab wounds. If the patient has an associated splenic injury and is hemodynamically stable, a laparoscopic splenorrhaphy can be attempted.

POSTSPLENECTOMY VACCINATION

All patients who undergo splenectomy and those that receive embolization should receive the pneumococcal vaccine Prevnar 13, Haemophilus influenza type B, and meningococcal vaccines 2 weeks postop. In the setting of unreliable follow-up, vaccinations should be provided on the day of discharge. The pneumococcal vaccine should be followed by Pneumovax 23 at least 8 weeks after the initial vaccination. Subsequent boosters for pneumococcal and meningococcal should be administered in 5 years. Seasonal flu vaccines should be provided to postsplenectomy patients as well. A recommended vaccination schedule is described in Table 2. Controversy exists about whether vaccinations should be provided to patients that have undergone embolization because short-term studies have shown relative immunocompetence and splenic function preservation in these patients. The validity of these studies is called into question as the best parameter to test for splenic function has not been determined as of yet. Furthermore, most of the current data are short-term with small sample sizes. Additionally, in the setting of trauma, patients may have an immunocompromised state, reducing the efficacy of vaccination, prompting more interest in posttraumatic splenic preservation.

RECOMMENDATIONS

Careful selection, CT scan imaging, and serial clinical examinations are crucial to the successful nonoperative management of patients with blunt splenic injuries. Angioembolization has furthered our ability to salvage a patient's spleen without an operation. Hemodynamic instability warrants urgent surgical exploration. Patients

TABLE 2 United States Centers for Disease Control and Prevention (CDC) Advisory Council on Immunization Practices Recommendations for Patients with Asplenia

Organism	Vaccine Dose #1	Dose at 4 Weeks	Dose at 8 Weeks	Dose at 5 Years
Streptococcus pneumoniae	Pneumococcal conjugate 13-valent [PCV13 (Prevnar 13)]	—	Pneumococcal polysaccharide 23-valent [PPSV23 (Pneumovax 23)]	Pneumococcal polysaccharide 23-valent [PPSV23 (Pneumovax 23)]
Haemophilus influenzae type B	Haemophilus b conjugate [Hib (ActHIB)]	—	—	—
Neisseria meningitidis	Meningococcal serogroup B [MenB (Bexsero)]	Meningococcal serogroup B [MenB (Bexsero)]	—	—
Neisseria meningitidis	Meningococcal conjugate [MenACWY-CRM (Menveo)	—	Meningococcal conjugate [MenACWY-CRM (Menveo)	Meningococcal conjugate [MenACWY-CRM (Menveo)

requiring surgical intervention are best managed with adequate exposure and mobilization. ABC, fibrin glue, and absorbable mesh wrap appear to have advanced the art of splenic salvage beyond the level achieved by topical hemostatic agents, suturing, and partial splenectomy. With these technical considerations combined with careful selection of candidates for nonoperative management, we have evolved to a point at which most patients with splenic injuries can undergo successful splenic salvage.

Suggested Readings

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Renal and Ureteral Traumatic Injuries

Michael W. Witthaus, MD, and Jill C. Buckley, MD

RETROPERITONEAL EVALUATION

The surgeon's initial evaluation is essential for the assessment of retroperitoneal trauma, i.e., history, physical exam, focused assessment with sonography in trauma (FAST), concomitant injuries, patient stability, mechanism of injury, and CT findings. Indeed, blunt trauma will have a different approach than penetrating trauma. The surgeon's repertoire consists of a milieu of clinical decisions based on the location of the retroperitoneal injury (zones I–III) (Fig. 1). Trauma injuries may be one or multiple locations: kidney, ureter, or both.

Evaluating the retroperitoneum for renal or ureteral injury in the stable patient is best accomplished by CT scan with IV contrast capturing three critical phases: arterial, nephrogram, and pyelogram. Evaluation is usually predicated by any gross or microhematuria. Even children (<16 years of age) should undergo a CT urogram if >50 RBC/HPF is appreciated on urinalysis. Retroperitoneal injury may be detected with either the immediate trauma presentation or completed in a delayed fashion once the patient's stability has improved. The surgeon must be cognizant of renal vein injuries due to the lowest detection sensitivity on CT imaging of all renal hilar anatomic structures.

Renal trauma is recognized routinely, whereas ureteral injuries can be more subtle. Ideally, ureteral injuries are identified on the delayed phase of the CT scan meant to detail the renal pelvis and ureteral anatomy. Intraoperative cystoscopy with retrograde pyelograms can be performed when a ureteral injury is suspected and no preoperative imaging was obtained. A postponed CT image is reasonable to rule out ureteral injury if patient stability was an initial concern precluding ureteral evaluation. The single-shot intravenous pyelogram (IVP) can be useful to identify the presence of a contralateral kidney and an apparent ureteral injury but is no longer algorithmically performed due to being hydration dependent and providing less anatomic detail than both the retrograde pyelogram or CT imaging.

The classification of renal injuries has evolved over the years by verifying appropriate patients for conservative management and improving the predictability of needing intervention (Table 1; Fig. 2). Further advancements have been observed with successful interventional radiologic techniques, which have largely supplanted the

isolated nephrectomy for segmental arterial bleeding at many institutions. For unstable patients with active bleeding from the kidney or renal hilum, operative intervention may be required, especially when interventional radiology is unavailable or unsuccessful at managing hemorrhagic shock.

Contrast extravasation on the delayed imaging is pathognomonic for a renal pelvis or ureteral injury. The presentation of gross hematuria, urinoma, or hydronephrosis may suggest ureteral injury. Patients with a drain in place can have a drain creatinine evaluated relative to serum creatinine levels. A significant fold increase is suggestive of a urinary leak.

The American Association for the Surgery of Trauma (AAST) classification of ureteral injuries has helped standardize the severity of injury (Table 2). However, additional factors have a consequence on the surgeon's choice for repair, for example, the location and the length of injury. Often, the first step is to perform cystoscopy and obtain a retrograde pyelogram. If the surgery is open or laparoscopic, then the ureter should be directly inspected. Placing a ureteral stent retrograde is always a safe course if there is suspicion of mild ureteral trauma. Of course, the patient's stability must always be considered. A transected ureter can be tied with a suture or clipped and a nephrostomy tube placed to temporize until the patient is safe for reconstruction. The nephrostomy tube should be placed relatively expeditiously as an obstructed unilateral system does not result in permanent injury in the first 24 hours, but a solitary kidney will result in significant electrolyte abnormalities in a short interval.

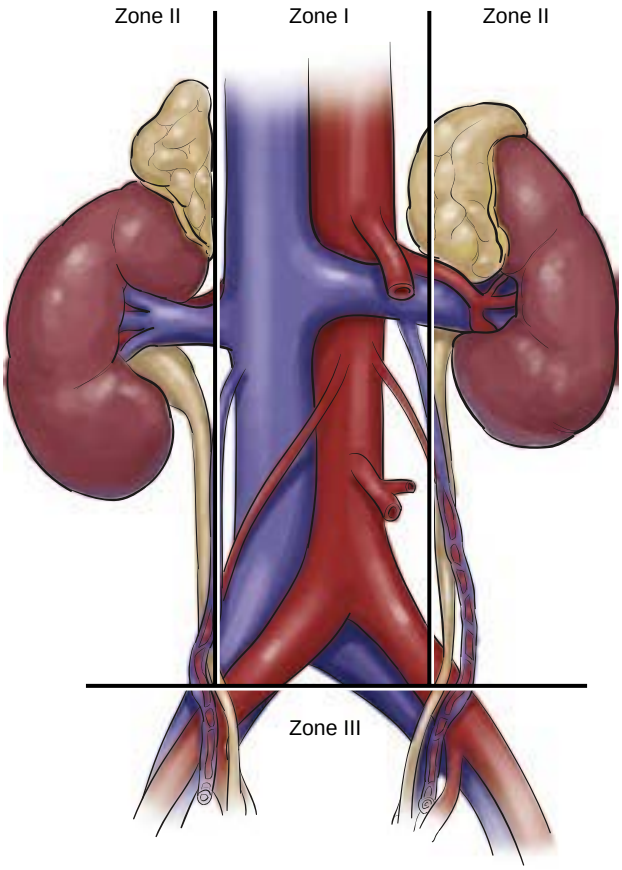


FIG. 1 Retroperitoneal zones: zone I is central; zone II is lateral; zone III is pelvic. *(From Rasmussen TE, Tai NR.* Rich's Vascular Trauma. *3rd Ed. Philadelphia: Elsevier; 2016.)*

RENAL

Indications for Nonoperative Management

Noninvasive management strategies should be the first step in managing hemodynamically stable patients with renal trauma. The renal injury grade's predictive value is indicative of the potential need for intervention (see Table 1). The standard initial management is bed rest, serial hemoglobin levels, and hemodynamic monitoring. Nonoperative management always contains active surveillance for potential clinical changes requiring blood transfusion with or without angioembolization. Furthermore, follow-up imaging should be obtained for deep lacerations (AAST IV–V) or clinical signs of complications: fever, worsening flank pain, or ongoing blood loss. Consideration should be made to place a ureteral stent or percutaneous nephrostomy tube if there is associated urinary extravasation with an enlarging urinoma or fever.

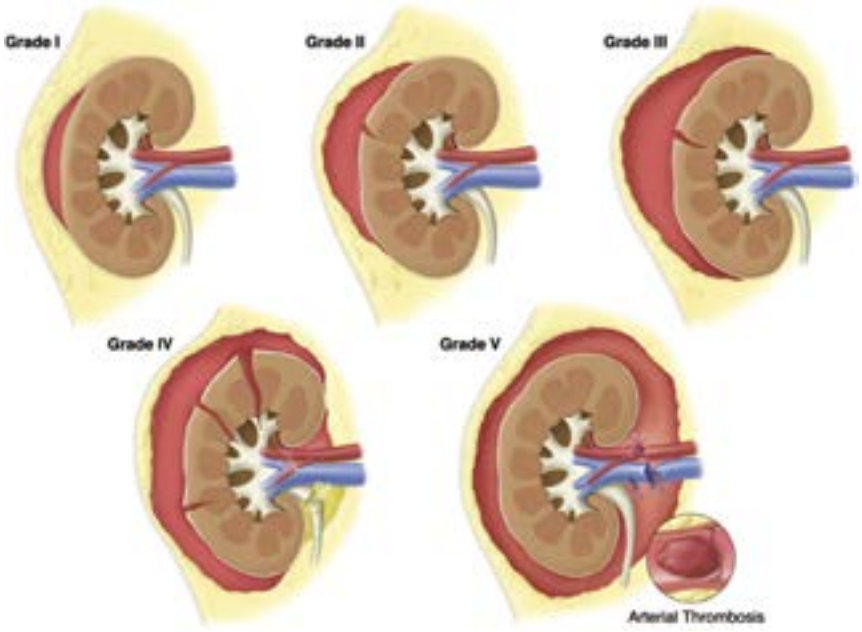


FIG. 2 AAST renal classification. *(From Buckley JC, McAninch JW: Revision of current American Association for the Surgery of Trauma Renal Injury grading system. J Trauma 2011;70:35.)*

TABLE 1 AAST Renal Classification

AAST Grade	AIS Severity	Imaging Criteria (CT Findings)	Operative Goals	Pathologic Criteria
I	2	• Subcapsular hematoma and/or parenchymal contusion without laceration	• Nonexpanding subcapsular hematoma • Parenchymal contusion without laceration	• Subcapsular hematoma or parenchymal contusion without parenchymal laceration
II	2	• Perirenal hematoma confined to Gerota facia • Renal parenchymal laceration ≤1 cm depth without urinary extravasation	• Nonexpanding perirenal hematoma confined to Gerota fascia • Renal parenchymal laceration ≤1 cm depth without urinary extravasation	• Perirenal hematoma confined to Gerota fascia • Renal parenchymal laceration ≤1 cm depth without urinary extravasation
III	3	• Renal parenchymal laceration >1 cm depth without collecting system rupture or urinary extravasation • Any injury in the presence of a kidney vascular injury or active bleeding contained within Gerota fascia	• Renal parenchymal laceration >1 cm depth without collecting system rupture or urinary extravasation	• Renal parenchymal laceration >1 cm depth without collecting system rupture or urinary extravasation
IV	4	• Parenchymal laceration extending into urinary collecting system with urinary extravasation • Renal pelvis laceration and/or complete ureteropelvic disruption • Segmental renal vein or artery injury • Active bleeding beyond Gerota fascia into the retroperitoneum or peritoneum • Segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding	• Parenchymal laceration extending into urinary collecting system with urinary extravasation • Renal pelvis laceration and/or complete ureteropelvic disruption • Segmental renal vein or artery injury • Segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding	• Parenchymal laceration extending into urinary collecting system • Renal pelvis laceration and/or complete ureteropelvic disruption • Segmental renal vein or artery injury • Segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding
V	5	• Main renal artery or vein laceration or avulsion of hilum • Devascularized kidney with active bleeding • Shattered kidney with loss of identifiable parenchymal renal anatomy	• Main renal artery or vein laceration or avulsion of hilum • Devascularized kidney with active bleeding • Shattered kidney with loss of identifiable parenchymal renal anatomy	Main renal artery or vein laceration or avulsion of hilum Devascularized kidney Shattered kidney with loss of identifiable parenchymal renal anatomy

Vascular injury is defined as a pseudoaneurysm or arteriovenous fistula and appears as a focal collection of vascular contrast that decreases in attenuation with delayed imaging.
Active bleeding from a vascular injury presents as vascular contrast, focal or diffuse, that increases in size or attenuation in delayed phase. Vascular thrombosis can lead to organ infarction.
Grade based on highest grade assessment made on imaging, at operation or on pathologic specimen.
More than one grade of kidney injury may be present and should be classified by the higher grade of injury.
Advance one grade for bilateral injuries, up to grade III.

From Kozar RA, Crandall M, Shanmuganathan K, et al. Organ injury scaling 2018 update: spleen, liver, and kidney *J Trauma Acute Care Surg.* 2018;85:1119–1122.

Indications for Interventional Radiologic Management

Angioembolization has become increasingly utilized in hemodynamically unstable patients as clinical skill has increased and institutional access has improved. Interventional radiology management includes patients with sizeable perirenal hematoma (>4 cm) or vascular contrast extravasation. Clinical outcomes of immediate angioembolization are comparable, but surgical intervention may be necessary for deep or complex renal lacerations (AAST III–V).

Surgical Indication

Patient instability, an acute abdomen, positive FAST exam, and CT findings suggestive of intraperitoneal pathology indicate operative evaluation (Table 3). Operative intervention is commonly performed with a midline vertical incision. On occasion, penetrating or blunt trauma can present in isolation of other intraperitoneal injuries and allows for alternative surgical approaches. Renal hilar injuries can be life-threatening and require immediate exploration.

TABLE 2 American Association for the Surgery of Trauma Ureteral Injury Scale

Grade	Injury
I	Hematoma; contusion or hematoma without devascularization
II	Laceration; <50% transection
III	Laceration; ≥50% transection
IV	Laceration; complete transection with <2 cm of devascularization
V	Laceration; avulsion with >2 cm of devascularization

Modified from Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling. III: Chest wall, abdominal vascular, ureter, bladder, and urethra. *J Trauma*. 1992;33(3):337–339.

TABLE 3 Indications for Operative Management of Renal Trauma

Absolute Indications	Relative Indications
Expanding pulsatile retroperitoneal hematoma	Urinary extravasation without viable tissue
Renal pedicle avulsion	Concurrent colon/pancreas/trauma exploration with incomplete staging or grade III or greater concurrent renal injury
Persistent/life-threatening shock or hemorrhage	Renovascular hypertension
Ureteropelvic junction disruption or avulsion	Failed embolization

The Trauma Ex Lap—Renal Injury

Technique

The patient is positioned supine with arms out, prepped from chest to pubis with sufficient vascular access, followed by a midline vertical incision. Assessment of the kidneys should be performed, depending on the degree of shock and damage control management. With renal hemorrhage, control of the renal hilum is paramount, and the first step is to obtain access. Immediate access to the bilateral renal hilum is performed by identifying the mesenteric vein (Fig. 3). The renal hilum is identified and isolated for clamping if necessary. Vascular clamps or Rummel tourniquets can be placed for vascular control. It is crucial to obtain vascular control before entering the retroperitoneal hematoma. If the patient is hemodynamically unstable from a kidney injury, a nephrectomy may be necessary. Knowing whether there is a contralateral kidney is essential. Intraoperative renal ultrasound, IVP, or palpation can be used to identify if bilateral kidneys are present.

The left renal hemorrhage can be managed with the Mattox maneuver (Fig. 4). The Mattox maneuver can help evaluate injuries to the left zones II and III. In addition, this conveniently exposes zone I in cases of aortic injury. If a pulsatile retroperitoneal hematoma is encountered, the exposure is performed quickly while the surgeon runs their hand laterally and posteriorly along the kidney. Then the kidney is lifted to the midline, which exposes the posterior hilum. The renal vessels are then controlled, then divided. The ureter is then taken last just above the iliac vessels on the psoas. The splenorenal ligament is avascular and requires division to avoid a splenic shear injury when removing the kidney. The adrenal can often be spared and is found within Gerota's fascia. The superior mesenteric artery is nearby and should be carefully avoided.

The Cattell-Braasch maneuver can be performed to obtain access to the right kidney (Fig. 5). The maneuver allows for evaluating the right zones II and III with the subsequent Kocher maneuver of the duodenum to obtain full access to the right renal hilum. However, not exploring the retroperitoneum is an option in circumstances of a nonpulsatile, nonexpanding retroperitoneum. Do not explore if this is encountered; leave the hematoma alone and obtain a delayed CT scan later. Avoiding exploration decreases the probability of nephrectomy while maintaining patient safety with the remaining options of angioembolization in the future, as well as ureteral stenting if needed.

Nephrectomy versus Renal Salvage

Technique

The dilemma in renal trauma is the decision to remove or repair. The patient in extremis is a considerably more straightforward decision because the patient's life should not be jeopardized to save a kidney. There is a significantly less postoperative risk when a nephrectomy is performed. In a non–life-threatening situation, renal preservation is the goal. The kidney has a remarkable ability to heal and, given time, will do so. Apart from grade V renal injuries, most are observed or managed without renal exploration. A ureteral stent, drain, or IR embolization may be required to manage a high-grade renal injury. A nephrectomy leaves considerably fewer nephrons for the patient in their life ahead and should only be done in life-threatening situations.

In a life-threatening situation where renal exploration is required, urologic expertise is highly valued. The urologist offers expertise with kidney management and repair, which can help collaboration between surgeons to ensure successful management of a renal injury. The kidney repair relies on understanding the segmental nature of the renal blood supply, which allows resection of devitalized parenchyma without compromise to the remaining parenchyma of the kidney. Diligent closure of the collecting system, followed by renorrhaphy, can salvage the remaining nephrons and avoid future kidney disease (Figs. 6 and 7). The renorrhaphy can be augmented with a rotational flap of omentum to support the closure (Fig. 8).

When the collecting system is entered, consideration of leaving a ureteral stent should always be made: entries are large or numerous, or there may be a delayed leak due to a projectile blast injury. Leaving a drain in these circumstances is sensible, whereas leaving a drain is seldom indicated with a nephrectomy alone.

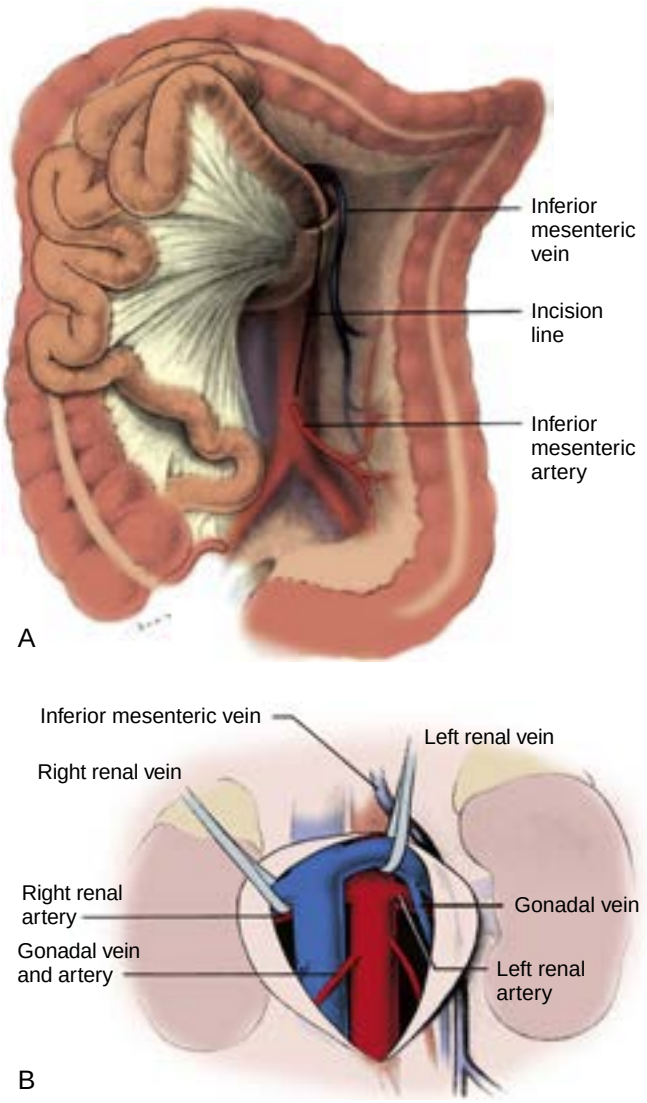


FIG. 3 Technique to obtain vascular control. **(A)** Exposure of the major vessels. **(B)** Relationship of the renal vasculature after incision of the posterior peritoneum over the aorta. *(From McNinch JW. Surgery for renal trauma. In: Novick AC, Stream SB, Pontes JE, eds.* Stewart's Operative Urology. *Baltimore: Williams and Wilkins; 1989.)*

Complications

Beware of aberrant renal hilar anatomy: multiple renal arteries, multiple veins, and gonadal vessels that do not always follow the rubric. If the kidney is repaired or embolized, there is a risk of delayed bleed, AV fistula, or pseudoaneurysm development. If the collecting system was repaired, there is a potential for a delayed urine leak, leading to a urinoma or perirenal abscess. Preparation allows for the best outcomes, and identifying the anatomy of the renal hilum on prior imaging is wise. Preparation includes knowledge of congenital anomalies such as a horseshoe kidney or a retroaortic renal vein, both of which can be unpleasant surprises.

Outcomes

Avoiding nephrectomy maximizes total nephrons and can result in the best clinical outcomes. There should be primary care follow-up for long-term chronic kidney disease screening: glomerular filtration rate (GFR), proteinuria, and hypertension. Hypertension can be exacerbated by renal scarring related to a Page kidney, which is renin-dependent and medically treatable.

URETER

Indications

Penetrating trauma is the most common etiology leading to ureteral injury. Relying on micro- or gross hematuria is not sensitive for identifying injury to the ureter, so high suspicion is needed. Ureteral injury is identified by either CT imaging (ideally with delayed images) or retrograde pyelogram. Once staged, a decision can be made on the management of the ureteral injury.

Indications for Ureteral Stent or Nephrostomy Tube Management

A ureteral stent should be placed for an identified ureteral contusion without a urinary leak in the trauma patient undergoing exploratory laparotomy. Nephrostomy drainage can be beneficial when a delayed ureteral injury is recognized or when severe urinary extravasation is present and maximal drainage is necessary to facilitate healing the injury. There are situations when both a ureteral stent and a nephrostomy tube will be used to optimize healing. The nephrostomy tubes are exchanged every 8 to 12 weeks to avoid infection.

Surgical Indication

Immediate repair of the ureter should be considered in the trauma patient undergoing exploratory laparotomy. Alternatively, ureteral repair may be performed if the injury is identified within 7 days of presentation. Generally, if the ureteral injury is identified after 7 days, a delayed repair is attempted several weeks after the urinary leakage and acute inflammation have resolved.

The course of the ureter traverses the retroperitoneum beneath the gonadal vessels, on top of the psoas, over the iliac vessels near the internal and external iliac bifurcation, which is the most reliable location for identification. The ureter blood supply varies by location; distally, the supply is lateral, then posterior as it travels over the iliac vessels, and then transitions to medially as the ureter travels to the renal hilum.

The Trauma Exploratory Laparotomy—Ureteral Injury

Open Technique

The patient is positioned supine with arms out, followed by a midline vertical incision. The ureters should be inspected if an injury has not been ruled out before the OR. Inspection of the ureters can be done visually or fluoroscopically. The ureter should be repaired if an injury is identified, relatively short in length, and the patient is stable. The ureter must be debrided to a bleeding edge to avoid future stricture. It should be noted that penetrating trauma can result in blast injury of up to 2 cm away from insult.

All repairs should use 4-0 or 5-0 absorbable interrupted sutures for a spatulated, water-tight, off-tension closure, and completed with at least a ureteral stent for optimal outcomes. A running suture technique should be reserved for elective clinical presentations. Permanent sutures within the urinary system should be avoided due to inherent lithogenicity resulting in ureteral obstruction or infection. The specific technique for ureteral repairs is based on length and location (Fig. 9). The patient in extremis is best managed with damage control and bailout: tying off the ureter, temporary urinary drainage, and delayed repair.

Proximal Ureter (Cephalad to Iliac Crest). The blood supply to the proximal ureter is found medial. Be aware that the main renal artery and vein will commonly be found anterior to the renal pelvis with the occasional caudal crossing vessel. A pyeloplasty may be required if a ureteropelvic junction (UPJ) is avulsed or severely

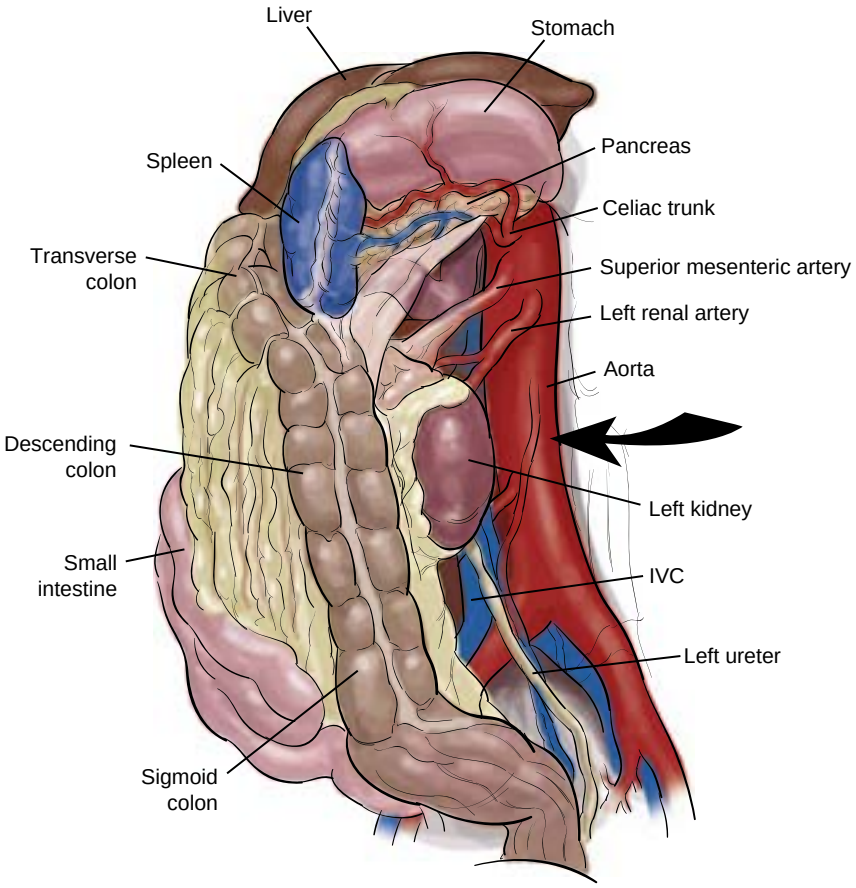


FIG. 4 Left medial visceral rotation to expose zone I and left-sided zones II and III vascular structures (Mattox). *IVC*, inferior vena cava. *(From Rasmussen TE, Tai NR.* Rich's Vascular Trauma. *3rd Ed. Philadelphia: Elsevier; 2016.)*

injured. UPJ disruptions are most commonly encountered with sudden deceleration injuries (blunt trauma), especially in pediatric patients.

The UPJ is anatomically the narrowest portion of the proximal ureter. However, the blood supply to the pelvis is robust, which can be helpful if a flap from the renal pelvis is required to keep the anastomosis off-tension. A ureteroureterostomy (UU) will be required if the injury is found more distal on the proximal ureter. The anastomosis requires spatulation of both ends with mucosa-to-mucosa apposition (Fig. 10). Generally, the spatulation should be performed opposite the blood supply to avoid devitalization. A tension-free anastomosis should be attained by mobilization distally; if necessary, a downward nephropexy can be performed to avoid tension.

Midureter (Caudal to Iliac Crest, Cephalad to Sacroiliac). The midureter is identified at the sacroiliac joint as it crosses over the iliac vessels and travels cephalad to the iliac crest. The cephalad blood supply comes from the medial portion of the ureter. The ureter should always be debrided to healthy tissue. Mobilization both caudally and cephalad is generally required.

The UU is most often performed procedure in the midureter in an acute setting. On occasion, a trans-UU is required. A trans-UU is accomplished by passing the injured ureter retrosigmoid and performing an end-to-side anastomosis. Rarely a trans-UU is indicated in the trauma setting and is contraindicated in patients with a history of urolithiasis due to the potential endoscopic access issues. If increased length is needed, the bladder can be mobilized, and a psoas hitch can be performed with subsequent transverse incising of the bladder with cephalad mobilization (Boari flap). In dire circumstances, the Boari flap can be spiraled for a great distance to reach the UPJ. The ureter is anastomosed in a separate location, and the bladder is then closed longitudinally.

Distal Ureter (Caudal to Sacroiliac). Most distal injuries are best managed with a ureteral reimplant (ureteroneocystostomy). To maintain the reimplant off-tension, performing a psoas hitch is often required (Fig. 11). The bladder is mobilized bilaterally, followed by a bladder hitch to the psoas muscle. The hitch is performed with an interrupted absorbable suture into the psoas muscle tendon. When placing the sutures, care is taken to avoid nerve entrapment of either the genitofemoral or femoral nerve. A ureteral stent and Foley catheter are essential for optimal healing.

The Delayed Ureteral Repair

Technique

The ureter can be approached by open surgical techniques such as the traditional Gibson or Pfannenstiel incisions. However, robotic ureteral reconstruction has become the mainstay for elective delayed ureteral repair. Advancements made have allowed for accessing even the most hostile abdomen. Positioning can achieve this in the lateral (or modified lateral) decubitus position for mid and proximal ureteral reconstruction. Port placement is midline to allow maximal caudal and cephalad mobilization of the ureter with one port carried slightly more lateral. Preoperative planning is imperative and requires appropriate imaging: a cystogram to measure bladder capacity for mobilization and an antegrade nephrostogram to identify the defect location and length.

Urologic expertise in ureteral reconstruction is indispensable. Often retroperitoneal hematomas lead to fibrosis and difficult dissection. The ureter is most reliably identified as it crosses over the iliac vessels; however, the addition of indocyanine green (ICG) has allowed for confirming location via retro or antegrade injection of the dye. Ureteroscopy is also invaluable for identifying healthy ureter at the time of reconstruction.

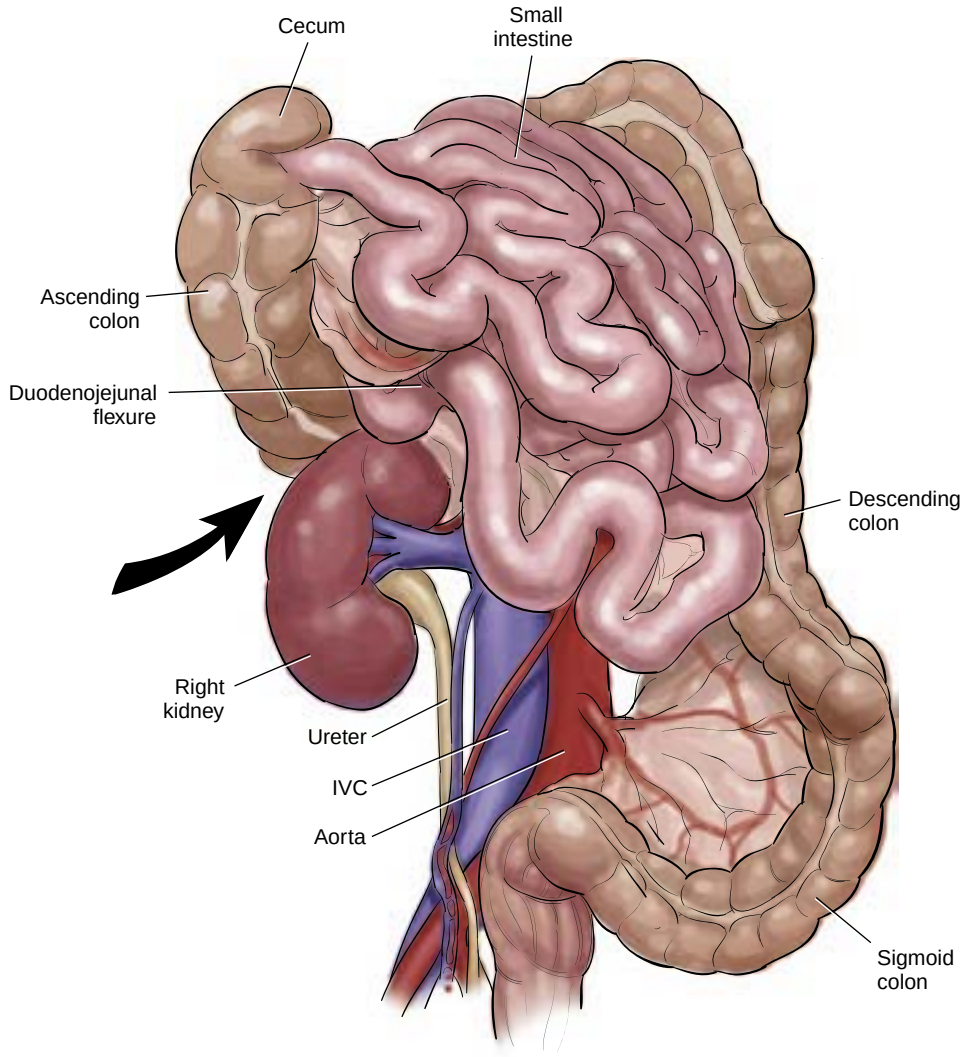


FIG. 5 Right medial visceral rotation to expose right-sided zone II and zone III vascular structures. Includes the Kocher and Cattell-Braasch maneuvers. *IVC*, Inferior vena cava. *(From Rasmussen TE, Tai NR.* Rich's Vascular Trauma. *3rd Ed. Philadelphia: Elsevier; 2016.).*

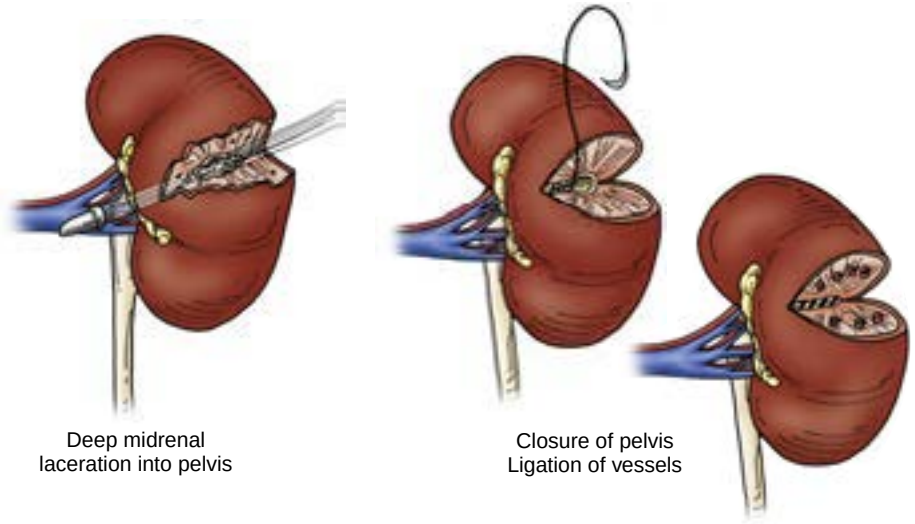


FIG. 6 Example of closure for traumatic penetrating renal injury. *(From Kim FJ, Molina WR, Biffl, WL. Kidney trauma [parenchymal and vascular injuries]: repair and nephrectomy. In: Cioffi WG, Asensio JA, Adams CA, et al., eds.* Atlas of Trauma/Emergency Surgical Techniques. *Philadelphia: Elsevier; 2014.)*

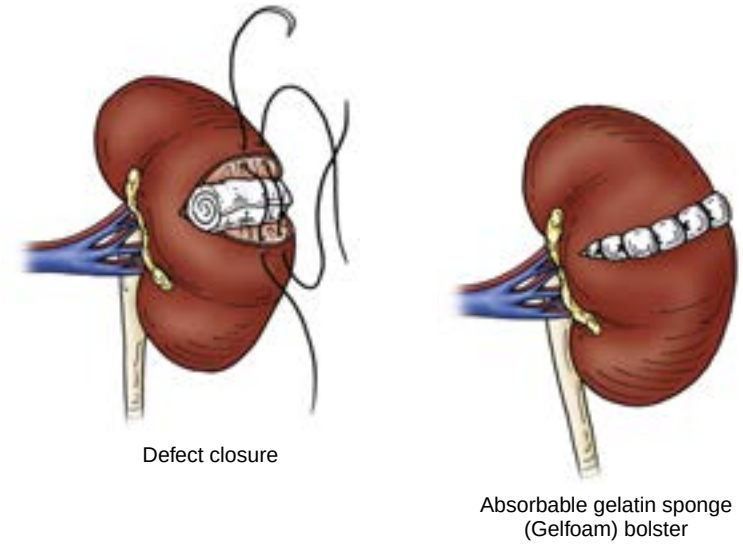


FIG. 7 Example of closure for traumatic penetrating renal injury with bolster. *(From Kim FJ, Molina WR, Biffl, WL. Kidney trauma [parenchymal and vascular injuries]: repair and nephrectomy. In: Cioffi WG, Asensio JA, Adams CA, et al., eds.* Atlas of Trauma/Emergency Surgical Techniques. *Philadelphia: Elsevier; 2014.)*

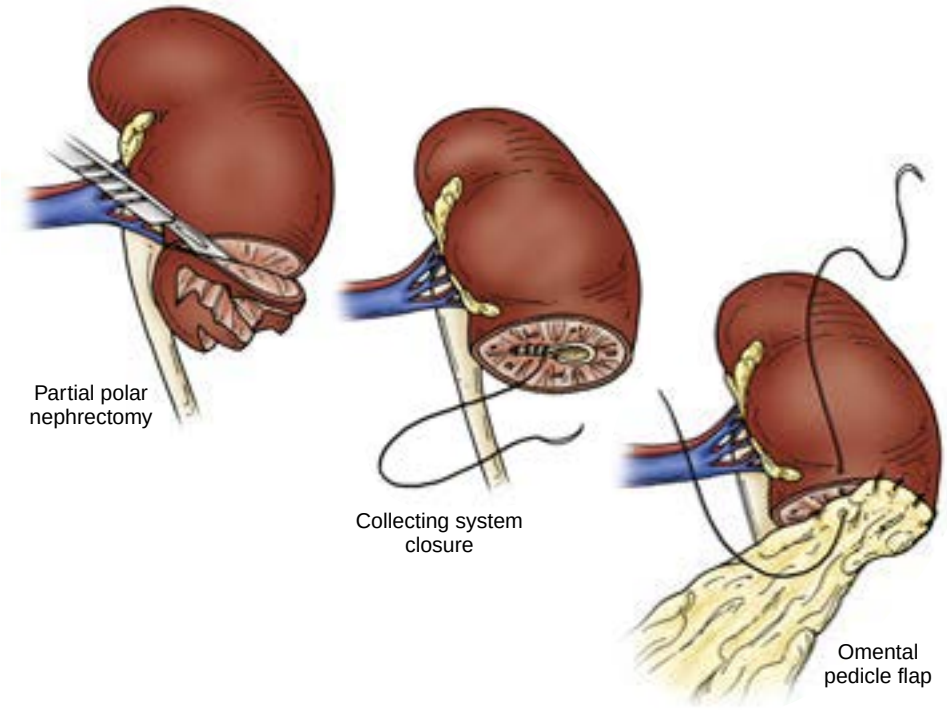


FIG. 8 Heminephrectomy for extensive injury. *(From Kim FJ, Molina WR, Biffl, WL. Kidney trauma [parenchymal and vascular injuries]: repair and nephrectomy. In: Cioffi WG, Asensio JA, Adams CA, et al., eds.* Atlas of Trauma/Emergency Surgical Techniques. *Philadelphia: Elsevier; 2014.)*

There are many troubleshooting techniques needed for delayed ureteral repair: downward nephropexy, bladder mobilization, psoas hitch, and bladder flaps. If the injury is on the right side, the appendix can be harvested and used as an interposition or an onlay flap. Additional tools include rotational flaps, such as the omentum, to buttress the repair. Further advancements have been made with buccal mucosal grafts for ureteroplasty, expanding the ureteral lumen as an onlay graft. Care must be taken to assure a healthy graft bed to quilt to or risk graft failure. The omentum is the ideal bed. Ureteral debridement to healthy tissue and confirmation of anastomotic perfusion with ICG is often performed to decrease the risk of potential ureteral stricture.

Ureteral Injury (>10 cm)

Rarely attempted in the acute setting, these injuries are best optimized with a controlled, delayed repair. Careful planning with complete access to the reconstructive arsenal is needed. Undeniably, a differential renal function imaging study can be helpful to determine whether the kidney is worth salvaging with a ureteral repair. Careful preoperative planning is often needed with an antegrade nephrostogram and cystogram to ensure adequate bladder capacity and confirm the extensive length of injury. Often distal and midureteral injuries can be approached with a bladder flap that can reach relatively high on the psoas at the expense of the patient's bladder capacity. Mobilization of the ipsilateral kidney may sometimes be required for a downward nephropexy to obtain a satisfactory anastomosis.

Ileal ureteral substitution (ileal ureter) can be achieved by utilizing a segment of the ileum at least 15 cm from the ileal-cecal junction. Depending on the length required, this can be a durable reconstruction for most patients, particularly with recurrent kidney stones, as this will serve as a "stone chute" that will pass a ureteral

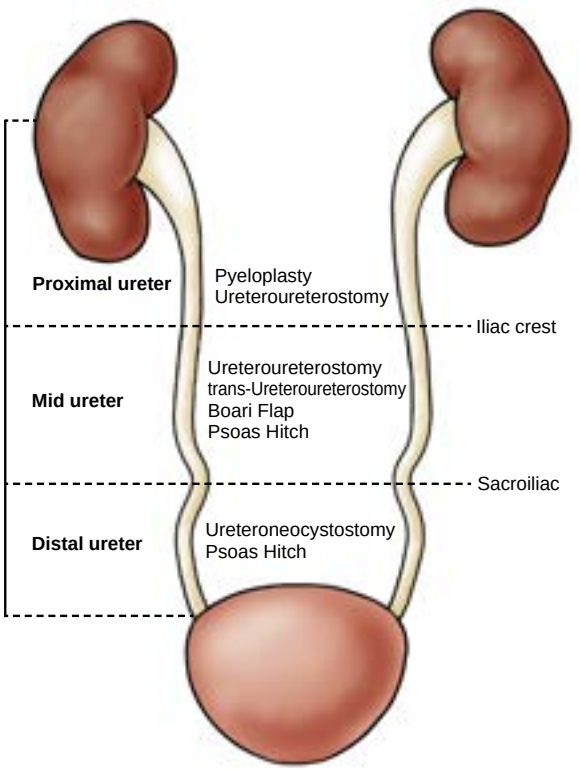


FIG. 9 Ureteral injury surgical repair technique based on location (proximal, mid, or distal).

stone without issue. Left-sided repairs require the ileal ureter vascular pedicle to be passed posterior to the sigmoid to maintain a retroperitoneal position. Autotransplantation of the kidney is an option for long ureteral injuries, especially when harvesting small bowel will be difficult or there are underlying reasons to avoid a bowel resection. For bilateral repairs, a reverse seven ileal interposition can be performed to accommodate complete upper tract drainage in bilateral ureteral obliteration cases.

Complications

Infections are the most common complications of ureteral injury repairs. Expert surgical technique is utilized to minimize the risk of urine leak. There is an inherent risk of ureteral stricture in all repairs. After surgical repair, patients are maximally drained to avoid complications: nephrostomy tube, ureteral stent, and Foley catheter. A drain is not usually required if the appropriate technique has been performed.

Outcomes

Sequential removal of urinary drainage tubes is prudent in the first 4 weeks postoperatively. Surveillance of the upper urinary tracts is mandatory due to the risk of silent obstruction of the kidney resulting in a nonfunctional renal unit. Surveillance can be accomplished with renal ultrasound screening and be advanced to CT or retrograde pyelograms if there is a concern. A MAG3 nuclear medicine study with and without Lasix can measure functional obstruction, which can provide valuable information when a patient has nonobstructing hydronephrosis. Special care should be taken in patients with prior pelvic radiation because these patients will have higher risks of complications and ureteral stricture occurrence.

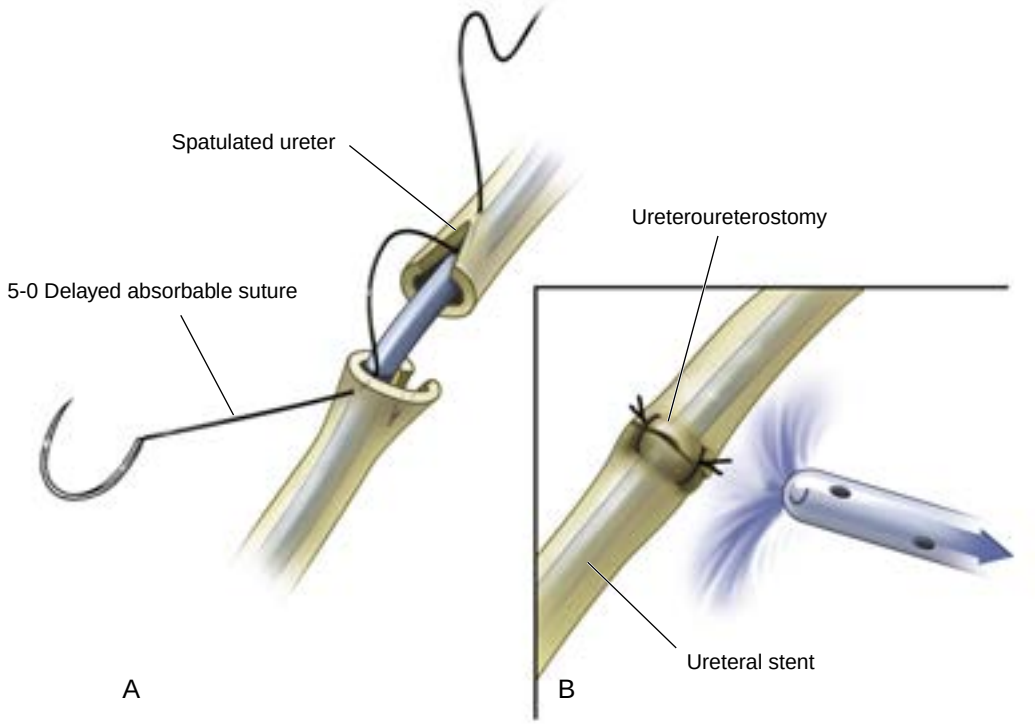


FIG. 10 Ureteral spatulation with mucosa-to-mucosa apposition over a ureteral stent.

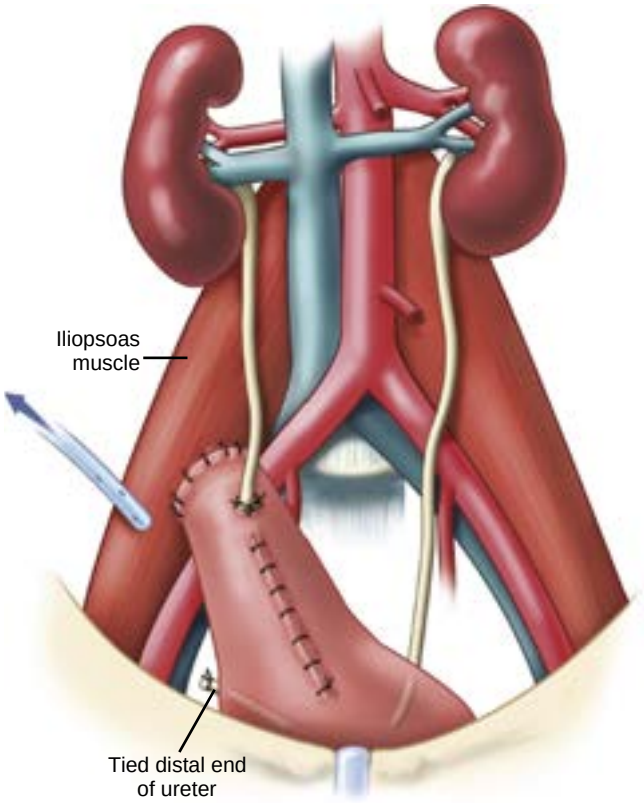


FIG. 11 Use of the psoas hitch for treatment of distal ureteral injuries. *(From Baggish M, Karim M, eds.* Atlas of Pelvic Anatomy and Gynecologic Surgery. *4th ed. Philadelphia: Elsevier; 2015.)*

Suggested Readings

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Tenets of Damage Control

Zachary Obinna Enumah, MD, PhD, MA, and Kent Allen Stevens, MD, MPH

INTRODUCTION

As the field of surgery has continued to evolve over the last several decades, the use and appropriateness of damage control operations (DCO) has become commonplace. The central tenets of a DCO include (1) controlling hemorrhage and exsanguination, (2) limiting contamination, and (3) maintaining adequate perfusion to end organs. The use of damage control surgery requires thoughtfulness, foresight, and a systematic approach to caring for the trauma or emergency general surgery patient, not all or whom should receive a DCO. The chapter is divided into three sections delineating the different stages of damage control: (1) preoperative, (2) intraoperative, and (3) postoperative. We conclude with remarks on the future of damage control, as well as important take-home points for practicing surgeons.

PHASE I: PREOPERATIVE DAMAGE CONTROL

Damage control before a patient even arrives at the hospital and trauma bay includes having perspective on the usefulness and appropriateness of a damage control strategy. It should not be used in every situation. Furthermore, much of the decision rests with the resources available (preoperatively, intraoperatively, and postoperatively) and the experience and comfort of the surgeon. For example, if a patient with an obvious vascular injury is being treated at a center without specialized or adequate vascular surgical capabilities, this patient may be better served with temporizing measures. Similarly, if one is practicing in an austere environment and pursuing a DCO for a patient whose needs may deplete a center's blood supply, judgment must be used with respect to the appropriateness of a DCO strategy because it is highly resource- and time-intensive (e.g., blood products, resuscitation products, labs, ICU beds, etc.).

In ideal circumstances, information about a patient is known before that patient's arrival in the trauma bay or at the hospital. This allows time for the trauma or surgical team to communicate with the emergency medical team, anesthesia, nursing, and blood bank to optimally prepare for the patient's arrival. Advanced Trauma Life Support (ATLS) protocols are followed with individual roles assigned to promote expedient but systematic care for the arriving injured

patient—if in the case of trauma. Upon arrival, ATLS protocols should be followed beginning with an expedient primary survey completed and then identifying and quickly determining whether a DCO strategy may be necessary given a patient's hemodynamic status and injuries. In certain circumstances, the use of adjuncts such as Focused Assessment with Sonography for Trauma (FAST) exam or portable radiography will help in the decision-making process. In all circumstances, good communication is critical to successful treatment of the patient.

Good communication will help alleviate obvious missteps in the resuscitation plan, which should include establishing appropriate IV access and initiating hemodynamic monitoring. For the choice of resuscitative fluids, evidence suggests that blood products are favored over crystalloid infusions when able and necessary. Excessive crystalloid transfusion, for example, may worsen coagulopathy given a net dilution of coagulation factors, and such volumes can have an inflammatory effect contributing to organ failure. Some centers have begun to revisit the use of whole blood transfusion for the bleeding patient who requires significant volume reexpansion, but the use of a 1:1:1 strategy of packed red blood cells (pRBCs), plasma, and platelets continues to be effective in treating the bleeding trauma patient. Lastly, the decision for operative intervention should be made expeditiously with the DCO strategy; if the patient condition and time permits, other preoperative adjuncts, such as CT, can be considered. Of note, the unstable patient may present with multiple wounds, each contributing individually or synergistically to their instability. In this situation, each wound should be considered and placed in the context of overall patient care. We use pelvic binders in a hypotensive patient with unstable pelvic fractures.

PHASE II: INTRAOPERATIVE DAMAGE CONTROL

If the decision is made to pursue an operative intervention, this can be approached in several ways: (1) damage control laparotomy, (2) damage control thoracotomy, and (3) damage control vascular surgery.

Damage Control Laparotomy

The surgeon should follow a systematic approach for managing the patient requiring a laparotomy. Usually, this patient is bleeding or has other significant signs of hypoperfusion, acidosis, hypothermia, and coagulopathy. We follow a systematic approach in identifying and managing wounds with additional maneuvers depending on the organ of interest.

- During initial exploration, a large midline incision should be utilized. Upon entering the abdomen, packs should be placed in all four quadrants.
- Removal of packs can either be in order of least likely area of hemorrhage to most, or vice versa. The important thing is to be systematic, so injuries are not missed.
- Hemorrhage should be controlled. Approaches to controlling hemorrhage varies on location and organ involved. Vascular injuries are discussed in the section, "Damage Control Vascular Surgery." Other organs are discussed here.

Liver

Liver injuries can be both readily apparent upon entry into the abdomen or occult. For easily recognizable injuries, direct suture ligation can be effective. We commonly use #1 chromic on a large needle ("liver stitch") for exposed liver or large lacerations and 4-0 Prolene suture for control of bleeding vessels or parenchyma. Suture ligation should be tight enough to control the bleeding but not too tight to induce tissue ischemia or, more commonly, pull through while tying. In other cases, coagulation using cautery or Argon can be effective, especially at controlling any raw surface injuries. In the case of injuries caused by a small projectile, a compression device constructed from a Penrose drain and red rubber can be effective in decreasing bleeding. For uncontrolled bleeding for which a source has not yet adequately been identified, a Pringle maneuver can be used, which involves clamping the porta. Bleeding despite a Pringle maneuver may indicate a retrohepatic inferior vena cava injury for which suture repair or packing should be pursued. Nonexpanding hematomas in the retroperitoneum should be left alone as opening them may lead to uncontrolled bleeding (Fig. 1).

Spleen

While percutaneous interventions with the rise of interventional radiology have demonstrated success up to grade IV splenic injuries, in the setting of damage control, major hemorrhage, or hemodynamic instability, a splenectomy should be performed. Delay in appropriate therapy can have major consequences.

Kidneys

Nonpulsatile, nonexpanding hematomas in zone 2 involving the kidneys should be left alone. Active, pulsatile, or expanding hematomas likely will require nephrectomy. Before opening Gerota's fascia in pursuit of a nephrectomy, the contralateral kidney should be identified and examined to ensure that it is normal in size and not injured.

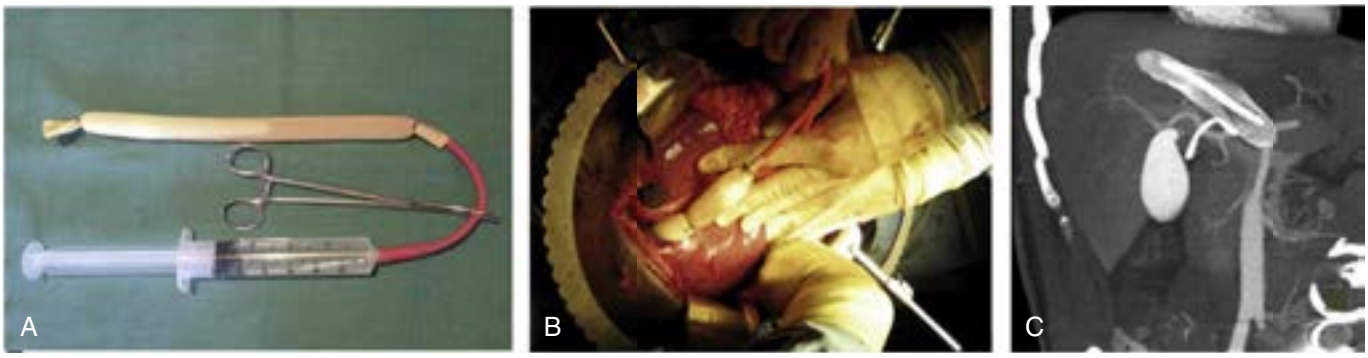


FIG. 1 **(A)** One-inch Fr Penrose drain and 12Fr red rubber catheter. **(B)** Deployed balloon device in penetrating liver injury. **(C)** CT image of deployed balloon device in penetrating liver injury. *(Adopted from Kodadek, LM, Efron DT, Haut ER. Intrahepatic Balloon Tamponade for Penetrating Liver Injury: Rarely Needed but Highly Effective.* World J Surg. *2019;43:486–489.)*

Pancreas

Priority in pancreatic injuries is to control bleeding, and this can often be managed with direct suture ligation. Secondary priorities include establishing appropriate drainage, and this should be obtained at the index operation to control any pancreatic leak. In rarer circumstances, trauma to the head of the pancreas may require a pancreaticoduodenectomy, which can be performed in the trauma setting. Reconstruction should not be undertaken in the index case but should be done at take back. Consulting a hepatopancreatobiliary surgeon can provide expertise in the reconstruction process and may lead to decreased complications.

Viscera

A main tenet of damage control surgery is to prevent contamination. Injuries to hollow viscous organs (e.g., stomach, small intestine, large intestine) should be managed to prevent contamination. This may involve direct two-layer repair, if the injury is small and the surrounding tissue healthy, or a segmental resection, if there is concern for more extensive injury. If performing a primary repair, one should be diligent in evaluating the surrounding tissue for hematoma and ischemic changes. If indicated, reconstruction should be delayed until the second-look laparotomy where a reexamination of all organs should be made to rule out a missed injury (Fig. 2).

DAMAGE CONTROL THORACIC SURGERY

Several indications merit the use of a thoracotomy for trauma. These include cardiac tamponade or other injuries identified on FAST, massive thoracic trauma or hemorrhage often identified during or after unilateral or bilateral chest tube placement, or high likelihood of intrathoracic injuries.

For cardiac tamponade, a left anterolateral thoracotomy can be performed in the 4th or 5th intercostal space from the sternum to the lateral chest wall, making sure to make a curvilinear incision as one moves more posterior. If not doing a clamshell thoracotomy, the right chest should still be decompressed with a thoracostomy to rule out a concomitant pneumothorax. In the setting of known tamponade, the pericardium should be opened first (before aortic cross-clamping) in a reverse T fashion to avoid injury to the phrenic nerve.

For direct injuries to the heart, these can be temporized with direct pressure, use of a skin stapler, or insertion and inflation of a Foley balloon. One should take caution not to exacerbate the size of the hole when using a Foley balloon. Formal closure can be

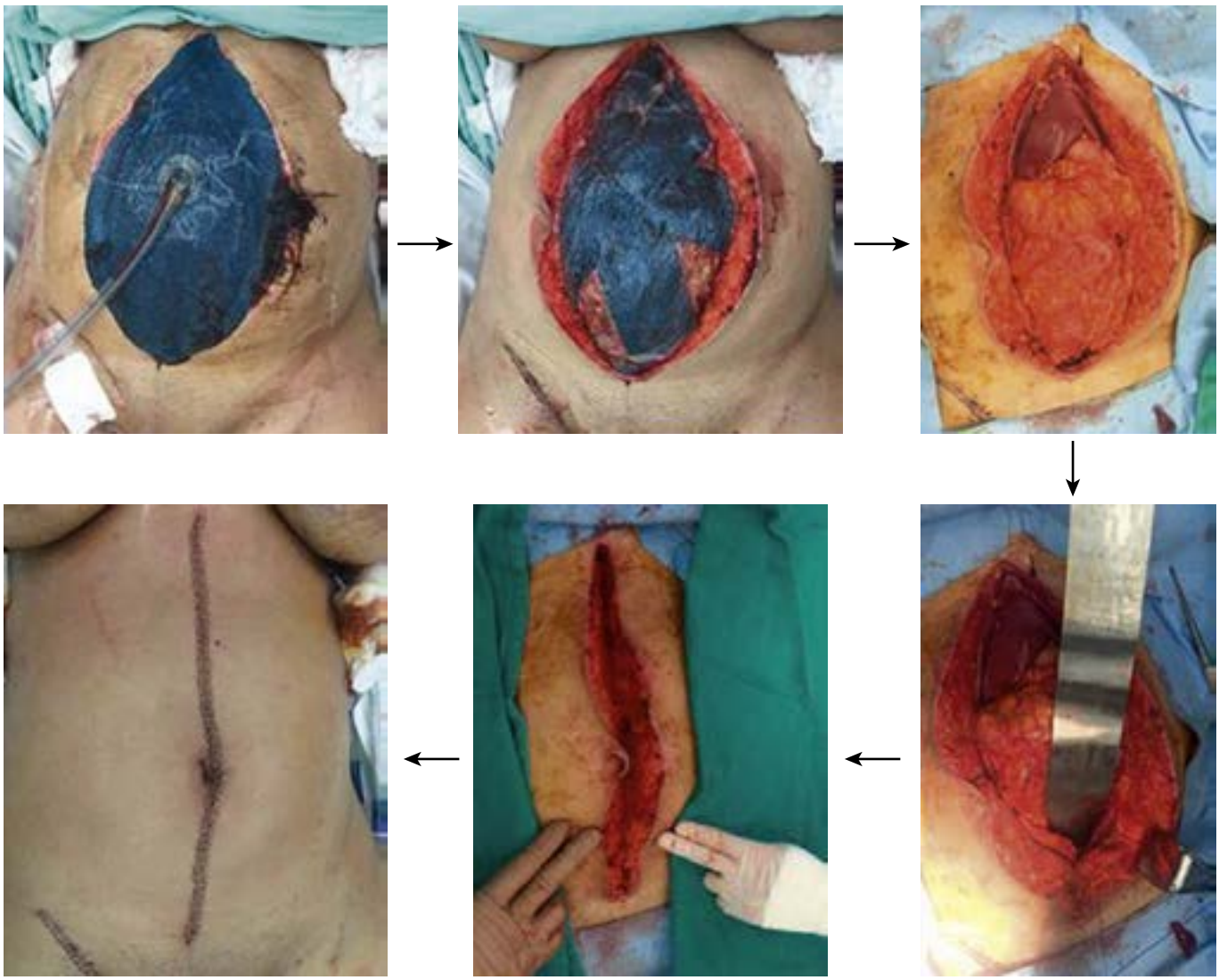


FIG. 2 Temporary abdominal closure.

attempted in the operating room with use of (pledgeted) sutures. Care should be taken to avoid coronary arteries when performing therapeutic maneuvers.

Massive pulmonary hemorrhage can be managed with anatomical (e.g., lobectomy, although this is rare) or nonanatomic (wedge) resections of the involved areas. For massive bleeding or refractory hemorrhage, hilar clamping or a hilar twist can be performed whereby the hilum of the affected lung is rotated 180 degrees. Division of the inferior pulmonary ligament up to the level of the inferior pulmonary vein is required for a hilar twist. Pneumonectomies should be avoided if possible as patients who undergo pneumonectomy have poor outcomes. In some cases, packing of the chest may be undertaken to facilitate transfer to the ICU. Although not as well understood as abdominal packing, one should monitor peak pressures routinely, as packing may have detrimental effects on lung expansion and barotrauma can result.

In rare circumstances where central access cannot be obtained through common approaches (e.g., subclavian, femoral, internal jugular), direct access in the right atrium can be used for resuscitation.

DAMAGE CONTROL VASCULAR SURGERY

Vascular injuries in the damage control setting come in many shapes and sizes and can include everything from a direct aortic injury to small mesenteric bleeding in the abdomen. Many patients with massive aortic injuries do not survive to make it to the hospital. Patients with aortic injury who do survive require repair. Recently, the use of a resuscitative endovascular balloon occlusion of the aorta (REBOA) has evolved as a technology to manage massive bleeding below the diaphragm.

Some large vessels cannot be ligated, such as the suprarenal IVC, superior mesenteric artery and vein, and iliac arteries. These must either be directly repaired or a temporary shunt can be placed for up to 3 days to restore flow. Vascular shunts can provide temporary reconstitution of flow during periods of resuscitation, while working on definitive repair or transfer to a higher level of care. The distal vessel or artery should be tested for back bleeding. Inadequate flow should prompt use of an embolectomy balloon catheter to rule out presence of thrombus or embolus. Systemic heparinization should be avoided given the patient's overall status; however, heparinized saline can be used to flush the proximal and distal vessels. Shunts should be secured with heavy sutures. Vessel debridement should not occur until formal reconstruction at the time of definitive repair. Doppler ultrasound can be used to serially monitor for signal and distant blood flow. Fasciotomies may be necessary if concern for prolonged ischemia.

Pelvic hematomas should be left alone or managed with interventional radiology unless there is an expanding or pulsatile hematoma. Smaller vessel injures, for example, to the mesentery, external iliac, or even the infrarenal IVC, can be ligated.

PHASE III: POSTOPERATIVE CARE AND ONGOING RESUSCITATION

Perhaps the most important aspect of damage control surgery is knowing when to leave the operating room and transfer the patient to an ICU to continue with resuscitation. Resuscitation must be aggressive and based on the patient's clinical condition and laboratory values. Goals include reversing coagulopathy, hypothermia, and acidosis—together known as the *lethal triad*.

Coagulopathy

Patients recovering in the ICU who underwent damage control surgery often are coagulopathic from recent massive hemorrhage and resuscitation with crystalloid fluids that dilute coagulation factors. When possible, transfusion with blood should be pursued. Evidence has long favored the use of a 1:1:1 transfusion strategy between pRBCs, plasma, and platelets. By the time a patient arrives at an ICU, transfusion should be continued and guided by laboratory values including full coagulation panel and the use of a thromboelastogram (TEG) (Fig. 3). TEG is a very useful dynamic tool that can be monitored in real time to assess which factors are needed. While expensive, these can be sent serially to monitor changes in a patient's underlying coagulopathy and to guide any further transfusion requirements. More recently, the use of whole blood resuscitation (rather than component parts) is regaining popularity for use in resuscitation.

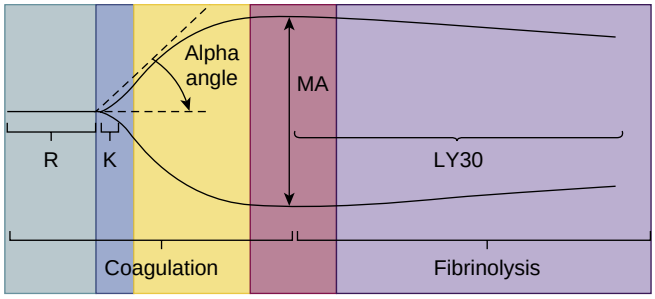


FIG. 3 Timeline of the evolving blood clot. *K*, Interval between reaction time and fixed value of clot firmness; *MA*, maximum amplitude; *R*, reaction time.

During the intraoperative and resuscitative phases, many patients are also hypothermic, which has long been associated with poor outcomes. In the trauma setting, mild hypothermia is temperature 36°C to 34°C, moderate is 34°C to 32°C, and severe hypothermia is <32°C. Hypothermia contributes to coagulopathy through multiple mechanisms including decreased enzyme activity, platelet function, and increased fibrinolytic activity. While fluids are often warmed before infusion into a patient undergoing damage control surgery, it would take a massive amount of fluid to just raise the core body temperature even by a single degree. Other passive and active adjuncts should be used when able including bear huggers, drying the patient, warm blankets, cavity lavage (intraperitoneal, intrathoracic), or, in the most extreme circumstances, extracorporeal warming through cardiopulmonary bypass.

Acidosis

Acidosis has many causes, but in the damage control setting, it is often a result of hypoperfusion causing a lactic acidosis. In and of itself, acidosis may have some advantages, such as improved dissociation of oxygen from hemoglobin. However, acidosis may have many detrimental factors, such as decreased cardiac contractility and poor function of vasopressors. Treatment with sodium bicarbonate can be used as a temporizing measure with the understanding that its administration does not treat the underlying cause. Importantly, administration of bicarbonate may have transient effects and increases on the pH and blood pressure, as a single ampule of bicarbonate has approximately the same sodium load (50 mEq) as one-third of a liter of normal saline. Caution must be taken, though, because sodium bicarbonate administration will lead to an increase in CO_2 levels that may lead to respiratory acidosis if CO_2 elimination cannot be increased (usually through increasing minute ventilation on the ventilator).

DEFINITIVE REPAIR

Following a period of resuscitation, patients should return to the operating room within 24 to 48 hours (unless clinically indicated earlier). A second-look laparotomy will provide an opportunity to reexamine for missed injuries and definitive repairs of hollow viscous, vascular, or other injuries. Importantly, counts during damage control laparotomy, especially if packing was left, are often

inaccurate. An abdominal x-ray should be obtained to rule out any retained foreign objects.

CLOSING REMARKS

In the acutely injured or exsanguinating patient, a stepwise approach to damage control can be life saving. Prompt identification of the unstable patient, aggressive resuscitation, surgical intervention, and definitive treatment combine to ensure the best possible outcome.

SUGGESTED READINGS

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Early Management of Pelvic Ring Disruption

J. Greg Mawn, MD, and Greg M. Osgood, MD

Simply stated, early detection and appropriate basic early interventions can save a life. Pelvis fractures can bleed significantly; first responders can preempt life-threatening bleeding without sophisticated technology or advanced training. Appropriately managed, a patient with a complex pelvic fracture may not require intensive care unit (ICU) admission and may not place undue stress on a health system. In the past 20 years, improvements in understanding simple interventions and teaching these to front-line providers have allowed primary emergency responders to save lives before orthopedic consultation. For this reason, expanded dissemination of these techniques to all trauma responders is integral to improving trauma outcomes.

EARLY MANAGEMENT OF PELVIC FRACTURES

Early management of pelvic fractures involves detection of patients at risk of sustaining this injury, appropriate radiographic evaluation and fracture classification, and rapid assessment of patients with life-threatening patterns. This early triage aids in efficient utilization of resources and immediate intervention in the appropriate patients. Most pelvic fractures are not life-threatening. Discerning the vulnerable patients with high-energy patterns with high degrees of morbidity and mortality within this diagnosis is imperative.

Mechanism of Injury in Pelvic Fractures

Pelvic fractures occur through both low-energy and high-energy mechanisms. The most common fractures of pelvic bones occur in falls from standing height. These fractures generally occur in elderly people with osteopenic or osteoporotic bone. The mechanism of injury is a direct impact through the greater trochanter or iliac crest, placing a lateral compression (LC) force across the pelvis. Typically, this generates a compression fracture through the sacral alar area and a corresponding, more displaced, anterior pelvic ring fracture through the superior and inferior ramus (Fig. 1). This fracture type occurs because of significant osteopenia. Although these are low-energy fractures and are rarely life-threatening, they may be devastating to the individual patient due to medical comorbidities and difficulty in mobilizing after the fracture.

In contrast, high-energy fractures to the pelvic ring occur through motor vehicle collisions, motorcycle injuries, falls from a height, and other mechanisms in which the pelvis is subjected to high velocity sudden impact. These fractures are characterized by larger degrees

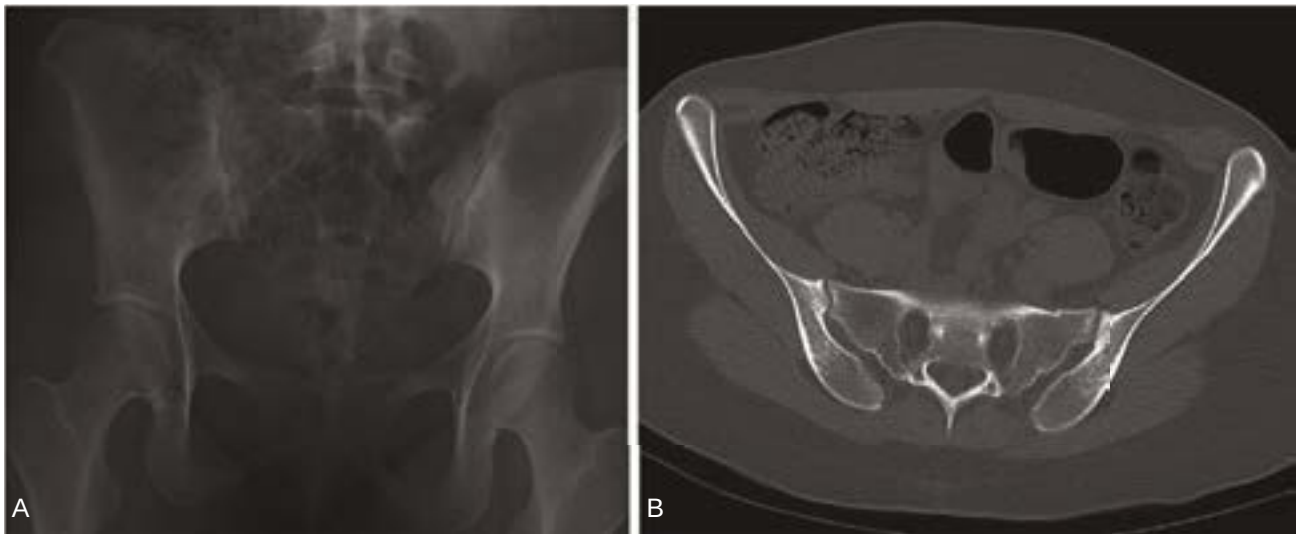


FIG. 1 **(A)** Anteroposterior radiograph of stable minimally displaced lateral compression pelvic fracture. **(B)** Axial CT image of sacrum shows left sacral alar compression fracture.

of displacement and generally occur in younger patients. They may involve LC, anteroposterior compression (APC), or vertical loading of the pelvic ring. Typically, these fractures occur through high-energy direct impact to the symphysis or greater trochanter, or indirect loading through the femur and femoral head, although crushing mechanism also occurs. Associated injuries and significant bleeding characterize these fractures; a high index of suspicion for this injury is required when patient presents with high-energy trauma to the abdomen and pelvic regions.

Relevant Patient History at the Time of Pelvic Trauma

Detection of pelvic trauma begins as the patient rolls into the trauma room. Pelvic trauma should be suspected after motor vehicle and motorcycle trauma, equestrian trauma, industrial injury, history of crushing mechanism, fall from a height, and other high-velocity injuries. The external signs of pelvic trauma include gross lower limb deformity, open wounds of the perineum and lumbosacral posterior torso (Fig. 2), bruising around the greater trochanters and thighs, and subcutaneous swelling about the pelvis. Internal degloving or separation of the skin from underlying fascia, the Morel-Lavallée lesion, often occurs about the thigh at the time of pelvic trauma (Fig. 3). This can cause significant unsuspected blood loss and may also complicate surgery if not addressed appropriately. Compressive dressings are the first intervention when this associated injury is detected. Another common presenting complaint on immediate presentation is lower limb neurologic dysfunction. Motor and sensory loss below the hips should raise suspicion of lumbo-pelvic trauma. The disturbing nature of this symptom to the patient makes it one of the first symptoms identified as the patient arrives in the trauma bay.

First responders should conduct a primary survey of the patient, assessing the ABCs of trauma response. Initial evaluation of the patient for sources of bleeding, the most common cause of hypotension in trauma, includes establishing whether there is pelvic and retroperitoneal bleeding. Bleeding from pelvic trauma occurs at lacerated vessels, but also from the large surface area of the fracture. Although providers often focus on arresting arterial blood loss, uncontrolled venous bleeding is a common source of hypotension. Veins do not contract or constrict, are thin-walled, and are difficult to access; therefore, venous bleeding is difficult to address directly without surgical intervention. Bleeding at fracture surfaces and venous bleeding can only be controlled by compression and stabilization of the fracture hematoma. Class III hemorrhage, with depression of systolic pressure, signifies a blood volume loss of 30%; in these cases, pelvic hemorrhage must be strongly considered. Focused abdominal sonography in trauma poorly identifies pelvic and retroperitoneal bleeding; therefore, a high index of suspicion of this problem is indicated. Computed tomography (CT) and angiography may be required to identify discrete vascular sources of hemorrhage.



FIG. 2 Posterior lumbosacral abrasions related to pelvic trauma.



FIG. 3 Large Morel-Lavallée lesion on the lateral thigh.

The events at the trauma scene are critical to patient outcome. Providers must know if there was associated external or perineal bleeding identified when the trauma occurred. In rushing to stabilize a patient with pelvic trauma, the clinician must identify all sources of external bleeding and open wounds as part of the initial survey; perineal and posterior wounds are often overlooked at the patient's peril (Fig. 4).

Before performing any surgical interventions, it is critical that the team assess the patient for prior abdominal and pelvic trauma, prior surgery in this area, prior laparoscopic or minimally invasive interventions, or radiation dosing in this area. These prior activities complicate all surgical procedures that address pelvic trauma.

IMMEDIATE ACTION SAVES LIVES: PRIMARY INTERVENTIONS

Advanced Trauma Life Support protocol mandates anteroposterior (AP) radiographs of the pelvis as part of the primary survey. Increasingly, CT of the body, and importantly the pelvis, is performed to identify life-threatening injury. The primary responder in pelvic trauma therefore should have preliminary radiographic imaging that identifies a pelvic fracture, allows some important generalizations on patient hemodynamic status, and signals the need for orthopedic consultation. If the patient's history and emergency radiographs suggest pelvic trauma, fracture, or dislocation, orthopedic consultation is warranted. The specialist's experience with immediate interventions and knowledge of common protocols for management is important in decreasing morbidity and mortality.

The next step in intervention is identifying the patient at risk from life-threatening hemorrhage from pelvic trauma. As stated, the combination of patient complaints, the history of the injury, and immediate visualization of the patient provide significant clues to this end. Radiographs that show gross displacement of the pelvis, gross asymmetry of pelvic bones, vertical shifting of the ilium on one side, and gross open book deformity of the pelvis warrant emergent placement of a circumferential pelvic sheet or binder; therefore, efficient circumferential physical examination of the anterior and

posterior lumbopelvic area and perineum (described later) is expedited and the compressive binder is applied. Rapid irrigation of large perineal wounds and packing improves the effect of a binder because large open wounds permit ongoing hemorrhage that cannot form a stable hematoma. The application of a pelvic compressive wrap or binder is lifesaving and should not be delayed (Fig. 5). It decreases the pelvic volume allowed for hemorrhage and applies a stabilizing compressive force at bleeding fracture surfaces and vessels. The technique of binder application is important in optimizing its effect and in minimizing the need for adjustment or reapplication.

Gentle realignment of the lower limbs with gross manual traction can improve binder effect. Bringing the heels together and internally rotating the lower extremities places the pelvis in optimal position. Commercially available binders attempt to simplify the steps of application; however, the principles of safe binder application must be followed. The first principle of binder application is centering the binder over the greater trochanters so that a compressive force is applied through inward force at the femoral heads. Improperly applied binders centered on the prominent iliac crest do not provide the best compression. The second principle is a wide, smooth surface of force application, roughly 20 cm in width, to distribute the required force over a large surface area of vulnerable skin. Wrinkles in sheets or binders must be avoided. Third, adequate compression should be applied; this often requires two to three responders to apply an effective binder when the patient is large. Two providers apply force at the greater trochanter, then one secures the binder. Finally, the patient with a binder must not be neglected. The skin beneath a binder is at risk due to initial trauma and then also due to binder compression.

There are few case reports of a binder causing or worsening a patient's injury. The question often arises if binders should be applied in the setting of LC injury, considering that the compressive force of the binder seems to only add to the internal rotation force of the patient's injury. If the patient's injury only involves internal rotation one hemipelvis (LC1 and LC2 injuries discussed later), the binder can be removed because it most likely does little to assist in hemorrhage control. If the patient's injury is a windswept pattern (LC3), the binder most likely can provide some benefit in stabilizing the pelvis and minimizing bleeding. A pelvic binder should always therefore be considered when pelvic fracture and hemorrhage is suspected as the source of hemorrhagic shock. Once the pelvic fracture pattern is appropriately identified, the binder may be removed if the provider determines it is not helping in the patient's care.

A binder may be left in place for 24 hours to allow fracture hematoma stabilization, but the skin must be checked around this time to assess for ongoing compromise. A binder may be left on after this point only if it is necessary for life-threatening injury. Prolonged application causes skin necrosis (Fig. 6) that can greatly affect surgical planning and patient outcomes.

A simple bed sheet is an effective universally available resource that all providers can learn to apply as a pelvic binder. Applied in this manner, it is referred to as a circumferential pelvic antishock sheet (CPAS). The same principles apply for sheet application: centering over the greater trochanters, wide surface of force application, effective compression and application, and vigilance (Fig. 7A,B). When these principles are followed, pelvic hemorrhage can be effectively controlled on the scene wherever pelvic trauma occurs. Access for internal fixation can be obtained by strategically cutting windows in the sheet before surgical preparation (Fig. 7C).



FIG. 4 Perineal wound associated with open fracture.



FIG. 5 Pelvic binder applied appropriately over greater trochanters and tightened.



FIG. 6 Early skin breakdown is seen directly over the right greater trochanter 24 hours after binder application.



FIG. 7 **(A)** Correct application of a circumferential pelvic antishock sheet. **(B)** A well-applied sheet secured with Kocher clamps compresses the pelvis. **(C)** Windows in the pelvic sheet allow access for conversion to anterior pelvic external fixation.

Physical Examination vs. Radiographs

The emergency imaging of the skeleton following high-energy trauma involves an AP pelvis radiograph, with or without axial CT of the pelvis. Although a great deal of information about a pelvic injury can be obtained through these standard radiographs, these images are merely snapshots of pelvic geometry that may belie the amount of pelvic instability and threat to the patient. A well-aligned pelvis on initial imaging may be the result of clothing, dressings, a compressive wrap or binder, or positioning at the time of radiograph, such as the cradling bed of the CT scanner. The pelvic injury and instability may be much greater than what appears on the films (Fig. 8). Stability of the pelvic ring should not be assumed when the history of injury suggests pelvic ring fracture, even when radiographs show a normal-appearing pelvis. Therefore, a careful physical examination is critical.

Physical examination follows in a standardized manner, involving circumferential inspection, palpation, gentle motion of the extremities, and complete neurovascular examination including examination of both lower extremities.

In the setting of high-energy trauma, multiple caregivers should be recruited to safely logroll the patient to inspect the posterior spine and pelvic region. The perineal area must be inspected with great care, looking for small punctate areas where bony fragments may have perforated the skin. Additionally, open fractures can occur through perforation through the rectum and genitourinary systems. For this reason, inspection and palpation of these sensitive areas is imperative; a speculum examination is warranted in women. Blood at the urethral meatus usually indicates urethral injury; this is best further investigated with retrograde urethrogram before Foley catheter insertion. The lower extremities should be inspected for subtle leg length inequality or abnormal rotational in either lower extremity. This may indicate significant displacement of one hemipelvis or upward displacement of one side of the pelvic ring, which allows limb shortening.



FIG. 8 **(A)** Anteroposterior pelvis radiograph on presentation in a binder. **(B)** Fluoroscopic examination under anesthesia demonstrates approximated symphysis at rest. **(C)** A moderate anterior force is applied, displacing the left hemipelvis laterally.

Palpation, specifically manipulative assessment of the pelvis, is important for these patients as well. AP compressive force is applied to patients in the supine position to detect subtle open book instability of the pelvic ring that is not identified on initial plain radiographs. In a similar manner, LC at the greater trochanters, detecting rotational instability of one hemipelvis, is essential. These maneuvers may disrupt pelvic hematoma and therefore should not be executed repeatedly. Gentle range of motion of the hips is indicated for these patients to detect fractures, soft tissue injury, or dislocation around the hip.

The neurovascular examination of a traumatized pelvis includes assessment of motor function and sensation from the waist down. Active hip, knee, ankle, and toe flexion and extension should be assessed. Lumbar and sacral roots must be tested for motor and sensory function. Rectal tone and perianal sensation should be tested at the time of rectal examination for open injury and hemoccult testing. Timely documentation of the neurovascular examination on presentation is important because the patient's examination may evolve after arrival.

Treatment of Open Pelvic Fracture Wounds

Open wounds may occur externally or internally, as previously mentioned. Antibiotics are first and foremost used to treat open wounds. Timely administration of antibiotics within 1 hour is essential in preventing infections at open fractures. First-generation cephalosporins should be administered for simple wounds; patients with large degloving injuries and wounds communicating with the bowel should also receive gram-negative coverage. External skin lacerations that do not extend to the abdomen, rectum, or vagina should be irrigated and closed, if small. Larger wounds may require operative exploration and treatment. Open wounds may allow significant ongoing bleeding. This may prevent stabilization of a pelvic hematoma. An open wound may also defeat the compressive forces of a pelvic binder; despite the binder's effect of decreasing the potential volume into which bleeding can occur, bleeding may continue through the open wound if it is not staunched. Careful emergency packing at open wounds should therefore precede application of the binder.

Traction Pins and Closed Reduction

Extremity traction can assist in stabilization of pelvic fractures by reducing and realigning anatomy and reapproximating surfaces that fit together. In the same manner, it can decrease the amount of bleeding at bony surfaces. Realignment and stabilization help to decrease patients' pain. Establishing normal anatomic relationships also helps in definitive treatment of the injury, considering that length will be more easily restored at the time of definitive fixation if traction has been in place.

Traction is most effective through application of skeletal traction pins through the distal femur, proximal or distal tibia, or calcaneus. Pin placement should be performed by skilled personnel only, considering that neurovascular structures are at risk in the locations of all properly placed pins. If skeletal traction is not possible, manual traction through the displaced extremity at the time of binder

application, internal rotation of the extremities, and taping the toes together assists in accomplishing the previously stated goals. Although skin traction apparatuses exist, they are generally ineffective at maintaining length and may cause soft tissue compromise if not appropriately applied and vigilantly attended to.

Binder Removal

Although a CPAS or binder provides essential support in minimizing pelvic hemorrhage, continued use beyond 24 hours can be detrimental. It obscures femoral access points, may impede access to the abdomen, and puts sustained pressure on skin, which inevitably leads to necrosis. For this reason, the skin beneath the binder should be inspected after 24 hours of application and the position must be altered if binder use is to continue.

Removal of CPAS or binder can exacerbate hypotension, so removal should usually be performed with supervision. This is easiest in the ICU setting, where the wrap can be removed, and the immediate effect can be observed on continuous monitors. Outside of the ICU, the provider should be ready to measure vital signs a few minutes after removal, and then later detecting tachycardic response or hypotension in response to the decreased pelvic pressure and increased volume. The binder is removed slowly and left in place beneath the patient, in case it needs to be rapidly reapplied. If the binder must be reapplied because of persistent lethal hypotension, adjusting the binder to a slightly different position may decrease skin injury. External fixation placed in the operating room setting should also be considered at this point to provide adequate pelvic stabilization, compression of the pelvic hematoma, and to minimize external soft tissue injury. Documenting the condition of the skin beneath the binder assists the providers in the patient's continuity of care, to communicate the risk of ongoing soft tissue injury.

Role of Pelvic Angiography

The role of pelvic angiography is individualized in each trauma hospital. The availability of resources and the timing of availability are important factors in determining its use. Each trauma hospital team establishes the potential role of angiography in treating pelvic hemorrhage. The success of pelvic binders in early management of hemorrhagic shock caused by gross pelvic hemorrhage has helped establish the role of angiography as an intervention that should be performed after the pelvic binder application, and after the emergency need for abdominopelvic surgery has been ruled out. Interventional radiography and specifically pelvic angiography have a role in addressing persistent arterial bleeding in patients who are persistently unresponsive to resuscitative efforts, who are already placed in a binder or external fixation, and who do not require surgical hemorrhage control (Fig. 9). Each hospital determines its decision tree or algorithm identifying the order of interventions and role of angiography based on available resources.

Role of Pelvic Packing in Emergency Control of Pelvic Hemorrhage

Some hospitals have access to surgeons educated in pelvic packing. When retroperitoneal hemorrhage is suspected as a source of hypotension and the patient is not responsive to binder application and primary resuscitative response with intravenous fluid and blood, pelvic packing can be considered. Especially in the setting in which exploratory laparotomy is underway for hemorrhage control, pelvic packing is a straight forward next step. The role of this step is protocolized, much the same as angiography, based on resources available within one's institution. Understanding of the pathoanatomy of pelvic hemorrhage is critical for successful pelvic packing. Retroperitoneal veins in the space of Retzius and retroperitoneum are responsible for much of pelvic hemorrhage and this pathology is addressed with pelvic packing. Three pads are forcibly packed against the hemorrhage on each side, along the pelvic brim and into the true pelvis, and posteriorly near the sacroiliac joint. The pelvis must be stabilized with a binder or an effective pelvic external fixator for this method to succeed.

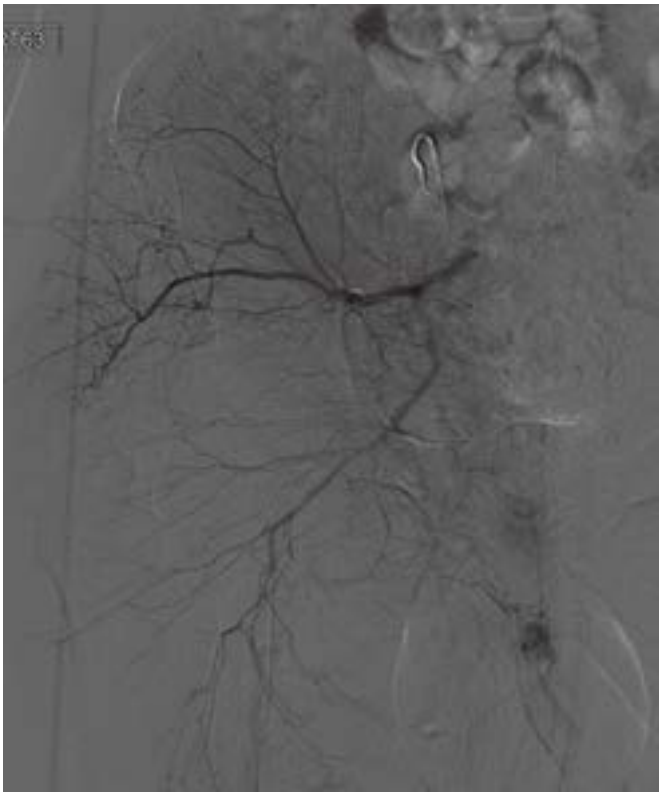


FIG. 9 Angiogram of the patient shown in Figure 10 demonstrating small anterior right pelvic bleed.

Systematic Radiographic Evaluation

The AP pelvis radiograph (Fig. 10A), when carefully inspected, reveals tremendous information about pelvic anatomy and pathology, its implications for instability and associated injury, and potential surgical challenges that can impair surgical stabilization. The first step in analysis is assessment of normal alignment of the body at the time of the radiograph. Central position of the spinous processes or equidistant and similar-appearing pedicles in the lumbar spine are the best indicators that the alignment of the body is normal at the time of x-ray exposure. Gross asymmetry is easily perceived, when present. Subtle asymmetry must be searched for through critical comparison of density and clarity of the sacral ala at the sacroiliac joint, appearance of sacral foramen, area/volume of the iliac fossa, visibility of the ischial spine, density of the quadrilateral surface, the shape of the obturator foramen, and midline position of the pubic symphysis. When a subtle difference is detected on a well-centered film, small posterior fractures and displacements and hidden anterior fracture lines are more easily perceived and explained.

A systematic evaluation of the AP radiograph includes inspection of the lumbopelvic junction, the brim of the iliac crests, the brim of the true pelvis, the foramen of the sacrum, the quadrilateral surfaces, iliac spines and tuberosities, superior and inferior rami, and the pubic symphysis. The evaluator looks for blurring of bone and joints at the lateral sacrum near the sacroiliac joint, and vertical and transverse fracture lines in the front of the pelvis. On a well-centered pelvic radiograph, displacement of the pubic symphysis generally occurs away from the side of the posterior injury on an LC fracture. Soft tissue shadows, often unappreciated on plain radiography, may



FIG. 10 **(A)** Anteroposterior pelvic radiograph. **(B)** Inlet radiograph of the pelvis. **(C)** Outlet radiograph of the pelvis.

show thigh and intrapelvic hematoma, bladder displacement, and intrapelvic air.

The CT scan solidifies diagnoses and suspicions drawn from the AP radiograph. The same anatomic regions previously reviewed on plain radiograph must be inspected in axial or reconstructed views. Visualizing *sequences* of images assists in localizing and measuring pathologic features. The bony volume of the sacrum and fixation corridors is best appreciated on CT. Fracture extensions into the lumbopelvic facet joints, that indicate increased lumbopelvic instability, are detected here as well. Three-dimensional reconstruction image quality is improving to the point that most features of pelvic fracture-dislocation can be clearly seen. It must be understood that most algorithms for reconstruction cause blurring of subtle fracture lines to the point of concealment. Soft tissues are further delineated with different contrast settings. Intravenous contrast medium that may have obscured plain radiography is better localized in CT planes. Despite the important information gleaned from the CT scan, advanced plain radiographs further assist the primary responder in quantifying risk of the injury to the patient and aid the orthopedic surgeon in operative planning.

The *inlet* pelvic radiograph (Fig. 10B) is performed by aiming the x-ray beam from anterosuperior to posteroinferior across the pelvis. The volume of the pelvis is best appreciated from this anterior-cephalad viewpoint. This view best delineates the brim of the true pelvis. It demonstrates internal and external rotational deformities and anterior or posterior displacement of the pelvis at the time of injury. Evaluation of this radiograph, like the AP view above and outlet below, starts by assessing if the patient is well-centered on the image. Visualization of compression fractures at the sacroiliac joint is improved from this perspective. Anterior pelvic fractures at the superior and inferior ramus and parasymphyseal region and their orientation (transverse in LC fractures and cephalocaudad in APC fractures) are more easily understood.

The *outlet* pelvic radiograph (Fig. 10C) is performed by aiming the x-ray beam from anteroinferior to posterosuperior across the pelvis. A true outlet superimposes the cephalad aspect of the symphysis over the S2 sacral body. Underappreciated on this view is the visualization of the sacral anatomy (necessary for surgical planning). Common features of sacral dysmorphism include mammillary processes, crenated sacral foramen, persistent sacral disk densities, and undulating sacroiliac joints. This view highlights the vertical displacement of one hemipelvis in relation to the other and the body during trauma. This can be measured by comparing the relative heights of the iliac crests, femoral heads, or ischial spines. Widening of the symphysis can be easily measured on this view. Appreciation of rotational deformity is also enhanced by comparing the symmetry of each obturator foramen oval.

The lateral sacral view or lateral reconstructions of the lumbopelvic region from the CT scan may prove important in assessment of injury. This projection allows improved evaluation when sacral fractures or lumbopelvic dissociations without pelvic ring disruption are suspected. U-shaped and H-shaped sacral fractures, among other isolated sacral patterns, and their associated sagittal plane (kyphotic) deformities are detected from this perspective.

Judet oblique radiographs, taken with 45-degree elevation of each hip, allow assessment of the acetabulum if fractures in the hip socket are detected on the AP projection. Fractures of the acetabulum can occur in combination with pelvic ring disruptions, most commonly when a lateral compressive or impaction force is applied through the greater trochanter as the mechanism of injury. If a patient's pelvic fracture does not extend to the acetabulum, Judet projections do not add significantly to the diagnosis and treatment of pelvic ring injury.

Classification of Pelvic Fractures

Several pelvic fracture classifications have evolved to improve communication and decrease morbidity and mortality risk to patients. Unfortunately, no classification is complete; some pelvic ring injuries escape classification.

The best classification system in the emergency department (ED) setting and among all trauma team subspecialists is the Young-Burgess classification of pelvic fractures (Table 1). This scheme correlates the trauma history and vector of force application against the pelvic ring to the radiographic findings of bony and soft tissue displacement on standard films. The force of displacement on the anatomy is linked to common patterns of fracture and dislocation. The classification simplifies vectors to those from APC, LC, or forces causing vertical displacement of one side of the pelvic anatomy (vertical shear [VS]).

Certain injuries are associated with each vector of force application. APC injuries are commonly associated with severe life-threatening hemorrhage, especially in the elderly. LC injuries commonly have associated head and thoracic trauma.

APC and LC injuries are divided into three subsets of increasing severity. APC1 fractures have minimal anterior widening at the symphysis or anterior pelvis, with insignificant ligamentous or bony disruption; these do not require surgery. APC2 injuries can be identified by more than 2.5 cm of anterior symphysial widening. They have disruption of the floor ligaments of the pelvis (sacrospinous and sacrotuberous ligaments) and anterior sacroiliac ligaments, but the strong posterior sacroiliac ligaments are intact. It is important to confirm that the posterior sacroiliac ligaments are intact on advanced imaging. APC3 injuries have ruptured all anterior and posterior pelvic ligaments; they are grossly unstable at one or both hemipelves, have significant intrapelvic hemorrhage, and require immediate intervention. A binder is indicated in the initial resuscitation of all APC injuries.

LC1 injuries have fractures through the sacral foramen or ala and corresponding anterior pelvic fractures of the superior and inferior rami, with internal rotation of one hemipelvis. This fracture is the most common pattern because it occurs when elderly fall from a standing position onto their hip. Young patients who sustain fractures in these anatomic regions, and therefore are classified as LC1, commonly have significant displacement and instability. Although elderly LC1 fractures are commonly stable and do not require surgery, young patients or those with good bone stock often have instability that can be confirmed on examination of the pelvis under anesthesia. LC2 disruptions have posterior fractures through the iliac wing and corresponding anterior rami fractures. LC3 patterns are fracture-dislocations known as the "wind swept" pelvis. They have the greatest instability due to internal rotation of one hemipelvis and external (AP-type) rotation of the opposite hemipelvis. LC3 injuries also have appreciable hemorrhage, and this is appropriately managed in the ED with a binder.

VS fractures are one large subset that demonstrate predominating vertical displacement of an entire hemipelvis proximally or distally. Distal displacement is very rare, but it is associated with significant nerve injury and often vascular trauma. Proximal vertical displacement is associated with proportional vascular injury and soft tissue damage to the iliolumbar ligaments, anterior and posterior sacroiliac ligaments, and anterior pelvic ligaments. Associated vascular injury is common, especially with significant displacement. Therefore, longitudinal traction on the shortened limb and binder application aids in management of pelvic hemorrhage in these patients.

It is clear from the Young-Burgess classification that AP3, LC3, and VS patterns (Fig. 11) are at the greatest risk of hemorrhage in general. These patients respond best to early pelvic binder application. AP2 injuries have a clear indication for binder protocol until surgical management. LC1 and LC2 injuries, once appropriately confirmed, probably do not benefit significantly from prolonged binder application.

Role of External Fixation

External fixation was often applied in the ED for pelvic ring fractures. With the rapid acceptance of pelvic binders and CPAS, ED external fixation is obsolete. Compressive wraps are reliable initial treatment. Sheets are universally available and inexpensive. External fixation therefore only has a significant role once 24 hours have passed. At this time, the patient is usually able to transport to the operating

TABLE 1 Young-Burgess Classification of Pelvic Fractures

Category	Common Characteristic	Differentiating Characteristic
LC1	Anterior transverse fracture (pubic rami)	Sacral compression on side of impact
LC2	Anterior transverse fracture (pubic rami)	Crescent (iliac wing) fracture
LC3	Anterior transverse fracture (pubic rami)	Contralateral open-book (APC) injury
APC1	Symphyseal diastasis	*Slight* widening of pubic symphysis and/or sacroiliac joint: stretched but intact anterior and posterior ligaments
APC2	Symphyseal diastasis or anterior vertical fracture	Widened sacroiliac joint; disrupted anterior ligaments; intact posterior ligaments
APC3	Symphyseal diastasis or anterior vertical fracture	Vertical displacement anteriorly and posteriorly usually through sacroiliac joint, occasionally through iliac wing and/or sacrum
VS	Symphyseal diastasis or anterior vertical fracture	Vertical displacement anteriorly and posteriorly, usually through sacroiliac joint, occasionally through iliac wing and/or sacrum
CM	Anterior and/or posterior, vertical and/or transverse components	Combination of other injury patterns: LC/VS or LC/APC

APC, Anteroposterior compression; *LC*, lateral compression; *VS*, vertical shear.
From Burgess AR, Eastridge BJ, Young JW, et al. Pelvic ring disruptions: effective classification system and treatment protocols. *J Trauma.* 1990;30:848–856.

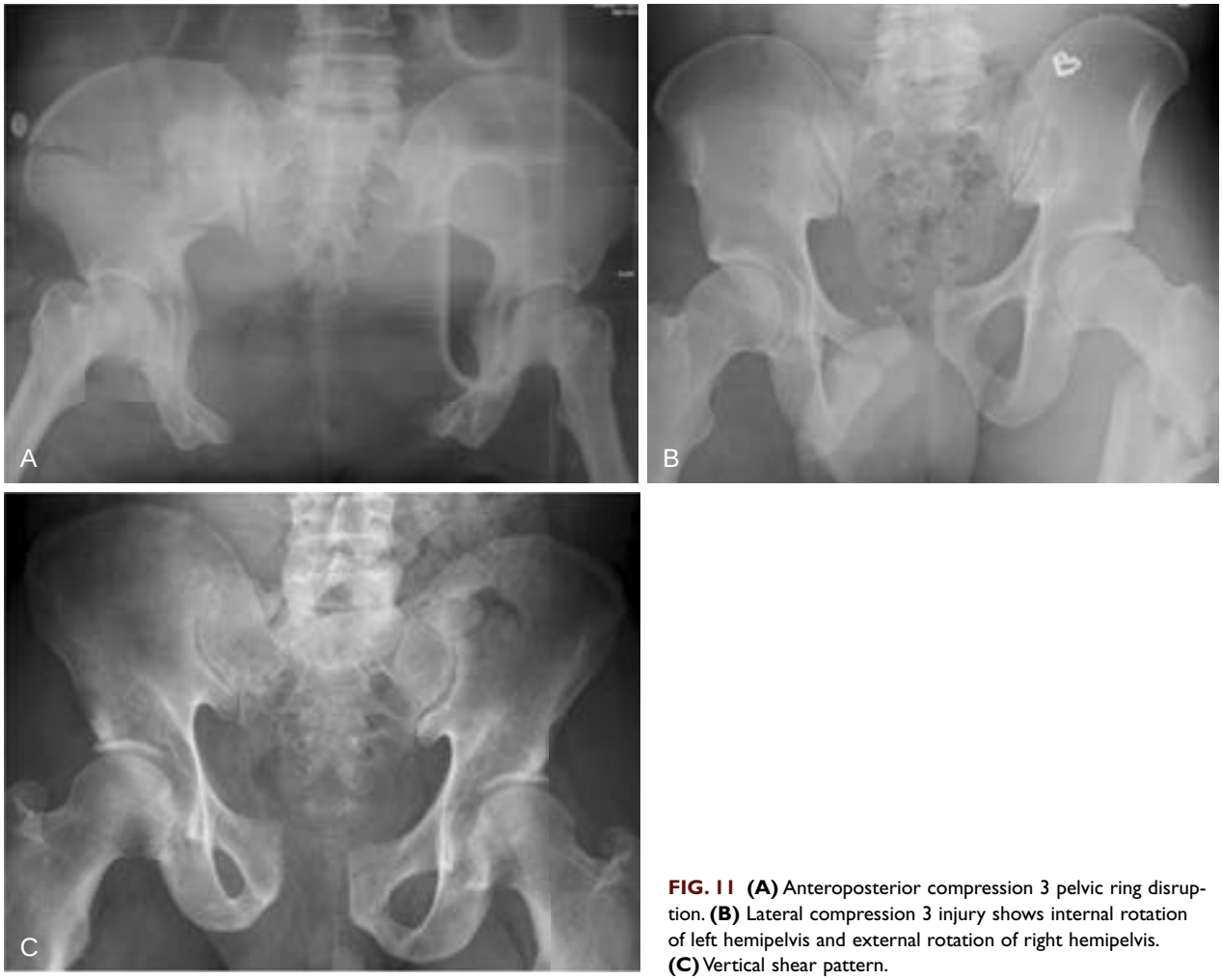


FIG. 11 **(A)** Anteroposterior compression 3 pelvic ring disruption. **(B)** Lateral compression 3 injury shows internal rotation of left hemipelvis and external rotation of right hemipelvis. **(C)** Vertical shear pattern.

room for fluoroscopic imaging and controlled sterile technique. External fixation applied in this environment is much more reliable than a frame applied in the ED. Additionally, recent acceptance of supra-acetabular two pin external fixation as a stronger compressive frame makes this the frame of choice (Fig. 12A); it must, however, be placed under fluoroscopic guidance. Definitive treatment of anterior pelvic instability can be effectively accomplished with external fixation (Fig. 12B). This is usually done once the patient is stable enough for surgery. This mode of fixation is usually selected over internal fixation when prior surgery or radiation complicates anterior open approaches, when an open fracture or gross contamination contaminate the anticipated surgical approach, or when other surgical incisions make standard approaches difficult.

Need for Definitive Surgical Stabilization of Pelvic Fractures

Definitive fixation of pelvic fractures should occur when the patient is stable enough for the approaches that are required for fixation. If limited open or percutaneous techniques are utilized, surgery does not have to be delayed. Large open approaches, including lateral window/iliac fossa approach, Pfannenstiel/Stoppa approach, and prone posterior open approach to the posterior ilium require consideration of other lines and tubes (diverting colostomy or chest tubes) and the ability of the patient to be placed in the proper position for surgery. The patient should be adequately resuscitated, signaled by a normalized lactate less than 2.5. Finally, stabilization of a complex pelvic injury may require more than one surgery as staged procedures to allow recovery from each component of surgical stabilization.

Hospital Admission in Pelvic Fracture

Although many pelvic ring fractures are indicated for surgery, minimally displaced fractures and fractures in relatively healthy individuals may not require hospitalization or operative fixation. Many LC1 and APC1 fractures can be observed briefly and discharged from the ED. Disposition to home requires that a patient have adequate assistance to mobilize out of bed, ambulate with some assistance, and accomplish activities of daily living. Pain must be adequately controlled and breathing should not be labored. Elderly patients often require brief social admissions to plan safe discharge and teach mobilization skills with physical therapy. Once a patient is appropriately dealing with the fracture discomfort and equipped to return home, he or she can be discharged.

Definitive Nonoperative Pelvis Fracture Care

Nonoperative care of a pelvic fracture requires demonstration that the fracture will not displace under physiologic loading during activities of daily living. Usually the injury AP, inlet, and outlet radiographs are repeated after the patient mobilizes out of bed. Most APC1 injuries allow bilateral lower extremity weight-bearing as tolerated (WBAT) with crutches or walker. Most LC1 injuries can accommodate partial/foot flat weight-bearing or WBAT on the injured side. The key in

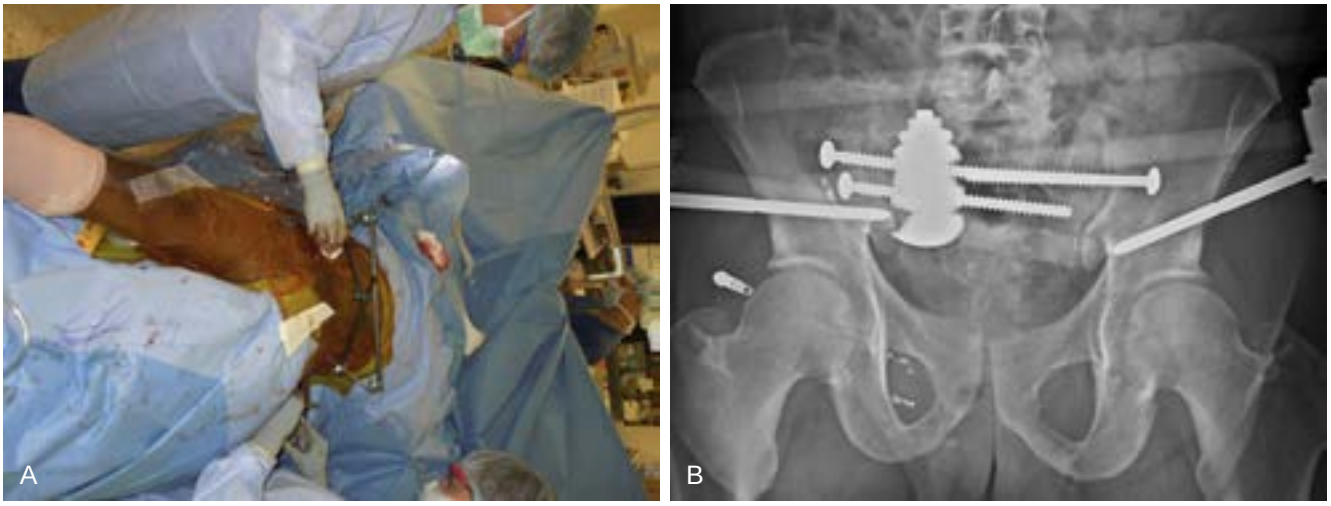


FIG. 12 **(A)** Clinical example of low anterior supraacetabular external fixation frame. **(B)** Definitive treatment radiograph of patient in Figure 10 using external fixation.

nonoperative management of pelvic fractures is serial radiographs demonstrating that minimal displacement occurs over the course of healing. This requires frequent office visits so that unacceptable displacement is detected before healing.

CONCLUSION

Management of pelvic fractures requires urgent recognition of life-threatening fracture patterns, which respond well to pelvic binder application in the setting of hypotension (APC2, APC3, LC3, VS). Many physical examination findings lead the clinician to suspect these injury patterns. The diagnosis is confirmed on systematic radiographic evaluation. Urgent gentle manipulative reduction and application of a compressive sheet or binder is accepted as the best front-line defense against life-threatening hemorrhage. The key to success in management of these injuries is a systematic approach to physical examination and patient evaluation, followed by stepwise use of resources to resuscitate the patient in anticipation of surgical stabilization.

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UROLOGIC COMPLICATIONS OF PELVIC FRACTURE

Hasan Dani, MD, and Misop Han, MD, MS

Pelvic fracture generally occurs with high-energy blunt trauma, most commonly with motor vehicle and motorcycle collisions, pedestrians struck by motor vehicles, industrial or work-related accidents, and falls. Although the incidence in the United States appears relatively stable over recent years, developing nations may have an increasing incidence of such injuries. Patients with pelvic fracture frequently have multiorgan system injuries, including of the head, chest, abdominopelvic organs, and major vessels. These injuries portend significant morbidity and mortality; open pelvic fractures are associated with a mortality rate as high as 45% in some series.

Injuries specific to the genitourinary tract include bladder rupture and urethral injury. Approximately 90% of blunt injuries to the bladder are associated with pelvic fracture. However, only 10% of pelvic fractures are associated with either bladder or urethral injury. These injuries can occur concurrently as well, with 10% to 29% of patients with bladder rupture also having urethral injury.

Urologic injuries are typically associated with disruption of the pelvic ring, particularly anterior disruption involving the symphysis and rami. Isolated fractures of the acetabulum generally do not result in urologic injury. Pelvic fracture urethral injury (PFUI) specifically has been shown to be more likely in patients with wider pubic diastasis or increased displacement of ramus fractures.

INITIAL EVALUATION

Initial evaluation should follow Advanced Trauma Life Support protocols, with priority to airway, breathing, and circulation. When appropriate, a thorough history and physical examination in communicative patients is sensitive for the diagnosis of pelvic fracture, though diagnosis will generally be made with plain radiographs in any patient with concerning mechanism or examination.

In patients with pelvic fracture, one should inspect for ecchymosis of the perineum or scrotum and blood at the urethral meatus, vagina, or rectum. Other signs and symptoms suspicious for urologic injury include gross hematuria, inability to void, distended bladder, and a high-riding prostate on digital rectal examination, though the

last finding is generally difficult to elucidate. The most reliable indicators for bladder injury and PFUI are gross hematuria and blood at the urethral meatus, respectively. Advanced diagnostics should only be undertaken in hemodynamically stable patients. The American Urologic Association (AUA) has recently published urologic trauma guidelines, which can help direct evaluation and management of suspected injuries.

IMAGING

Retrograde cystography is the best test for diagnosis of bladder rupture. This can be performed either with plain films or computed tomography (CT), with sensitivity and specificity for both approaching 100%. In the trauma setting, generally CT cystogram will be performed. Regardless of the modality, the bladder should be filled with at least 300 mL of diluted contrast or until the patient reaches capacity by report. This should be done through the Foley catheter by gravity instillation rather than manually via syringe. Clamping of the catheter to allow intravenous contrast to accumulate in the bladder is not an appropriate evaluation for bladder injury as it does not provide adequate distention. If it is being performed with plain radiographs, cystogram should include anteroposterior and oblique views of both the full bladder and postdrainage.

Patients with pelvic fracture and gross hematuria should undergo retrograde cystogram. If the mechanism is concerning for pelvic trauma in a patient without evidence of pelvic fracture, gross hematuria still warrants a retrograde cystogram. Other indications include pelvic ring fracture with other signs of bladder injury such as inability to void, suprapubic pain, or findings concerning for urinary ascites (e.g., abdominal distention, significant intraperitoneal free fluid on imaging). Though microscopic hematuria in the setting of pelvic fracture has a low likelihood of bladder injury, some have advocated for imaging in patients with greater than 30 red blood cells per high-powered field on urine microscopy.

Retrograde urethrogram (RUG) is generally preferred to cystourethroscopy for the diagnosis of PFUI in the trauma setting. The exception is in female patients due to their shorter urethra, which is best evaluated with cystourethroscopy. However, the incidence of PFUI in female patients is very low due to a lower incidence of pelvic fractures and smaller risk of urethral injury when pelvic fracture is present.

RUG can be performed in the trauma bay or radiology suite. The patient is positioned obliquely approximately 45 degrees with the bottom leg flexed and the top leg straight. It can instead be performed with the patient supine if other injuries preclude oblique positioning. A 14Fr catheter is placed into the distal urethra, and the balloon is filled with 1 to 3 mL of fluid. The penis is placed on stretch. Plain radiographs are taken after instillation of 20 to 40 mL of contrast.

In patients with pelvic trauma and blood at the urethral meatus, RUG should be performed. Blind placement of the catheter before performing RUG is discouraged when PFUI is suspected but may be necessary in the severely unstable patient. In this situation, a pericatheter RUG can be performed once the patient is stable. If blind catheter placement is difficult in a patient with pelvic fracture without initial concern for PFUI, RUG should be performed if not done previously.

BLADDER INJURY

Bladder injury in the setting of pelvic fracture usually occurs due to shearing forces tearing the bladder at its fascial attachments. Occasionally, bone fragments can directly lacerate the bladder. Based on the distribution of extravesical contrast during cystogram, injuries can be classified as extraperitoneal in 60% of cases or intraperitoneal in 30% of cases, with the remainder having both intraperitoneal and extraperitoneal injuries.

Intraperitoneal injuries tend to occur from pelvic trauma to a full bladder, resulting in rupture of the dome of the bladder. On cystogram, contrast is seen in the peritoneal cavity, notably outlining loops of bowel (Fig. 1). Conversely, extraperitoneal rupture results in a flame-shaped extravasation of contrast in the perivesical space. If fascial planes are disrupted, extraperitoneal contrast can spread to the retroperitoneum, scrotum, penis, abdominal wall, and thighs (Fig. 2).

Intraperitoneal bladder rupture allows free spillage of urine into the peritoneal cavity and can result in peritonitis, sepsis, azotemia, and death if not treated promptly. These injuries warrant immediate operative exploration and repair. Extraperitoneal injuries, however, are most often managed conservatively with catheter drainage to

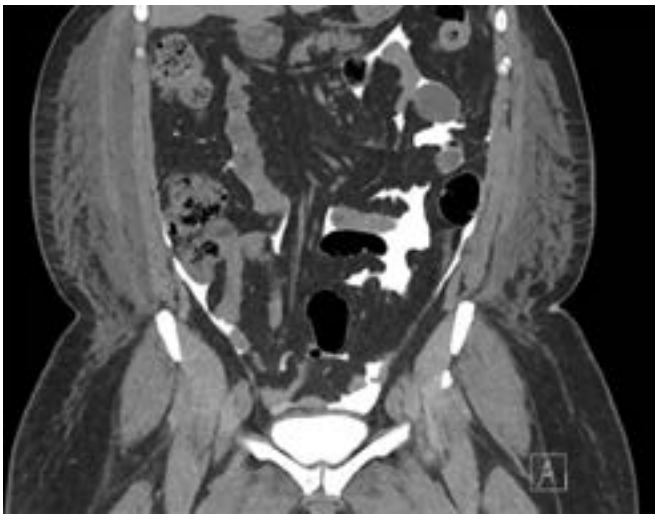


FIG. 1 CT cystogram demonstrating intraperitoneal bladder rupture with contrast outlining bowel loops.

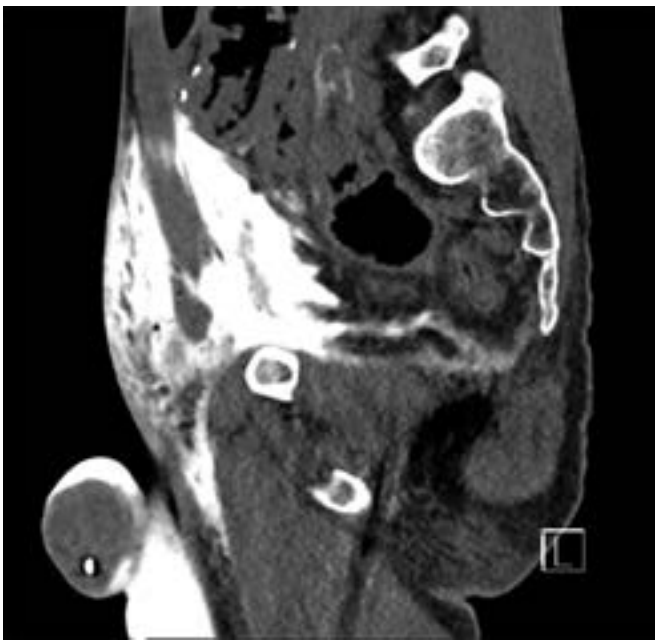


FIG. 2 CT cystogram demonstrating extraperitoneal bladder rupture with contrast tracking into retroperitoneum, anterior abdominal wall, penis, scrotum, and thighs.

allow the bladder to heal. The currently available literature suggests that catheter drainage of uncomplicated extraperitoneal injuries does not increase urologic complications compared to operative repair. A large catheter such as a 22Fr catheter should be used to ensure adequate drainage. Antibiotics should be considered to reduce risk of infected pelvic hematoma or abscess. The catheter is maintained for approximately 2 weeks, and a follow-up cystogram is performed to confirm resolution of the urine leak before catheter removal.

Scenarios do exist in which extraperitoneal injuries should be managed operatively. Complicated extraperitoneal injuries include those with concurrent lacerations of the rectum, vagina, or bladder neck, bony spicules in the bladder, or significant hematuria resulting in clot obstruction of the catheter. These situations necessitate primary repair to prevent complications such as fistula, urinary incontinence, and nonhealing of the bladder. Similarly, if conservative management with catheter drainage has failed after approximately 4 weeks, operative repair should be considered. Lastly, if a patient is undergoing an open reduction and internal fixation (ORIF) or abdominal exploration for other reasons, primary bladder repair should also be considered in the same setting. Although there is not clear supporting evidence, bladder repair is performed in the setting of ORIF to reduce theoretical risk of hardware infection.

When planning operative repair of the bladder, a lower midline incision provides excellent exposure for both intraperitoneal and extraperitoneal repair, though a transverse Pfannenstiel incision can also be used. Entry into the peritoneal cavity allows easy visualization of the dome of the bladder if concerned for intraperitoneal injury. However, there can often be multiple sites of injury, and thus complete inspection of the extraperitoneal bladder is also warranted. Bladder exploration is undertaken by making a longitudinal midline incision on the anterior wall of the bladder. The ureteral orifices should be inspected for efflux of urine. If any concern for injury, one should consider intubation of the ureters with a 5Fr feeding tube or retrograde pyelogram.

Bladder lacerations should be repaired in two layers with slowly absorbable suture. The first layer incorporates the mucosa and muscularis, and the second layer incorporates the muscularis and serosa. A closed suction drain should be placed in the pelvis and the bladder drained with a Foley catheter. The placement of a suprapubic tube (SPT) is generally unnecessary. Follow-up cystogram should be performed in 10 to 14 days to confirm healing of the bladder before catheter removal.

URETHRAL INJURY

PFUI is caused by shearing forces disrupting the urethra at bulbomembranous junction in the posterior urethra. This area is vulnerable relative to the immediately more proximal and distal urethra, which are anchored by the prostate and perineal membrane, respectively. Extravasation of contrast outside the posterior urethra on RUG is diagnostic of PFUI. If contrast reaches the bladder, this suggests partial disruption of the urethra. In more severe cases of complete disruption, there will be no opacification of the bladder.

The goal of PFUI management is to perform prompt urinary drainage in the acute setting and minimize long-term morbidity from urethral stricture disease, urinary incontinence, and erectile dysfunction.

Primary surgical repair of PFUI is not recommended due to high rates of complications. These patients suffer from high rates of urinary incontinence and erectile dysfunction, and significant urethral strictures requiring further surgery still occur in 69% of patients. Exceptions include patients with concurrent rectal or bladder neck injury; these patients should undergo primary repair to reduce risk of fistula and incontinence. Posterior urethroplasty is a complex operation that generally should be performed by reconstructive experts. Given the rarity of female PFUI, data are limited but do suggest that female patients should undergo early primary repair within the first 7 days, particularly if there is concurrent vaginal laceration.

If a partial urethral disruption is diagnosed on RUG, it is reasonable for a single attempt at blind catheter placement. This is successful in 50% of cases. The current literature does not suggest that a failed attempt at blind catheter placement will convert a partial disruption into a complete disruption. Regardless, this should be performed by an experienced team member.

In cases of complete urethral disruption or failed catheter placement, an alternative approach to urinary drainage, such as SPT placement or primary endoscopic urethral realignment, should be undertaken quickly. SPT placement is the preferred initial treatment for most PFUI cases according to the AUA guidelines. SPTs can be placed expeditiously in these frequently unstable patients. Furthermore, SPT provides a long-term solution if planning delayed reconstruction in several months, but it also allows useful access that might be needed if planning primary realignment later in the acute setting. When placing an SPT for PFUI, one should be mindful that the bladder may be displaced from pelvic hematoma. Use of ultrasound guidance or even open placement of an SPT should be considered if percutaneous placement is difficult. The AUA guidelines state that SPT may be placed even in patients undergoing ORIF of pelvic fracture, as there is no current evidence to suggest that SPT increases risk of hardware infection.

Primary endoscopic urethral realignment can be considered for hemodynamically stable patients. This can be performed in the first week after injury, allowing time to bring the patient to the operating room during the daytime with appropriate staff in a controlled setting. Primary realignment is best performed with two urologists utilizing cystoscopy and fluoroscopy to realign the urethra and place a urethral catheter. Prolonged attempts should not be attempted as this may increase complications and delay other care the patient requires. If primary realignment is successful, the urethral catheter should be maintained for 4 to 6 weeks, and a pericatheter RUG or voiding cystourethrogram should be performed at time of catheter removal.

The literature is conflicting regarding the benefit of primary realignment over SPT. A meta-analysis in 2019 suggested similar long-term urethral stricture rate between primary realignment and SPT, but the quality of included studies was found to be very poor. Most studies agree that the majority of patients undergoing primary realignment will still develop urethral strictures, but these strictures may be less complex and more easily managed in the future. Rates of erectile dysfunction and urinary incontinence are similar in patients undergoing initial SPT or primary realignment. A prospective, multicenter study is currently ongoing by the American Association for the Surgery of Trauma to further compare SPT versus primary realignment for PFUI.

The risk of subsequent urethral stricture disease after PFUI ranges from 45 to 100%. Erectile dysfunction occurs in approximately 50% and is typically severe. Urinary incontinence is rare, with only 5% of patients experiencing long-term symptoms. Patients should be followed by urology for at least one year following injury to monitor and treat these likely complications.

CONCLUSION

Urologic injuries associated with pelvic fracture are uncommon but have the potential for devastating acute and long-term morbidity. Appropriate and timely management in the trauma setting can minimize the risk of complications such as abscess, sepsis, renal failure, fistula, and chronic voiding dysfunction. It is essential to establish prompt urinary drainage. Early collaboration among surgical services can optimize care for these complex patients. Outpatient follow-up with urology after convalescence is necessary to monitor for complications and improve quality of life.

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Spine and Spinal Cord Injuries

Khaled M. Kebaish, MD, FRCS, and Andrew Harris, MD

INTRODUCTION AND EPIDEMIOLOGY

The incidence of spinal cord injury (SCI) is between 25 to 59 cases per million in the United States, a rate higher than other developed countries. Among the general population, most cases of SCI are caused by motor vehicle accidents (48.3%), followed by acts of violence (12%) and sports-related injuries (10%). In those older than 60 years old, however, falls are the leading cause of SCI. Recent trends show that, overall, 55% of SCI cases occur in the cervical spine, with a rising predominance of upper cervical lesions (C1–C4) with patients being discharged from the hospital as ventilator-dependent. Current estimates suggest that 48.7% of SCI is neurologically complete at presentation, a number that has been decreasing slightly as the prevalence of gunshot-related injuries decreases and falls in the elderly increases.

Though comparison of affected age groups is complicated by differences in reporting, several predominant trends are clear. Males are the most commonly affected gender, at approximately 80% of cases and a 4:1 incidence ratio compared with females—a disparity that has remained constant over time. In addition, the highest-risk age groups are the late teens and 20s, though recent data have showed that the mean age of patients affected by SCI is increasing as the US population ages.

INITIAL EVALUATION AND MANAGEMENT

Due to the magnitude of injury necessary to damage the spinal cord, SCI is commonly comorbid with multiorgan injury, which can complicate or even prohibit a thorough history and physical examination. Nonetheless, the initial evaluation of a patient with SCI is identical to other trauma patients in accordance with Advanced Trauma Life Support guidelines. Airway, breathing, and circulation are assessed as part of the primary survey, followed by complete evaluation in a secondary survey. Overt signs of SCI in the secondary survey include flaccid paralysis, hemodynamic instability with bradycardia, priapism, lack of response to painful stimuli in the lower extremities, and paradoxical breathing—all of which require prompt evaluation and application of appropriate algorithms to determine if imaging and/or surgical treatment is warranted.

Aside from the maintenance of airway, breathing, and circulation, the immediate chief concerns in patients with SCI are (1) avoiding movement that could worsen the condition by pathologic motion of displaced vertebral elements and (2) minimizing deleterious effects of the secondary injury cascade by maximizing blood oxygenation and tissue perfusion. Within 2 to 3 hours after injury, disruption of arterioles by mechanical disruption and vasoconstriction causes ischemia in the grey matter of the cord. Following this insult to fragile tissue of the central nervous system is the release of cytokines, inflammation, and apoptotic cell death primarily over the next 24 to 48 hours, though these processes can continue to cause damage for up to 3 weeks after injury.

In the acute phase of injury, maintaining an appropriate airway is essential to maintaining oxygen delivery to the damaged spinal cord. Patients with cervical spine injury are at increased risk of airway compromise because of the risk of development of localized edema, neck hematoma, disruption of the innervation to respiratory musculature, and concomitant pulmonary injury. Thus, throughout the acute evaluation, one should remain vigilant in monitoring for signs of acute respiratory failure and consider positive pressure ventilation. Hypotension (<90 mm Hg systolic), even for brief periods of time, should be avoided as it is associated with significantly worse outcomes, though this can be especially difficult in the setting of neurogenic shock. Attention should also be given to transferring these patients to an appropriately specialized center equipped to treat patients with SCIs, as early transfers to such centers have been associated with improved outcomes and reduced complications.

After completion of the primary and secondary survey, the National Emergency X-Ray Utilization Study (NEXUS) criteria are commonly used to determine if radiographic imaging is warranted for a patient with suspected cervical SCI. According to these criteria, patients who are alert and nonintoxicated who lack midline cervical pain, neurologic symptoms, or distracting injury do not require further imaging. The negative predictive value of these criteria is 99.8% for ruling out a cervical spine injury. No such validated criteria exist for ruling out the need for imaging in cases of suspected lumbar SCI; however, the same concepts can intuitively apply to the thoracolumbar spine above the level of the spinal cord.

Patients with neurologic symptoms or who fail the NEXUS criteria will usually require imaging, which will be discussed later in this chapter. Symptomatic patients should also receive a thorough physical examination to identify motor and sensory deficits that can aid in localizing the injury. Detailing specific deficits in these patients is important and has shown to be associated with prognostic value and decreased complications. The American Spinal Injury Association (ASIA) classification system is widely used for classifying physical examination symptoms in these patients. This scale uses a 0 to 5 point scale to evaluate 10 different muscle groups bilaterally, and each of the resulting 20 scores are added to determine the total ASIA motor score. Sensation is also evaluated on a 0 to 2 scale in all dermatomes. Lastly, the ASIA scale classifies SCI overall as complete SCI (A), sensory incomplete (B), motor incomplete (C and D), and normal (E) (Table 1). The combination of the ASIA impairment scale with the ASIA motor score comprises the best description of a patient's neurologic status after SCI.

Incomplete SCI is also commonly classified into syndromes based on the level of injury and neurologic tracts involved. Central cord syndrome is the most common, accounting for 9% of SCI overall. The defining characteristics of this syndrome include tetraparesis with arms weaker than the legs and a variable amount of sensory loss that does not affect the face. Cervicomedullary syndrome results from injury from the lower medulla to C4, and presents with respiratory difficulty, spinal shock, sensory deficit between C1–C4, and facial sensory loss from damage to the ascending tract of the spinal trigeminal nerve. Space-occupying lesions such as disc fragments, hematoma, or fractured vertebrae can cause anterior cord syndrome, which presents with complete paralysis due to disruption of the corticospinal tract and preservation of vibration and light touch. Posterior cord syndrome is more rare and presents with tetraparesis and profound sensory loss with preservation of pain and temperature sensation. Brown Sequard syndrome is another commonly described syndrome, involving hemisection of the spinal cord classically in patients with penetrating injury. The syndrome presents with ipsilateral paralysis, ipsilateral vibration, loss of light touch sensation, and contralateral pain and temperature loss. Conus medullaris syndrome can be caused by burst fractures of T12 or L1 and will result in paraparesis along with loss of bowel and bladder function, sensory loss in the legs, and sparing of perianal sensation. With more distal injury, cauda equina syndrome can also occur as a traumatic injury, presenting with saddle anesthesia and bowel and bladder dysfunction. Of note, the prognosis for cauda equina syndrome caused by traumatic injury to the spinal column has a higher rate of recovery due to the higher resistance to injury found in lower motor neurons. In addition to the classically described syndromes, SCI can also be caused by prolonged hypotension and watershed infarction. Though rare, SCI due to hypotension and ischemia can occur in the absence of cerebral ischemia and is best diagnosed by MRI.

IMAGING

CT scanning is the imaging modality of choice in acute SCI and has proven to be more sensitive and specific than radiographs in diagnosing vertebral column fracture or dislocation following blunt trauma. In patients who are found to have SCI at a single level, imaging of the entire spinal column should be obtained, as 10% to 40% of patients will present with multiple noncontiguous fractures. In patients with cervical spine injury, if high-quality CT scans are available, three-view radiographs are not required; however, if high-quality CT is not available, level I evidence supports three-view radiographs (anteroposterior, lateral, odontoid views) as an additional test.

Performing MRI in trauma patients is challenging, time intensive, and not readily available at all centers. In patients who have clearly defined symptoms that correlate with CT findings, most would argue against the use of MRI in the acute setting. In patients who have neurologic symptoms without findings on CT scan, however, MRI may be useful to identify occult cord compression from time-sensitive pathologies such as critical disc herniation or epidural hematoma. Because MRI can accurately depict cord compression and signs of cord injury (hemisection, transection, edema, hemorrhage, ischemia), current recommendations suggest that MRI may be performed, when feasible, before surgical intervention for a potential added benefit in surgical decision making, though evidence is weak to support this recommendation. In patients who have pain without neurologic findings, MRI may identify ligamentous injury as the cause of pain, though ligamentous injury does not necessarily imply spinal instability. MRI has also shown utility in predicting long-term neurologic outcomes through a prognostication score when combined with clinical symptoms, though the validity of these predictions have yet to be established.

SCI without radiographic abnormality (SCIWORA) is a syndrome that presents almost exclusively in children. The most accepted current definition of SCIWORA has come to encompass CT and radiographs only, as cases of SCI almost always have pathologic findings on MRI. Nonetheless, both complete and incomplete SCI may present as SCIWORA, and surgeons should be aware of this presentation of SCI. Current recommendations involve up to

TABLE 1 The American Spinal Injury Associations (ASIA) International Standards for Neurologic Classification of Spinal Cord Injury Impairment Scale

Grade	Classification	Motor	Sensory
A	Complete	No motor function	Complete deficit
B	Incomplete	No motor function	Incomplete deficit
C	Incomplete	Motor function is preserved – more than half of key muscles below the neurologic levels have a grade less than 3/5	Incomplete deficit
D	Incomplete	Motor function is preserved – more than half of key muscles below the neurologic levels have a grade less than 3/5	Incomplete deficit
E	Normal	Normal motor	Normal

12 weeks of bracing, and MRI in this population of patients has been shown to hold prognostic value.

SELECTION OF SURGICAL CANDIDATES AND TIMING OF SURGERY

Disruption of osteoligamentous structures associated with the majority of SCIs has the potential to cause permanent neurologic impairment. Therefore, the goal of surgical intervention in patients with SCI is to reduce compressive forces on the spinal cord and restore normal anatomical alignment. Though a variety of injury patterns may occur, we will describe the classic isolated injuries. Patients with multiple fracture patterns or cord compression present at multiple levels may warrant more complex treatment algorithms.

Cervical Spine

Injuries to the cervical spine can be classified as craniocervical (occiput to C2) or subaxial (C3-T1) injuries. The most cranial of these injuries is atlanto-occipital dislocation. Though usually fatal due to the level of the injury or associated vertebral artery injury, patients who survive this traumatic dislocation are treated with occiput to cervical fusion. Infrequently, these traumatic dislocations may also require decompression of associated damaged nerves. Unilateral fractures of the occipital condyle can be treated with a cervical collar for 6 to 12 weeks. C1 fractures commonly occur as a burst-type fracture of the anterior and posterior arches, originally described as double fractures through each arch and known by the eponym Jefferson fracture. Though other variations of C1 fractures exist, they are typically treated by halo vest immobilization for 6 to 12 weeks. C2 fractures are divided between those affecting the odontoid process and all other fractures. Type I odontoid fractures occur at the tip of the dens, type II fractures occur at the base, and type III fractures occur at the body of the axis. Type I fractures are stable and can be treated with immobilization with a cervical collar. The management of type II odontoid fractures is somewhat controversial, as there is a high risk for nonunion without surgical treatment, but surgical treatment is both risky and invasive at this level. Current accepted indications for surgical management of type II odontoid fractures include patients with instability, cord compression with neurologic deficits, and high risk of nonunion (smoking, osteoporosis, etc.). Surgical treatment options include odontoid screw fixation and posterior atlantoaxial arthrodesis. Nonoperative management may be considered for patients without these symptoms and <5 mm displacement. Nonoperative treatment options include nonrigid orthosis (collar, cervicothoracic orthosis) or rigid cervical orthosis (halo vest). Type III odontoid fractures may be treated effectively with cervical collar immobilization. Hangman's fractures (HF) are bilateral fractures of the C2 pars interarticularis and are similarly classified as one of three types based on the degree of subluxation of C2 on C3 and angulation of the C2 vertebral body. Type I HF exhibit <3 mm translation and may be successfully treated with a cervical collar. Type II HF are defined as those with >11 degrees of angulation and >3 decrees of translation, and may require surgical fixation if deemed unstable, though the definition of stability varies between authors and there is no consensus. Type III HFs are defined by severe angulation and facet dislocation of C2–C3 and generally require surgical fixation. Nonoperative management of these fractures includes either cervical collar or halo vest, and surgical treatment options anterior C2–C3 interbody fusion, posterior C1–C3 fusion, and bilateral C2 pars screw osteosynthesis (Table 2).

Subaxial cervical spine fractures can be classified using several classification schemes; the Arbeitsgemeinschaftfür Osteosynthesefragen (AO) classification and subaxial cervical spine injury classification system (SLICS) are the most commonly used. The SCLICS (Table 3) takes into consideration the morphology of the fracture, integrity of the discoligamentous complex, and neurologic status of the patient. Each of these domains is scored from 0 to 2/4 from intact to most severely damaged, and the decision to operate is dictated by the overall summative score. Overall score of <4 indicates nonoperative management, while overall score of >5 necessitates operative treatment. Fractures with a score of 4 using SCLICS may be treated operatively or nonoperatively. Nonoperative management of these fractures is similar to craniocervical fractures. When indicated, surgical fixation for subaxial fractures may be performed through an anterior, posterior, or combined approach, taking into account the need for decompression, stabilization, and reconstruction (Fig. 1).

Ideally, surgical decompression should be performed before 24 hours after injury in cases of cervical SCI. To date, the 2012 Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) study is the largest study to evaluate the effect of early surgical decompression after SCI on long-term outcomes. The results of the STASCIS study showed that decompression before 24 hours was associated with a grade 2 improvement on the ASIA scale at 6 months. These findings are backed by a large amount of preclinical evidence supporting the advantages of early surgical decompression. In addition, a recent meta-analysis published in 2019 confirms that, in patients with complete traumatic cervical SCI, surgical decompression within 24 hours is more often associated with a clinically and statistically significant improvement when compared with late surgery. When feasible given

TABLE 2 Craniocervical Fracture Types and Recommendations for Treatment

Fracture Location	Recommended Treatment
Atlanto-occipital dislocation	Occiput to cervical fusion
Unilateral occipital condylar fracture	Cervical collar for 6–12 weeks
C1 fracture	Halo vest immobilization for 6–12 weeks
C2 fracture	
Odontoid (type I)	Cervical collar immobilization
Odontoid (type II)	Surgical vs. nonsurgical treatment depending on displacement and patient comorbidities
Odontoid (type III)	Cervical collar immobilization
Hangman's (type I)	Cervical collar immobilization
Hangman's (type II)	Surgical fixation if unstable
Hangman's (type III)	Surgical fixation

TABLE 3 Subaxial Cervical Spine Injury Classification System (SLICS)

Characteristic	Points
MORPHOLOGY	
No abnormality	0
Compression	1
Burst	2
Distraction (e.g., facet perch, hyperextension)	3
Rotation/translation (e.g., facet dislocation, unstable teardrop or advanced-stage flexion compression injury)	4
DISCOLIGAMENTOUS COMPLEX (DLC)	
Intact	0
Indeterminate (e.g., isolated interspinous widening, MRI signal change only)	1
Disrupted	2
NEUROLOGIC STATUS	
Intact	0
Root injury	1
Complete cord injury	2
Incomplete cord injury	3
Continuous cord compression in setting of neurodeficit	+1
Score	**Interpretation**
<4	Nonoperative treatment
4	Operative versus nonoperative
>5	Operative treatment

the limitations of the treatment facility and comorbid injuries in these patients, the goal should be for surgical decompression to be performed in <24 hours.

Thoracolumbar Spine

Traumatic injury at the level of the thoracic spine is less common, due to the added structural support of the ribs and sternum. Thus, when injury at this level does occur, it is frequently severe and associated with neurologic deficits. The majority of thoracic injuries occur at the thoracolumbar junction. Isolated lumbar SCI is less common, mainly due to the fact that the spinal cord typically ends between L1–L2. Surgical decision making in thoracolumbar SCI is also dependent on the stability at the level of the injury.

The three-column model of the spine proposed by Denis in 1983 is the basis for conceptualizing variations in thoracolumbar injury and the resulting loss in mechanical stability. (Fig. 2). The three-column model has subsequently been used to develop the AO classification of spinal injury (1994), and more recently, the thoracolumbar injury classification and severity score (TLICS) (2005). Under the AO classification, thoracolumbar spinal injuries are classified as compression injury (group A), distraction injury (group B), and translation or rotation injury (group C) (Fig. 3). This classification system depicts increasing injury severity from category A to C and associated increased likelihood of requiring surgical stabilization. In general, type A injuries are limited to the anterior column, and type B and C injuries affect two or three columns. Because type A injuries are generally stable, they can be treated with a thoracic-lumbar-sacral orthotic (TLSO) brace, while type B and C injuries are inherently less stable and will usually require operative management. The TLICS score considers injury morphology, posterior ligamentous complex injury, and the patients' neurologic status. The score of each domain is added, with higher score indicating more severe injury, and the total score determines if surgical vs. nonsurgical management is warranted.

In stable fractures that are treated with TLSO bracing, patients are followed with radiographic imaging to ensure bony union across the fracture site. Follow-up visits should include surveillance for progressive kyphosis or loss of vertebral body height as indicators of treatment failure. When surgical stabilization is warranted, the approach may be anterior, posterior, or combined, and this decision is commonly dictated by skill and preference of the spine surgeon. There is currently no consensus on the preferred approach. Surgical decompression may be done either directly (i.e., laminectomy) or

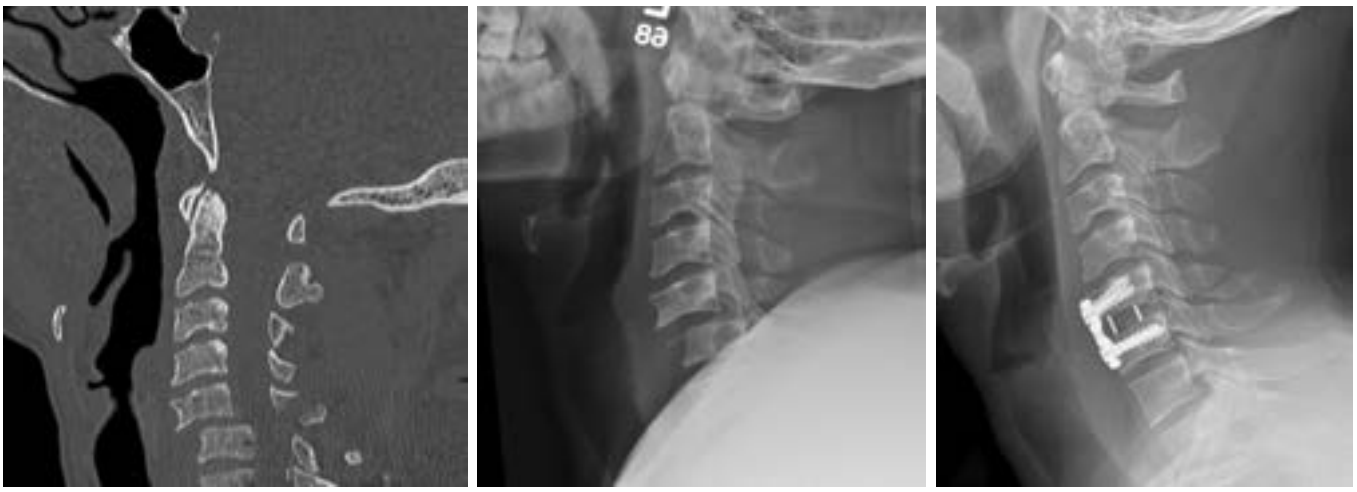


FIG. 1 Subaxial cervical spinal cord injury case example. This patient presented to the ED as a pedestrian vs. motor vehicle accident. CT scan and radiographs demonstrated C5–C6 bilateral jumped facets with relative anterolisthesis of C5 on C6 with complete spinal cord injury at C6 level (ASIA A). The patient was reduced in the ED using serial traction. Later that day, the patient had definitive fixation with a C5–C6 anterior cervical discectomy and fusion (ACDF).

indirectly by reducing the fracture, and multiple methods of vertebral fusion and reconstruction exist.

The optimal timing of decompression in thoracolumbar SCI has not been studied as rigorously as with cervical SCI. Best evidence supports that surgical decompression <72 hours after injury for thoracic fractures is associated with decreased days on a ventilator and in the intensive care unit, and the risk of respiratory issues is reduced; however, similar benefits to long-term neurologic outcomes with early surgical intervention in lumbar SCI have not been well-established. It is the author's recommendation that, when indicated, surgical intervention for cases of thoracolumbar SCI is performed at the earliest possible time given the patient's other associated injuries and comorbid conditions.

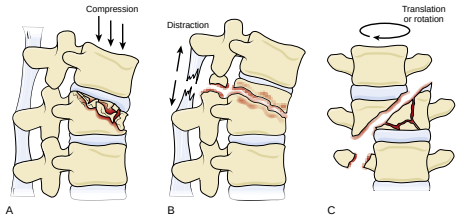


FIG. 2 The three-column model of Denis divides the spinal column into anterior, middle, and posterior columns. The anterior column is composed of the anterior longitudinal ligament, anterior annulus, and anterior portion of the vertebral body. The middle column is composed of the posterior portion of the vertebral body, posterior annulus, and posterior longitudinal ligament. The posterior column is composed of the posterior ligamentous complex, facet joints, neural arch, and interspinous ligament.

MEDICAL MANAGEMENT

Hemodynamic Support

Patients with SCI are at risk of hemodynamic compromise from several etiologies. Bradycardia and other arrhythmias may result from injury to the autonomic nervous system; hypotension can result from neurogenic shock; and concomitant hemorrhage, tension pneumothorax, cardiac tamponade, or sepsis may all occur and contribute to hypotension. As such, substantial evidence supports current recommendations to keep mean arterial pressure between 85 and 90 mm Hg for the first 7 days after injury in patients with SCI. IV fluids should be utilized judiciously, as these patients are at high risk of pulmonary edema, and early consideration should be given to vasoactive agents. There has yet to be a preferred algorithm developed to guide fluid resuscitation in patients with SCI.

Traditional mean arterial pressure goals in the acute setting following traumatic SCI are recommended between 85 and 90 mm Hg for 7 days after injury. Still, emerging evidence suggests that spinal cord perfusion pressure, measured using an intrathecal catheter, may be a more adequate gauge of spinal perfusion. Squair et al. conducted a multicenter prospective observational clinical trial of 92 patients to determine optimal hemodynamic goals for patients with acute ACI. They found that, overall, adherence to target spinal cord perfusion pressure goals and not mean arterial pressure was linearly related to improved neurologic outcomes. Ultimately, their recommendation is to target a spinal cord perfusion pressure of 60 to 65 mm Hg in the acute setting.

Corticosteroids

Among the more contentious topics within the field of SCI is the use of methylprednisolone sodium succinate (MPSS) in the treatment of acute SCI. MPSS is a synthetic glucocorticoid that exhibits anti-inflammatory effects through interference with cytokine signaling and arachidonic acid metabolites. The theoretical basis for its use in SCI comes from numerous studies in animal models that have shown enhanced neuron survival after the use of MPSS; however, high-dose glucocorticoids come with increased risk of infection and gastrointestinal bleeding in patients with SCI. For many years, it was common practice to administer MPSS within 8 hours of SCI, but this

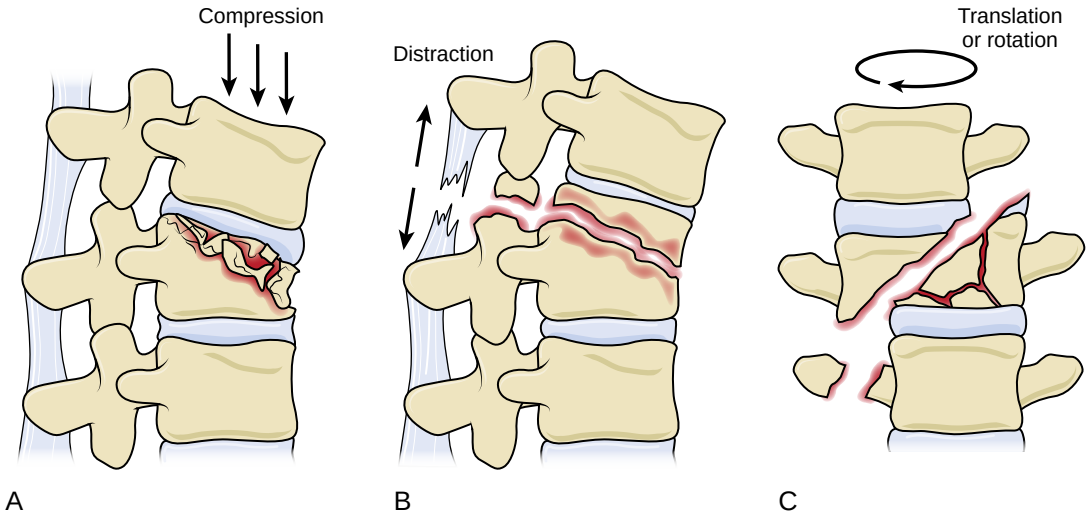


FIG. 3 AO classification of thoracolumbar spinal injury categorizes thoracolumbar spinal injury by mechanism of compression **(A)**, distraction **(B)**, and translation or rotation injury **(C)**.

has proven to be a complex issue that continues to be debated even in the face of several large randomized trials, and the subsequent debate has brought to light the heterogeneity of the population of SCI patients. The National Acute Spinal Cord Injury Study (NASCIS) has conducted three trials (NASCIS I, II, III), spanning from 1984 to 1997, and the findings of these trials have served as the basis for other prospective studies and current guidelines. The most recent guidelines are the result of a joint effort between AOSpine, the American Academy of Neurological Surgeons, and the Congress of Neurological Surgeons published in 2017. Their recommendations are to consider a 24-hour infusion of high-dose MPSS within 8 hours of SCI (30 mg/kg bolus + 5.4 mg/kg/h for 23 hours). In addition, the AOSpine recommendations are to avoid MPSS after 8 hours of SCI and to the avoid 48 hour-long infusions that were once recommended. These recommendations are based on evidence suggesting a small benefit in motor recovery when MPSS is administered within 8 hours of injury, and that the possible drawbacks (GI bleeding, infection) outweigh the benefits after 8 hours and with 48-hour infusions. Still, it should be recognized that other organizations, such as the American Academy of Neurology, continue to recommend against the routine use of high-dose methylprednisolone following acute SCI after meta-analyses showing increased risks of GI hemorrhage and respiratory tract infection without significant functional benefit.

Recently, there has been renewed interest in examining methylprednisolone in combination with other agents, such as erythropoietin, to potentially further attenuate immune-regulated neuroprotection against cellular injury and apoptosis following acute SCI. Although preclinical studies have shown some promising results for erythropoietin in combination with methylprednisolone, a pilot randomized controlled trial published by Ganjeifar et al. did not show any significant functional differences at 1-year post-SCI between patients receiving methylprednisolone vs. methylprednisolone plus erythropoietin.

Alternative Neuroprotective and Neuroregenerative Agents

Several alternative neuroprotective agents have been studied in SCI with an aim to attenuate the secondary injury in SCI, including minocycline, Riluzole, AC-105, SUN13838, granulocyte-colony stimulating factor, and Cethrin. Although there has been promising preclinical evidence, several clinical trials have failed to demonstrate significant clinical benefit of these agents.

COMPLICATIONS AND REHABILITATION

Patients with SCI are at risk for a handful of short- and long-term complications due to both direct neurologic injury and concomitant injuries. In the subacute setting, patients may experience spinal shock, neurogenic shock, or respiratory failure, which may require fluids, vasopressors, and/or mechanical ventilation. In the intensive care unit, common complications are dysphagia, venous thromboembolism, infections, and stress gastroduodenal ulcers—all of which are managed in line with standard medical therapy. Long-term complications include complications due to immobility (pressure sores, leg edema, obesity), denervation (spasticity, urinary retention, constipation, temperature dysregulation, autonomic dysreflexia, and orthostatic hypotension), and the development of psychiatric conditions (depression, anxiety, and sleep disorders).

Rehabilitation After Acute Spinal Cord Injury

In part due to the challenges of conducting prospective controlled studies in patients with SCI, there is a lack of agreement among clinical practice guidelines for postinjury rehabilitation. Rehabilitation goals are often complex and should be individualized to each patient. Physical and occupational therapists should be an integral part of caring for these patients even before transferring to the rehabilitation unit, and both patients and their families should be educated on the importance and goals of rehabilitation efforts to maximize the potential for long-term recovery. Updated clinical practice guidelines for rehabilitation were published in the Journal of Neurology and Physical Therapy in 2020. The authors recommend postacute care in the institutional and community setting and moderate to high-intensity walking training in individuals who are able after central nervous system injury. They also recommend virtual reality walking and circuit training. Similar guidelines published in 2017 by AOSpine and the American Academy of Neurologic Surgeons (AANS) also recommend psychosocial rehabilitation and place a strong emphasis on early rehabilitation once medically stable.

PROGNOSIS

Providing a reliable prognosis to patients and their families is an important component of caring for patients with SCI. The most important prognostic factors to consider are the level of neurologic injury, ASIA impairment scale grade, age at injury, and appearance of the spinal cord on MRI, with early mortality seen in high cervical lesions, increased age, more severe neurologic deficits, and edema or hemorrhage on T2 MRI. A handful of disability measurement scales exist for categorizing patient's impairments and monitoring improvement, and the Spinal Cord Independence Measure (SCIM) is among the most common. The SCIM takes into account self-care (0–20 score), respiratory and sphincter management (0–40), and mobility (0–40), with the final score ranging from 0 to 100. The mortality rate of SCI patients is difficult to generalize overall, with a large systematic review showing median survival of between 35.4 days to 36.5 years. On average, however, the mortality associated with SCI is highest between 6 to 12 months after injury, with the greatest threat being pneumonia and sepsis. It is estimated that 13% of patients are employed at 1 year following the initial insult. The average lifetime costs attributed to the care for patients with SCI vary from $1.1 million in elderly patients with less severe injuries to $4.8 million in younger patients with high cervical injuries.

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Evaluation and Management of the Patient with Craniomaxillofacial Trauma

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GENERAL CONCEPTS

The maxillofacial skeleton is composed of three distinct regions: the upper face, midface, and lower face (Fig. 1). The upper facial skeleton is predominately made up of the frontal bone, supraorbital rims, and lateral orbital elements. The midface includes the medial, inferior, and inferolateral orbit, as well as the nasal complex, zygomata, and maxilla. The lower facial skeleton is represented by the mandible and its associated temporomandibular joints. It is helpful to consider these facial skeletal thirds when discussing the evaluation and management of craniomaxillofacial injuries, as injuries may involve a single portion of the facial skeleton (e.g., isolated frontal sinus fracture) or all portions of the facial skeleton (e.g., panfacial fracture).

The bones that comprise the facial skeleton are supported by vertical and horizontal skeletal buttresses (Fig. 2). These buttresses assist with the dispersion of forces such that energy is dissipated before being transmitted to the intracranial structures or cervical spine. The vertical buttresses of the facial skeleton include the nasomaxillary (medial), zygomaticomaxillary (lateral), pterygomaxillary, and posterior mandibular (Fig. 3). These points of skeletal fusion support the bones of the midface and lower face. The horizontal buttresses of the facial skeleton include the frontal, zygomatic, maxillary,

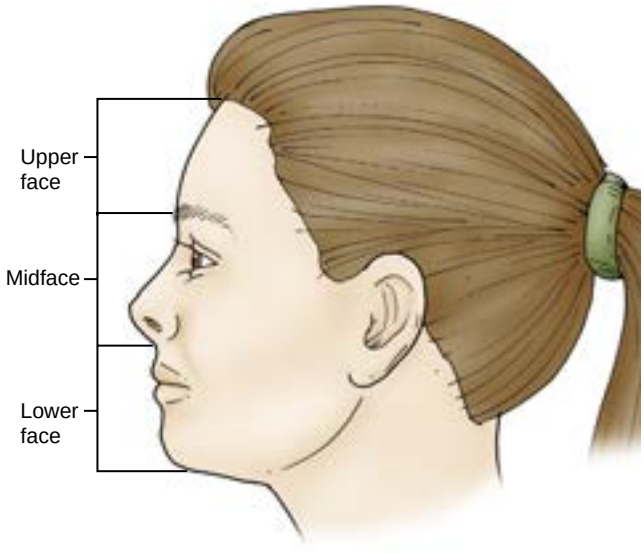


FIG. 1 Regions of the maxillofacial skeleton. *(Adapted from Avery LL, Susarla SM, Novelline RA. Multidetector and three-dimensional CT evaluation of the patient with maxillofacial injury.* Radiol Clin North Am. *2011;49:183–203.)*

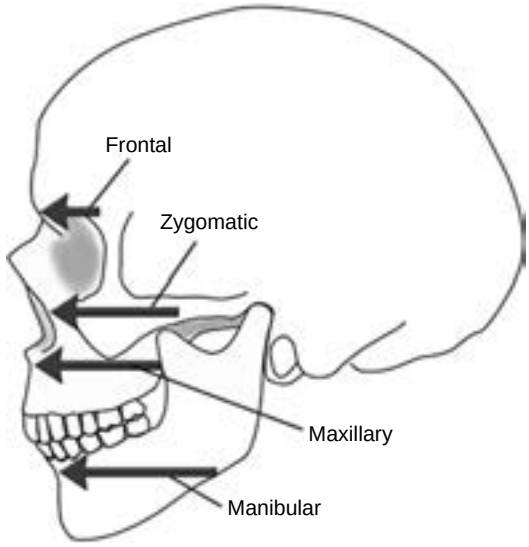


FIG. 3 Horizontal skeletal buttresses. *(Adapted from Avery LL, Susarla SM, Novelline RA. Multidetector and three-dimensional CT evaluation of the patient with maxillofacial injury.* Radiol Clin North Am. *2011;49:183–203.)*

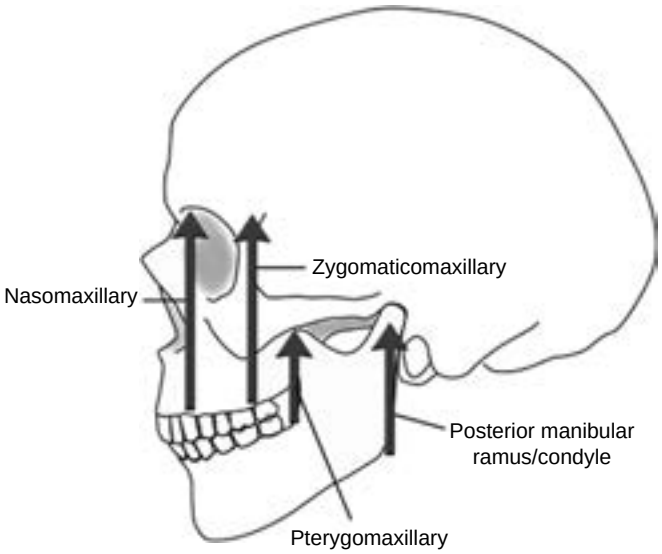


FIG. 2 Vertical skeletal buttresses.

and mandibular and offer support to the associated bones and their articulations.

The surgeon initially managing acutely injured patients would be well served to know the regions of the face and the associated buttress. Although the finer anatomy of the facial bones is relevant for operative management of these injuries, an understanding of the regional gross anatomy and biomechanical principles can assist the trauma surgeon with recognizing patterns of injury and effectively communicating the types of injuries to the craniomaxillofacial surgeon.

The discussion that follows will focus on the constituent parts of each third of the facial skeleton, the patterns of injury that commonly occur within each, and the clinical signs and symptoms associated with injuries to these regions, whether in isolation or concomitantly with other fractures.

EMERGENT MANAGEMENT OF CRANIOMAXILLOFACIAL TRAUMA

Craniomaxillofacial trauma can present with three life-threatening emergencies that need to be managed before all else: (1) airway, (2) hemorrhage, (3) aspiration. These are part of the crucial initial assessment and management of all trauma patients—ABCs, ATLS, C-spine precautions, and ruling out cranial, thoracic, and abdominal injuries.

Airway

Swelling and bleeding in the nasopharynx and oropharynx can result in an unstable and obstructed airway. The patient may present with stridor, hoarseness, and inability to tolerate secretions. Rapid assessment and plan for intubation, emergent cricothyroidotomy, or tracheostomy should be performed. A protected and stable airway will also lessen the risk of aspiration of oral secretions, gastric contents, and blood.

Hemorrhage

Ongoing bleeding from the scalp, face, sinuses, and from within the skull is life-threatening. Visualization and direct control with direct pressure or ligation may be required. Although rare, consultation with interventional radiology for selective embolization of injured vessels needs to be considered.

UPPER FACIAL INJURIES

The frontal bone, which comprises the upper facial skeleton and provides the contour of the forehead, superior orbital rim, and orbital roof, is a prominent feature of the facial skeleton, particularly in children. The frontal bone has a central, air-filled cavity known as the frontal sinus, which is bounded anteriorly and posteriorly by thin pieces of frontal bone. Frontal sinus pneumatization does not occur until the age of 7, which influences the patterns of frontal injuries seen in children (e.g., linear bone fractures) versus those of adults (frontal sinus fractures). Frontal sinus fractures may involve the anterior wall of the sinus (anterior table fractures), the posterior wall of the sinus (posterior table fractures), or both. Patients with

frontal bone injuries often present with lacerations over the forehead or eyebrows with associated edema. Isolated upper eyelid ecchymosis may be consistent with an orbital roof injury (the orbital roof represents a portion of the floor of the frontal sinus and is comprised of the orbital plate of the frontal bone). Rhinorrhea is a worrisome clinical finding in these patients, as it suggests a complex injury that involves the posterior table of the frontal sinus with associated dural injury. Patients may describe salty nasal drainage, and presence of cerebrospinal fluid can be confirmed with a beta-2-transferrin test.

Evaluation should include a careful inspection of the forehead and scalp, examination of the eyes, particularly to assess visual acuity and extraocular movements, and inspection of the nose to identify rhinorrhea. Relevant consultations should include craniomaxillofacial surgery and possibly neurosurgery and ophthalmology.

Isolated anterior table fractures of the frontal sinus without significant displacement or comminution rarely require operative intervention. In contrast, displaced injuries of the anterior table (Fig. 4), particularly those that violate the integrity of the nasofrontal outflow tracts (which allow for sinus drainage into the nose), or displaced posterior table fractures are complex injuries that often require multidisciplinary management. In patients with posterior table injuries, the evaluating clinician should consider the likelihood of intracranial vascular injury and dural injury with cerebrospinal fluid leak. Pneumocephalus on CT is one sign suggestive of a posterior table injury and may be helpful for diagnosis in situations where a nondisplaced fracture exists.

TREATMENT OF UPPER FACIAL INJURIES

The surgical access to the frontal bone and sinus is through a coronal incision. It is important to identify the periosteum and protect it early in the surgical exposure because it may be needed for a pericranial flap. The pericranial flap is a valuable source of vascularized tissue that can be used for obliteration of the frontal sinus, repair of dural injuries, coverage of hardware, and as a base for skin grafting.

Nondisplaced anterior wall fractures without nasofrontal duct obstruction can be observed. Depressed anterior wall fractures with resultant deformity can undergo open reduction and internal fixation to improve contour. Fractures that result in obstruction of the nasofrontal duct require either complete removal of the mucosa and obliteration of the duct with bone graft, or removal of the posterior wall and cranialization of the entire sinus. In the setting of mucosal stripping, burring of the bone should also be performed to completely remove microscopic mucosal invaginations. Nondisplaced posterior wall fractures without nasofrontal duct obstruction can also be observed. Displaced posterior wall fractures may have dural injuries that will need exploration and repair in a combined operation with neurologic surgery colleagues.

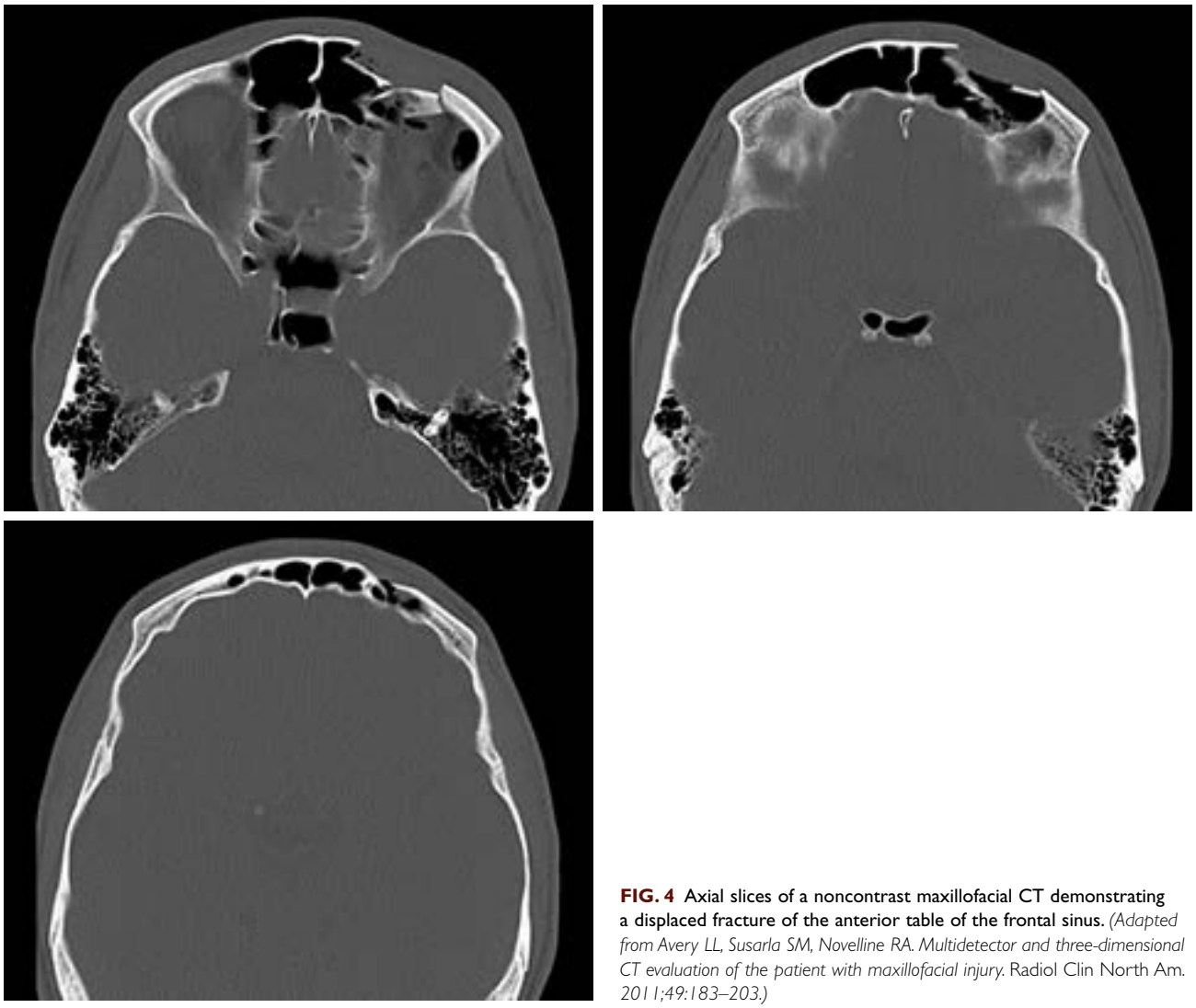


FIG. 4 Axial slices of a noncontrast maxillofacial CT demonstrating a displaced fracture of the anterior table of the frontal sinus. *(Adapted from Avery LL, Susarla SM, Novelline RA. Multidetector and three-dimensional CT evaluation of the patient with maxillofacial injury.* Radiol Clin North Am. *2011;49:183–203.)*

MIDFACIAL INJURIES

The midface is arguably the most complex bony anatomy of the facial skeleton, as it is composed of many small bones with important soft tissue structures. The nasal, orbital, zygomatic, and maxillary regions are components of the midface, and midface injuries often include multiple regions. Patients with midfacial injuries often present with a clinical history of direct trauma to the midface or eyes. Clinical symptoms may include double vision, decreased vision, periorbital edema and ecchymosis (Fig. 5), nasal bleeding/congestion, cheek or upper lip swelling, facial asymmetry due to loss of nasal or zygomatic projection, malocclusion, and paresthesia to the lower eyelid, cheeks, and upper lip (suggestive of infraorbital nerve injury).



FIG. 5 Midfacial injury.

Clinical evaluation of patients with midfacial injuries should systematically assess four distinct areas: the nasal complex, the orbit, the zygoma, and the maxilla. Evaluation of each area should focus on assessment of soft tissue injury (frequently with associated lacerations to the nose, eyelids, or cheeks), as well as distinct findings associated with specific bony injuries. Nasal bone fractures often present with swelling and tenderness to palpation over the nasal root, with associated crepitus. An intranasal examination is important to assess the position of the septum, identify any sources of intranasal bleeding (which may require packing or urgent airway management), and septal hematoma. Orbital examination should focus on palpation of the external orbital rim, which is comprised of the frontal bone, zygomatic bone, and maxilla, to assess for discontinuities or stepoffs. Close evaluation of the eye (visual acuity, double vision, extraocular movements, etc.) is paramount, as many patients with orbital fractures will have altered vision or injuries to the ocular adnexa. Patients with zygomatic injuries may complain of cheek swelling, loss of cheek projection, cheek numbness, or difficulty opening their mouth (trismus). The latter finding suggests impingement of the zygomatic arch on the temporalis muscle/coronoid process of the mandible, consistent with a displaced zygomatic arch fracture or displaced zygomaticomaxillary complex (ZMC) injury. Patients with maxillary fractures often have associated intranasal and/or intraoral bleeding, malocclusion, dental/dentoalveolar injury, or facial asymmetry.

Radiographic assessment of midfacial injuries should be systematic and focus on identifying patterns of injury rather than specifying which particular bones are fractured. Given the complex interbony connections within the midface, it is more useful to know the patterns of injury that are commonly seen than it is to describe each bone or portion thereof that is injured. Fortunately, there are well-established classifications for complex injuries in the midface that can aid the trauma surgeon with communicating the findings to the facial trauma specialist.

Injuries of the nasal region can be commonly classified as isolated nasal bone/septal fractures and the more complex naso-orbito-ethmoid (NOE) fractures. Nasal bone fractures are very common due to the thin bony support and prominent position of the nasal complex as a central component of the face. Radiographically, nasal bone fractures can be identified by the degree of displacement, laterality, and associated soft tissue swelling (Fig. 6). Deviation of the septum or septal hematoma should also be evaluated as one reviews the

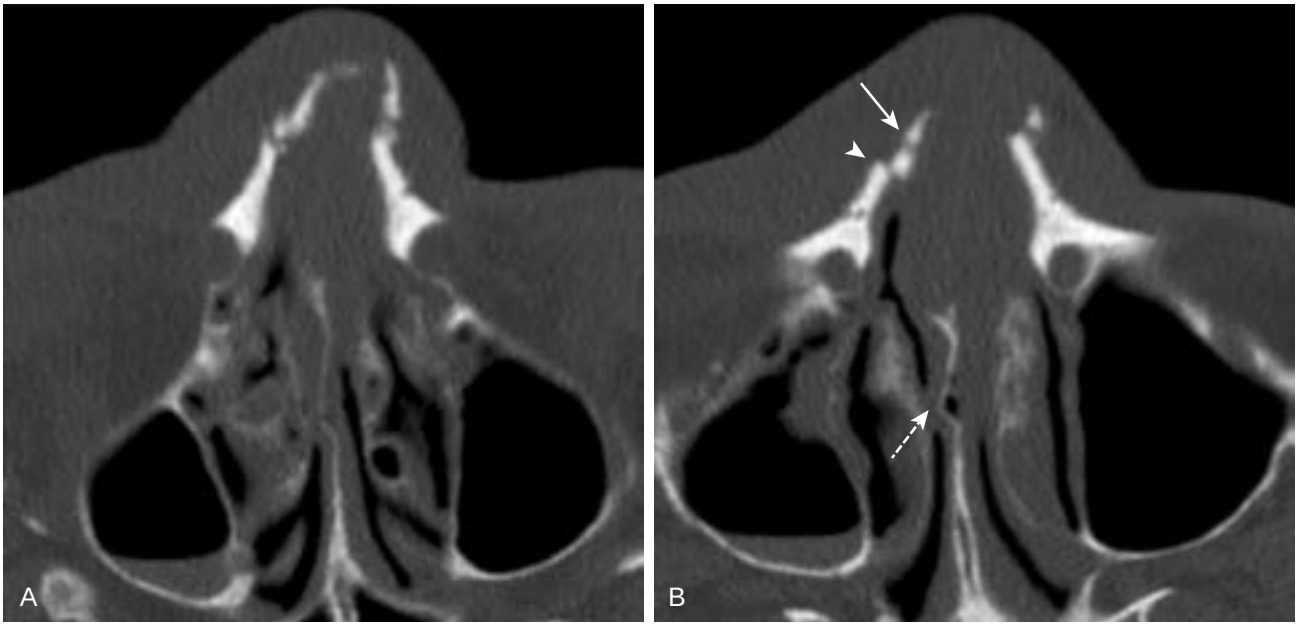


FIG. 6 **A** and **B,** Axial slices of a noncontrast maxillofacial CT demonstrated displaced nasal bone fractures. **B,** Significant displacement of both the right frontal process of the maxilla *(arrowhead)*, right nasal bone *(solid arrow)*, and bony nasal septum *(dashed arrow)*.

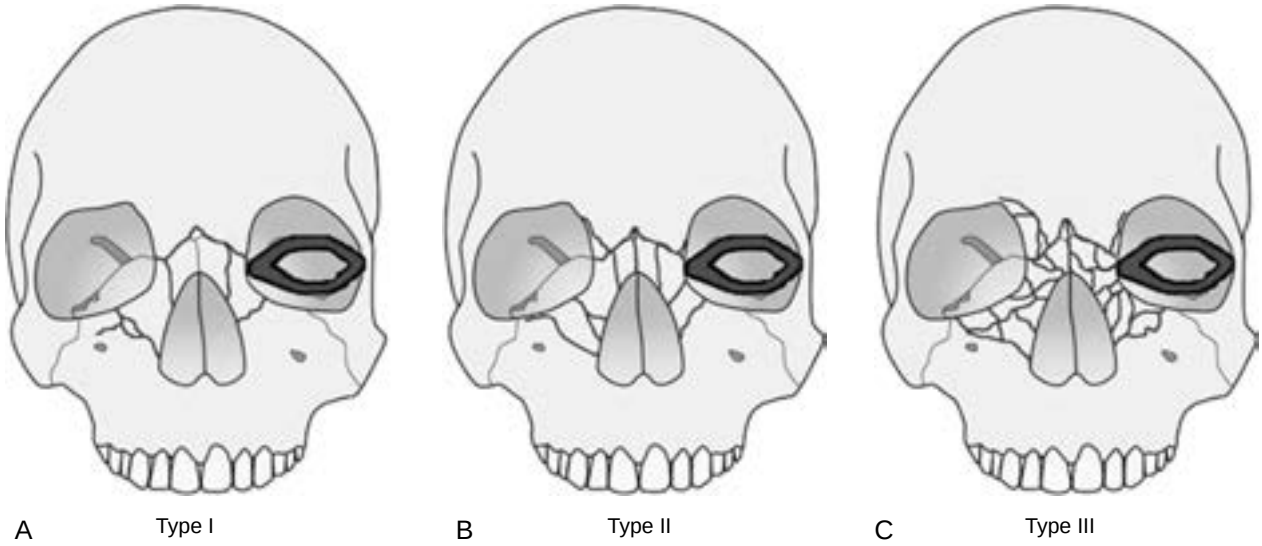


FIG. 7 The Markowitz-Manson classification of nasoorbitoethmoid (NOE) fractures. This classification scheme is based on the integrity of the medial canthal tendon (MCT) attachment to the NOE complex. **(A)** In type I injuries, the tendon remains attached to a large central NOE fragment. **(B)** In type II injuries, there is a higher degree of comminution of the central fragment, but the MCT remains attached to the bone. **(C)** In type III injuries, there is a high degree of comminution, and the MCT attachment to the bone needs to be reestablished during reconstruction.

relevant imaging. Higher energy injuries will cause greater displacement or comminution. The highest energy injuries will include the medial orbit resulting in NOE complex fractures that involve the nasal bones, inferior medial orbital rim, and the medial orbital wall, which is comprised of the ethmoid bones. Damage to the medial canthal tendons can cause increased distance between the medial canthi (telecanthus) and has important implications for management. The Markowitz-Manson classification system is based on the severity of fractures and the integrity of the medial canthal tendon complex (Fig. 7).

Orbital injuries are frequently encountered in patients of all ages and may occur in conjunction with nasal injuries, frontal bone injuries, and zygomaticomaxillary injuries. Isolated orbital fractures can involve any of the four walls of the orbit (roof, floor, medial, or lateral), but most frequently involve the orbital floor and medial wall (Fig. 8). These injuries may be associated with entrapment of the extraocular muscles, herniation of the periorbital soft tissues into the adjacent air-filled spaces (ethmoid or maxillary sinuses), and globe injuries. Muscle entrapment is a surgical emergency and can present with extraocular movement restriction, oculocardiac reflex/trigeminovagal reflex (sinus bradycardia), severe nausea, and eye pain. Forced duction testing should be performed preoperatively and at the end of an orbit operation to assess any restricted eye movements in sedated patients.

Zygomatic injuries are often described as injuries to the different articulations of the zygoma. However, the trauma surgeon should be cognizant of the regional anatomy and the components of a ZMC injury. The zygoma articulates with the frontal bone, maxilla, lateral wing of the sphenoid bone, and the temporal bone via the zygomatic arch. In a complete ZMC fracture, all four articulations are disrupted, which may result in varying degrees of displacement of the zygoma, loss of cheek projection, or facial widening. Incomplete fractures of the ZMC will involve one or more articulations but not all. A simple classification scheme for ZMC fractures is based on the degree of injury to the various articulations, with minor injuries being those with involvement of only one articulation and more major injuries involving all four articulations (Fig. 9), with or without comminution of the zygoma proper.

Maxillary fractures have been classically characterized by the Le Fort designation (Fig. 10). Le Fort I injuries are those that separate the maxilla from the remainder of the midface. Le Fort II injuries,

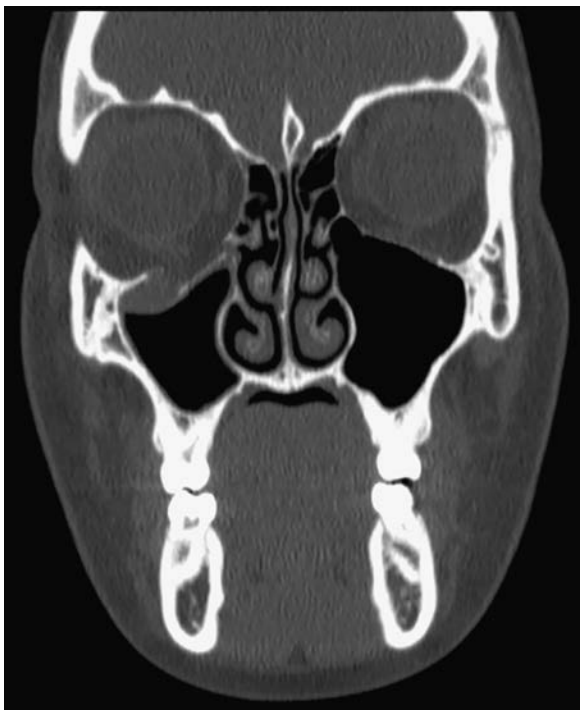


FIG. 8 Orbital injury.

or "pyramidal fractures," separate the maxilla and nasal complex from the surrounding midfacial structures. Le Fort III fractures, or "craniofacial dysjunction," separate the midface from the skull base in its entirety. Regardless of the level of injury, patients with maxillary fractures commonly present with midfacial swelling, pain, and subjective complaint of malocclusion. Physical findings will include malocclusion, intraoral or midfacial ecchymoses, maxillary mobility, and facial paresthesia related to the infraorbital or nasopalatine nerves. Characteristic imaging findings are associated with the level of injury, but strictly speaking, all Le Fort fractures will involve injury to the pterygoid plates. It should be noted that, though classically

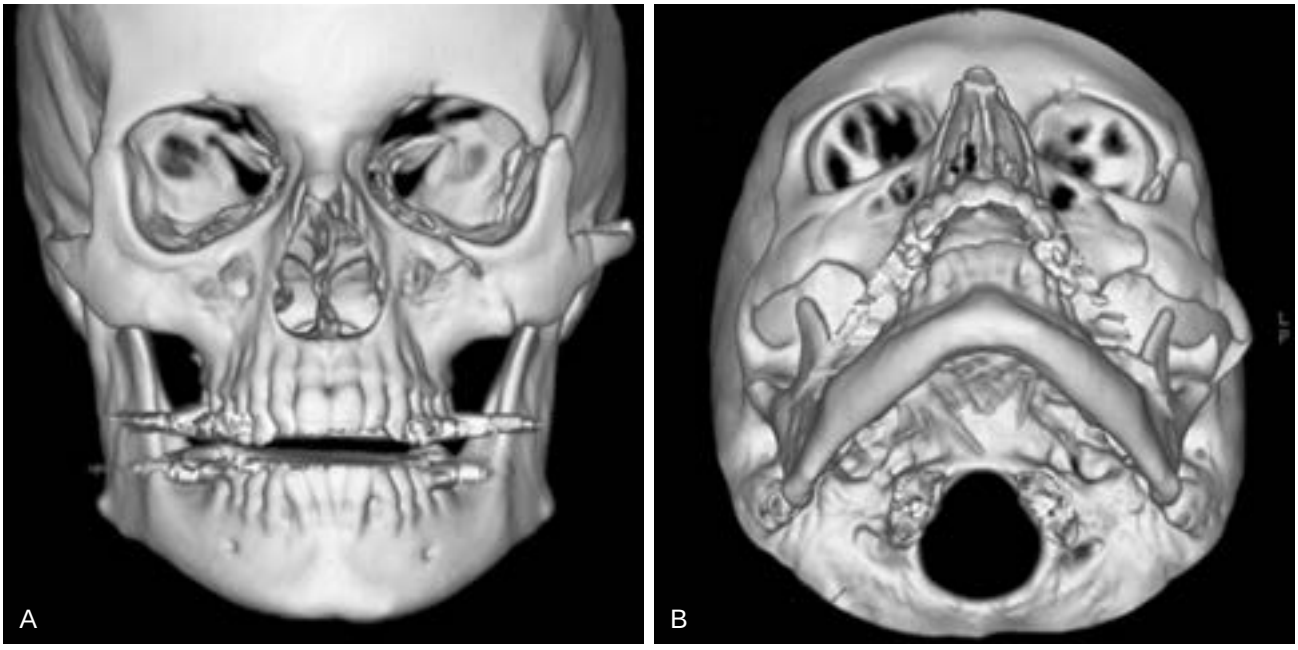


FIG. 9 Three-dimensional computed tomographic reconstructions of a patient with a displaced left zygomaticomaxillary complex (sometimes referred to as an orbitozygomatic) fracture. **A,** Displacement in the frontal plane, most notably at the inferior orbital rim and frontozygomatic suture. **B,** Displacement at the zygomaticomaxillary buttress and zygomatic arch, as viewed from below.

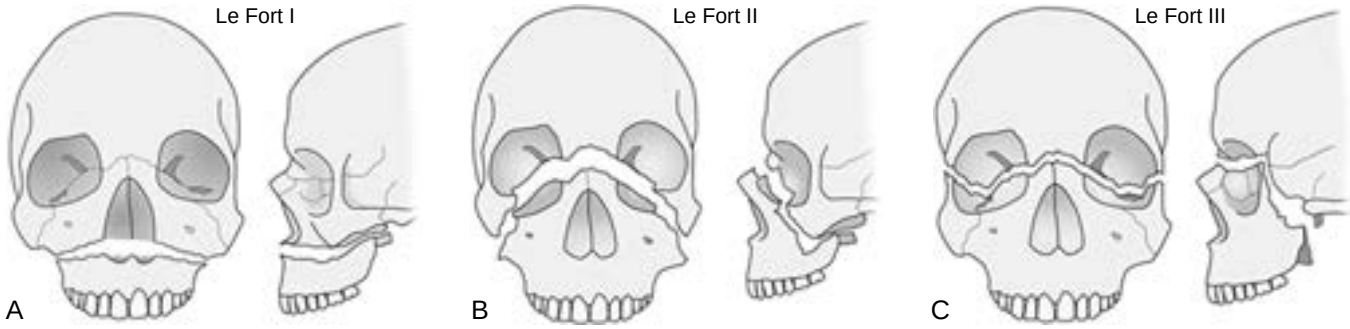


FIG. 10 (A–C) Le Fort classification of maxillary injuries.

described as bilateral injuries, Le Fort fractures can occur unilaterally or asymmetrically (e.g., Le Fort I injury on one side, Le Fort II on the other). In addition, patients with high-energy mechanisms may present with multilevel Le Fort injuries (Fig. 11).

TREATMENT OF MIDFACE FRACTURES

Naso-Orbital-Ethmoid Fractures

Surgical indications for NOE are both functional (cerebrospinal fluid rhinorrhea, persistent epistaxis, disruption of nasolacrimal system, medial orbital entrapment) and aesthetic (displaced NOE complex and telecanthus). For most cases, there is adequate time to determine the extent of all injuries, start antibiotics, and plan for operative intervention. More urgent indications relate to neurologic or ophthalmologic function. Similar to other parts of craniomaxillofacial reconstruction, NOE injuries should be approached in terms of the objectives and the approaches of surgical repair. Additionally, multidisciplinary (neurosurgery, otolaryngology, and ophthalmology) evaluation and treatment is crucial to patient care. Starting cranially and progressing caudally, the frontal sinus floor and posterior wall fractures may need exploration and repair. Cerebrospinal fluid leaks that have not resolved with conservative measures and time need to be repaired at this time. Displaced and widened NOE bones need to be reduced and either splinted or fixated into proper position, which also relates to reestablishing normal intercanthal distance (normal is about 30 mm), and frontal and profile appearance. Entrapped medial orbital tissues should be carefully reduced while protecting the globe. Lastly, the nasolacrimal drainage system should be repaired and stented to establish continuity.

Depending on the extent of the structures involved, there are several surgical approaches to address NOE injuries: existing traumatic lacerations, transconjunctival approach ± transcaruncular extension, medial canthal and lateral nasal approach, and coronal flap. If the NOE fracture fragments are unstable with reduction and splinting, they will require fixation. Internal transnasal wiring is placed superior and posterior to the posterior lacrimal crest to provide the appropriate vector of fixation and avoids injury to the nasolacrimal system. Alternatively, low-profile miniplates can be spanned from the frontal bone to the maxilla to achieve fixation.



FIG. 11 Multilevel Le Fort injury. *(Adapted from Avery LL, Susarla SM, Novelline RA. Multidetector and three-dimensional CT evaluation of the patient with maxillofacial injury.* Radiol Clin North Am. *2011;49:183–203.)*



FIG. 12 Right mandibular parasymphysis fracture. The fracture extends through the dentoalveolar segment, with a visible laceration and stepoff in the occlusal plane between the right mandibular lateral incisor and canine *(arrow)*.

Zygoma Fractures

The surgical approach to a displaced arch that needs reduction alone could be performed through either a temporal Gillies incision or intraoral Keen incision. Often times, the periosteum surrounding the arch is sufficient to stabilize it after reduction. Displaced zygoma fractures that involve the arch, frontozygomatic suture, zygomaticosphenoid suture, inferior orbital rim, and maxilla require multiple approaches to the craniofacial skeleton. Coronal incision, brow incision, lower lid incision, and intraoral incision may all be used in combination. Anatomic reduction of the fracture lines and sutures, particularly the sphenozygomatic suture, is of critical importance before fixation to restore facial width and projection. The orbital floor can also be displaced in ZMC fractures and should also be explored and fixed as necessary to prevent diplopia, enophthalmos, and orbital dystopia.

Maxillary Fractures (Le Fort Patterns)

The first step in surgical correction of maxilla fractures is to obtain appropriate centric occlusion held in place with temporary maxillomandibular fixation (MMF) with either rapid screws or Erich arch bars. Through an intraoral gingivobuccal approach, the maxillary fracture is exposed, reduced, and fixated with plates and screws along the medial and lateral buttresses. Postoperative MMF is not required if rigid fixation is used. Associated fractures of the nasofrontal junction and orbital rims may be exposed through coronal and upper and lower eyelid incisions as necessary.

LOWER FACIAL INJURIES

Lower facial skeletal injuries involve the mandible and its associated alveolar housing. As the only mobile bone within the face, the mandible is arguably the most complex bone and presents a unique reconstructive challenge when injured. The most common causes of mandibular fractures are motor vehicle accidents, assaults, and falls. The clinical history is often diagnostic, as patients will relate an injury mechanism whereby their chin or lower face was directly struck and will complain of an altered bite, intraoral bleeding, and lower lip or tongue paresthesia.

Physical examination of the patient with mandibular trauma often reveals an intraoral laceration or fractured teeth (Fig. 12). Sublingual hematoma is often associated with injuries of the dentate mandible. Patients with subcondylar fractures may have deviation of the mandible to the side of the fracture when opening their mouth. Patients with bilateral subcondylar fractures often present with an anterior open bite (i.e., the maxillary and mandibular incisors do not occlude). When evaluating patients with mandibular injuries (or maxillary injuries), it behooves the practitioner to ask the patient if their bite feels different and how so. Patients often can provide a description of how their teeth fit together before the injury.

Although many plain film imaging techniques have historically been described for imaging of mandibular injuries, multidetector CT scans have largely replaced plain films as the technique of choice for evaluation. Three-dimensional reformations of maxillofacial CT scans with 1 mm cuts are often helpful for demonstrating the fracture with the affected dentition in the same image. Finally, as the mandible is a single, contiguous bone connecting two joints, forces distributed at the site of injury may result in coup or countercoup injuries with bilateral fractures. These are often not immediately evident on clinical examination but should be carefully ruled out on imaging (Fig. 13).

TREATMENT OF MANDIBLE FRACTURES

Similar to treatment of maxillary fractures, the first step in mandibular fracture repair is establishing appropriate centric occlusion and centric relation. Mandibular fractures can be managed through a combination of MMF and rigid internal fixation. Nondisplaced and stable fractures of the symphysis, body, angle, ramus, and condyle may be successfully managed with MMF alone. It should be noted that patients will lose between 10 to 20 pounds while on a liquid diet during their 4 to 6 weeks of treatment. Displaced fractures require open reduction internal fixation through either an intraoral or external approach. Patients who receive plate-and-screw fixation should be counseled to maintain a soft diet for 4 to 6 weeks during healing, maintain meticulous oral hygiene with chlorhexidine rinses 3 to 4 times per day, and to quit smoking.

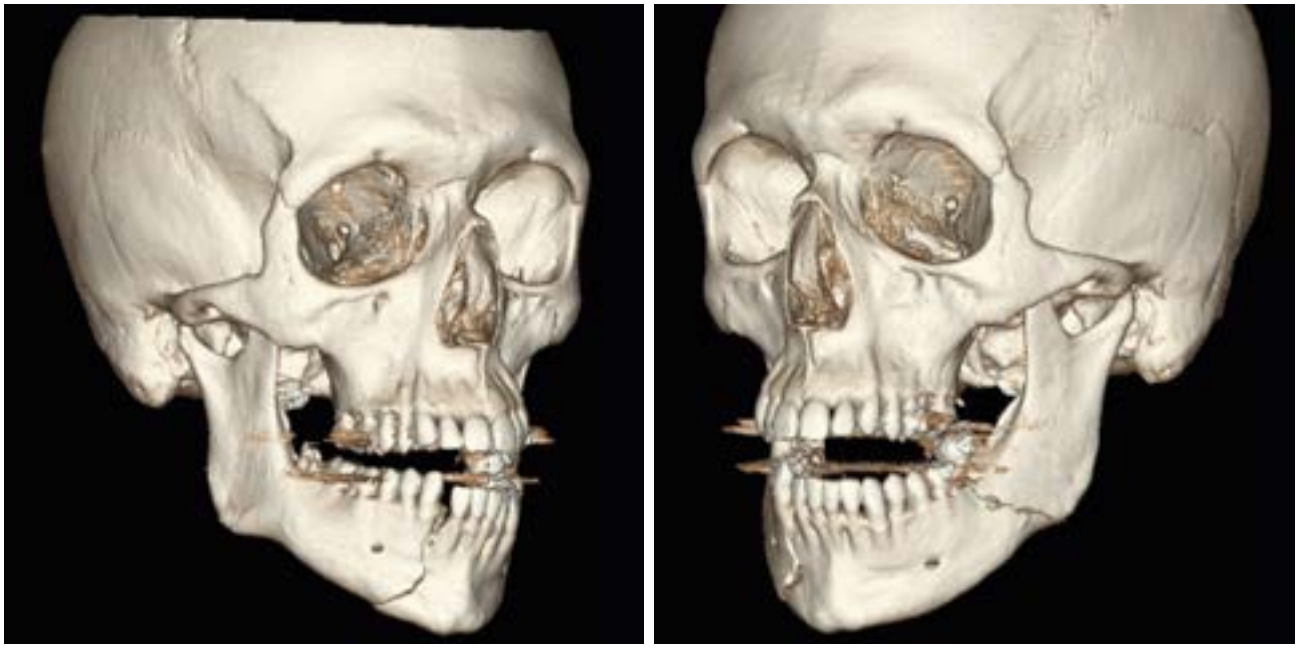


FIG. 13 Three-dimensional reformations of maxillofacial computed tomographic scans for mandibular injury. *(Adapted from Avery LL, Susarla SM, Novelline RA. Multidetector and three-dimensional CT evaluation of the patient with maxillofacial injury.* Radiol Clin North Am. *2011;49:183–203.)*

SOFT TISSUE INJURIES

Facial skin defects secondary to trauma can be several centimeters wide involving regions in which obtaining appropriate aesthetic and functional results can be challenging. For example, lesions in the lower eyelid need to be reconstructed appropriately so as not to cause ectropion, or pulling down, of the lower eyelid. The blood supply to the face is robust, and all tissues should be preserved for potential soft-tissue closure following a traumatic injury. The wound should be cleaned of all debris and irrigated. All tissue should be handled meticulously and closed loosely, with monofilament sutures if there is concern for ischemia or infection.

Small superficial defects of the facial skin can often be closed primarily after an elliptical incision. Such an incision must be short and made in the direction of the facial skin-tension lines. If the wound cannot be closed primarily, the next option would be a local tissue flap based on a random blood supply, such as a transposition or rhomboid flap. Full-thickness skin grafts can be used instead if they match the thickness and color of the skin at the wound site. The best skin graft donor site for facial reconstruction is the region above the clavicle, as both the color and the texture of the skin there match that of the facial skin. Defects in the face >5 cm often require large fasciocutaneous rotation flaps from the cervical and deltopectoral region. In rare instances in which local or regional tissue cannot cover exposed critical neurovascular or bony structures, reconstruction with free tissue transfer may be necessary.

CERVICAL SPINE AND INTRACRANIAL INJURIES

In addition to assessment of the upper, middle, and lower facial skeletons, the traumatologist should have a high suspicion for cervical spine or intracranial injury in the patient with craniomaxillofacial trauma. Among patients evaluated with craniomaxillofacial trauma, 5% to 10% have a concomitant cervical spine injury and up to 50% may have an intracranial injury. Upper facial injuries are associated with lower cervical spine and intracranial injuries. Midfacial injuries, particularly unilateral injuries, are associated with basilar skull fractures and intracranial injuries. Upper cervical spine injuries are often seen with mandibular fractures.

CONCLUSION

The evaluation and management of the patient with craniomaxillofacial trauma is based on a fundamental understanding of anatomy. It is the interaction of the bones of the facial skeleton with the overlying soft-tissue envelope that creates an interesting dynamic for the reconstructive surgeon to deal with in the setting of trauma. Adherence to basic surgical principles regarding bone stabilization and soft-tissue handling will assist the reconstructive surgeon in optimizing clinical outcomes in the treatment of these patients undergoing trauma to the craniomaxillofacial skeleton.

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Penetrating Neck Trauma

Anna M. Ledgerwood, MD, and Charles E. Lucas, MD

The anatomy text defines the neck as being the structure that connects the head to the torso. The cervical vertebrae make up the bony connection that allows the neck to be involved in flexion, extension, and rotation. The neck may be divided into bilateral anterior and posterior triangles by the sternocleidomastoid (SCM) muscles. Treatment of posterior triangle injuries focuses primarily on hemostasis for active bleeding from superficial wounds and complex reconstruction of soft tissues for deep wounds. When assessing patients with gunshot wounds to the posterior triangles, one needs to be sure that the missile did not injure the structures within the anterior triangles.

The anterior cervical triangles can be divided into three zones (Fig. 1). Zone 1 is sometimes referred to as the "thoracic outlet" and extends from the first rib to the clavicles. A decision to explore zone 1 injuries would be made on the basis of confirmed injury to a named vessel, the trachea, or the esophagus. Zone 2 of the anterior triangles extends from the cricoid cartilage to the angle of the mandible. Formerly, all patients who had penetration of the platysma muscle in zone 2 underwent mandatory exploration. Most zone 2 injuries are now treated nonoperatively. Zone 3 of the anterior triangles extends from the mandible to the base of the skull. The decision to explore zone 3 injuries would be based upon angiographic evidence of arterial injury. This clinical classification of penetrating neck wounds by zone is an outgrowth of historical data when most penetrating neck wounds were caused by knives. Current data show that many penetrating neck wounds are caused by missiles; consequently, the surgeon must determine whether the missile that entered in one zone has traversed into one or both of the other zones, which mandates that decision making be made according to all of the zones in which the missile has entered.



FIG. 1 The anterior cervical triangle may be divided into three zones. Zone 1, the thoracic outlet, extends from the first rib to the cricoid cartilage. Zone 2 extends from the cricoid cartilage to the angle of the mandible. Zone 3 extends from the mandible to the base of the skull.

Most challenges regarding the care of penetrating neck wounds relate to injuries in the anterior triangles. These challenges include (1) emergency airway control, (2) hemostasis for active bleeding, (3) emergent operative intervention for nonbleeding injuries, (4) choice of diagnostic studies for patients not requiring urgent operation, (5) decision making regarding the need to explore or observe stable patients, (6) optimal exposure for patients requiring operation, and (7) care of specific injuries (Box 1).

EMERGENCY AIRWAY CHALLENGES

Potentially life-threatening airway injuries may be caused by tracheal or cartilaginous rupture, soft tissue compression of the airway from adjacent arterial injury, or active hemorrhage into the tracheal-bronchial tree due to a vascular airway fistula. Signs and symptoms of acute airway challenges might include hemoptysis, stridor, hoarseness, subcutaneous air, air hunger, or patient's refusal to lie down, which would interfere with expectoration of airway blood. The stable patient with hemoptysis wishes to sit up and lean forward to efficiently expectorate blood present within the airway. Forcing the patient to lie flat on the stretcher should be avoided until all preparations have been made for a rapid sequence intubation (RSI).

Ideally, RSI is performed in the operating room by experienced anesthesia personnel so that the team can proceed directly to operation. When excessive bleeding into the oral cavity is present, one should attempt a nasotracheal intubation (Fig. 2). When bleeding

BOX 1 Priorities in Care of Penetrating Neck Wounds

1. Emergency airway control
2. Hemostasis for active bleeding (anterior or posterior)
3. Urgent operation for nonbleeding life-threatening wounds
4. Urgent diagnosis for patients who are stable
5. Decision to explore or observe stable patients
6. Exposure of internal organs
7. Specific treatment of the injured organs

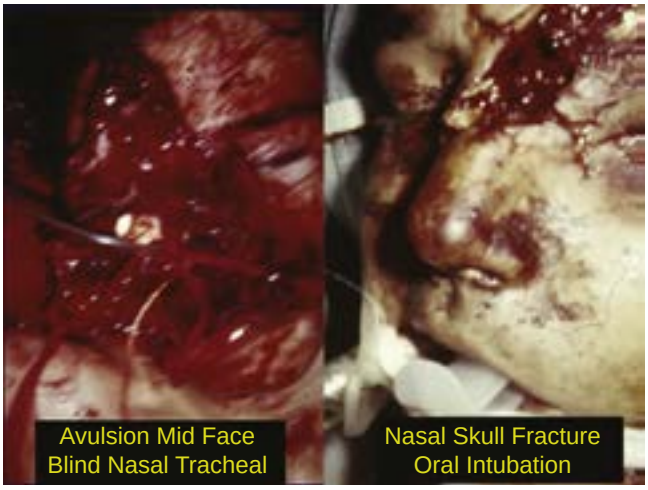


FIG. 2 Establishing an emergency airway may be difficult with head and neck trauma. A patient with a destructive injury to the nose and mouth *(left)* had placement of a nasotracheal airway by an experienced anesthetist who followed the bloody bubbles and prevented an emergency coniotomy that was about to begin. The patient with injury to the proximal nose and forehead requires oral intubation to prevent injury to the frontal lobe in association with a fracture of the cribriform plate *(right)*.

obscures the hypopharynx, a fiber-optic nasotracheal intubation may be accomplished by experienced personnel. When severe nasal fractures or lower forehead fractures are present, the intubation should be accomplished by the oral route to prevent injury through a fractured cribriform plate into the frontal lobe (see Fig. 2). When both the oral and nasal route of intubation are compromised, one should proceed directly to a coniotomy (cricothyroidotomy) or, in a less urgent situation, a rapid tracheostomy.

Significant preintubation hemoptysis portends an arterial-tracheal fistula. When present, the balloon on the endotracheal tube, once inserted, should be inflated at or below the site where the potential fistula is most likely located. Likewise, when a coniotomy is performed, the tracheostomy tube balloon should be positioned at the suspected site of a fistula or more distally. Once airway control is achieved, immediate neck exploration is performed.

HEMOSTASIS OF EXTERNAL BLEEDING

Once the airway has been established, control of significant external bleeding becomes the next priority. Significant nonpulsatile bleeding is likely coming from a major venous injury. This can usually be controlled by direct digital pressure over the site where the suspected venous perforation is located. Pulsatile bleeding indicates an arterial injury. This may be controlled by direct external pressure or by placing the gloved finger through the penetrating wound where the pulsation can be palpated down to its origin at the arterial perforation. Direct digital pressure is maintained throughout the trip to the operating room, the anesthetic induction, the rapid wound preparation, and during the incision until the dissection reaches the injured artery. Neck wraps and compresses should never be used because they are ineffective and potentially dangerous.

URGENT OPERATION IN NONBLEEDING PATIENTS

Once airway control has been obtained in patients who no longer have external bleeding, a decision must be made as to whether the patient needs an urgent operation. That decision is often made on the basis of so-called hard signs indicative of a major injury. These signs would include a pulsatile hematoma, continued external oozing, cervical crepitus, hoarseness, air bubbles within the wound, dyspnea, stridor, air hunger, or large soft tissue wounds that need surgical closure (Box 2).

BOX 2 Hard Signs for Operative Exploration

1. Pulsatile hematoma
2. Continued external oozing
3. Cervical crepitus or air bubbles in wound
4. Dyspnea, stridor, air hunger
5. Hoarseness
6. Large wounds needing reconstruction

URGENT DIAGNOSTIC EVALUATION

Many patients without the need for emergent or urgent operative intervention should have diagnostic studies performed to exclude potential injuries to important structures. Such patients may have soft signs, including continued superficial bleeding thought to be from the skin or subcutaneous tissues, a history of major bleeding before arrival in the emergency department, blood-streaked sputum, or cervical swelling. The first component of this urgent investigation is a thorough physical examination of the neck, including an intraoral examination looking for blood or mucosal injury of the pharynx or hypopharynx. Chest auscultation and examination for tracheal deviation will help identify a pneumothorax or a mediastinal shift. Physical examination by itself, however, will not identify subtle injuries to important structures, such as the carotid arteries, trachea, or esophagus. Small injuries to the trachea or esophagus may be identified by endoscopic examination. CT angiography will usually identify an arterial injury, although formal arteriography may be necessary when CT angiography is questionable.

NECK EXPLORATION VERSUS OBSERVATION

The decision to perform exploration of a penetrating neck wound in a stable patient without obvious signs of injury has undergone major modifications over the past two decades. Formerly, patients with wounds that penetrated the platysma muscle in zone 2 underwent neck exploration. This guideline led to a large number of negative operations. Currently, most surgeons would explore penetrating zone 2 injuries for those patients who had evidence of organ injury, hematoma, continued oozing, or suspicion for a tracheal or esophageal injury. Consequently, most patients with penetrating zone 2 injuries are treated nonoperatively. This nonoperative approach for zone 2 injuries is also implemented for most patients in military conflicts.

OPERATIVE EXPOSURE

Most penetrating neck wounds are best explored through an ipsilateral incision along the anterior border of the SCM muscle (Fig. 3). The incision is extended through the platysma into the deeper planes; the trachea and thyroid gland are retracted anteriorly, whereas the neurovascular bundle and esophagus are displaced posteriorly. This exposes the tracheal-esophageal groove and allows the operator to identify when further dissection is needed anteriorly or posteriorly. Superficial crossing veins are divided and ligated, as is the omohyoid muscle; this facilitates unimpeded dissection into the deeper tissues.

When a zone 3 injury requires repair of the internal carotid artery at the base of the skull, the mandible may be detached posteriorly to the angle and subluxated anteriorly to facilitate a direct primary repair. When the injury involves zone 1 structures in the thoracic outlet, the incision can be extended inferiorly as a median sternotomy, thereby giving excellent exposure to the trachea, innominate artery, left common carotid artery, subclavian artery, subclavian



FIG. 3 Unilateral penetrating neck wounds are best explored through an incision along the anterior border of the SCM muscle *(left)*. When bilateral injuries are present, bilateral incisions anterior to the SCM muscles are preferred *(right)*. Combining the two distal portions of the incision above the manubrium is not recommended.

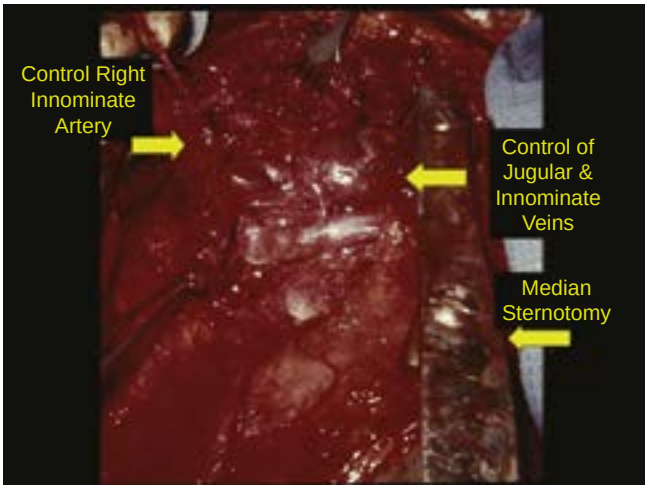


FIG. 4 This patient had a penetrating wound involving the innominate artery, which was exposed and repaired by extending the anterior SCM incision into a median sternotomy, providing exposure to the innominate arteries, internal jugular vein, subclavian vein, and superior vena cava.



FIG. 5 This patient had an anterior cervical incision extending down to the mid-portion of the sternum where the sternum was divided on the left side in the fourth interspace to lift the left upper rib cage anteriorly and laterally to repair a subclavian artery injury near the aorta. This incision, sometimes referred to as a Ravitch flap, is associated with significant morbidity.

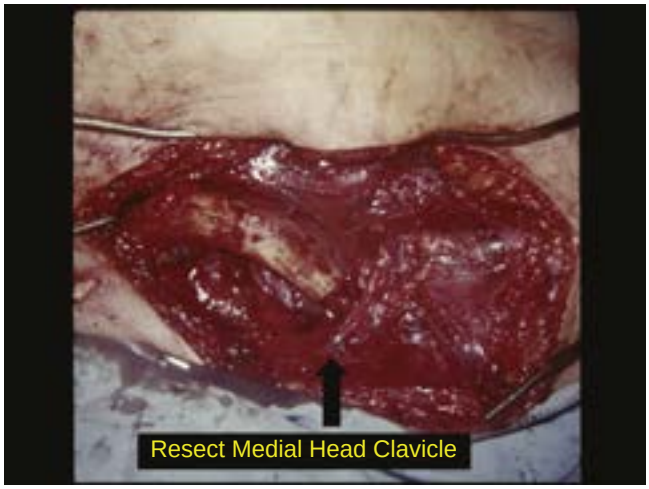


FIG. 6 This patient sustained an injury to the thoracic outlet with perforation of the innominate artery right subclavian artery junction, which was approached by resection of the medial half of the clavicle, which provides excellent access to these vessels.

vein, innominate vein, and superior vena cava (Fig. 4). When the injury involves the subclavian artery just beyond its origin from the aortic arch, the median sternotomy incision can be extended laterally in the left fourth interspace and the clavicle divided so that the left anterior chest wall can be rotated anteriorly and laterally as a Ravitch flap (Fig. 5). Likewise, when the injury involves the subclavian artery posterior to the clavicle, the medial half of the clavicle can be resected, giving excellent exposure to both the subclavian artery and vein (Fig. 6).

REPAIR OF SPECIFIC INJURIES

Venous Injuries

Venous injuries are the most common cause of non–life-threatening hemorrhage from penetrating neck wounds. Small veins, including the external jugular vein, are best ligated. The internal jugular vein can often be repaired primarily with wounds that involve less than 30% of the circumference. This should be done with a fine, nonabsorbable suture. When there are large through-and-through wounds to the internal jugular vein, the vein should be ligated; this is well-tolerated.

Arterial Injuries

During neck exploration for suspected arterial injury, intraoperative dissection should begin above the clavicle in the neurovascular complex to free up the proximal common carotid artery. Active bleeding can be controlled by digital pressure over the perforation as dissection is carried distally. The distal segment of the artery is then dissected and controlled. Small arterial injuries due to pellet wounds from shotgun blast can easily be repaired with a single 5-0 nonabsorbable suture for each of the pellet holes (Fig. 7). When evaluating

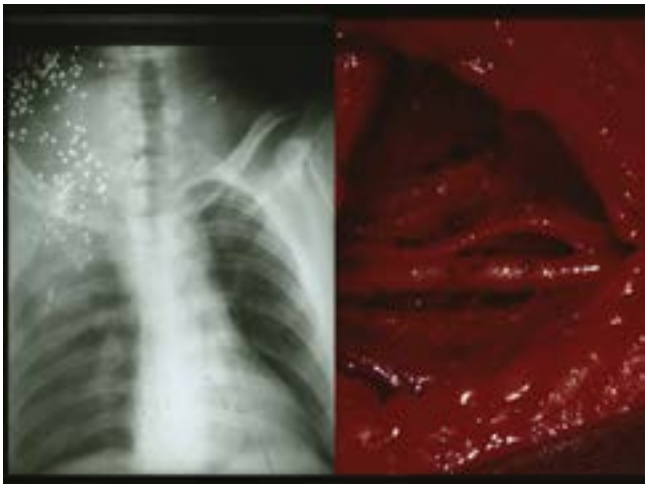


FIG. 7 This patient had multiple pellet wounds from a distant shotgun wound to the neck *(left)*. He had a number of pellet holes in the carotid artery, which could be easily repaired with single 5-0 nonabsorbable sutures for each pellet hole *(right)*.



FIG. 8 This patient sustained a pistol wound to the right common carotid artery *(left)*. The injury was resected, and an end-to-end anastomosis was performed *(right)*.

a patient with multiple pellets within the neck, CT angiography will usually identify a defect. Through-and-through gunshot wounds to the carotid artery are usually low velocity and can be treated by resection of the injured segment, followed by an end-to-end anastomosis with a running 5-0 nonabsorbable suture (Fig. 8). More extensive injuries, possibly due to a higher velocity missile, will require resection of a longer segment of artery necessitating a reverse saphenous vein graft. Prosthetic grafts in this situation are avoided unless there is no other option because the patient has an occluded saphenous vein. Installation of a small amount of dilute heparin proximally and distally circumvents the need for total body heparinization. Injured branches of the external carotid artery in zone 2 are best ligated. When the proximal internal carotid artery is totally disrupted, the intact external carotid artery can be swung over and anastomosed to the distal internal carotid artery to facilitate cerebral perfusion.

When patients present with disruption of the internal carotid artery at the base of the skull, distal ligation may be the best option, particularly when the patient has no preoperative neural deficit, and there is good back bleeding (Fig. 9). Controversy exists about the wisdom of repairing a carotid artery injury in a patient who has a preoperative neurologic deficit. The authors recommend repair in this setting, since those patients who subsequently succumb from brain ischemia will have diffuse cerebral edema on postmortem examination without evidence of hemorrhage into the ischemic brain.

Injury to the vertebral artery is uncommon and typically occurs following a gunshot injury. The injury will be suspected on the basis of a CT angiogram and can be confirmed by angiography (Fig. 10). This artery is surrounded by bone so that treatment of a vertebral artery injury would be by proximal ligation at its origin from the

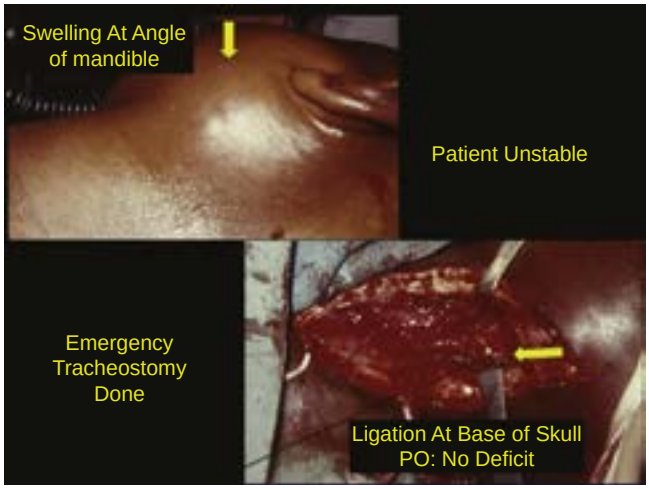


FIG. 9 This patient had a penetrating wound near the base of the skull, which was associated with a large hematoma at the angle of the mandible *(left)*. Exploration revealed a perforated internal carotid artery at the base of the skull with good back bleeding so that proximal and distal ligation could be performed without causing any neurologic deficit *(right)*.

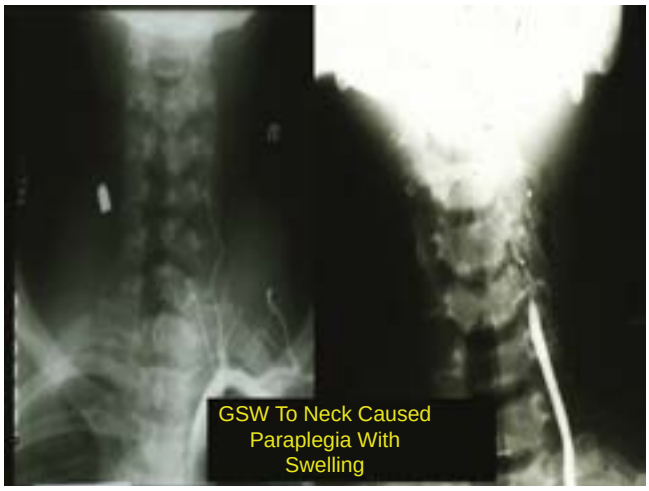


FIG. 10 This patient presented with a GSW through zone 2, which traversed posteriorly and caused paraplegia *(left)*. Arteriogram revealed occlusion of the vertebral artery, which was ligated at its origin on the left subclavian artery and distally where it was approached through cervical vertebrae 1 and 2 *(right)*.

subclavian artery and, if necessary, distal ligation approaching the artery between vertebrae C1 and C2.

Esophageal Injury

Exposure of the injured esophagus through the anterior SCM approach permits the esophagus to be freed up from the trachea anteriorly and the prevertebral fascia posteriorly. Sometimes the mobilization of the esophagus is facilitated by placing a Penrose drain around the esophagus. The presence of the nasogastric tube within the esophagus facilitates digital identification and safe mobilization of the esophagus. Once mobilized, most unilateral stab wounds can be repaired in two layers, being certain to incorporate the full-thickness mucosa and muscular layers in the inner layer and tension-free interrupted 4-0 permanent sutures for the outer layer (Fig. 11). When bilateral esophageal perforations are present, the esophagus can be rotated to facilitate repair of the contralateral side; alternatively, when the injury on the ipsilateral side of the esophagus is large, the contralateral perforation can be closed from the intraluminal approach. Following closure, an esophageal drain should be left in place, and the drainage should be monitored for amylase. The likelihood for an esophageal cutaneous fistula is low, but once a fistula is identified, nasogastric tube feedings are instituted while the fistula closes over the ensuing 3 weeks. When an esophageal fistula occurs in association with nearby vascular injuries, it is important for the drain to be left in place since there can be unevacuated leakage from the esophagus that may digest the repair of the associated venous or arterial injury (Fig. 12).

Pharyngeal Injury

Perforations of the pharynx and hypopharynx are often suspected when blood is seen on deep oral examination and may be confirmed at the time of operation by following the wound tract to the area of perforation. Primary closure with full-thickness inverted absorbable suture provides for hemostasis and a secure closure.

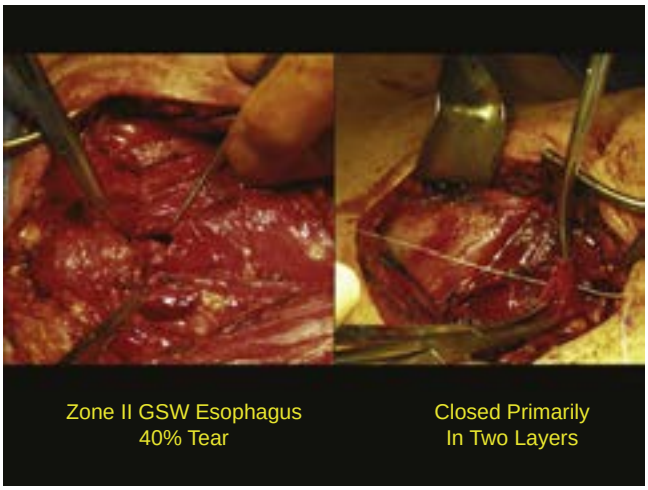


FIG. 11 This patient had a stab wound that, upon exploration, revealed a 40% transection of the lateral esophagus, which was repaired by a two-layer simple closure *(left)*. This patient had repair of a carotid artery and jugular venous injury, but an esophageal injury was missed. Patient developed an abscess that, at the time of exploration, showed that the carotid artery repair and the venous repair had been digested by the esophageal juices *(right)*.

Tracheal and Cartilaginous Injuries

Using the anterior SCM approach, the trachea can be freed up posteriorly by dissection in the tracheal-esophageal groove. Posterior perforations of the trachea can be repaired with either running or interrupted 3-0 absorbable sutures with the knots tied on the outside. When identifying a posterior tracheal perforation, one must be on the alert for an associated anterior esophageal perforation. Closure of perforations of the anterior trachea often requires that sutures be placed in the interspaces above and below the perforated tracheal rings, and the knots are tied on the outside. Cartilaginous injuries, likewise, can be repaired with sutures heavy enough to go through the cartilage and provide apposition. Some cartilaginous injuries are best left alone and allowed to heal by second intent. A tracheostomy is added to protect the airway and decrease airway resistance from the intact glottis. High tracheostomy insertion at the second ring is preferred when the actual injury is located distal in the trachea. These patients typically do not require ventilatory support.

Thyroid Injuries

Many wounds that cause tracheal injury will also cause injury to the thyroid. When the injured portion of the thyroid gland is located lateral to the trachea, hemostasis may be obtained by simple sutures or electrocoagulation. When the injury goes through the thyroid gland into the trachea, that portion of the thyroid is best resected; alternatively, the thyroid may be divided at the isthmus and rotated off the trachea to facilitate a primary tracheal repair.

Miscellaneous Injuries

Injuries to the recurrent laryngeal or vagus nerve following a penetrating wound are rare. If injury is a result of a gunshot wound, the nerve is unlikely to be completely severed and is best left alone to regenerate over time. If the injury is due to a stab wound with complete severance, a primary approximation using fine absorbable sutures is recommended. The results of such repairs are not known.

Injuries to the thoracic duct may be recognized by the presence of lymph within the operative field. The duct should be freed up at its insertion into the venous angle so that it can be isolated, divided, and ligated at each end.

Suggested Readings

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Blunt Cardiac Injury

Anna M. Ledgerwood, MD, and Charles E. Lucas, MD

Blunt cardiac injury (BCI) can occur in any patient who sustains a significant impact to the chest. Clinical manifestations may encompass a wide spectrum of injury patterns ranging from simple myocardial bruise to rupture of a ventricle and death. The myriad injuries include minor electrocardiogram (ECG) abnormalities, complex arrhythmias, cardiac failure, septal rupture, valve rupture, coronary artery thrombosis, pericardial rupture, and chamber wall rupture.

INCIDENCE

The incidence of BCI varies widely (8%–71%) due, primarily, to the lack of a gold standard for diagnosing BCI after major thoracic injury. The diagnosis of myocardial contusion was often suggested in patients who had blunt thoracic injury with sternal fracture and elevated cardiac enzymes. Most likely this was overdiagnosing BCI in patients who had no cardiac symptoms. Autopsy series of injured patients who die at the scene, however, show a relatively high incidence of BCI from a ruptured heart and pericardial tamponade.

MECHANISM OF INJURY AND PATHOPHYSIOLOGY

BCI should be considered in any patient with a high-speed impact to the thorax from a motor-vehicle collision, bicycle or motorcycle crash, falls greater than 10 feet, blast injuries, assaults, and crush injury to the chest. Any mechanism such as a direct precordial impact, a compression or crush between the sternum and spine, or a deceleration/torsion force causing a cardiac tear at a fixed point such as between the right atrium and vena cava can cause BCI. Even an abrupt compression of the abdomen causing a significant and sudden rise in venous pressure that is transmitted to the right heart can result in cardiac rupture. This hydrostatic pressure can also produce rupture of the pericardium at its diaphragmatic attachments. Most patients with blunt thoracic injury, however, have no BCI. In contrast, most patients with cardiac chamber rupture die at the scene and seldom present alive to the emergency department.

CLINICAL DIAGNOSIS OF BCI

There are no signs or symptoms specific for BCI. The most common complaint is chest pain, which could be due to the associated thoracic injuries including rib fractures, sternal fractures, or chest wall contusions. The presence of associated thoracic trauma, however, should raise suspicion for BCI. Likewise, auscultatory findings of a thrill, murmur, or rub should raise suspicion for BCI, but they usually are not present. Hypotension may accompany BCI but is usually from other causes such as a tension pneumothorax, spinal cord injury, or hemorrhagic shock.

The use of ECG and cardiac enzymes to diagnose BCI in the emergency department has been extensively studied. Velmahos and coworkers determined that the combination of a normal ECG and troponin 1 level on admission and 8 hours later rules out the diagnosis of significant BCI. They prospectively evaluated 333 consecutive patients with major blunt trauma and defined significant BCI as the presence of cardiogenic shock, arrhythmias requiring treatment, or posttraumatic structural deficits. They noted that all 131 patients with normal serial ECG and troponin 1 levels had no significant BCI. Only 44 patients (13%) had significant BCI and, of those, 34% had both abnormal ECG and troponin levels. They reported that 22% of their patients with only an abnormal ECG and 7% of their patients with only an abnormal troponin level developed a significant BCI. However, 43 of their 44 patients with significant BCI had an abnormal ECG on admission.

Testing for creatinine kinase-MB isoenzyme and the use of radionuclide angiography have not been helpful in diagnosing BCI. The initial chest radiograph is helpful in ruling out a tension pneumothorax and/or a hemothorax that may be a source of blood loss and hypotension. A careful physical examination confirming movement of the lower extremities and the presence of rectal tone before giving drugs for intubation rules out spinal cord injury as a cause of hypotension. The FAST examination helps determine whether there is any cardiac activity in the patient who presents without vital signs and identifies if there is fluid in the pericardial sac in patients who present with vital signs. A transthoracic echocardiogram or a transesophageal echogram is recommended for those patients who have abnormal ECGs on admission. These studies provide information regarding the cardiac function.

BCI INJURY SEVERITY

The American Association for the Surgery of Trauma has identified an organ injury scale for BCI. A grade 1 BCI is identified by ECG abnormalities, such as nonspecific ST or T-wave changes, premature atrial or ventricular contractions, or persistent sinus tachycardia. Grade 2 BCI includes patients with heart block or ischemic changes without cardiac failure. Grade 3 injury includes patients with sustained arrhythmias, septal rupture, valvular incompetence, papillary muscle dysfunction, distal coronary artery occlusion without heart failure, or blunt pericardial laceration without cardiac herniation. Grade 4 BCI includes patients with septal rupture, pulmonary or tricuspid incontinence, papillary muscle dysfunction, distal coronary artery occlusion with cardiac failure, rupture of the right or left atrium or the right ventricle, or aortic or mitral valvular incompetence. Grade 5 BCI includes patients with proximal coronary artery occlusion, left ventricular perforation, or rupture of more than one chamber.

TREATMENT OF BCI

Grade 1 Injury

Patients with a grade 1 BCI will have only ECG abnormalities and should be observed by continued monitoring until the ECG abnormalities have corrected. This typically occurs within 24 hours. The treatment of associated injuries resulting from the blunt force has a higher priority.

Grade 2 Injury

Patients with grade 2 BCI have heart block and/or ischemic changes and need to be monitored until ischemic changes resolve and the ECG pattern returns to normal. Arrhythmias should be anticipated and treated promptly. Close monitoring and serial assessment of troponin levels should continue while associated injuries are treated. Resolution often occurs within 48 hours. Inotropic support is not needed unless the patient worsens and develops evidence of heart failure.

Grade 3 Injury

Patients who have BCI associated with ventricular arrhythmias with or without an anatomic defect such as septal rupture, papillary muscle dysfunction, or distal coronary artery blockade without heart failure need to be monitored closely for progression to cardiac failure. Even patients who have a blunt pericardial rupture can be followed

nonoperatively if this does not interfere with cardiac output and total body perfusion. If the patient with grade 3 injury has evidence of pericardial fluid, be careful to look for any evidence of pericardial tamponade and treat promptly with pericardiocentesis or, if necessary, open pericardiotomy. This type of symptomatic injury in patients with grade 3 BCI is potentially life-threatening and requires careful observation and seldom requires operative intervention.

This type of a grade 3 BCI was recently treated in a 23-year-old man who was found on the embankment of the freeway after ejection from the back seat of an SUV that struck a semi-truck at high speed. He was awake and could answer questions but had a Glasgow Coma Score (GCS) of 12. His palpable systolic pressure was 100 torr. He had multiple abrasions and contusions but, on arrival to the emergency department, was moving all extremities. Shortly after arrival, he became hypotensive (87/57 mm Hg), tachycardic (145 beats/min), and tachypneic (22 breaths/min) with a GCS of 8. He was resuscitated, and his FAST examination of the chest and abdomen was negative. Initial chest radiograph suggested left lung contusion (Fig. 1). Subsequent computed tomography (CT) of the chest confirmed bilateral hemothoraces with small pneumothoraces, left pulmonary contusion, bilateral rib fractures, and nondisplaced sternal fracture (Fig. 2). He also had fractures of thoracic T12 vertebra, fracture of the transverse processes of L1–L3, and nondisplaced fracture at the base of the dens. The abdominal CT scan demonstrated a grade 3 liver injury and a grade 2 splenic injury (Fig. 3). Blood studies showed an arterial pH of 7.16, a lactate of 5.9 mmol/L, an alcohol of 165 mg/dL, and a troponin of 1.67 ng/mL. Bilateral tube thoracostomies yielded 750 mL of blood on the right and 150 mL on the left. The ECG showed sinus tachycardia with ST elevation.

Repeated episodes of hypotension in the intensive care unit were treated with blood and crystalloid solution, to which he responded. He gradually improved over the next 12 hours when his pH was 7.3, the troponin was 2.53 ng/mL, and the elevated liver enzymes began to normalize. The transthoracic echo examination showed "normal left ventricular size with slight increase in left ventricular wall thickness with mildly decreased left ventricular systolic function." He had global hypokinesis, and the left ventricular ejection fraction was 45% to 50%. Throughout day 1 and into day 2, he had a fever (39.2°C), remained tachycardic (130 beats/min), and required continued resuscitation with crystalloid, packed red cells, and fresh-frozen plasma. By day 2, his troponin had risen to 2.53 ng/mL, and his abdomen was full and difficult to evaluate.

Laparotomy at this time revealed 400 mL of blood. He underwent gastrostomy tube placement, tracheostomy, and bronchial alveolar lavage, which returned a gram-positive cocci and gram-negative coccobacilli, for which he was appropriately treated. He progressed to severe respiratory distress (partial pressure of oxygen/fraction of inspired oxygen <100%) even though his troponins and liver enzymes normalized. He remained tachycardic for the next 10 days but, by day 14, his pH and blood gases normalized. Repeat transthoracic ECG (TTE) at this time showed normal left ventricular

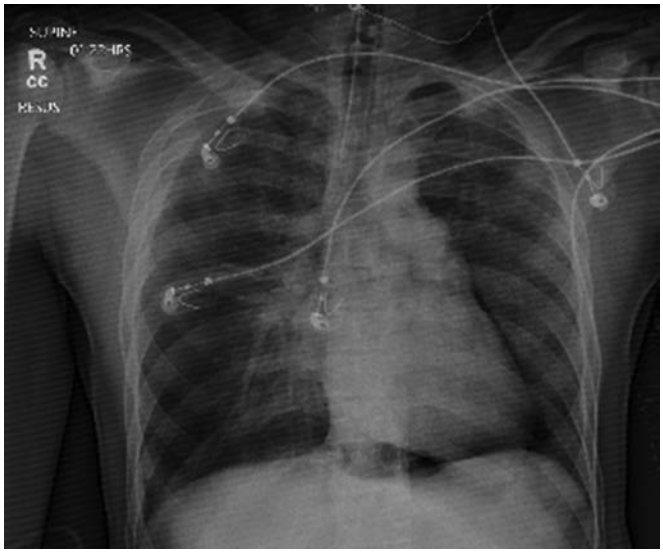


FIG. 1 Initial chest radiograph in a patient with grade 3 blunt cardiac injury demonstrated a small left pulmonary contusion but did not show significant hemothorax to explain his hypotension after arrival in the emergency department.

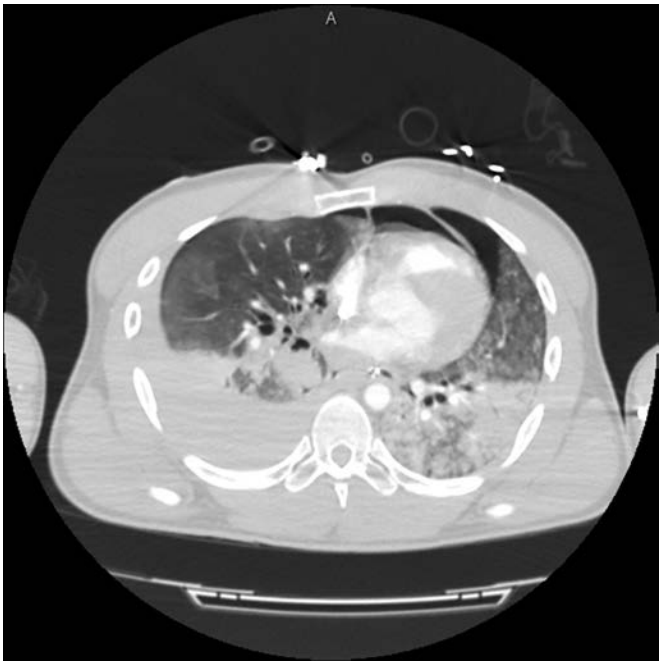


FIG. 2 Chest CT scan in a patient with grade 3 blunt cardiac injury demonstrated a left pneumothorax, bilateral hemothorax, and showed the pulmonary contusion.



FIG. 3 Abdominal CT scan in a patient with grade 3 blunt cardiac injury showed a grade 3 liver injury and a grade 2 splenic injury but no obvious reason for the patient's hypotension.

function with an ejection fraction of 60% to 65%; the right ventricular size and function were normal. He slowly improved, so that by day 39, his chest tubes, tracheostomy tube, and percutaneous endoscopic gastrostomy tube had been removed, and he was able to tolerate an oral diet, and he was transferred to the rehabilitation center. The long-term result was good. This example of grade 3 BCI, sometimes referred to as severe myocardial contusion, may produce prolonged tachycardia, ST segment changes, elevated troponin, and impaired cardiac function, but it usually responds to supportive care while the associated injuries are treated.

Grade 4 Injury

Grade 4 BCI associated with septal rupture, valvular incompetence, or chamber rupture of the right ventricle, either atrium or the right atrial appendage often die at the scene; when arriving at the hospital alive, prompt diagnosis and therapy are needed. The diagnosis of valvular incompetence or papillary muscle dysfunction shows a reduced ejection fraction or dyskinesis. Likewise, patients with distal coronary artery occlusion will have evidence of cardiac ischemia and inotropic compromise, which can be documented by TTE. These patients need to have myocardial support but usually do not require operative intervention unless there is chamber rupture. An example of a patient requiring operative intervention follows.

This young man was found outside his vehicle after an MVC. He was confused, drowsy, tachycardic (115 beats/min), and hypotensive (systolic blood pressure, 80 mm Hg). He was given Narcan with little immediate improvement in his drowsiness, but when he arrived in the emergency department, his pressure rose (144/109 mm Hg), but the tachycardia (120 beats/min) persisted. His GCS was 10. He moved all four extremities, thus ruling out spinal cord injury. His blood alcohol was 76 mg/dL, and he had a positive drug screen for benzodiazepine and cannabinoids. Chest radiograph demonstrated normal lungs but a globular heart (Fig. 4). A CT of the chest showed pericardial effusion (Fig. 5), and CT of the abdomen showed hepatomegaly with edema around the liver and gallbladder (Fig. 6). The troponin level on arrival was 0.057 ng/mL. Shortly after admission to the surgical intensive care unit, he became hypotensive (89/66 mm Hg) and did not respond to a fluid bolus. The arterial pH was 7.19. He was taken to the operating room for laparotomy and was found to have yellow, cloudy ascites with a very large, edematous, purple-looking liver of undetermined etiology. No specific treatment was done,

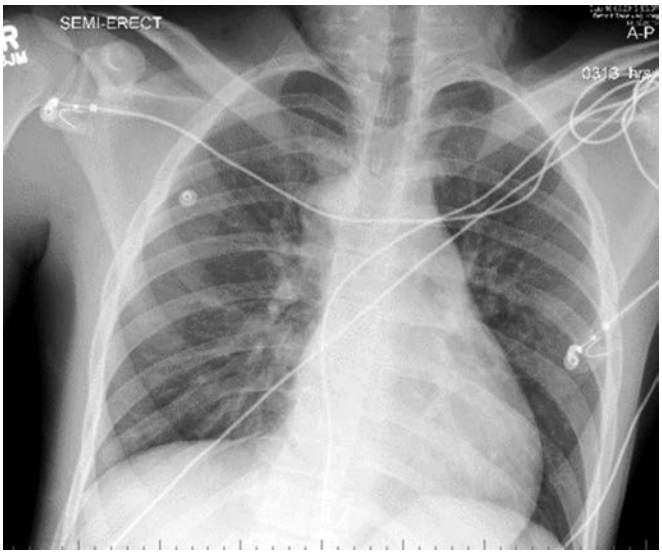


FIG. 4 Admission chest radiograph in a young man who developed a grade 4 blunt cardiac injury following a motor vehicle collision showed a globular heart.



FIG. 5 CT scan of the chest in a young man with a grade 4 blunt cardiac injury demonstrated a pericardial effusion.



FIG. 6 Abdominal CT in a patient with grade 4 blunt cardiac injury demonstrated significant hepatomegaly and edema around the liver.

and he returned to the intensive care unit, where a repeat troponin level was 1.56 ng/mL; the liver enzymes including bilirubin were normal. TTE demonstrated a large pericardial effusion, thus explaining his recurrent hypotension. A difficult transabdominal pericardial window was performed with return of a large amount of bloody effluent, which led to a sternotomy, pericardiotomy, and primary repair of a 4-mm hole in the right atrial appendage. Postoperatively, his troponin level was 3.97 ng/mL, but his vital signs stabilized, and the transient rise in his liver enzymes returned to normal. He had an uneventful recovery.

The rarity of this type of BCI led to the delay in recognizing pericardial tamponade, which should have been detected on an initial FAST examination and confirmed on the CT scan. Definitive care should have included a transthoracic pericardiocentesis followed by a prompt left anterior thoracotomy. The engorged purple liver in this patient was caused by impaired hepatic venous return because of the pericardial tamponade.

Grade 5 BCI

BCI associated with rupture of the left ventricle or more than one heart chamber is highly lethal. The vast majority of these patients

(>80%) have been injured in motor vehicle collisions, biking mishaps, motorcycle crashes, or pedestrian/vehicular mishaps; less common causes would include thoracic crush injury, falls from major heights, and other events that exert a great force on the chest. Chamber rupture is more likely to occur in the right atrium or ventricle (65%) followed by the left ventricle with few patients having rupture of more than one chamber. The lethality of this syndrome is reflected by the fact that most patients die at the scene or receive cardiopulmonary resuscitation at the scene only to be declared dead at the time of arrival in the emergency department. The force of the impact is so great that almost all such patients have major associated injuries and very high injury severity scores.

The typical scenario of BCI with chamber rupture was seen in a 21-year-old restrained front seat passenger in a vehicle that struck a tree at 80 mph. She was unresponsive at the scene, was intubated, and had cardiopulmonary resuscitation during her 20-minute trip to the hospital. Upon arrival, she had pulseless electrical activity with no cardiac movement per ultrasound and was declared dead. Injuries identified at autopsy included fractures to the right humerus, left femur, 10 right ribs, six left ribs, in addition to atlanto-occipital separation, bilateral pulmonary contusions, and rupture of the right hemidiaphragm, liver, and spleen. She had a 0.3 cm laceration of the apical portion of the right ventricle and numerous lacerations of the right atrium with bilateral hemothorax. This patient's mechanism of injury, attempted resuscitation by emergency medical services, and subsequent death are typical for patients with ventricular rupture or rupture of more than one chamber.

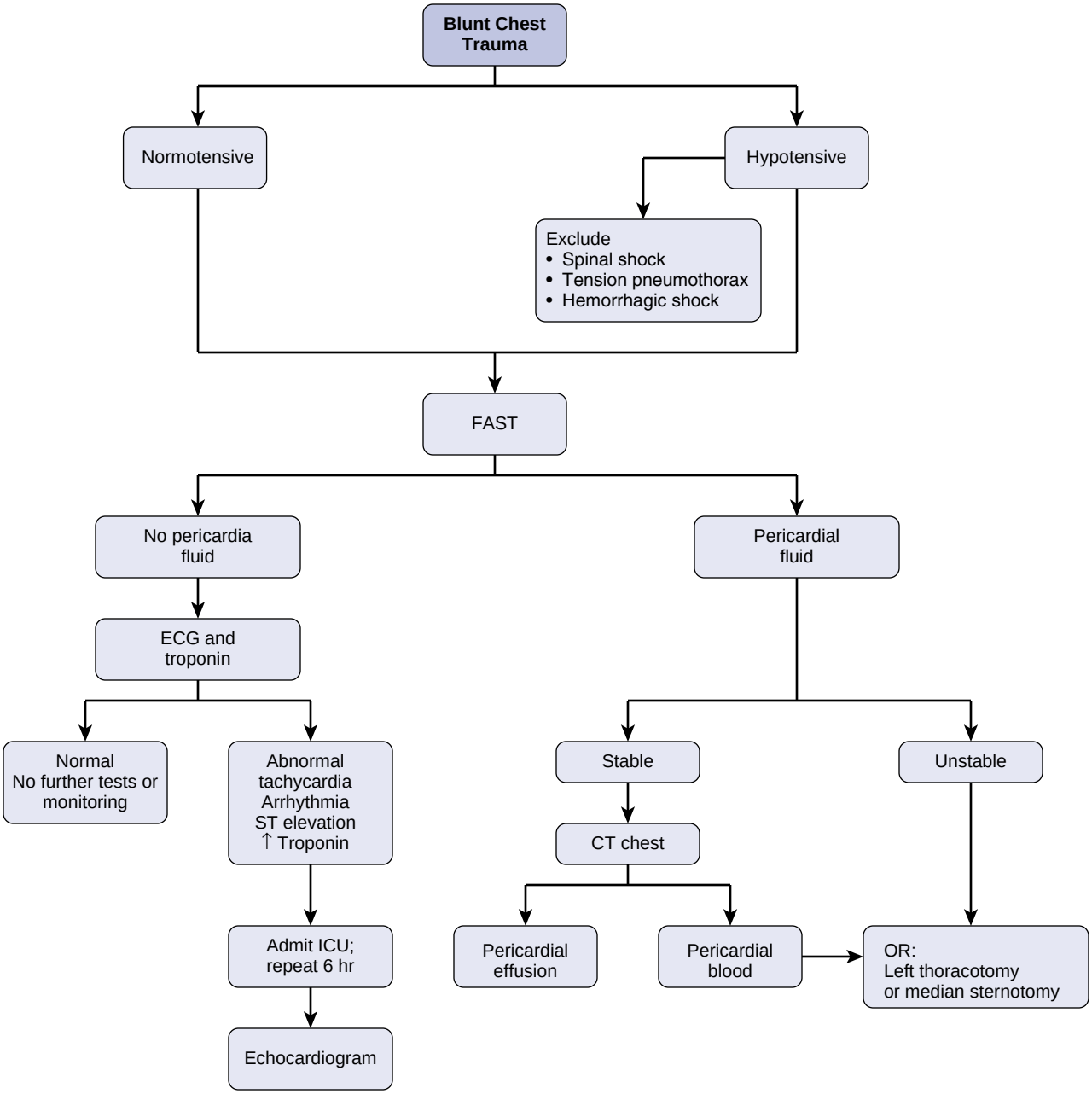


FIG. 7 Algorithm for diagnosis and management of blunt cardiac injury. *CT*, Computed tomography; *ECG*, electrocardiogram; *ICU*, intensive care unit; *OR*, operating room.

COMMOTIO CORDIS

Commotio cordis is sudden death from cardiac arrest associated with no anatomic structural damage to the heart identified at autopsy. This condition occurs in young people typically after a blunt blow to the chest inflicted during competitive sporting activity. Direct impacts from a baseball or hockey puck have caused this sudden death. These patients have no underlying congenital cardiac disease, cardiomyopathy, or other preexisting abnormalities. This condition appears to be caused by the impact transmitted to the heart inducing ventricular fibrillation during a phase of ventricular excitability such as cardiac repolarization. This unusual event is most often refractory to cardiopulmonary resuscitation and defibrillation. These patients present to the hospital in cardiac arrest and the FAST examination will show no cardiac activity and no pericardial fluid.

LONG-TERM FUNCTION AFTER BCI

There have been few studies that have evaluated the long-term effects of BCI. The studies that have been done show that most of these patients do well and require no further treatment.

ALGORITHM FOR DIAGNOSIS AND MANAGEMENT OF BCI

Any patient who presents with blunt thoracic trauma should be suspected of having BCI despite its rarity (Fig. 7). The patient who presents without vital signs should have a FAST examination done to determine if there is cardiac activity. In the absence of cardiac activity nothing further should be done and the patient should be pronounced dead. The patient who presents normotensive after blunt thoracic trauma should have a FAST examination done as part of the secondary survey. If the heart is beating and there is no pericardial fluid, the patient should have an ECG and troponin measurements. If both ECG and troponin are normal, no further tests or monitoring for BCI is indicated. However, if the ECG and/or troponin is abnormal with findings such as tachycardia, arrhythmia, and/or ST elevation, the patient should be admitted to the intensive care unit and the ECG and troponin levels repeated in 6 hours. An echocardiogram should be done within that first 24 hours. These patients will usually remain stable and will have correction of their abnormal ECG and troponins within the first 24 to 48 hours. If the echocardiogram is abnormal, it should be repeated in 48 to 72 hours. Treatment of the BCI in this setting is supportive. The tachycardia is best treated with a β-blocker and any pulmonary injury is treated with ventilatory support.

The patient who presents with blunt thoracic trauma and is hypotensive presents a real challenge. The initial examination and chest radiograph should exclude spinal cord injury, a tension pneumothorax, or other sites of hemorrhage including the chest or fractures. The FAST examination is most helpful in determining whether there is fluid in the pericardial sac. If there is pericardial fluid and the patient is stable, a CT of the chest is recommended to determine whether the fluid resembles a serous pericardial effusion from an underlying medical condition or blood. Some patients may have a comorbid condition leading to pericardial fluid, which is typically serous as occurs in renal failure. If the pericardial fluid has the appearance of blood, and the patient is stable, immediate operation is indicated. If the patient is unstable and has pericardial fluid, the patient should have pericardiocentesis on the way to the operating room. Recommended operation is a left anterolateral thoracotomy, which provides rapid access for pericardiotomy and repair of most BCI. We do not recommend a transabdominal pericardial window that, in the presence of BCI, leads to rather sudden blood loss and does not facilitate expedient repair. We recommend either a definitive median sternotomy or a left thoracotomy. The pericardium is then opened parallel to the phrenic nerve. The blood is evacuated and the heart examined for injury. Most of these patients will have a small injury involving the atrium or the atrial appendage. A simple primary repair including clamping of the atrial appendage followed by ligation, and control of the bleeding. Repair of the atrium and/or the ventricle can be done with a 2-0 silk suture on a noncutting needle. Bleeding is controlled with digital pressure while the sutures are being placed. Some surgeons prefer pledgeted sutures. The main objective is to control bleeding. If a left thoracotomy is done which limits access to the heart, the incision could be carried across the sternum into the right chest as a clamshell thoracotomy. Occasionally, there may be bleeding from the pericardial sac itself so that there is blood in the pericardial sac but no rupture of the heart. The pericardium should be approximated leaving the nonapical part of the pericardial sac open for about 3 to 4 cm to permit egress of any postoperative pericardial blood. Successful therapy of BCI requires definitive management of the other injuries including the pulmonary injuries, which are usually severe.

Injuries to the coronary vessels are very unusual and include coronary artery contusion or rupture. Rupture of a valve or papillary muscle may also occur. These injuries would probably be detected on an echocardiogram and would require cardiopulmonary bypass for repair. Cardiopulmonary bypass should be available for repair of any chamber rupture but has not been found to be useful for cardiac support alone.

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ABDOMINAL COMPARTMENT SYNDROME AND MANAGEMENT OF THE OPEN ABDOMEN

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Abdominal compartment syndrome (ACS) is a surgical emergency and the final common anatomic and physiologic pathway of sustained abnormal elevations in intraabdominal pressure leading to a progressive cascade of visceral malperfusion, organ failure, and death. This condition is most frequently seen among critically ill medical and surgical patients at risk for elevated intraabdominal pressures as a result of altered physiology, underlying diagnoses, and need for substantial resuscitation. Patient morbidity and mortality can be significantly high if the diagnosis is overlooked and surgical therapy delayed. Awareness of the syndrome's pathophysiology, strategies for prevention, and both operative and perioperative management is essential for the practicing general surgeon.

INTRODUCTION AND PATHOPHYSIOLOGY

ACS is the pathologic event caused by progressive and sustained elevations of intraabdominal pressure leading to organ dysfunction and end-organ failure. The abdominal cavity is limited by the relatively fixed space confined by the abdominal wall, diaphragm, and bony surfaces (spine, costal margin, pelvis). Although soft and distensible under normal conditions, the intraabdominal pressure can increase exponentially as the space contained by the abdominal wall and diaphragm is inundated with additional noncompressible volume (e.g., caused by progressive visceral edema during massive resuscitation). This can rapidly progress to true ACS. There are several identified risk factors associated with the development of intraabdominal hypertension (IAH) and progression to ACS.

Primary ACS has been defined as disease or pathologic processes that originate in the abdomen (e.g., a patient who has substantial peritoneal hemorrhage), while secondary ACS results from a pathologic process that originates from a systemic process. Conditions associated with secondary ACS commonly develop as a consequence of increased capillary permeability (sepsis, large-volume resuscitation, massive transfusion, inflammation). A common example is a patient with septic shock or severe burns who has received massive crystalloid infusion in the setting of a profound capillary leak leading to overwhelming visceral, abdominal wall, and retroperitoneal edema. In patients undergoing emergency abdominal surgery, ongoing resuscitation needs after closure can cause elevations in intraabdominal pressure that similarly will compromise tissue perfusion, cardiac output, and pulmonary compliance. ACS can also present as a recurrent phenomenon after abdominal closure as a result of subsequent resuscitation needs (e.g., sepsis from a complicating condition) and is associated with substantial morbidity and mortality.

PREVENTION

Interventions aimed at limiting progression of elevated intraabdominal pressures before developing ACS should be part of the provider's repertoire of methods for managing IAH. Several strategies can be considered to facilitate the reduction of IAP and manage refractory IAH. Evacuation of space-occupying masses and collections, decompression of intraluminal content, improvement in abdominal wall and diaphragm compliance, and optimal fluid management are plans of action that can be employed.

Nasogastric and rectal tube decompression are straightforward maneuvers that have been shown to reduce IAP. In addition, intestinal promotility agents can be administered as an adjunct to assist with the evacuation of intraluminal content and gas. These maneuvers can be particularly useful in settings of gastric or intestinal obstruction, severe dysmotility, or abnormally large fecal burden.

Placement of percutaneous drainage catheters into space-occupying collections can be an effective method of lowering intraabdominal pressure if there is a substantial volume drained (e.g., ~1 L) and in some cases can be performed at the bedside under image guidance. Drainage of a hematoma should be coordinated after evaluating the patient and addressing any ongoing source of bleeding (e.g., with CT or angiography), correcting any associated coagulopathy to minimize the risk of bleeding as the lesion is decompressed, and planning for additional surgical therapy if bleeding worsens substantially or the patient develops ACS despite drainage.

It should be noted that the methods described have been shown to reduce intraabdominal pressure but may only be temporizing and should not be considered a definitive therapy for refractory IAH or ACS. If the patient has severe IAH or true ACS, prioritizing the nonsurgical measures described may delay definitive surgical decompression and lead to worsened outcomes.

DIAGNOSIS

Clinical Findings

The clinical diagnosis for IAH or ACS is often challenging. Abdominal distension and "soft" or "tense" character often do not correlate with underlying abdominal pressure, and peritonitis is less commonly present until late in the course unless it is resulting from the inciting etiology (e.g., bowel perforation). Although physical examination is unreliable for ruling in or excluding the presence of severe IAH or ACS (and should not be used as a single metric in the presence of significant physiologic risk, poor mental status, or states of immunosuppression), the pathophysiologic mechanisms present in progressive IAH and ACS can manifest as other clinically relevant findings that may assist with early diagnosis.

Elevations in intraabdominal pressure that approach what is considered IAH will cause compression of the intraabdominal inferior vena cava, decreasing venous return to the heart, decreasing cardiac preload, and leading to systemic hypotension. Pressure transmitted through the diaphragm from the abdomen leads to compression of the thoracic cavity, loss of compliance, and increasing peak airway and plateau pressures on the mechanical ventilator. This can lead to an inability to adequately ventilate the patient, increased risk of barotrauma from compensatory increases in ventilator pressures, and compressive atelectasis, all resulting in poor gas exchange presenting as refractory hypoxia and hypercarbia.

Decreased urine output, declining glomerular filtration rate (GFR), or increased creatinine levels can indicate worsening renal function caused by a combination of poor systemic perfusion and direct pressure compression on the renal system. Intestinal and solid organ ischemia are late findings in ACS and present as metabolic acidosis with increasing lactate levels, renal failure, or abnormal liver function tests (LFTs) (Table 1).

Grading Severity and Measurement of Abdominal Pressure

The World Society of Abdominal Compartment syndrome has developed a grading schema that defines the severity of IAH and ACS and further recommends frequent monitoring of intraabdominal pressure every 4 to 6 hours in patients considered at risk for ACS (Table 2). Trans-bladder pressure monitoring is a standard modality

TABLE 1 Clinical Implications of Intraabdominal Hypertension

Cardiovascular	Pulmonary	Renal	GI	CNS
↑CVP	↓Compliance	↓Renal perfusion	↓Blood flow	↑ICP
↓Preload	↑Paw	↓Urinary output	↑LFT	↓CPP
↓Cardiac output	↑Atelectasis	↓GFR	↑Lactate	
Cardiac arrest	Respiratory failure	Renal failure	Intestinal ischemia	Cerebral edema

CNS, Central nervous system; *CVP*, central venous pressure; *GFR*, glomerular filtration rate; *GI*, gastrointestinal; *LFT*, liver function test; *Paw*, peak airway pressure.

for the measurement of intraabdominal pressure. The standard technique for bladder pressure measurement involves instillation of 25 mL of normal saline via a Foley catheter connected to a transducer placed at the midaxillary line at the level of the iliac crest (0 mm Hg) in an entirely supine and relaxed patient (Fig. 1). It is ideal to obtain the minimum pressure reading when the abdominal wall/musculature is relaxed at the end of expiration. The use of sedation, analgesia, or even neuromuscular blockade may be necessary for patients with abdominal guarding, ventilator dyssynchrony, agitation, or contraction. In obese patients, baseline IAP can be somewhat higher than in non-obese individuals and should be interpreted with consideration, though the consequences of a delay in definitive management of ACS support aggressive management if the diagnosis is likely. A patient found to have sustained IAH >20 mm Hg in the setting of new or

TABLE 2 Grading of Intraabdominal Hypertension

	Intraabdominal Pressure	
Grade	**mm Hg**	**cm H_2O**
Grade I	12–15	16–21
Grade II	16–20	22–27
Grade III	21–25	28–34
Grade IV	>25	35
ACS	Sustained IAP >20 mm Hg with associated new organ dysfunction/failure	

ACS, Abdominal compartment syndrome.

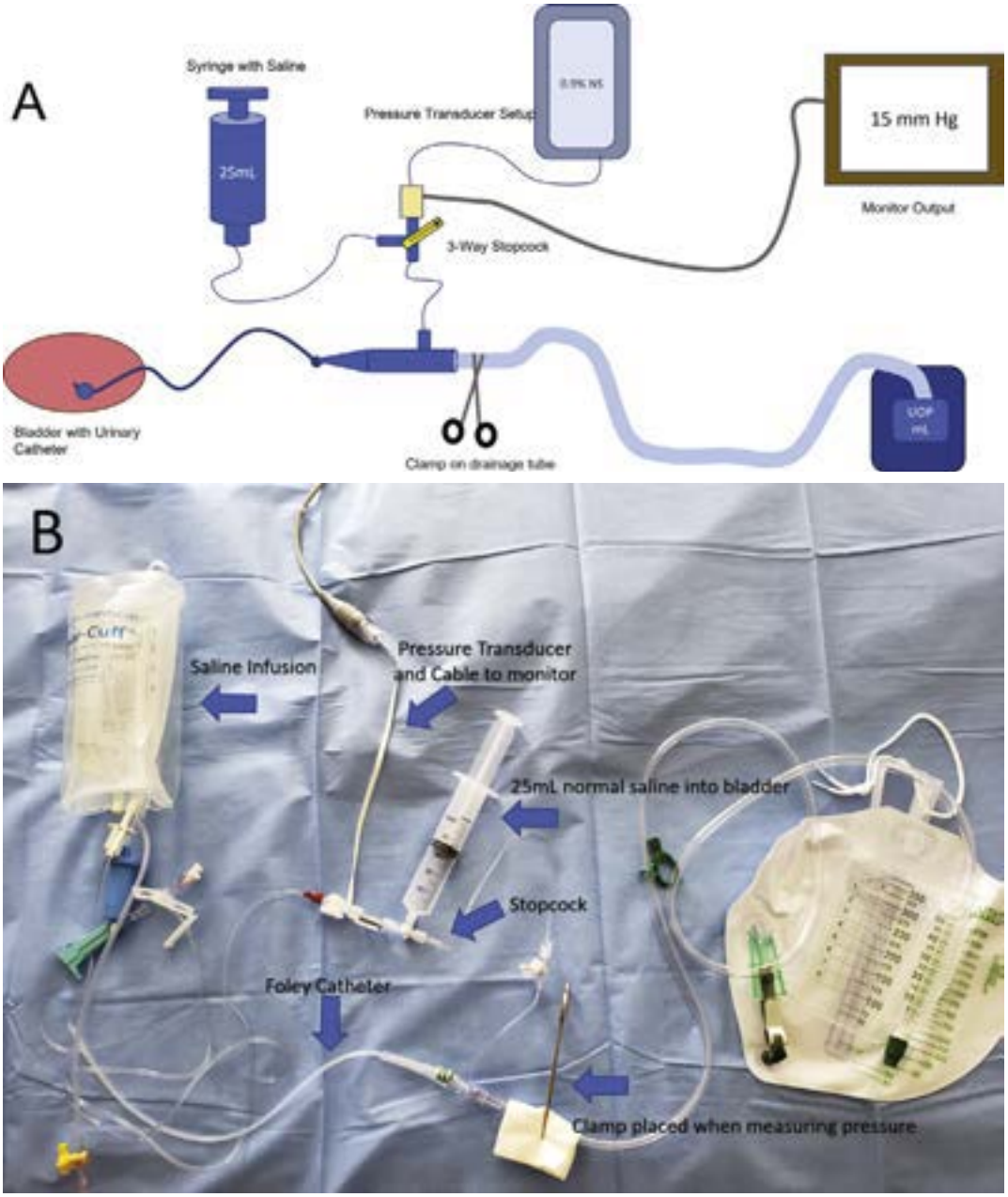


FIG. 1 Schematic and visual demonstration of setup for bladder pressure measurement. Note the clamp placed on the urinary drainage side that allows for pressure transduction to the monitor, the three-way stopcock that allows the switch between the measured 25 mL of saline instilled into the empty bladder via syringe, and the pressure transducer setup for measurement (with its attached pressure bag of saline).

worsening organ dysfunction meets the definition of ACS, and prompt intervention is warranted.

SURGICAL INTERVENTION AND TECHNIQUE

Decompression of the Abdomen

Definitive management for ACS is an emergent decompressive laparotomy. Ideally performed under controlled conditions in the operating room, inability to transport due to hemodynamic instability, respiratory compromise, severel y elevated intracranial pressures, and other barriers to transport may warrant a bedside surgical decompression. The primary objective for bedside surgical decompression is relieving escalating intraabdominal pressure in the setting of severe IAH and ACS; this often confirms the diagnosis if hemodynamics or ventilator mechanics improve substantially on opening of the abdominal fascia. The complexity of the bedside procedure will depend on coexisting abdominal pathology, available resources, and institutional experience; however, bedside laparotomy is fundamentally a damage control procedure. Surgical equipment, staff, and physical space to perform the procedure with necessary personnel are often much more limited than in the operating room. Consideration ahead of time and planning with the operating room staff to develop a transportable standard set of instruments for such emergencies will save valuable time and confusion and aid in expediting care in time-sensitive scenarios. In some settings, a hybrid approach is needed in which a sharp laparotomy and temporary abdominal dressing is rapidly performed at the bedside with very limited equipment, and the patient is transported to the operating room once the acute hemodynamic or pulmonary decompensation resulting from ACS is improved (potentially immediately) for further exploration and management (e.g., if a bowel resection or debridement of infected tissue is needed).

The immediate goal of decompressive laparotomy is to release the tension on the abdominal compartment (Fig. 2). This is achieved with a generous midline abdominal incision involving both skin and fascia over the majority of the abdomen and should be adequate to allow the egress of abdominal fluid and edematous bowel. More limited laparotomy can be inadequate for complete release of pressure (analogous to extremity compartment syndrome) and a risk for failure of initial therapy and for recurrent ACS. Close communication with the anesthesiologist, intensivist, and/or respiratory therapist can be helpful to establish the diagnosis of ACS by demonstrating improvements in hemodynamics, ICP, peak airway pressures, cardiac output, or oxygenation. If minimal to no improvement in these parameters are observed, extending the midline incision of both skin and underlying fascia should be performed to ensure adequate decompression. If possible, exploration of the abdomen should be performed to evaluate associated intraabdominal pathology. Surgical management of ACS is fundamentally a damage control strategy. Strategic priorities (in addition to the focus on abdominal decompression) align with those in emergency laparotomy for trauma and emergency general surgery and are primarily focused on stabilizing the patient's physiology. They are, in order based on the time sensitivity of needed intervention: (1) control of [surgically addressable] hemorrhage, (2) control of contamination, and (3) reconstruction of anatomy. In damage control scenarios, these serve as landmarks for reevaluation of the patient's current physiologic state and expected course (e.g., vasopressor trend, acidosis, hypothermia, need for abdominal packing, anticipated resuscitation needs, coagulopathy, adhesion formation, other time-sensitive interventions) and for deciding whether to proceed with the next planned step of surgical therapy.



FIG. 2 Decompressive laparotomy revealing massive bowel edema and dilation contributing to abdominal compartment syndrome.

Temporary Abdominal Closure

Temporary abdominal closure comprises a set of techniques that allow the surgical procedure to be paused with the abdominal fascia remaining open, which avoids reexacerbating IAH, allows for safe and rapid transition to other time-sensitive patient needs (e.g., warming, resuscitation, angiography, other surgical procedures), and allows for "second-look" explorations when the conditions of the viscera are in evolution or it is not yet safe to proceed with the next step in surgical therapy. Now commonly used across multiple specialties, the techniques and materials used have developed over time.

Although commercialized negative pressure wound therapy vacuum-assisted closure devices are a mature technology now widely available and utilized for temporary abdominal closure across multiple surgical specialties in many hospital systems, several noncommercialized methods are still utilized in selected scenarios or settings with variable resource availability. Regardless of the approach used, the temporary abdominal closure technique should provide adequate visceral protection, allow drainage of intraabdominal fluid, mitigate fascia edge retraction, and prevent redevelopment of IAH and compartment syndrome.

Skin-Only Closure

Earlier surgical techniques employed skin-only closure, which was achieved by placing penetrating towel clips 2 cm apart or using a continuous running monofilament suture to approximate the skin edges (Fig. 3). This is effective for rapid abdominal closure and does protect the viscera, however it did not sufficiently allow for expansion of the abdominal contents in many patients at risk for IAH and (because of skin tension) retains significant risk for recurrent ACS despite open abdominal fascia. Additionally, skin closure–based techniques do not allow the egress of abdominal fluid (without drain placement), do not prevent abdominal wall musculature and fascial edge retraction or adhesions to the lateral abdominal wall (increasing difficulty of subsequent closure attempts and worsened loss of abdominal domain), and cause considerable damage to the edges of the skin.

Silo and Vacuum Type Temporary Closure Methods

A landmark innovation in management of patients with emergency abdominal surgical needs, the Bogota bag was first described by surgeons in Colombia (Fernandez et al., 1996). In resource-deprived areas, the use of this technique is an inexpensive yet effective option for temporary closure. The technique, on which subsequent techniques have been based, prioritizes prevention of IAH and uses a sterile x-ray cassette cover or a durable 3-L sterile irrigation bag cut to size as a nonadherent and easily distensible protective cover over the viscera. This transparent protective layer is approximated



FIG. 3 Penetrating towel clips used for temporary "skin-only" closure *(left)* and postclosure radiograph demonstrating the resulting limited view caused by overlap and obstruction from the clips *(right)*.

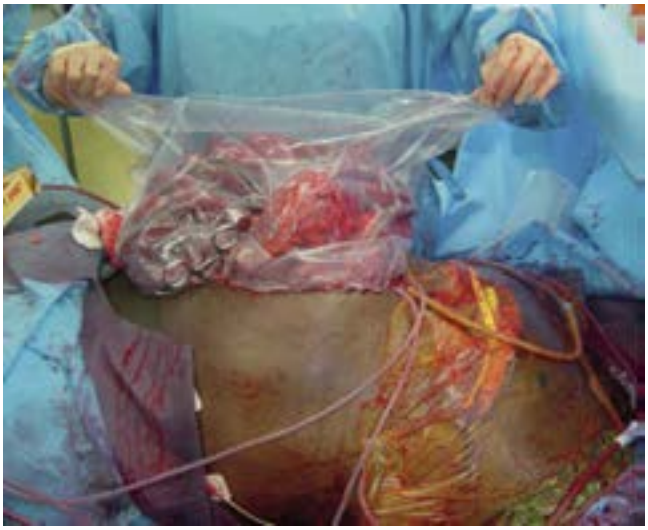


FIG. 4 Bogota bag with sterile x-ray cassette cover before outer adhesive dressing placement.

circumferentially to the skin or fascial edges using running small bites of heavy monofilament sutures. Closed-suction drains can then be placed along the plastic covering–skin interface to allow for continuous abdominal drainage. Finally, an adhesive drape can be placed (though not strictly necessary) over the drain and bag complex to further secure the closure (Fig. 4). This technique is effective and inexpensive and remains a useful tool in resource-limited settings (e.g., during transport or when suction may not be available). The primary disadvantages are that it does not prevent either fascial retraction and loss of domain or adhesion formation to the anterolateral abdominal wall (increasing the difficulty of subsequent operative intervention and attempts at fascial closure). It additionally carries a risk of inadvertent bowel injury during the suturing process (often under time pressure in a field of swollen viscera) and is more labor-intensive than more recent iterations of the technique.

The *Barker vacuum pack* represents a subsequent development of the concepts demonstrated in the Bogota bag. This technique uses a sterile polyethylene sheet fenestrated throughout with small holes using scissors or a scalpel. The key difference in this technique is sterile non-adherent sheet is placed *under* the fascia directly between the viscera and the anterolateral abdominal wall, preventing adhesion formation. Next, a layer of saline-soaked towels is situated in the midline defect over the fenestrated sterile sheet, allowing effective fluid drainage. Two Jackson-Pratt closed drains are placed over the towels and sandwiched with a second set of towels on top. Finally, a large adhesive sterile drape is placed over the abdomen. The drains are then connected to continuous wall suction in the postoperative period, which aids in limiting fascial retraction (Figs. 5 and 6).

Contemporary commercialized negative pressure wound therapy systems, such as the AbThera vac, have become widely available. This combines many of the components of the constructed vacuum-assisted dressing described earlier with the benefit of being contained in a prepackaged, ready-to-go unit (see Fig. 5). It employs a polyurethane foam enveloped within a fenestrated and non-adherent polyethylene sheet positioned entirely over the viscera contents in a subfascial placement, with the goal of improving the fluid transit through the non-adherent layer. A second foam sponge is placed on top of the protective sheet, and an adhesive drape secures the sheet and foam in place. A suction tubing is attached via a "lily pad" adaptor to the adhesive covering layer and is connected to a self-contained, pressure-regulated negative pressure pump system and fluid collection chamber. The advantages of this approach are similar to the Barker vacuum pack with additional gains in efficiency through ease of equipment identification and availability (especially if working with a team that does not commonly deal with open abdomen cases), consistency in application technique (especially for surgeons who less commonly perform this procedure), and portability of the vacuum device over wall-suction or ad hoc portable suction containers. The major advantage, even for teams and surgeons that frequently manage open abdomens, is the time savings gained from systemization of the process, which can allow more rapid transitions to the next intervention or phase of the case and may be lifesaving in very physiologically compromised patients.

Abdominal Closure

Approach and Strategy

Once the acute resuscitative phase of care is complete, hemorrage and contamination sources controlled, and surgical reconstruction complete, the abdomen is closed. The timing of this transition is frequently indicated by evidence of physiologic convergence and normalization, such as weaning of vasopressors, decrease in resuscitative fluid requirements, improvement in indicators of tissue perfusion, and resolution of coagulopathy. In the ideal setting, the abdomen will be primarily closed as soon as the patient's physiology permits; however, large-volume resusucitation often produces visceral congestion that remains too high a volume for the patient's abdominal wall. This viscera will begin to form adhesions at variable timings based on the patient's underlying comorbidities, physiologic state, and degree of malnutrition and immunosupression, making attempts at manipulation increasingly likely to cause injury and enteroatmospheric fistula. Additionally, the longer a patient's abdomen is open, the more retracted the lateral abdominal wall musculature becomes, leading

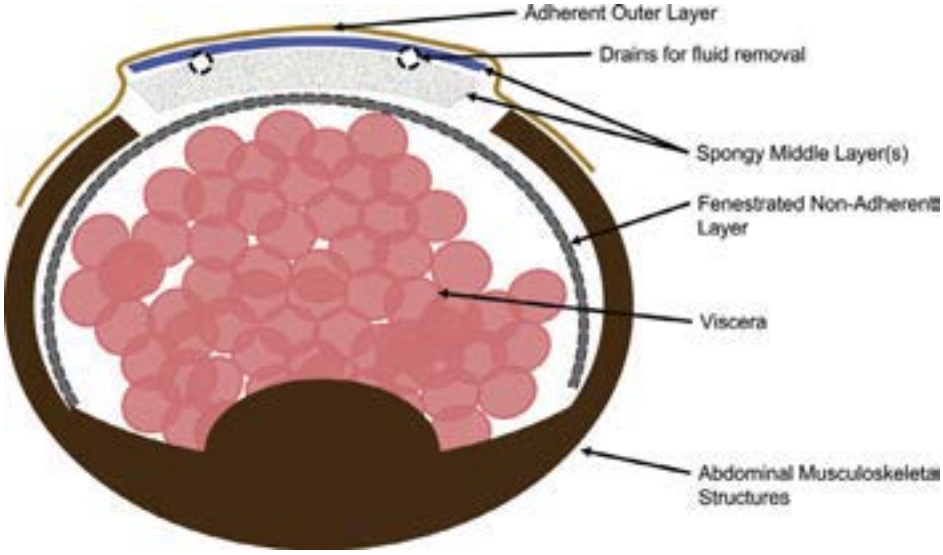


FIG. 5 Schematic representation of vacuum type temporary abdominal closure (e.g., Barker pack or AbThera). The essential components are illustrated on an abdominal cross-section: an inner nonadherent layer is fenestrated to allow fluid to flow through it; a spongy layer (e.g., consisting of loosely folded gauze, operating room towels, or a commercially made wound vac sponge) is positioned above the nonadherent layer between the open abdominal muscles to improve fluid flow and help prevent abdominal wall retraction from the effect of the suction; an outer adherent layer contains the negative pressure and provides additional support of the laminated closure structure; drains may be placed within the spongy middle layer(s) and attached to suction, or a "lily-pad" device placed external to the adherent outer layer can be connected to a commercial wound vac.

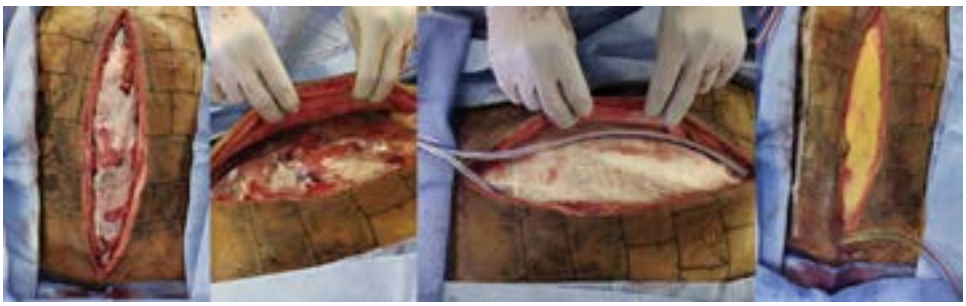


FIG. 6 Example construction of a vacuum-type temporary abdominal closure (e.g., Barker pack). This dressing is constructed with a fenestrated x-ray cassette cover placed over the viscera to protect the lateral abdominal wall, loose Kerlix gauze placed as the middle spongy layer containing two 19Fr channel drains to provide suction and fluid removal, and an Ioban adherent dressing placed over the top to seal the closure. The drains are positioned between folds of the spongy middle layer to improve their functions of maintaining suction and fluid removal and are best sealed by means of a "mesentery" folding of the adherent dressing around the drain tube to prevent air leak. Alternatively, the drains may be brought out the skin if this method is not feasible.

to a loss of domain and enlargement of the fascial gap that further limits the ability to achieve primary closure. Rates of primary closure are highest and complications are reduced if the patient can be made anatomically and physiologically optimized to attempt closure within 7 days. The main theraputic strategies that address these major challenges and allow for consistent primary closure are precision of fluid management in both the resucitative and postresuscitative phase, early definitive source control in the case of significant contamination, and early (and frequent if needed) return to the operating room to progress surgical care as soon as anatomically and physiologically possible. However, despite even optimal management, a significant portion of patients will have significant challenges to achieving primary abdominal closure.

Primary Abdominal Closure

For patients who are able to sufficiently clear the resuscitative fluid burden and related visceral edema and maintain preserved abdominal muscular domain, primary approximation of the fascia is optimal. Though many methods are described, in these cases we prefer to use an interrupted closure of #0 or #1 polydioxanone or polyglycolide-trimethylene carbonate (commercially known as PDS or Maxon). These suture materials have the benefit of being absorbable but they retain tensile strength for a more extended time than other commonly used absorbable sutures (approximately 40–90 days), allowing increased time for fascial healing while decreasing potential risks for infection or suture granuloma with permanent suture material. We avoid using a continuous suture in these cases, as a single stitch failure or small area of fascial necrosis would allow the closure to open entirely, resulting in a large dehiscence or evisceration that requires additional surgery or complex wound care rather than a small area that can often be managed with comparatively simple local wound care alone (Fig. 7). More importantly, careful attention to a consistent and meticulous technique is more critical to the viability of the closure than the individual method chosen. Maintaining the principles of consistent bites (depth, contour, and travel) to evenly spread the tension, taking appropriately deep fascial bites (neither too shallow to hold the stitch nor so deep that they generate additional wound tension), and selecting the appropriate patient and setting to attempt primary closure (e.g., tension is minimized to the degreee possible, fascia is overall intact, the patient is optimized

physiologically) will maximize the patient's chance of successfully healing the abdominal closure.



FIG. 7 Complete fascial dehiscence after partial failure of a continuous running primary abdominal closure.

Retention Sutures

Even in the setting of optimal surgical and perioperative management of patients with an open abdomen, not all patients have a clearly delineated method for abdominal closure. Retention sutures are a risk-reduction strategy sometimes used for patients who are felt to be at increased risk of poor fascial healing (Fig. 8). It is most useful in patients who have the abdominal wall domain to primarily close the fascia but additionally have substantial risk factors for fascial dehiscence and would poorly tolerate additional operative management in the setting of evisceration (or may be unable to rapidly access surgical care). It is important to consider that these sutures (commonly heavy #2 nylon), placed either in interrupted or mattress fashion through the skin and fascia lateral to and across the midline wound (ideally in the preperitoneal space to avoid unnecessary contact with the viscera), *do not reduce the risk of fascial dehiscence and wound opening,* rather they *reduce the risk of evisceration* in the event that the fascial closure fails. This may be of significant benefit in settings in which patients are cared for with limited access to surgical services, either because of availability of surgeons or facilities or as a result of postoperative care delivery in a location where time-sensitive access to surgical care is logistically difficult. This technique may have significantly less utility in settings with robust access to surgical care or a patient population that has lower rates of risk factors for fascial dehiscence. Additionally, although it is sometimes a worthwhile tradeoff for the risk reduction of evisceration, retention sutures are substantially uncomfortable and cause skin breakdown, pressure necrosis, and wound complications.

Progressive Closure Techniques

In the setting of potentially reversible loss of abdominal domain and initial inability to primarily close fascia, several techniques have been described to address the progressively fixed and lateralized abdominal wall. Sequential fascia closure is commonly practiced in which interrupted closure of the most superior and inferior portions of the wound are performed until the tension increases to a point that is not longer able to be approximated, and the remainder of the

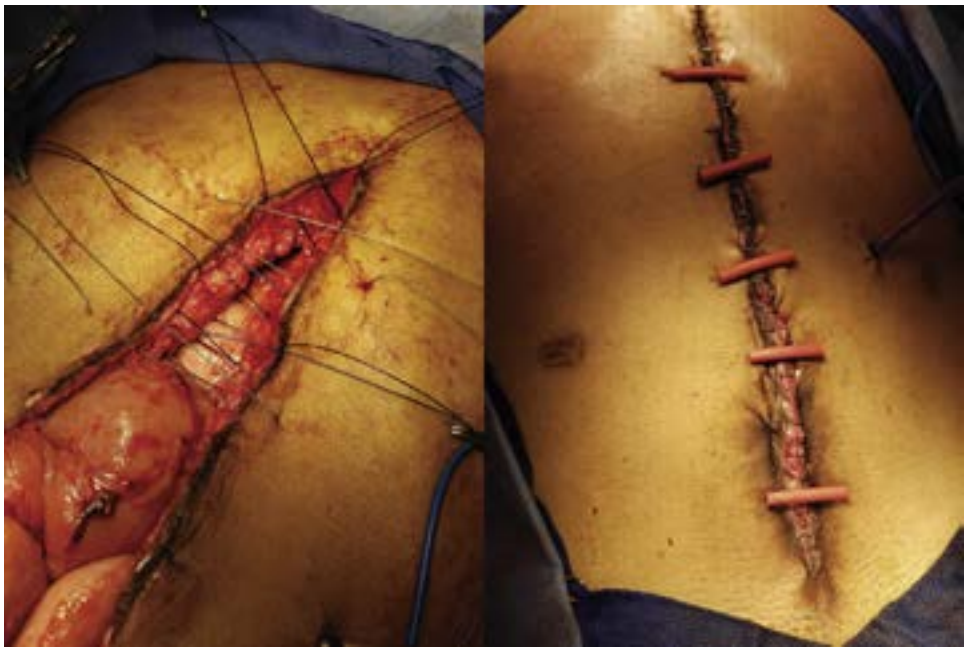


FIG. 8 Placement of retention sutures in support of an interrupted primary abdominal fascia closure. Retention sutures are ideally placed through the fascia but remain extraperitoneal to limit contact with and trapping of viscera. These may be placed in simple interrupted arrangement using sections of red rubber catheter to protect the soft tissue *(as shown)* or alternatively in mattressed fashion with the visible portion of the sutures running parallel to the wound. Other commercially available or improvised materials may alternatively be used as available in place of the red rubber catheter to reduce the impact of the heavy suture on the skin.

defect is redressed with a temporary closure aparatus. The technique is repeated on the next operative episode, until the fascia is either fully closed or a small(er) bridging mesh is used. This may limit progressive fascial retraction to some degree, though it comes at the expense of loss of intraoperative visualization (as a result of bulging viscera through a progressively smaller defect) and concentrates the tension of the closure on the stress point of the stitch most closely positioned to the open defect (rather than balanced across the entire wound). It is not clear that this technique improves closure rates or time to closure over serial vac dressing changes with optimized fluid management.

A technique that similarly aims for progressive closure is well described by the Denver group. A protective layer of white wound vac sponge is placed directly over the bowel. Interrupted full-thickness fascia bites using heavy monofilament sutures are placed 5 cm apart starting inferiorly and superiorly and met in the center of the incision to prevent lateral retraction of the fascia (Fig. 9). If fascia closure is not achieved at this particular time, the patient sequentially returns to the operating room every 48 hours until primary closure is achieved. One particular disadvantage of this technique includes a "piano wire" effect by which the firm and tense monofilament sutures cause deep pressure necrosis of the fascia and may injure the underlying bowel. Additionally, repeated fascia injury is imminent as the repetitive placement of sutures, in turn, can theoretically increase the risk of fascia dehiscence, evisceration, and hernia defect formation. Other progressive closure techniques include the use of elastic bands or sutures (or notably a pair of interlaced ¼-inch Penrose drains) attached to either the skin or fascia to place continuous gradual tension across the wound and achieve progressive closure, even between operative episodes. Commonly referred to as a *Jacob's ladder,* this technique has many described variations and multiple commercial devices designed to take advantage of the principle of *sequential static tension* to achieve closure of many types of wounds. Although it has been shown to achieve impressive results in selected cases; it is also relatively labor-intensive, may cause skin breakdown, and for most patients may not achieve closure significantly more consistently or rapidly than other techniques.

Tissue Rearrangement and Mesh: Hernia Repair Techniques to Achieve Closure

An alternative to progressive attempts at closing a retracted fascia is to use techniques common to abdominal wall reconstruction to achieve either primary or bridging closure. The timing of this should be balanced against the estimated degree of visceral edema that may be reduced with further diuresis as the inflammatory state of the patient improves, and ideally only employed if fascial retraction and loss of domain have progressed past what gains are expected from further fluid optimization. Consideration for the strategic goal of the technique used should strongly be tuned to the long-term effects of any potential tissue rearrangement; a technique that exchanges a substantial long-term risk of a potentially unfixable abdominal wall hernia for primary fascia closure in the index admission may not be in the patient's best interest. Caution should be exercised and experienced judgment consulted when considering any tissue rearrangement option as an adjunct to management of the emergency surgery patient with the open abdomen.

Elevation of fascio-cutaneous (subcutaneous tissue down to but not including the anterior abdominal wall fascia) flaps is an adjunct that has versatile use in managing the open abdomen. It allows a few centimeters of fascial advancement and may be employed to reduce tension or achieve a safe primary closure when the residual defect is less than 5 to 8 cm. Additionally, it may be used to advance healthy tissue over a bridging fascial closure to avoid the need for prolonged wound care or skin grafting. Although the risk of raising these flaps is relatively low, fascial planes are typically able to be raised again in the reoperative setting with only a modest increase in difficulty, and flaps of moderate size are often well perfused in emergency surgery patients. Risks predominately consist of flap/skin ischemia and necrosis and infection under the flap; caution should be exercised in patients with small-vessel vascular disease, diabetes, significant smoking history, thin subcutaneous tissue, and larger flaps—all of which increase these risks and could lead to substantial tissue loss.

More complex tissue rearrangements including separations of components (e.g., retrorectus dissection with transversus abdominus release) have been described for achieving primary closure in the index admission for the emergency surgery patient population, however they should be used sparingly and only in the setting of substantial experience with the techniques and management of their complications. Even a more limited myofascial release (e.g., of the external oblique) can substantially limit subsequent surgical repair options if the abdominal closure in the index admission fails. It is important to consider the compounding of risk factors in an emergency surgery patient with an open abdomen who is not able to be primarily closed compared with such a complex repair in the elective setting.

A more conservative strategy—conceptually a damage control approach for the abdominal wall—is the use of a bridging mesh to allow preservation of the native tissue planes (Fig. 10). The goals of such a strategy are to preserve fascial integrity, limit further retraction of the abdominal musculature, prevent abdominal fluid/protein losses and protect the viscera, facilitate epithelial closure (either with advancement flaps or skin grafting), and avoid compromise of future abdominal wall reconstruction attempts. This technique can be used for small and large-size defects and used as the primary alternative for patients who are unable to be closed with fluid optimization serial vacuum dressing changes or in combination with other described techniques such as progressive closure. When choosing the type of mesh for closure in this setting, biologic or absorbable biosynthetic mesh is preferred over permanent synthetic mesh, which should be avoided as infectious, fistula, and intestinal erosion complications



FIG. 9 Denver Group technique for progressive fascial closure.

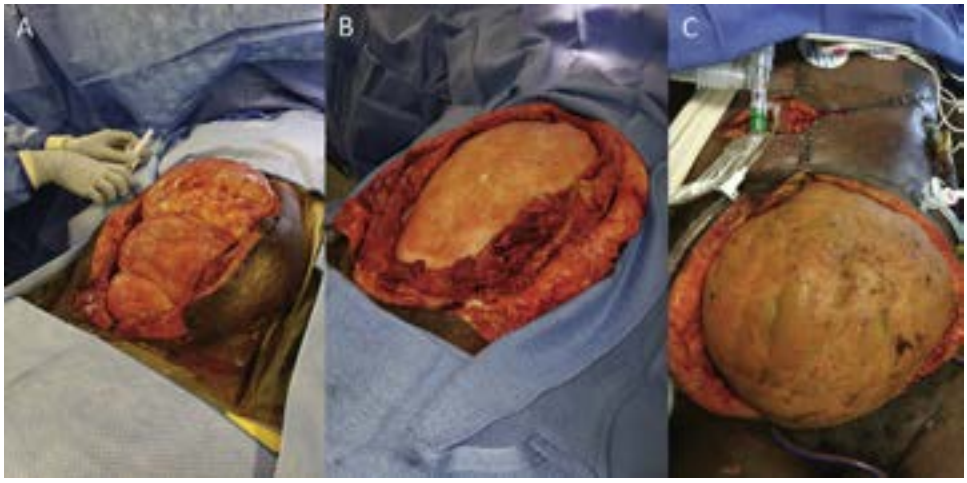


FIG. 10 Bridging closure of a retracted abdominal wall with mesh. Open abdomen with refractory edema and loss of abdominal wall domain **(A).** Closure can be achieved with a bridging mesh such as a biologic crosslinked bovine acellular dermis **(B)** or an absorbable synthetic Vicryl mesh **(C).** Wound care can proceed with wet to dry or wound vac–type dressings. Once the mesh is well-incorporated with healthy granulation tissue, a skin graft may be applied.



FIG. 11 Split-thickness skin graft at initial placement **(A)** and at several months postoperatively **(B).** Graft may be placed on incorporated mesh or directly on granulated viscera. Over time, the area of the graft will begin showing signs of separation and softening of the underlying adhesions. Interval elective hernia repair may be completed once this occurs, typically between 6 and 12 months post–abdominal closure. *(From Berlew C. Chapter 234. In: Cameron JL, Cameron AM, eds. Current Surgical Therapy, 12th ed; Philadelphia: Elsevier; 2017.)*

are high in this particular group of patients. The ability of a biologic mesh to incorporate as it slowly degrades and is replaced by native tissue is an attractive property that may minimize infection-related complications typically seen with non-absorbable synthetic material, particularly in operative trauma and emergency surgery patient populations who often have a significant degree of contamination or bioburden. A biologic or absorbable synthetic mesh can also serve as a substrate for tissue ingrowth in settings in which the retracted overlying subcutaneous tissue and skin cannot cover the wound and facilitate epithelial closure with a subsequent skin graft (Fig. 11).

MANAGEMENT OF THE OPEN ABDOMEN IN THE INTENSIVE CARE UNIT

Nutritional Support

In combination with critical illness, an open abdomen can contribute to a hypercatabolic state, which leads to high energy expenditure, severe protein loss, and significant lean body mass turnover. This results in worsened malnutrition, immunocompromise, an elevated risk for infection, poor wound healing, longer length of stay in the intensive care unit, and increased mortality. Therefore, optimizing the nutritional status of a patient with an open abdomen should be a priority for the healthcare team. The American Society for Parental and Enteral Nutrition (ASPEN) recommends that all patients with a critical illness have an assessment of nutritional risk to facilitate a strategic plan for nutritional therapy. The NUTRIC score is a nutritional risk assessment tool validated for critically ill patients that can be used to calculate the risk of adverse events that can be mitigated with nutritional support; a score >5 identifies patients at high risk. Early enteral nutrition within 24 to 48 hours should be considered in all patients with an open abdomen unless contraindicated. Patients who require ongoing massive fluid resuscitation, those who have increasing or high-dose vasopressor requirements, and those left in intestinal discontinuity preclude attempts at early enteral feeding. Evidence has shown that early enteral nutrition is associated with increased rates of earlier fascial closure, lower rates of fistula formation, decreased infectious complications, and reduced mortality.

The benefits of early enteral nutrition with an open abdomen are consistent with the findings from a multi-institutional trial sponsored by the Western Trauma Association. Intravenous total parental nutrition should be considered for those who have a contraindication to enteral nutrition or are unable to meet at least 60% of daily nutritional intake. Timing for initiating supplemental total parental nutrition is variable and dependent on preexisting nutritional status, risk of malnourishment, and the patient's overall clinical course. The ideal timing for initiating supplemental total parental nutrition in patients considered at low nutritional risk who cannot meet caloric goals is 7 days. This attempts to avoid the adverse outcomes associated with overfeeding. Conversely, providing total parental nutrition on days 3 to 4 is recommended in patients labeled as high nutritional risk and unable to receive enteral nutrition as outcomes have shown to be superior with an earlier start.

Nutritional support is part of the foundational management shown to improve recovery and overall patient outcomes with an open abdomen. Strategic planning on the mode and delivery of nutritional support should coincide with planning for abdominal closure and consider other patient factors such as the ability to swallow, mental status, and ease of subsequent percutaneous enteral access. If the decision is made for surgically placed enteral access, this should be performed at the time of closure.

Fluid Management

Fluid management can be a difficult challenge to manage in patients with an open abdomen. Patients with conditions leading to ACS and requiring management with an open abdomen often require large volumes of fluid resuscitation and ongoing maintenance to support significant gastrointestinal, peritoneal, and insensible losses. There can also be substantial differences in these requirements depending on the inciting etiology. Careful and ongoing attention to the individual patient's physiology is critical to successfully navigating a difficult pathway to recovery. Fluid mismanagement can lead to considerable setbacks and undesirable outcomes. Strict and frequent measurements of fluid intake/outtput allow the clinician to treat fluid balances with precision. Insensible fluid losses from the open peritoneum combined with direct losses caused by large-volume drainage from the abdomen should not be overlooked in fluid calculations. Although important to strictly monitor, measurement of urine output is not a consistently reliable parameter for fluid status in the complex critically ill population. Hemodynamic response to fluid, although more consistent, can also lead to overresuscitation when used as a sole indicator of hypovolemia. Optimal management requires interpreting multiple dynamic parameters that may include urine output and hemodynamic response to volume. Still, in complex cases, hemodynamic bedside echocardiography, arterial waveform analysis, or direct measurement of hemodynamics with a pulmonary artery catheter may substantially improve the precision of fluid and vasoactive medication management. Excessive fluid administration is a risk factor for recurrent ACS, leading to visceral congestion and bowel edema and making attempts at primary fascia closure challenging to obtain. Once resuscitation is accomplished and physiologic parameters are converging, maintaining the balance in which tissue hypoperfusion is avoided while agressively eliminating the retained resuscitative fluid volume that is no longer of benefit to the patient significantly reduces risk of avoidable anatomic and physiologic complications.

Direct peritoneal resuscitation (DPR) is an adjunctive modality first utilized during damage control surgery in the setting of traumatic hemorrhage. Limited data support the utility of DPR in decreasing the need for crystalloid administration, attenuating the inflammatory response, reducing bowel edema, and achieving early primary fascia closure rates. The technique, which is similar to that used in constructed open abdominal vacuum dressings, involves instilling the abdominal cavity with a hypertonic dextrose-based dialysate solution. A large-bore drain is left in the abdominal cavity and used as a conduit for dialysate instillation. A sterile sheet is then placed over the viscera and the closed-suction drains overlying the sterile covering. A large adhesive drape is then placed over the abdomen to create a temporary abdominal closure. Continuous lavage and drainage are performed postoperatively via the drainage system until return to the operating room.

Sedation and Analgesia

Pain and agitation are common problems encountered in most critically ill surgical patients and negatively affect patient outcomes. Patients with an open abdomen may be more susceptible to evisceration or recurrent ACS when actively writhing from pain or extreme agitation. Pain control and management of agitation are essential to avoid these potential complications. Utilization of the Richmond Agitation-Sedation Scale (RASS) to quickly assess sedation and agitation can guide the desired level of sedation. A RASS goal of 0 (alert and calm) is ideal but not always achievable; however, selected patients may benefit from extubation with an open abdominal dressing in place between abdominal explorations. The objective should focus on providing an appropriate comfort level for the patient while minimizing the adverse effects of deeper and prolonged sedation levels that are associated with increased incidence and severity of delirium, prolonged ventilator dependence, and more days in the intensive care unit.

COMPLICATIONS

Risk Factors and Management Strategy

The incorporation of temporary abdominal closure into surgical practice and the advancement of perioperative and operative management techniques to optimize its utility have significantly reduced complications and improved survival in patients with disease processes that increase the risk of ACS. As with any other technique, however, there are a set of risks when using these techniques that should be recognized and considered. The development of large hernia defects, dense adhesions, and enteroatmospheric fistulas are among the known surgical complications that cause significant postoperative morbidity. Complications most commonly occur in patients with elevated anatomic risk factors (e.g., compromised tissue integrity, persistent contamination/infectious source, substantial adhesions, obesity, multiple injuries requiring repair, multiple prior abdominal surgeries) and physiologic risk factors (e.g., persistent shock, poor cardiac function, smoking, steroids, connective tissue disease, immunosupression, malnutrition, diabetes, ascites), but they can occur in any patient. This underscores the importance of having meticulous respect for tissue and surgical technique (such as attempting an anastomosis on edematous and fragile bowel), paying close attention to management of fluid status and nutritional support, and aggressively monitoring the progress of physiologic landmarks and returning to the operating room to complete the operative phase of care as soon as they are reached.

Before final closure of the abdomen, reconstruction of intraabdominal anatomy should be completed. Gastrointestinal and biliary continuity should be restored, and all anastomotic connections or diverting stoma should be created and matured. Management of high-risk surgical anatomy should be considered, particularly if the abdomen was open for a prolonged period or a bridging mesh was required for closure. Adhesions contributing to internal hernia or significant lumenal narrowing should be lysed if safe to do so to avoid postoperative obstructions that place the patient between the risk for complications with early reoperation (in what is often a high risk, severely adhesed field with friable tissue) or prolonged obstruction that may lead to severe dysmotility and intestinal failure if reoperation is delayed for an extended period. Enteral access should be considered if the patient is likely to have difficulty resuming sufficient oral intake or if the position of the stomach is likely to make

subsequent percutaneous access challenging. Consideration for prophylactic cholecystectomy or appendectomy may be warranted for selected patients with favorable anatomy who are likely to have prolonged and substantial reoperative risk profiles.

Enteroatmospheric Fistula

One of the more challenging complications for both the patient and surgeon is the development of an enteroatmospheric fistula. In contrast with enterocutaneous fistulae, this abnormal communication tends to have a relatively large-diameter defect and is directly between the intestinal lumen and the external environment. The lack of a tract through other tissue that would help contain the drainage increases the risk for sepsis because of formation of undrained intraabdominal collections and makes spontaneous closure highly unlikely. Uncontrolled spillage of intestinal content into the wound in this scenario commonly leads to failure of the fascial closure or mesh, skin breakdown, and inability to progress out of the critical care environment as a result of complex and often customized wound care management. Risk factors that have been associated with the development of enteroatmospheric fistula include large-volume crystalloid administration, multiple abdominal reexploration, intestinal anastomosis, and large bowel resection.

Early Management and Sepsis Control

As with enterocutaneous fistulae, management of enteroatmospheric fistulae focuses on control and direction of drainage, anatomic characterization, wound care, fluid/electrolyte/nutritional planning, and consideration of long-term operative strategy. Sepsis control is predominately achieved by selection of a robust pathway for diversion of enteric contents to prevent their accumulation. When acute surgical intervention is needed, the goal is not to repair and take down the fistula but rather to transform an uncontrolled fistula into a controlled (ideally ostomy-like) fistula. There is no one standard procedure for controlling a fistula, and the most appropriate set of techniques often evolves throughout the early course: Combinations of techniques such as tube diversion (e.g., insertion of a large Malecot tube into the fistula), sump drain placement into posterior collections, wound vac therapy, wet-to-dry dressings, and maturation of the fistula to the skin can be utilized to control fistula output (Fig. 12). Excision and direct repair of fistula defects is described but only rarely successful; resection and reanastomosis can achieve a more definitive result when feasible, though the majority of patients have visceral adhesions too severe to safely accomplish this on initial admission. **Most importantly, as the chance of failure to achieve controlled drainage with any individual technique is high in these patients, surgical planning should tend to be conservative and particularly**



FIG. 12 Cannulation of poorly mobile enteroatmospheric fistula for initial drainage control in the setting of delayed presentation of anastomotic failure and a partially frozen abdomen **(A).** Enteral access (g tube) is achieved with endoscopic assistance. Temporary support packing with laparotomy pads achieved progression to more favorable positioning of an otherwise relatively nonmobile posterior fistula over time that subsequently allowed for effective pouching **(B).**

thoughtful with respect to how to avoid worsening the problem if serial attempts are unsuccessful. Judgment as to the sequence of operative contingencies that (with consideration to the patient's current physiologic state and underlying comorbidities) minimizes overall risk is critical to sucessfully navigating these complications.

Wound Care Techniques

Throughout the duration of the fistula, well-designed and consistently maintained wound care is critical to fistula management. Uncontrolled output is highly caustic and causes recurrent wound infections, causes skin breakdown, and is responsible for the majority of pain symptoms with fistulae. A dedicated and experienced multidisciplinary wound care team should be consulted for all patients with enteroatmospheric and enterocutaneous fistulae. Early in the course, bedside wound management is often insufficient to adequately address the needs for controlled drainage and to design a robust wound care plan. A thorough washout and assessment in the operating room can aid in identification of the fistula anatomy and areas that may need additional operative management (e.g., tube placement, significant debridement, or drainage). For enteroatmospheric fistula in the middle of a large wound with loss of abdominal muscular domain, control of drainage is often especially challenging, even once granulation of the posterior and internal spaces effectively prevents intraabdominal accumulation of collections of enteral contents. Purposely manufactured or improvised "chimney" appliances can be used alone or in addition to tube drainage of the fistula lumen to isolate the drainage into an ostomy appliance and allow for granulation and skin grafting of the surrounding wound (Fig. 13). An alternate technique that we have found helpful in select difficult cases involves suturing a pediatric silo conduit to the ostomy opening for enteral diversion, circumferentially excising surrounding tissue when needed, placing a white sponge and black foam around the wound base, and applying negative-pressure wound vac therapy (Fig. 14). A split-thickness skin graft is then applied after 7 to 10 days, providing a stable epithelialized flat surface for long-term placement of an ostomy appliance bag.

Characterization of Fistula

Once initial source control is achieved, the fistula is anatomically and functionally characterized. This can be as an adjunct to developing a drainage and wound care strategy and to assist with nutritional planning and both short- and long-term surgical decision making. Anatomic mapping, for example, CT with enteral contrast, or fluoroscopic sinography if not clear from operative exploration can provide insight into the path of the fistula and its location along the gastrointestinal tract. A distally located intestinal fistula is more likely to remain with modest output and allow enteral nutrition without severe fluid and electrolyte loss versus a more proximally located fistula. Understanding the response of the fistula output to enteral nutrition often requires a trial of feeding when its behavior is unclear. Although much less likely with an enteroatmospheric fistula than a enterocutaneous fistula with a long narrow tract, a distal fistula with well-controlled drainage may functionally perform as would a new ileostomy and (after a period of adjustment) allow the patient to eat. Most often, however, enteroatmospheric fistulae will tend to substantially increase in output with even small volumes of enteral intake and rapidly lead to dehydration and electrolyte derangements. In these cases, a prolonged course (e.g., 6–12 months) of total parenteral nutrition will be required before the patient is safe to undergo operative fistula takedown (and typically concomittant complex hernia repair).

CONCLUSION

IAH is commonly encountered when managing patients with time-sensitive, severe illnesses, especially those with life-threatening abdominal surgical conditions. Strategies of prevention (particularly decisions for when to use damage-control surgery and a balanced, frequently titrated resuscitation and fluid-removal strategy) are the most important to avoid progression to ACS that often leads to devastating complications for the patient. A high index of suspicion is necessary for early recognition and timely intervention to prevent severe morbidity and mortality. For patients requiring management of an open abdomen, attentive and precise management of fluids, nutrition, and operative planning will reduce the risk of severe complications. These principles increase the likelihood of achieving safe abdominal closure, rapid return to normalized anatomy and physiology, and critically avoiding recurrent ACS. Even with optimal management, complications should be anticipated and managed with experienced judgment. Avoiding the traps of utilizing too optimistic, too pessimistic, or impatient strategies when complications happen and maintaining focus on long-term goals is essential to successfully managing these complex and dynamic patients. Although long-term care of patients with difficult abdominal wall defects or enteroatmospheric fistulae may benefit from care by surgeons and institutions with significant and ongoing experience managing and treating these issues, the acute management of patients with conditions predisposing to ACS is a core competency in emergency general surgical care. Given the common occurrence of IAH, the profound morbidity and mortality caused by development of ACS, and the relatively consolidated operative care in the early phase of such illness, surgeons managing severe abdominal trauma and emergency abdominal surgery should maintain a working knowledge of strategies for damage control and management of the open abdomen.

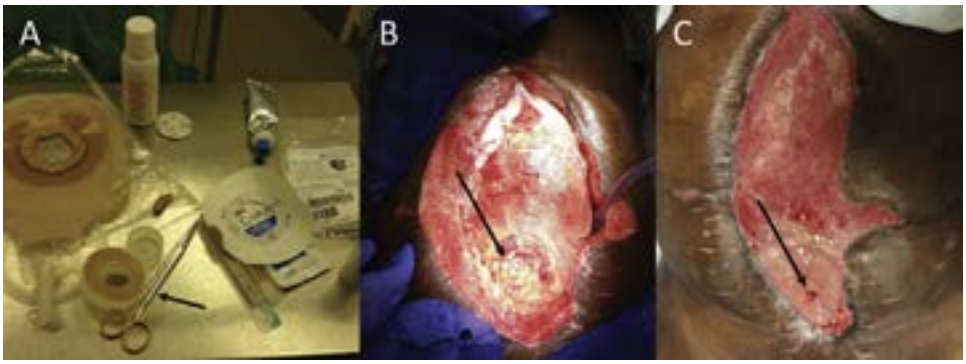


FIG. 13 Back-table assembly and progressive placement of a commercial "chimney" diversion apparatus. The *black arrow* demonstrates the device in **(A)** with putty lining for improved seal and scissors for reference size. *Black arrows* in **(B)** and **(C)** show the location of the fistula with progressive granulation and contraction of the overall wound.



FIG. 14 Silo technique for management of enteroatmospheric fistula from a complex Pfannenstiel wound in the setting of large pannus **(A).** A silo conduit is anastomosed to the mucosa of the enteroatmospheric fistula **(B)** to control output and allow for a negative pressure wound vac to hold suction and improve granulation. **(C)** A split-thickness skin graft is placed on the surrounding granulated wound after 7 to 10 days. **(D)** Successful healing of the skin graft allows for subsequent pouching.

Suggested Readings

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Abdomen That Will Not Close

Stephen L. Barnes, MD, and Jacob A. Quick, MD

The open abdomen as a component of staged surgical intervention, damage control surgery, or as a treatment strategy for abdominal compartment syndrome can be lifesaving when applied in the appropriate clinical setting. Use of the open abdomen should not be undertaken lightly as the rate of complications (hernia, fistula, infection) can be significant and increases linearly with duration of temporary abdominal closure. Timing of closure and the technique by which the open abdomen is addressed have both been debated widely and numerous strategies for management have been adopted. Modern resuscitation strategies, including limiting crystalloid and goal-directed resuscitative practices coupled with fixed-ratio blood product resuscitation have reduced, but not eliminated, the need for an organized approach to open abdomen management. The overarching goal of managing the open abdomen should be primary fascial closure during the index hospitalization.

INDICATIONS FOR THE OPEN ABDOMEN

Indications for utilization of the open abdomen fall into five major categories. Surgeons should be prepared to effectively utilize the open abdomen when clinically indicated in the following clinical scenarios.

Abdominal Compartment Syndrome

Compartment syndrome is a late manifestation of uncontrolled intraabdominal hypertension. It is most commonly associated with aggressive resuscitation and has a high risk of mortality. The acute treatment of abdominal compartment syndrome is utilization of the open abdomen through a generous midline incision and temporary abdominal closure that does not result in recurrent compartment syndrome.

Damage Control Surgery

Physiology is king and should drive the decision to leave the abdomen open during a laparotomy. After achieving major source and/or hemorrhage control, a truncated surgical procedure with temporizing measures, such as packing or vascular shunt placement is performed, followed by a temporary closure technique. The patient is then returned to the operating room once coagulopathy and physiology have corrected for definitive repair and closure.

Second-Look Laparotomy

In cases of flow-related ischemia, with or without embolectomy or bypass, a planned "second look" allows for assessment of viability once flow has been improved or reestablished.

Loss of Domain

When visceral edema or retroperitoneal hemorrhage/edema result in loss of domain and the abdomen is unable to be closed, the abdomen will require temporary abdominal closure. In these cases, an overly tight closure would have a high risk of developing compartment syndrome. As edema resolves, the abdomen may be closed primarily.

Failure to Achieve Source Control

In cases where source control is not felt to be adequate at the index operation, a short period of resuscitation and use of the open abdomen may be warranted. A secondary washout may be warranted to achieve adequate control of infection in severely and grossly contaminated cases. Usually associated with septic shock and disrupted physiology, the planned use of second look solely for secondary washout should be rare. Infection control in the majority of cases can be achieved at the index operation.

TEMPORARY CLOSURE TECHNIQUES

Many strategies have been employed for the management of the planned open abdomen. The ideal strategy should contain the intraabdominal viscera, protect it from mechanical injury, prevent bowel desiccation, minimize abdominal wall tissue damage, prevent contamination of the peritoneal cavity, control egress of peritoneal fluid, be applied rapidly, be able to be reapplied or revised multiple times, and be cost effective. However, the ideal system does not exist. Recent expert consensus statements recommend negative pressure dressings for the open abdomen and find their use to result in higher rates of primary closure, which can be achieved through both commercial devices and materials readily available in most operating rooms.

The ideal characteristics of temporary closure techniques should:

- Contain the intraabdominal viscera
- Protect viscera from mechanical injury
- Prevent bowel desiccation
- Minimize abdominal wall tissue damage
- Prevent contamination of the peritoneal cavity
- Control egress of peritoneal fluid
- Be rapidly applied and reapplied or revised
- Be cost effective

The underlying reason for the open abdomen, the patient's clinical condition, and the suspected duration of temporary closure are all factors in deciding which method to employ. Clinical judgment of expected duration is important in choosing the most applicable temporary abdominal closure technique.

Short Term

Short-term use of the open abdomen is most commonly utilized in the damage control setting or planned second-look laparotomy. In many cases, the viscera are easily contained within the peritoneal cavity, and a single return to the operating room is anticipated with definitive closure at that time. When domain is maintained but the abdomen is to be left open, simple use of a slush basin drape or an x-ray cassette drape will provide ample coverage and protect the viscera. Ensure that all viscera are included within the plastic aids in maintaining domain, as the plastic barrier prevents visceral adhesion to the peritoneum (Fig. 1A). Next, a folded radiopaque towel or laparotomy pad may be placed around a nasogastric tube to manage abdominal fluid effluent, and create negative pressure under an occlusive dressing. Before applying the occlusive dressing, a partial or complete skin closure may be completed dependent upon indication for the open abdomen (Fig. 2). This "homemade" negative pressure dressing, often called a Barker pack, has been described by many and can be most effectively utilized in the setting of planned second look, as it can be quickly and easily constructed with materials available in any modern operating room. Documentation of number and location of laparotomy pads or other materials left in the peritoneal

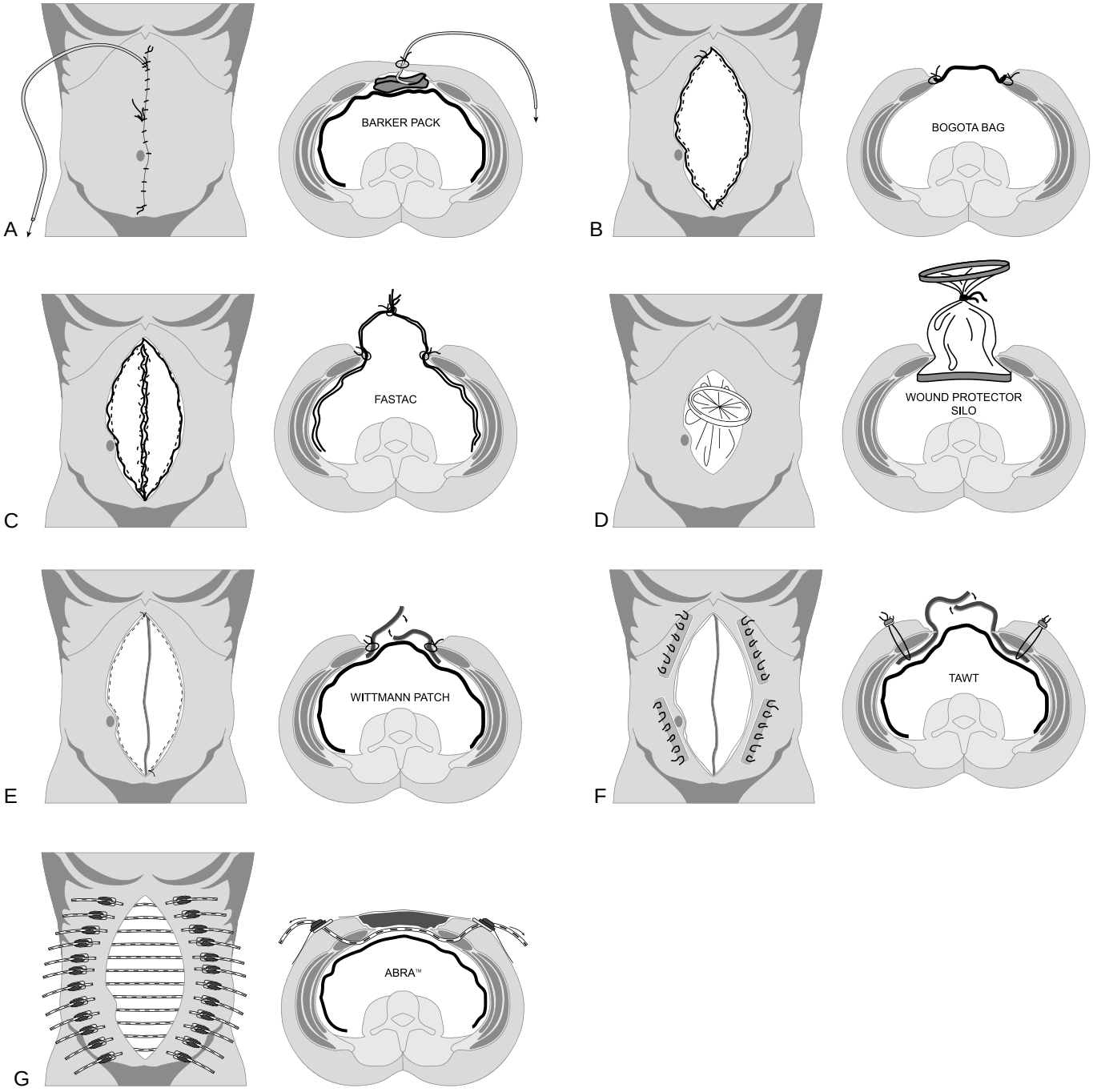


FIG. 1 **(A)** Barker pack. An x-ray cassette drape is cut and fenestrated laterally. It is then placed into both gutters, both subcostal spaces, and the pelvis to create a wide adhesion barrier between the entire viscera and the abdominal wall. A nasogastric tube is then placed within surgical towels. The skin is closed as appropriate to avoid compartment syndrome, and a self-adhesive dressing is then placed over the closure. The nasogastric tube is then placed to suction. **(B)** Bogota bag. A sterilized IV bag is opened and sewn to the fascial edges. **(C)** FASTAC. The abdomen is sequentially closed by fixing the midpoint of a thick plastic drape to the bilateral fascial edges. The drape is placed laterally to prevent adhesions, while the medial portion is sutured together. The medial aspect is sequentially tightened by rolling until the fascia is ready for primary closure. **(D)** Wound protector silo. A large wound protector may be placed to house edematous viscera. It is closed at the opening with suture or an umbilical tape. **(E)** Wittmann patch. Viscera are covered by a barrier dressing, followed by hook-and-loop sheets sewn to fascial edges. The hook-and-loop sheets can then be advanced easily, as they are self-adhering. **(F)** TAWT (transabdominal wall traction). A Wittmann patch is utilized in a similar manner; however,it is fixed to the abdominal wall via transfascial sutures that do not incorporate the fascial edges. Bolsters are utilized to protect the skin. **(G)** ABRA. A silicone barrier is placed over the viscera, followed by attachment of multiple button skin anchors. Next, thick elastomeric sutures are delivered in a transfascial manner across the wound. The elastomers can then be tightened without return to the operating room.



FIG. 2 Barker pack utilized for temporary closure. In this case, domain was preserved by temporarily closing the skin. Negative pressure is applied to the nasogastric tube after skin closure and coverage with an occlusive dressing.



FIG. 3 Bogota bag placement. A sterilized saline bag is cut to form a thick plastic sheet, which is sewn to the fascia. Gauze dressings or vacuum-assisted dressings are then applied.

cavity should be written on the patient for improved communication at time of planned takeback.

First described by Oswaldo Borraez, the Bogotá bag is another time-tested method to gain initial closure in patients with preserved domain. This involves affixing a sterile 3 L IV fluid bag to the fascia or the skin following laparotomy in an inlay position (Fig. 1B). A downside to the Bogotá bag is that it requires fixation to the fascia or skin, which may require subsequent debridement, creating a larger defect to close at a later date (Fig. 3). Suturing the bag to the skin also fails to prevent visceral adhesion to the peritoneum, lessening the likelihood of closure with further operations.

Long Term

Visceral edema, caused by mesenteric venous thrombosis, aortic aneurysm rupture, resuscitation techniques, pancreatitis, or other entity, may result in viscera that reside outside of the peritoneal cavity. In these cases of loss of domain, the use of a negative pressure system is recommended by professional societies.

Although the commercial negative pressure devices are effective in the long-term management when multiple returns to the operating room are anticipated, we find the use of the FASTAC technique or plastic patch to be very effective in cases where when multiple takebacks are anticipated due to the patient's overall condition and loss of domain (Fig. 1C). A thick plastic drape is cut in two pieces and folded into multiple layers. The plastic sheets are then sewn to the fascia bilaterally with enough intraperitoneal plastic to reach the gutters bilaterally, which prevents the viscera from adhering to the anterior abdominal wall. The two medial edges of the plastic sheets are then sewn together in the midline to retain the viscera while not creating compartment syndrome. Simple wet dry dressings are then placed over the plastic sheets to keep the subcutaneous tissues moist. The clear plastic drape allows for daily inspection of the peritoneal cavity, repetitive entry as needed, and sequential bedside tensioning for staged reduction of the defect size over time. As the patient's condition improves and fluid is mobilized, the midline plastic can be reduced in size with a running suture, allowing for fascial edges to return to the midline. Once the defect can no longer be brought together by the plastic sheets, the patient is ready for primary closure. If effectively secured to the fascia with the extensions into the peritoneal cavity to separate the viscera from the abdominal wall, no adhesions will be present at the time of final operation, allowing for easy closure (Fig. 4).

Several additional sequential closure strategies have been employed to address patients with loss of domain. In cases where the viscera extend above the fascia and skin, the abdominal silo promotes reduction in bowel edema and may facilitate closure in patients with severe abdominal compartment syndrome. The silo closure technique has been employed for decades in pediatric surgery as treatment for gastroschisis and omphalocele. The key principle of silo creation involves creating a cylinder that will enclose and elevate the viscera above the abdominal wall. The silo itself may be of a variety of materials, including fashioned plastic, commercial mesh, or a large wound protector that is unfurled and sutured closed at the top opening (Fig. 5). Benefits of the wound protector silo include the absent need for suture fixation to the fascia or skin and an ease of sequential tightening, either with suture or ties, by simply twisting the plastic (Fig. 1D). Wound protectors come in variety of sizes and therefore make them versatile options for silo creation and may be best suited in the diminutive adult or in pediatric cases with shorter overall laparotomy length.

The Wittmann patch utilizes a plastic visceral adhesion barrier, commonly an x-ray cassette drape or bowel bag, followed by plastic sheets of hook-and-loop fasteners sewn to the fascial edges (Fig. 1E). The Velcro-like device can then be opened and closed with relative ease. It may remain in place for several return trips to the operating

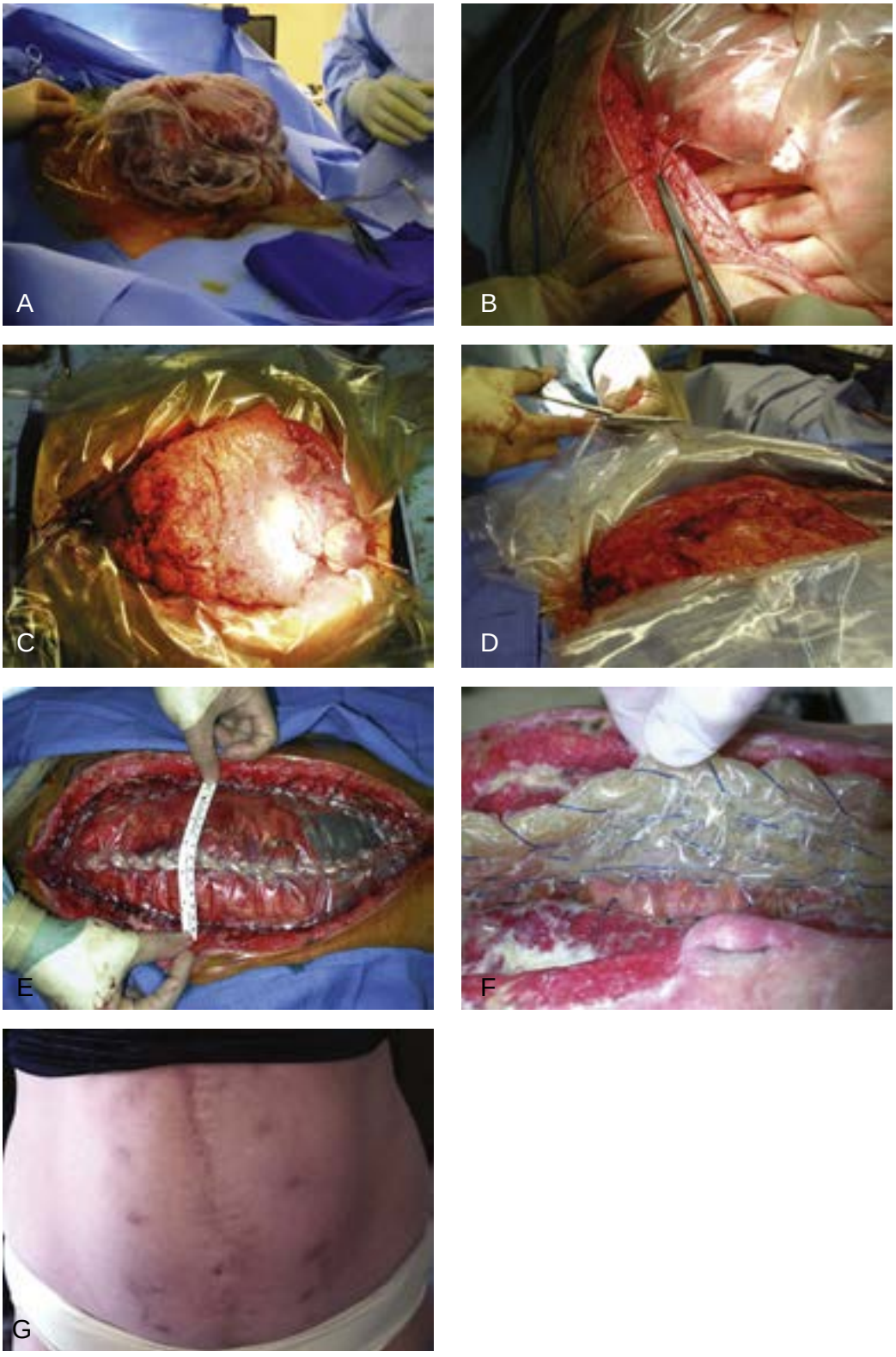


FIG. 4 FASTAC method of sequential closure. **(A)** Initial laparotomy for compartment syndrome with loss of domain. **(B)** A thick plastic drape is folded to 4-fold thickness and the midpoint is sewn to the fascia bilaterally. **(C)** The interior flaps are placed laterally within the gutters, while the medial flaps are utilized to cover the exposed viscera. **(D)** Medial flaps are trimmed to allow enough space for the eviscerated contents. **(E)** Medial plastic flaps are closed in the midline to provide closure. **(F)** Over time, the medial flaps are sequentially tightened by suturing the flaps. This results in fascial advancement and eventual ability to primarily close. **(G)** The patient in Figure 4A at 5 months postclosure. This incremental bedside closure technique allowed for definitive closure at postoperative day 18.

suite, with sequential and progressive closure at each stage. To manage abdominal fluid, a negative pressure system may then safely be applied above the patch. Frequent gauze dressing changes may also be effective at managing effluent but carry a risk of skin irritation and breakdown. The Wittmann patch has shown successful primary closure in up to 80% of patients, with a relatively low complication rate. One potential issue is that, like the Bogotá bag, it is sutured to the fascial edge and therefore results in the need for debridement and tissue loss at a crucial location necessary for successful closure of the midline wound. To avoid potential tissue destruction from suture and tension along the fascial edge, a technique developed at Cook County Hospital anchors the patch to the lateral rectus sheath and distributes tension to the obliques. Dubbed the transabdominal wall traction (TAWT) system, it places transfascial sutures parallel to the lateral rectus border to secure the Wittmann patch in an underlay fashion (Fig. 1F). To protect the skin, padded aluminum strips prevent erosion of the sutures through the abdominal wall. Although limited data exist, the TAWT appears to be effective at achieving primary closure, with reports rates of up to 100%. The TAWT's complexity and time-consuming nature may preclude its use at the initial damage control procedure.

Increasing in complexity, the ABRA (Abdominal Reapproximation Anchor System, CJ Medical, Truro, UK) requires placement of a number of transfascial, elastomeric retention sutures. The elastomers are then sequentially tightened at bedside or during repeated operations to achieve closure (Fig. 1G). The system includes all the necessary components, including a visceral silicone sheet, skin button anchors, and elastomers. To manage the abdominal fluid effluent, a vacuum-assisted wound dressing is often utilized above the elastomers. Several studies show primary fascial closure rates of up to 100% with the ABRA system. Potential issues include skin complications and bowel injury secondary to the elastomers as they may create lines of tension across the viscera. This can be mitigated by a variety of techniques, including tension distribution methods to protect the bowel.



FIG. 5 Silo method of addressing loss of domain. In this case, a 3 L saline bag creates a cylindrical silo to allow visceral edema to subside.

PERIOPERATIVE STRATEGIES FOR SUCCESS

The risk of complications related to temporary abdominal closure increases linearly with the time the abdomen is open. Once the decision is made to leave an abdomen open, focus should be on limiting the duration to definitive closure. Intraoperatively, surgeons should employ precise and expedient techniques and decision making, while limiting operative time and effectively addressing the immediate needs of the patient. Damage control operative and resuscitation techniques, including the use of massive transfusion and enhanced-recovery protocols, will decrease resuscitation needs and shorten time to reaching resuscitation goals. These techniques will thus shorten the time to definitive closure.

When choosing a temporary closure method, surgeons should ensure that none of the viscera are allowed direct contact with the abdominal wall, as this is the key to successful delayed closure (Fig. 6). Failure to properly place the plastic adhesion barrier between the viscera and the abdominal wall will significantly limit the ability to close the abdomen primarily.

It is crucial to employ goal-directed postoperative resuscitation techniques to avoid the prolonged open abdomen. While the use of crystalloid is inevitable, it should be limited. Hypertonic saline has been shown to decrease postoperative inflammatory states after major abdominal surgery but at the cost of hyperchloremia. Judicious use of hypertonic saline works to increase serum osmolarity, which reduces interstitial edema and improves microvascular circulation. These properties result in less overall volume administration, while maintaining end-organ perfusion, leading to quicker resolution of acidosis and earlier return to the operating room.

For the patient with edema and loss of domain, particular attention to fluid balance is required to achieve primary fascial closure. If not in discontinuity, early enteral feeding can help improve osmotic pressure and help promote fluid mobilization. We find when using sequential closing devices, such as the FASTAC, that a daily negative balance of 1500 to 2000 mL allows for reduction in visceral volume and can be used as a guide for when to sequentially tighten the device.

In operations where bowel is left in discontinuity, it is important for the surgeon to recognize the limitations of gastric decompression. Although enteral feeding is contraindicated in cases of discontinuity, nasogastric decompression is limited in its efficacy to decompress the entire proximal bowel. Postpyloric decompression may have better overall results. Without effective decompression, bowel distension risks perforation and contributes to intraperitoneal volume, which decreases likelihood of closure. In all but the rarest cases, patients should have intestinal continuity reestablished within 48 hours of the initial operation. When that is not possible, early ostomy formation may be considered.

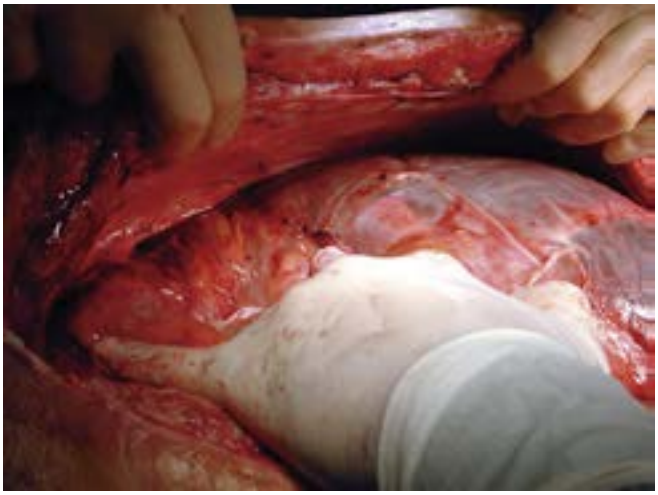


FIG. 6 Following 2 weeks of sequential using the FASTAC method, adhesions are present between loops of intestine and the omentum but none to the peritoneum. Adequate and complete visceral coverage with a plastic barrier is a crucial component to successful primary closure.

SPECIAL CONSIDERATIONS

It is imperative that surgeons do not burn bridges during the initial or subsequent operation leading up to definitive closure. This is especially true when primary closure is not anticipated during the initial hospital stay. In those cases, particular attention should be paid to maintaining abdominal wall integrity and, when necessary, violating it thoughtfully to ensure closure and reconstruction success thereafter.

Ostomies are common in patients who have undergone damage control surgery and can present a challenge. When an ostomy is necessary in the setting of an open abdomen, it should be placed as lateral as possible to avoid the detrimental effect on tissue advancement techniques that may be necessary following patient convalescence. This is contrary to standard practice, which typically places the ostomy within the rectus fascia. It is important to avoid the semilunar line, as large hernias may result. The ostomy can typically be accommodated in the temporary closure or sequential closure method of choice. As in most of the previously discussed techniques, a plastic visceral protection drape should be placed into the bilateral colonic gutters as usual, with the ostomy swept laterally above the plastic to prevent intestinal adhesion to the abdominal wall.

Similarly, when drains are utilized, they should be placed laterally through the obliques to avoid potential issues with tissue advancements during any abdominal wall reconstruction that occurs. Patients requiring an open abdomen often have prolonged courses and long-term needs for enteral nutrition access. It is important to avoid transabdominal feeding tubes in the early stages of the open abdomen and use nasoenteral methods until time of definitive closure.

DEFINITIVE CLOSURE

In most cases, patients should return to the operating room within 48 hours of the initial operation. If at 48 hours the patient is not physiologically corrected, surgeons should give strong consideration for reoperation at that time. In this case, the goal would not be closure but to delineate any causes for continued physiologic derangement. This is especially true for cases in which visceral viability was ever in question or ischemic resections have taken place. If upon reoperation the patient is found to have ongoing ischemia, enterotomy, or other malady, temporary closure techniques should again be used and the clock restarts.

Once patients have improved parameters, such as normalized base deficit, lack of vasopressor requirements, and net negative fluid balances, they should return with plans to primarily close the fascia. However, if upon return to the operating room, the abdomen is unable to be closed primarily, multiple options exist. The first is to return to the intensive care unit and resuscitate to achieve a net negative fluid balance for the next 48 hours, with plans for reoperation and an additional attempt at primary closure. Although this plan's success is dependent upon a variety of factors, surgeons must be acutely aware of not only the resuscitation strategy but also the likelihood of the plan's success. This strategy may result in multiple return trips to the operating suite but should not continue indefinitely, as risk of morbidity and mortality increases with each reoperation.

Creation of subcutaneous flaps may have some utility dependent upon the anatomy of the abdominal wall. In thin patients, release of the skin from the anterior rectus fascia for a distance of 2 to 3 cm may lessen tension and gain up to 2 cm of domain to achieve fascial closure. This is a relatively low-risk and expedient technique for wounds that are nearly able to be primarily closed but overall has limited utility in larger wounds.

The goal should be to primarily close the abdominal fascia and skin. But for patients whose abdomen cannot be closed even after judicious and accurate resuscitation, appropriate timing, and use of the temporary and sequential closure techniques described earlier, several secondary options exist. Skin-only closure may be possible in some instances, with the obvious downside of a planned hernia repair later. Biologic mesh may also be utilized in cases where the skin can be closed overlying the mesh. When the skin cannot be closed, biologics should be avoided as they tend to rapidly degrade with negative pressure dressings and increase risk of fistula formation. Polyglactin (Vicryl, Ethicon Inc., Raritan, New Jersey) and other absorbable synthetic meshes may also be utilized, with or without a polyvinyl alcohol or silicone-based negative pressure dressing initially, followed by secondary intention closure or eventual skin grafting. Absorbable synthetics are relatively inexpensive and typically stand up to negative pressure and dressing changes better than biologic mesh. Permanent mesh has been suggested by some but is not recommended by the authors. We prefer staged primary closure or skin grafting, as permanent mesh is likely to result in chronic infection and fistula formation when used in the open abdomen scenario.

Although tempting, major abdominal wall reconstruction should not occur during the initial hospitalization. Component separation, retrorectus, or transversus abdominis release techniques should be reserved after a period of convalescence. We prefer to wait at least 6 months after wound closure, either by secondary intent and granulation or skin grafting. This will allow the inflammatory process to subside and visceral adhesions to release. When the skin (grafted or otherwise) can be physically separated from the underlying viscera, definitive reconstruction may be undertaken. This can be assessed in clinic by pinching the skin and lifting it from the viscera. Reentry before this time period may result in significant morbidity and mortality rates.

CONCLUSION

When applied in the appropriate clinical setting, the open abdomen can be a lifesaving intervention. Indications for the open abdomen are the same in both adults and children. Negative pressure wound therapy has become the recommended management strategy with higher reported primary closure rates and can be achieved through both commercial and noncommercial methods with similar results. Novel closure techniques should be based on anatomy, treatment

goals, available resources, suspected duration, and cost. The goal of management of the abdomen that will not close (or should not be closed) is definitive primary fascial closure during the index hospitalization. For the few patients in which this cannot be achieved, planned hernia and staged closure is a viable option.

Suggested Readings

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Management of Vascular Injuries

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INTRODUCTION

Vascular injuries are time-sensitive, and a delay in recognition or treatment can have adverse outcomes, including death from bleeding or from extremity or organ ischemia. An initial and often lifesaving sequence of steps for the management of severely injured patients is provided by the American College of Surgeons Advanced Trauma Life Support (ATLS) guidelines. These guidelines provide a structured approach that includes establishing an airway, tending to oxygenation and ventilation (i.e., breathing), gaining intravenous access, and initiating resuscitation (i.e., circulation). In the obviously exsanguinating patient, control of hemorrhage with manual pressure or a tourniquet precedes the usual "ABC" sequence. The surgeon charged with managing the polytrauma patient should be knowledgeable of causative mechanisms, potential concurrent injuries, diagnostic modalities, and anatomic/surgical exposures. The goals of this chapter are threefold: evaluation, diagnosis, and open surgical treatment of vascular injuries.

INITIAL EVALUATION AND PREPARATION

Evaluation and Stabilization

The American College of Surgeons ATLS guidelines are useful in structuring what can otherwise be a chaotic initial management phase of the injured patient. Immediate steps should be taken to stop external bleeding with manual pressure or a tourniquet, and in some instances by placing hemostatic dressing and compressive wrap. Resuscitative thoracotomy with aortic clamping is indicated in a small number of severely shocked patients with evidence of pericardial tamponade, those with left-sided chest trauma, or those who lose vital signs from hemorrhagic shock. Endovascular bleeding control and afterload support can be accomplished with transfemoral placement of a resuscitative endovascular balloon occlusion of the aorta (REBOA) device, which can be done before or at the same time as the patient is being intubated.

The patient should be kept warm to avoid coagulopathy, and for those who have lost a significant amount of blood, a blood product–based transfusion should be initiated (e.g., whole blood or an equal ration of packed red blood cells, platelets, and cryoprecipitate). In most scenarios of hemorrhagic shock, a strategy of permissive hypotension reduces further bleeding. Extremity deformities/fractures should be reduced or "brought to length" as soon as possible and reassessed for perfusion with continuous-wave Doppler imaging and measurement of an injured extremity index.

Diagnosis

Vascular injury can result from a wide range of blunt and penetrating mechanisms, from seemingly minor to obviously severe. As such, there are many different types of injuries and varying clinical presentations that require the surgeon to apply an organized approach using physical examination and diagnostic imaging tools to diagnosis the problem. Blunt injuries resulting from an acceleration-deceleration and/or crush injury to the vessel are typically the result of or accompanied by an orthopedic fractured or dislocation (Table 1). Blunt vascular trauma requires a great deal of kinetic energy or force, often stemming from a motor vehicle crash, a fall, or a crush injury. In contrast, penetrating injuries from a knife, firearm projectile, or other type of fragment are more likely to transect the vessel. Depending on the velocity, penetrating projectiles may also cause significant damage to neighboring vessels and soft tissue structures (i.e., concussive effect).

The diagnosis of a vascular injury starts with documenting a history of the event and performing a physical examination. Understanding the mechanism and recognizing soft versus hard signs of vascular injury (Box 1) will help with quickly ruling in or ruling out vascular injury. The patient should be exposed for examination of the extremities, with an eye directed toward detecting deformities or asymmetry, diminished or absent pulses, and the presence or absence of pallor or reduced capillary refill. Continuous-wave Doppler imaging is an extension of the physical examination that allows for detection and a qualitative assessment of arterial and/or venous signals (e.g., strong biphasic signal, versus a weak and monophasic signal, versus no signal). Used in conjunction with a manual blood pressure cuff, the Doppler imaging allows for calculation of a more objective assessment of perfusion, the *injured extremity index* (also termed the *ankle brachial index for lower extremities*).

TABLE 1 Patterns of Associated Musculoskeletal and Other Structures with Specific Vessel Injury

Vessel	Musculoskeletal	Other
Carotid artery	Cervical spine Mandible, Le Fort II/III facial fracture Skull base	Vertebral vein Carotid artery Trachea, esophagus
Vertebral artery	Cervical spine (vertebral foramina) Skull base	Jugular vein Carotid artery
Subclavian artery or vein	Clavicle Sternum, manubrium	Thoracic duct (left) Brachial plexus, recurrent laryngeal nerve
Axillary artery or vein	Shoulder, proximal humerus	Brachial plexus Axillary nerve
Brachial artery or vein	Midhumerus Biceps, triceps	Ulnar nerve Median nerve
Radial or ulnar artery	Elbow fracture or dislocation Radius, ulna, wrist Forearm and hand flexor tendons	Distal radial nerve (sensation) Ulnar nerve
Thoracic great vessels	Sternum, manubrium	Innominate vein Recurrent laryngeal nerve
Descending aorta	Thoracic spine Posterior rib fracture or dislocation Diaphragm	Esophagus Lung Left subclavian vein (blunt)
Abdominal aorta or vena cava Suprarenal Infrarenal	Thoracic or lumbar spine T12–L2 (with or without spinal cord) L2–sacral fractures	Zone I retroperitoneal hematoma Stomach, transverse colon, pancreas Duodenum, small bowel
Portal vein or superior mesenteric vein	Lumbar spine fracture or ligament injury Rib fracture	Zone IV retroperitoneal hematoma Duodenum (second or third portion), head of pancreas Portal triad (hepatic artery, common bile duct)
Renal artery or vein	Lumbar spine Posterior rib fracture or dislocation	Zone II retroperitoneal hematoma Kidney, proximal ureter, adrenal or gonadal vessels
Iliac vessels	Pelvic fracture Sacral fracture Sacroiliac joint disruption	Zone III retroperitoneal hematoma Cecum (right), sigmoid colon (left) Bladder, ureters
Femoral artery or vein	Pelvic fracture Acetabulum Proximal to mid-femur	Femoral nerve, sciatic nerve (rare) Inguinal ligament Spermatic cord
Popliteal artery or vein	Dislocated or "floating" knee Distal femur, proximal tibia	Tibial nerve Calf compartment syndrome
Tibioperoneal vessels	Tibia, fibula Ankle fracture or dislocation	Tibial nerve, peroneal nerve (foot drop) Calf compartment syndrome

From Cronenwett JL, Johnston KW. *Rutherford's Vascular Surgery.* 8th ed. Philadelphia: Saunders; 2014: 2427.

An injured extremity index of less than 0.9 is abnormal, suggestive of a flow-limiting arterial injury and an indication for further diagnostic evaluation. A widened mediastinum observed on chest x-ray or peritoneal fluid seen on a focused assessment with sonography in trauma (FAST) examination are also soft signs of vascular injury that require additional diagnostic imaging. Duplex ultrasound is a quick and noninvasive modality that is particularly well-suited to detect extremity vascular injury, while contrast-enhanced computed tomography (i.e., CT angiography [CTA]) is optimal for evaluating the torso, junctional, and cervical regions for vascular injury. If the contrast bolus is dosed and timed appropriately, CTA is also useful in detecting most forms of extremity vascular injury (i.e., extremity runoff).

Preparing the Operating Room

Before proceeding to the operating room, the surgeon should be aware of what level of technical support and operative tools are available. It is important to communicate with and alert the anesthesia and operating room teams as to what is expected as far as planned diagnostic and therapeutic procedures, equipment needs, and anticipated resuscitation requirements. If a formal vascular repair/reconstruction is anticipated, the surgical team should be familiar with the operating room setup as well as needed instruments and supplies. Preparation of and coordination with the operating room team are as essential as the anatomic exposure and technical repair of the injured blood vessel(s).

BOX 1 Signs of Vascular Injury

Hard Signs

Pulsatile bleeding
Expanding hematoma
Presence of a thrill or bruit
Evidence of ischemia including the 6 Ps (pain, pallor, paresthesia, poikilothermia, paralysis, pulselessness)

Soft Signs

History of significant hemorrhage
Injury in proximity to a major vessel
Nonexpanding hematoma
Diminished or asymmetric pulses
Unexplained hypotension or tachycardia

Many medical centers have established hybrid operating rooms that combine fixed fluoroscopic imaging units with the traditional capabilities of the "open" operating room. This setup reduces the time and risk associated with transporting an injured patient between an "imaging-only" interventional radiology suite and the operating room. Many of the newer hybrid operating rooms have imaging capability that includes cone-beam CT (CBCT), which can also be used for cursory imaging of the brain, chest, and abdomen. The surgeon, operating room nurses, and surgical technologists should be familiar with open vascular and catheter-based supplies such as wires, sheaths, catheters, and stent grafts.

Endovascular storage areas or "cores" are generally organized in a manner that allows easy access to wires, catheters, stents and stent grafts, balloons, and coils. Recent efforts have been made to define a more focused, trauma-specific inventory to help centers with fewer resources or less experience access and use endovascular approaches more efficiently. As noted, it is important for the surgeon to communicate with the anesthesiology team regarding anticipated blood loss, clamp/ischemic times, and reperfusion. In addition, the patient's condition (hypothermia, coagulopathy, and or severe acidemia) may change the approach to one in which faster damage-control techniques are used rather than performance of more time- and resource-consuming definitive operations. Multiple specialties may be involved in caring for a polytrauma patient with vascular injury, and coordination and sequencing of procedures among these providers is essential to optimize care and outcomes.

Once on the operating room table and asleep, the patient should be prepped widely in anticipation of the need to achieve vascular exposure, possibly through an incision that is remote from the site of injury, and the potential need for routing a bypass through extraanatomic locations. The injured extremity should be prepped circumferentially, most often to include the foot and toes, and the contralateral limb should be prepped in case there is a need to harvest the saphenous vein to use as a vascular conduit.

MANAGEMENT PRINCIPLES

Damage Control

Vessel Ligation

Although the focus of this chapter is repair and restoration of perfusion, ligation of vascular injury is a useful damage-control maneuver to consider for some severe patterns of injury. The redundancy of blood flow to certain areas of the body allows surgeons in austere settings or those treating severely compromised patients to quickly ligate a bleeding vessel instead of spending operative time and resources pursuing repair. Ligation is better tolerated with smaller, more distal arterial injuries, such as tibial and forearm level injuries, and with injuries to distal branch vessels of the mesentery and external carotid. Patients will also tolerate ligation of many types of venous injuries, especially those that are smaller, more distal, and part of a redundant circulation.

The consequences of vascular ligation can be quickly assessed in the operating room with the use of continuous-wave Doppler imaging, which in many cases will detect a decreased arterial signal indicating a relatively ischemic but still viable extremity or end organ. If ligation renders an extremity or end organ without an arterial Doppler signal, then the surgeon and anesthesiology team will need to consider whether pursuing placement of a temporary shunt or performing a more extensive vascular repair is indicated on a case-by-case basis. Ligation of proximal extremity vascular injuries, even those likely to lead to an amputation, may be the better choice in patients whose injury severity and or physiologic derangements make vascular repair unwise.

Temporary Vascular Shunts

Temporary vascular shunts can be used instead of ligation to quickly restore perfusion when immediate repair is not possible or advisable. Their use is standard during carotid artery revascularization; however, the use of shunts has been popularized and expanded for damage control during vascular injury. Vascular shunts can remain patent without systemic anticoagulation for 4 to 6 hours, especially when placed in more proximal, high-flow vessels. Patency for longer periods (24 hours or more) has been reported, but the incidence of thrombotic complications, such as embolization and occlusion, increases as shunts are in place beyond the 4- to 6-hour mark. Temporary shunts are useful in the management of arterial and venous injuries, although the inherently low flow state of the venous circulation makes shunt thrombosis more likely when used as a bridge for these types of injuries. Overall, the use of temporary shunts has allowed for staged vascular repair and a reduced need for immediate ligation, and it has extended the surgeon's ability to save an injured/ischemic limb or organ.

Several types of shunts are available in different lengths and configurations that allow them to be secured within the vessel (Table 2). These devices can be considered as short "in-line" shunts that lay inside the vessel or its original location (i.e., in situ) or as longer "looped" shunts that form outside of the vessel's anatomic course. Some shunts have balloons or bulbs on their ends to facilitate positioning and stabilization, while others can be secured with specialized vascular clamps (i.e., "shunt clamps"). If a commercially supplied shunt is not available, one can use other types of sterile tubing of appropriate diameter as a substitute. When using a modified chest or nasogastric tube as a vascular shunt, care should be taken to avoid injuring the vessel with an inappropriately sized shunt or with rough, freshly cut edges.

Before shunt removal, one should perform more proximal and distal dissection in anticipation of needing to debride or remove several centimeters of the vessel edge such that the repair is performed to a normal/uninjured segment. Care should also be taken to remove thrombus from the proximal and distal components of the injured vessel by releasing clamps and allowing forebleeding and backbleeding. Heparinized saline solution should be used to flush the vessel surface and instilled into the inflow and outflow vessels. One should have a low threshold to use a Fogarty thrombectomy catheter to confirm thorough thrombus removal after shunt removal before performing the vascular repair and restoring flow.

Balloon Occlusion

In some scenarios, it may not be immediately possible to establish sufficient operative exposure that will allow for positioning and placement of atraumatic vascular clamps. In these situations, application of direct manual pressure or placement of pressure with a surgical instrument such as a sponge stick or smaller Kittner blunt dissecting device may allow one to stop the bleeding long enough to achieve more complete operative exposure and clamping. Placement and inflation of a Fogarty catheter (Edwards Lifesciences, Irvine, CA) can also be used to temporize inflow and backbleeding until more

TABLE 2 Shunt Types

Manufacturer	Type	Features	Composition	Sizes
Bard	Straight	± bevel tip; ± side holes; ± balloon tip	Polyvinyl chloride (± latex balloon)	Diameter: 9Fr (balloon), 10Fr, 12Fr, 14Fr, 16Fr
	Javid	Tapered ± loop		Length: 13 cm
	Brener	Tapered with side arm		
	Burbank	Tapered; depth markings		
	Cardinal	Argyle ± loop; kit with four sizes	Polyvinyl chloride	Diameter: 8Fr, 10Fr, 12Fr, 14Fr Length: 11 inches (loop), 6 inches (straight)
Integra	Sundt	± loop; steel reinforcement ± nonreinforced segment; cone-shaped ends	Silicone elastomer	Diameter: 3 × 4 mm, 3 × 5 mm, 4 × 5 mm Length: 30 cm (loop), 10 cm (straight)
LeMaitre	Pruitt	F3 ± T-port; color coding; depth marks; balloon with safety sheath; kit with four sizes	Polyurethane (latex balloon)	Diameter: 8Fr, 9Fr, 10Fr, 12Fr, 14Fr Length: 31 cm (outlying), 15 cm (inlying), 13 cm (inlying)

From Rasmussen TE, Tai NR. *Rich's Vascular Trauma*. 3rd ed. Philadelphia: Elsevier, 2016. Data from manufacturer websites:
www.bard.pv.com/_vascular/product.php=37.
www.kendall-ltp.com/Kendall-LTP/pageBuilder.aspx?topicID=67419&breadcrumbs=81035:0,67418:0.
integralive.com/Neurosurgeon/Neurosurgeon-Product-Detail.asp.
www.lemaitre.com/medical_shunts.asp.

complete vascular isolation can be completed. Fogarty catheters are sized from 2Fr to 7Fr, which correspond to balloon diameters from 2 to 14 mm. When using the Fogarty catheter for bleeding control, a three-way stopcock should be placed on the end of the catheter to allow the balloon to remain in place once the small tuberculin syringe has inflated the balloon. Use of sequentially smaller and more pinpoint manual occlusion of the bleeding site should help the surgeon visualize, expose, isolate, and eventually repair or ligate the injured vessel.

Balloons can also be placed using traditional endovascular means (i.e., transfemoral access and sheath placement) to attain proximal arterial control. Placement of endovascular balloons above (transjugular) and below (transfemoral) has also been described to isolate large venous (i.e., vena cava) injuries and facilitate repair. Large-diameter over-the-wire balloon catheters such as Coda (Cook Medical, Bloomington, IN), Reliant (Medtronic, Minneapolis, MN), and GORE Molding & Occlusion Balloon (GORE, Newark, DE) can be used for occlusion of large vessels such as the aorta or vena cava. However, these devices require large sheath access, a long leading 0.035-inch wire, high-quality fluoroscopic imaging, and an experienced endovascular skill set. Lower-profile endovascular balloon occlusion catheters such as the ER-REBOA (Prytime Medical, Boerne, TX) have been developed to facilitate placement in emergent settings. This device has a trauma-specific indication and features that eliminate the need for fluoroscopic-guided placement and a separate guidewire.

Definitive Repair

The following sections provide a brief account of vascular injury in the extremities and the cervical and torso regions. Surgeons should be familiar with the incisions and retractor positions needed to access vessels in these various anatomic regions. Although the incisions and operative exposures are different, the technical principles of vascular exposure, dissection, control, and repair or bypass are similar whether the injured vessel is in the extremity, neck, or torso.

Vascular injury should be approached by ample surgical incision(s) that allow exposure of anatomic structures and vessels above and below the injury site with the intent to obtain proximal and distal control. There are cases when exposure of the injury directly through the wound is acceptable, but this approach is best for less severe forms of trauma and cases in which thrombosis and not hemorrhage is the problem. Regardless, of the operative exposure, one should anticipate the need to control bleeding with vascular forceps, atraumatic clamps, or a finger or Kittner device until proximal and distal control can be accomplished.

Once inflow and outflow are controlled, one should assess the segment by fully opening and removing injured and nonviable vessel wall and thrombus. Debridement to healthy vessel wall is especially important after temporary vascular shunt removal in cases in which the shunt has been secured with heavy ties. Although thrombus at the injury site may be removed with forceps and saline flush, a Fogarty thromboembolectomy catheter should be passed proximal and distal to ensure that more extensive, remote clot is removed from the inflow and outflow vessels. If the patient's overall injury pattern permits, intravenous heparin should be given. Whether or not systemic anticoagulation is used, heparinized saline (1000 units/L) should be flushed on the surface of the newly debrided and healthy vessel wall and infused into the inflow and outflow circulations (i.e., local and regional heparin use).

Small focal injuries can be repaired primarily with permanent, monofilament suture if the lumen of the vessel is not compromised. Larger injuries require extension of the arteriotomy for inspection of endpoints and patch angioplasty repair. In the case of some sharp lacerations the debrided vessel, ends can be mobilized to relax tension and allow an end-to-end anastomosis. Most often, the extent of injury results in the need to remove or debride a length of vessel. In these cases, restoration of flow should be established with an in-situ interposition graft sewn end-to-end to healthy edges of the proximal and distal vessel. Multiple conduits can be used for vascular reconstruction in the appropriate setting. Depending on factors such as the anatomic location of the injury, degree of wound contamination, and surgeon preference, a bypass can be performed to route flow around the injury zone. In these cases, the anastomoses may be performed to the uninjured inflow and outflow vessels using an end-to-side configuration. As noted, the saphenous vein is the preferred conduit

and can be used in the reverse or nonreverse configuration if the valves are lysed.

Lower Extremity

The femoral vessels emerge from the pelvis under the inguinal ligament and into the femoral canal, medial to the femoral nerve. The common, deep, and proximal superficial femoral arteries are approached with anterior longitudinal incisions, often using identification of the inguinal ligament as a first and orienting step in the dissection. A more lateral anterior incision on the thigh can be made to isolate the second and third portions of the deep femoral artery, whereas the mid and distal superficial femoral arteries should be approached from medial incisions on the thigh anterior to or above the sartorius muscle. Similarly, the above and below knee popliteal spaces with corresponding vessels are most often approached from a medial exposure (Fig. 1). This will require hip external rotation with alternating knee extension and flexion using a small soft bump above the knee joint. Unstable concomitant fracture should be addressed simultaneously in coordination with orthopedic surgery. In rare cases, a posterior approach to the popliteal artery can be used to isolate and repair an injury. The medial approach is also used to expose the posterior tibial and peroneal vessels in the posterior deep compartment of the leg, whereas the anterior tibial artery is approached from a more lateral leg incision and dissection between the extensor muscles of the anterior compartment.

The negative consequences of ligating the femoral or popliteal artery in the setting of trauma are such that establishing perfusion with a repair or bypass is the preferred approach. In contrast, the redundant nature of the tibial and peroneal arteries is such that only one needs to be patent to maintain viability of the foot and toes. Although the premise of "more perfusion is better" is true, one need not spend time attempting to reconstruct a small tibial or peroneal artery injury if one or two of the remaining are uninjured tibial arteries and patent. As noted, continuous-wave Doppler imaging is especially useful in these situations to ascertain the status of the other tibial vessels and overall perfusion to the foot and toes.

Fasciotomy should be considered following repair of lower-extremity vascular injury. A longitudinal incision on the medial leg is used to expose and release the posterior superficial and posterior deep compartments, while a similar incision on the lateral leg is used to decompress the anterior and lateral compartments. To ensure a complete fasciotomy, one should clearly identify and divide (i.e., "take down") the fascia attached to the medial edge of the tibia that covers the posterior deep compartment (medial exposure) and visualize the intermuscular septum that divides the anterior compartment from the lateral compartment through the lateral exposure. Prophylactic fasciotomy is recommended in younger patients and those with greater than 3 hours of ischemia or concomitant crush injury or fracture. A preemptive fasciotomy should also be considered in patients who will remain intubated or sedated and unable to respond to serial physical examinations of the leg. Surgeons should also have a low threshold to perform a fasciotomy if the patient will be transferred to a different facility or echelon of care following the index operation.



FIG. 1 Distal comminuted fracture of the femur associated with distal superficial femoral and popliteal artery and vein disruption. Bypass of both the artery and vein was facilitated through a medial thigh and leg incision and tunneled anatomically behind the knee *(not shown)*. Coordination with orthopedic surgery is essential for management of concomitant bony injuries.

Upper Extremity

The axillary artery emerges from the thoracic outlet at the lateral margin of the first rib and extends to the lateral edge of the teres major muscle. Proximal control may be obtained using a supraclavicular approach to the subclavian artery or an infraclavicular incision through the clavipectoral facia deep to the pectoralis minor, which affords a more distal exposure. Disarticulation or partial resection of the clavicle allows more complete exposure and control of the artery, although this maneuver can result in chronic pain and instability of the collar bone. One should be mindful that proximal control of the axillosubclavian arterial segment can be obtained using balloon occlusion if the patient is relatively stable and imaging and endovascular equipment are available. While exposing axillary vessels, one should be mindful to avoid injury to the cords and peripheral nerves of the brachial plexus, which are located lateral and posterior to the axillary vessels.

The brachial artery begins at the lower margin of the teres major muscle and extends through the anterior compartment of the arm alongside the median nerve (Fig. 2). The basilic and brachial veins take a similar course and are often injured along with the artery. Exposure is performed through a longitudinal incision inferior to the biceps, an approach that can be extended from the axilla to the antecubital fossa. If the artery is injured (or clamped) distal to the origin of deep brachial, some degree of perfusion to the forearm and hand will be maintained via collateral circulation. As with other scenarios of vascular trauma, continuous-wave Doppler imaging can be used to assess perfusion distal to the brachial artery injury or clamp site to estimate perfusion and viability.

The brachial artery gives rise to the radial, ulnar, and interosseus arteries near or immediately distal to the antecubital fossa, which can be exposed by curving the longitudinal incision into a short transverse incision in this location. The proximal radial and ulnar arteries can be exposed through this "lazy S" incision in the antecubital fossa and more distally by a longitudinal incision on the palmar aspect of the forearm (see Fig. 2). The ulnar is usually deeper and is commonly crossed by the median nerve. Like vascular injuries of the leg, it is only necessary to have one axial artery patent to maintain viability of the hand and fingers. If both the radial and ulnar arteries are injured, repair or reconstruction of the larger, dominant vessel (usually the ulnar) should be performed. Also, like injuries of the leg, distal venous injuries of the forearm can be ligated.

Cervical Region

The management of cervical vascular injury is approached differently depending on the suspected location in relation to one of three anterior zones (Fig. 3). The most proximal zone (zone I) extends from the thoracic outlet to the cricoid cartilage. The middle or second zone is between the cricoid cartilage and the angle of the mandible, and zone III is most distal extending above the angle of the mandible to the skull base. Carotid and vertebral injuries can occur, and contrast CT imaging is the diagnostic choice for all three zones. However, if treatment is needed, vascular injuries in zones 1 and 3

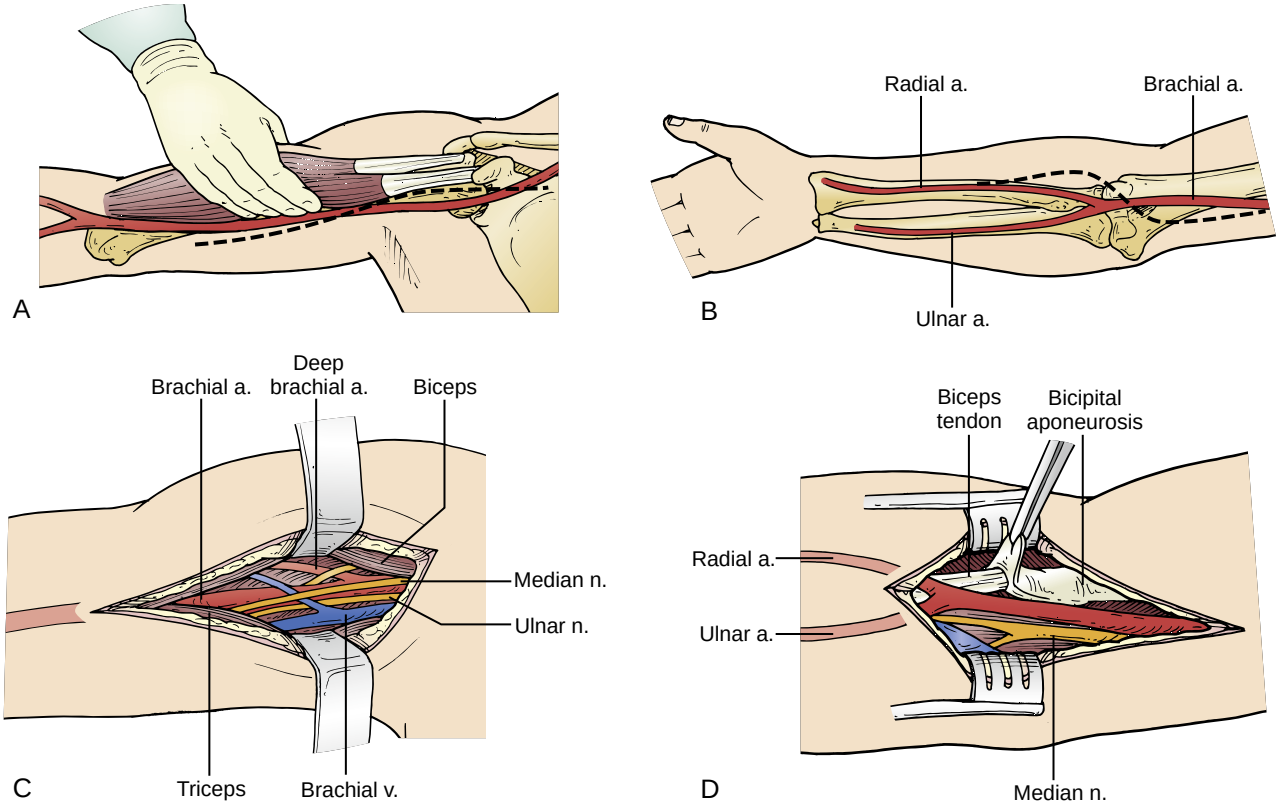


FIG. 2 Exposure of the brachial artery. **(A)** The incision for the brachial artery should lie just inferior to the biceps muscle. **(B)** A " lazy S" incision can be used to traverse the antecubital fossa. **(C–D)** Note the close association between the brachial artery in the median nerve. *(From Cronenwett JL, Johnston KW.* Rutherford's Vascular Surgery. *8th ed. Philadelphia: Saunders; 2014: 2493.)*

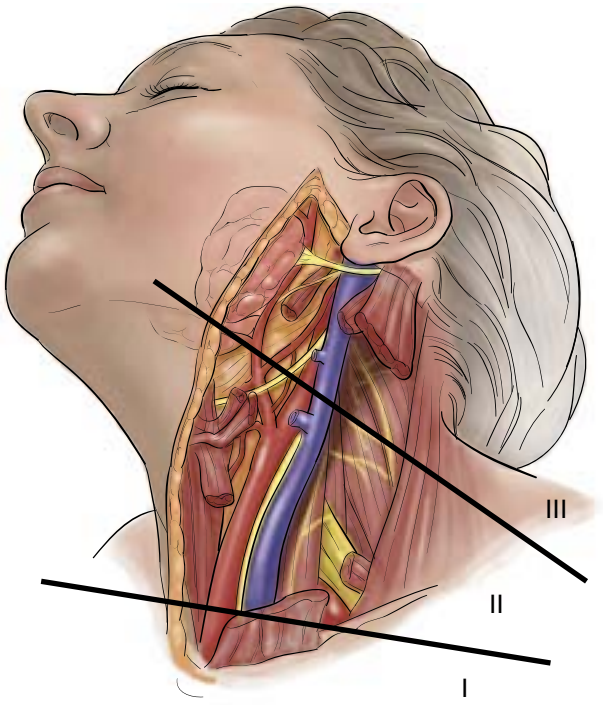


FIG. 3 Carotid zones of the neck. Zone I extends from the sternal notch to the cricoid cartilage. Zone II extends from the cricoid cartilage to the angle of the mandible. Zone III extends from the angle of the mandible to the base of the skull. *(From Rasmussen TE, Tai NR.* Rich's Vascular Trauma. *3rd ed. Philadelphia: Elsevier; 2016.)*

are more commonly managed with endovascular techniques (e.g., stent grafts, coils) than injuries to vessels in zone II.

Traditional teaching has been that one should explore all penetrating zone II injuries, whereas in the absence of hard signs, injuries in zones 1 and 3 can be observed. With the ready availability of CT imaging, this paradigm is changing such that in the absence of hard signs of vascular injury, one can now manage penetrating zone II wounds without an operation. Regardless of injury zone, in the setting of penetrating cervical trauma, one must be vigilant about the potential for and workup of cranial nerve and/or aerodigestive injuries in this region.

Zone I vascular injuries with signs of bleeding indicate damage to the proximal common carotid or another arch vessel. In this case, if an open approach is selected, one should use a median sternotomy to identify and control the proximal aspects of the great vessels. A partial sternotomy can be performed by dividing the superiormost aspect of the manubrium beginning in the sternal notch. This hemisternotomy can be extended laterally on either side in the fourth or fifth intercostal spaced and/or cephalad along the anterior sternocleidomastoid muscle to facilitate proximal and distal exposure, respectively (Fig. 4). The cervical incision allows one to identify structures in the zone II carotid sheath. In rare cases in which there are zone II injuries on both sides, a collar incision that crosses the midline can be used to control the structures of both carotid sheaths. Vascular injuries in the distal zone III are more difficult to expose and often require nasotracheal intubation, anterior subluxation of the mandible, and/or mandibulotomy.

Focal partial-thickness injuries to the common and internal carotid arteries can be repaired with a patch angioplasty technique using vein or bovine pericardium. If a more extensive repair is needed, an interposition graft should be fashioned using an autologous conduit such as saphenous vein if obtained quickly and is of

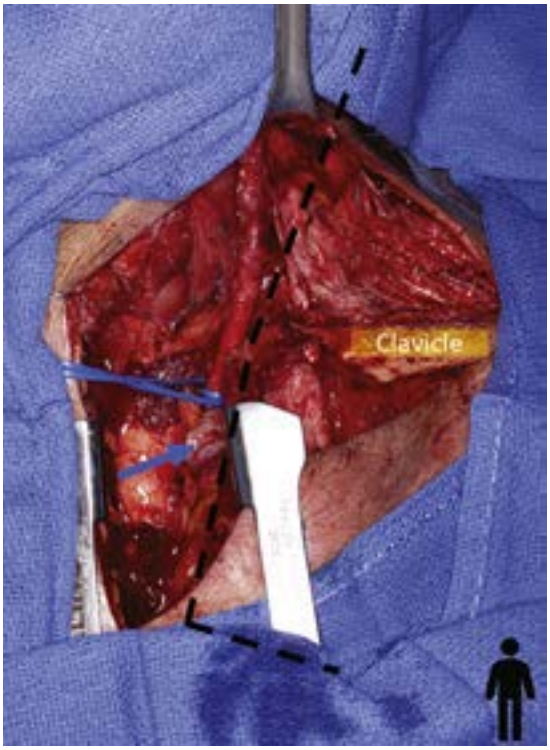


FIG. 4 Exposure of the left carotid artery with a left lateral cervical incision and a sternotomy for proximal control *(dashed lines tracing surgical incisions)*. The innominate vein *(blue arrow)* is preserved and circumferentially mobilized to expose the origin of the left carotid artery *(encircled with a vessel loop)*.

good quality and caliber. If vein is not available and the wound is not overly contaminated, one can use a properly sized synthetic conduit such as Dacron or expanded polytetrafluoroethylene (ePTFE).

To maintain perfusion to the ipsilateral brain and reduce the risk of stroke, repair is the preferred approach for injuries to the internal carotid artery. Anticoagulation is important during repair of carotid injuries, and systemic heparin should be used if possible. If intravenous heparin cannot be used because of concomitant injuries, one should use heparinized saline as previously described as a local and regional adjunct to prevent platelet aggregation and clot formation. Frequent backbleeding from the internal carotid artery can also be used to prevent thrombus accumulation. External carotid injuries should be ligated as a matter of expediency, whereas repair or interposition graft replacement of an injured internal jugular vein is preferred to prevent venous hypertension in the brain, especially if both jugulars are injured. If time or the patient's condition does not permit repair, the jugular vein may be ligated as a damage-control maneuver.

Vertebral artery injuries most often occur in conjunction with fracture of one or more cervical transverse processes. Exposure of the proximal vertebral artery (V1 segment) proceeds like that of the common carotid, with a slightly more lateral extent. Open operative exposure of the foraminal or extradural portions of the vertebral artery (V2 and V3 segments) is more challenging and may require compression of the vessel against or within the transverse foramina. Care must be taken to avoid injury to the phrenic nerve and thoracic duct during exposure of the proximal vertebral artery, and a closed-suction drain should be left in place if one suspects a ductal or esophageal injury.

The vertebral artery is small and difficult to expose and repair; therefore, endovascular techniques are preferred in the management of this injury pattern. If one does explore or encounter a proximal (V1 segment) injury, primary repair can be attempted, or the artery can be ligated at its origin from the subclavian and transposed onto the common carotid to maintain antegrade perfusion. The redundant nature of posterior brain circulation is such that ligation is usually tolerated without significant morbidity. For this reason, one can have a low threshold to ligate a vertebral artery injury if the patient's condition or technical limitations do not permit repair. In these cases, one should be mindful of the size and patency of the contralateral vertebral and carotids before ligating the injury. It may also be useful to maintain the patient's blood pressure at a higher than normal level at the time of ligation and during the first postoperative day or two to maximize perfusion to the brain.

The term *blunt cerebrovascular injury* (BCVI) applies to carotid and vertebral arteries, and its diagnosis is dependent on recognition of concomitant injuries, clinical suspicion, and appropriate imaging. Treatment of BCVI is dictated by injury severity as defined by Biffl's grading score (Table 3) as well as local institutional protocols. Low-grade injuries (grades 1 and 2) are generally managed nonoperatively with antithrombotic or antiplatelet agents and surveillance imaging, whereas grade 3 injuries more commonly require some form of interventional treatment, most commonly an endovascular approach (Fig. 5).

Torso

Vascular injuries within the torso (chest, abdomen, and pelvis) often present as noncompressible hemorrhage and are associated with a high rate of mortality. Management is dictated by the patient's hemodynamic status and findings on physical examination and imaging studies. Patients with hemodynamic collapse or witnessed cardiac arrest need surgical exploration such as resuscitative thoracotomy with aortic cross-clamping. Penetrating injury to the thoracic cavity can cause injury to the aortic arch and branch vessel. Median sternotomy is the most versatile for exploring the arch and great vessels, with the exception of the proximal left subclavian artery, which is better accessed from a fourth-interspace anterolateral thoracotomy performed through the inframammary crease. To optimally expose the ascending aortic arch via the median sternotomy, one may choose to ligate the overlying innominate. The left anterolateral thoracotomy approach can be extended across the sternum for a clamshell thoracotomy if one requires access to the right chest (Fig. 6).

Resuscitative left anterolateral thoracotomy facilitates repair of most cardiac injuries and affords manual cardiac massage if needed. In rare instances in which one anticipates the need for hypothermic cardiac arrest, the cardiac surgery team should be alerted as soon as possible. The descending thoracic aorta and pulmonary hilum can also be approached via a left anterolateral thoracotomy. If hemodynamically stable, the patient may be placed in the right lateral decubitus position and a more formal left posterior lateral thoracotomy performed for more inferior injuries or those to the pulmonary parenchyma. Injury to the large veins of the mediastinum or pulmonary hilum should be repaired or patched if possible.

Management of blunt thoracic aortic trauma is dictated by injury grade based on contrast CT imaging. Most commonly, the aortic tear occurs in the descending portion at or immediately distal to the ligamentum arteriosum. Injuries range from mild forms such as a small intimal tear (grade 1) or a confined intramural hematoma (grade 2) to more severe forms such as a contained pseudoaneurysm (grade 3) or a free aortic rupture (grade 4). Urgent repair is indicated for grade 3 and 4 injuries, a maneuver that is now most frequently accomplished by placement of an endovascular stent-graft (Fig. 7). Patients with grade 1 and 2 injuries should be admitted to the intensive care unit for monitoring of blood pressure and heart rate to prevent episodes of high shear stress that will extend or worsen the injury. Re-imaging should be performed for these patients within the first few days after injury to re-evaluate the injury and check for progression and the need for endovascular repair.

TABLE 3 Screening Criteria for Blunt Cerebrovascular Injury

	Denver Criteria*	Memphis Criteria†	Modified Criteria‡ (odds ratio)
Signs and symptoms	Arterial hemorrhage or expanding hematoma	Neurologic examination findings not explained by brain imaging	GCS score <6 (1.98)
	Cervical bruit	Horner's syndrome	
	Neurologic examination findings inconsistent with head CT findings	Neck soft tissue injury (seat belt sign, hanging, or hematoma)	
	Stroke on follow-up head CT		
	Focal neurologic deficit		
Risk factors	Le Fort II or III fracture pattern	Le Fort II or III fracture pattern	Le Fort II or III fracture pattern (3.7)
	Basilar skull fracture with involvement of the carotid canal	Basilar skull fracture with involvement of the carotid canal	Petrous fracture (2.64)
	Diffuse axonal injury with GCS score <6	Cervical spine fracture	Diffuse axonal injury (3.09)
	Cervical spine fracture		
	Near-hanging with anoxic brain injury		

*Modified from Biffl WL, Moore EE, Ryu RK, et al. The unrecognized epidemic of blunt carotid arterial injuries: early diagnosis improves neurologic outcome. *Ann Surg*. 1998;228(4):462–470.
†Modified from Miller PR, Fabian TC, Croce MA, et al. Prospective screening for blunt cerebrovascular injuries: analysis of diagnostic modalities and outcomes. *Ann Surg*. 2002;236(3):386–395.
‡Modified from Biffl WL, Moore EE, Offner PJ, et al. Optimizing screening for blunt cerebrovascular injuries. *Am J Surg*. 1999;178(6):517–522.
CT, Computed tomography scan; *GCS*, Glasgow Coma Scale.
From Cronenwett JL, Johnston KW. *Rutherford's Vascular Surgery*. 8th ed. Philadelphia: Saunders; 2014: 2442.

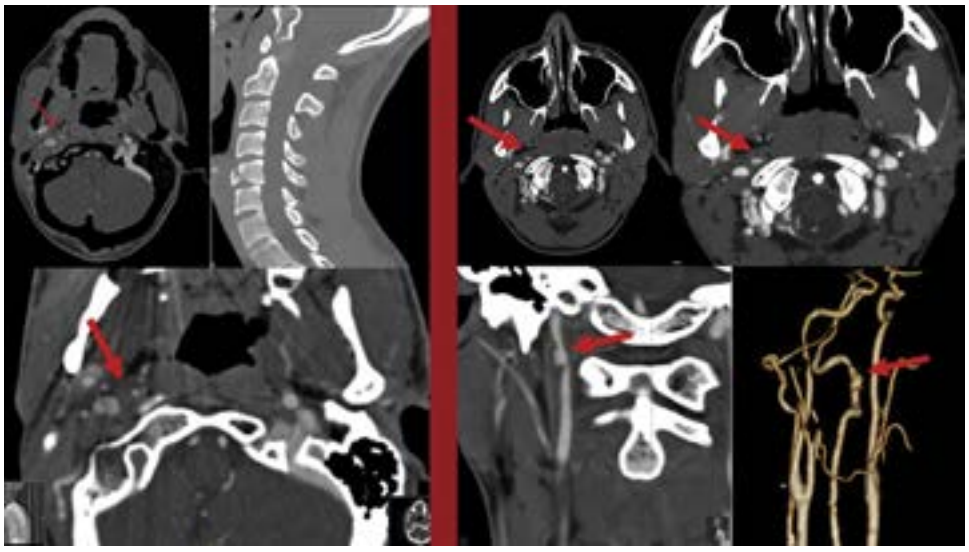


FIG. 5 CT angiogram images *to the left of the red bar* demonstrate a low-grade blunt cerebrovascular injury involving the right internal carotid artery (dissection without luminal compromise indicated by the *red arrows*) associated with a cervical spine fracture. *To the right of the red bar,* this injury evolved over several days to grade 3, a pseudoaneurysm.

Abdomen and Pelvis

In general terms, injuries resulting in class III or IV shock that are associated with a penetrating wound(s) or evidence of intraperitoneal blood on a FAST examination are best managed with emergency laparotomy. Refinements have been made such that some forms of vascular disruption associated with solid organ injury and pelvic fracture can be effectively managed with nonoperative means leaning heavily on modern, blood product–based resuscitation techniques (e.g., damage-control resuscitation). Guidelines are maintained by civilian organizations and the military's trauma system to assist surgeons in navigating the various nonoperative scenarios used to manage abdominal and pelvic bleeding.

Laparotomy for hemoperitoneum is performed through a generous midline incision, quickly placing sponges in the four quadrants of the abdomen to compress and stem bleeding. The falciform can be ligated and divided so a retractor system can be placed under the ribs of the inferior thoracic aperture to open the costal margin for

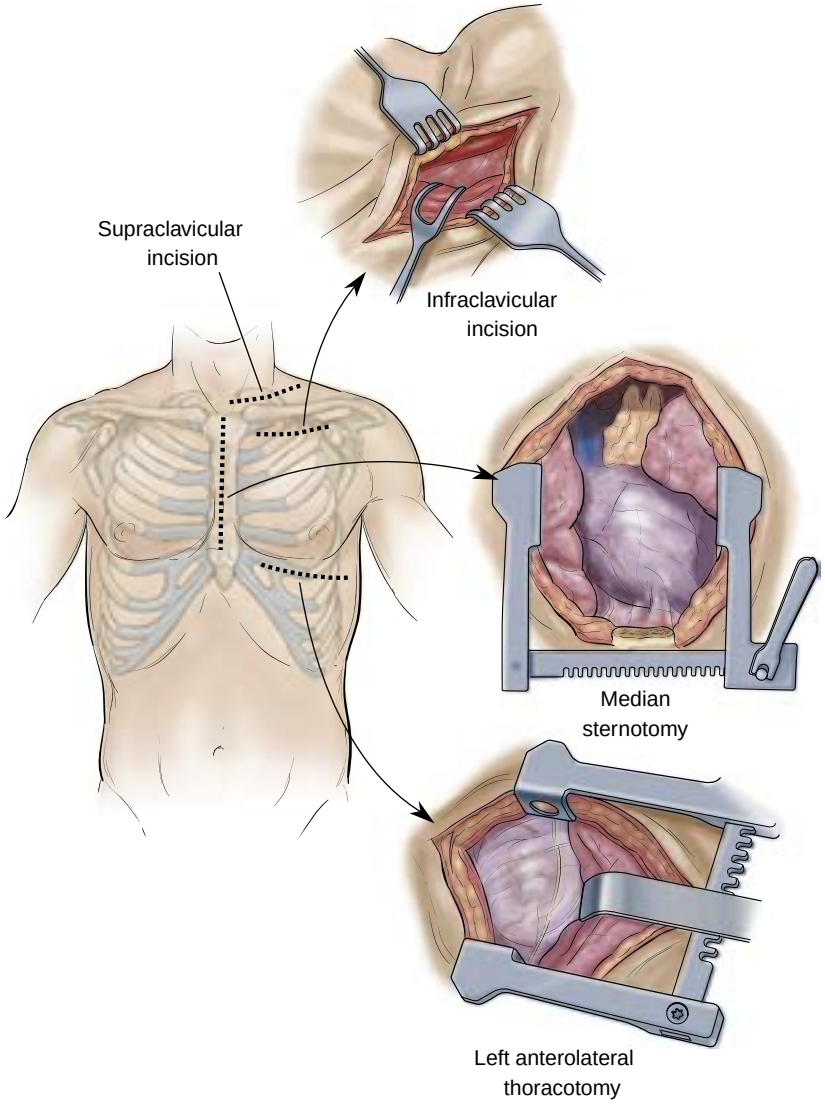


FIG. 6 A left high anterolateral thoracotomy extended across the sternum allows expeditious access to the thoracic cavity. *(From Rasmussen TE, Tai NR.* Rich's Vascular Trauma. *3rd ed. Philadelphia: Elsevier; 2016.)*

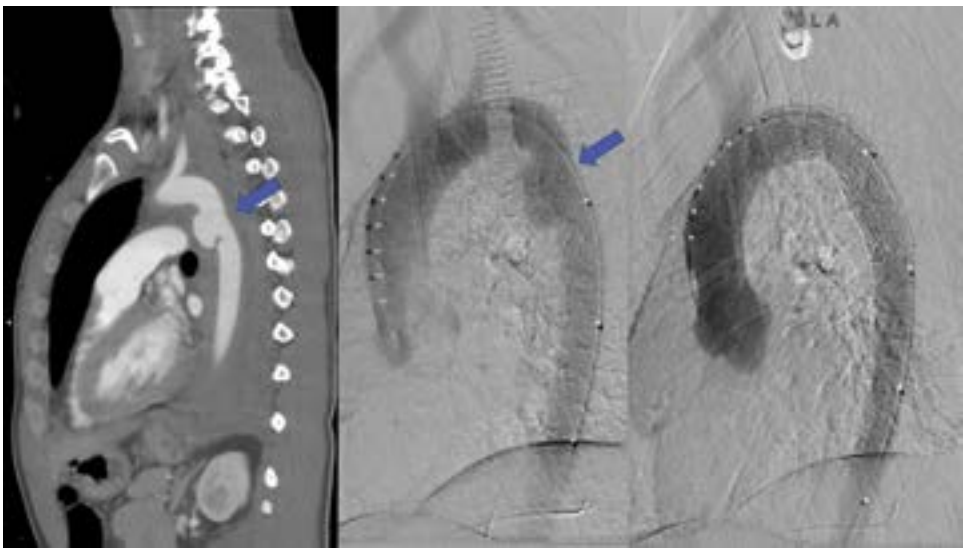


FIG. 7 *Left to right:* Grade 3 blunt cerebrovascular injury *(blue arrow)* diagnosed on CT angiography and repaired with an endovascular thoracic stent graft. The final image *(right)* demonstrates placement of a stent graft covering the left subclavian artery with no filling of the pseudoaneurysm.

thorough exposure. These maneuvers should be performed in communication with the anesthesia team to optimize the timing of blood product and pharmacologic resuscitation and avoid ill-timed blood loss and needless variations in pressure. As the abdominal packs are sequentially removed, one will identify the location(s) of bleeding and begin to make decisions about how best to approach, control, and ultimately manage the problem.

Vascular disruption and bleeding from the spleen is first controlled by manual pressure to assess the extent of injury. Small, low-grade injuries can be managed without removing the organ, whereas higher-grade injuries, those in older patients, and those associated with other severe injuries require splenectomy. Similarly, vascular disruption within the liver parenchyma is managed with compression that requires division of the coronary and triangular ligaments to free the organ from diaphragmatic attachments and allow its segments to be pressed together. Unlike the spleen, resection of a liver segment(s) to control bleeding is rare and should be avoided in favor of techniques to control the liver circulation (e.g., portal isolation and Pringle maneuver) and manually compress the parenchyma.

Intraperitoneal bleeding from larger axial or mesenteric vessels should be initially controlled manually until the inflow and outflow vessel(s) can be identified and dissected for more precise exposure and control. Small injuries to vessels in the distal portions of the mesentery can be ligated, whereas injuries to proximal mesenteric vessels should be more completely dissected and considered for primary repair or, for more extensive injuries, reconstruction using patch angioplasty or interposition graft placement.

Retroperitoneal bleeding is considered in three zones and requires different operative approaches depending on location and whether the hematoma is expanding (Fig. 8). Zone I hematomas are central and indicate bleeding from the aorta, vena cava, or the proximal portion of their branch vessels. As a rule, all zone I hematomas should be explored, a maneuver best accomplished with a left medial visceral rotation or Mattox maneuver to optimize exposure and control the aorta and its visceral branches (Fig. 9A). An inframesocolic exposure can be used if the zone I hematoma is small and confined to the infrarenal portion. If the hematoma is on the right side and appears to be from the vena cava, the Cattell-Braasch maneuver (right medial visceral rotation) should be performed to elevate and retract the entire right colon cephalad to expose the infrarenal and juxtarenal vena cava (Fig. 9B). Caval injuries should be repaired primarily if possible. However, if primary repair will cause a greater than 30% narrowing of the lumen, the vena cava should be repaired with patch angioplasty or rarely, in the setting of trauma, an interposition graft using a large-diameter prosthetic conduit (Fig. 10). Ligation of the infrarenal vena cava is an acceptable damage-control maneuver but should be coordinated with anesthesia team that can start or maintain resuscitation through large-bore resuscitation lines above the diaphragm.

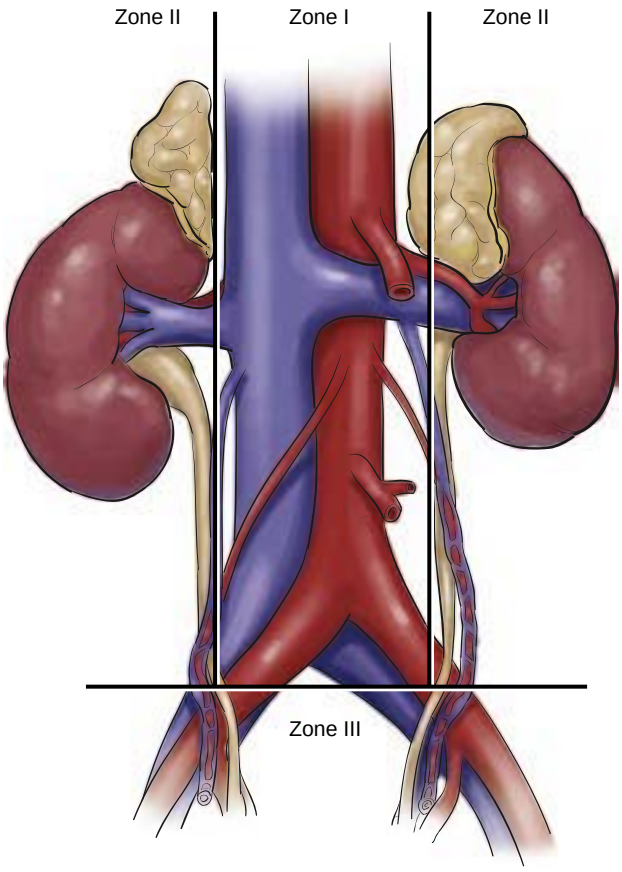


FIG. 8 Retroperitoneal zones and major vasculature within each zone. *(From Rasmussen TE, Tai NR.* Rich's Vascular Trauma. *3rd ed. Philadelphia: Elsevier; 2016.)*

Zone II hematomas are those in the lateral gutters and should be observed unless expanding or associated with major penetrating injury. This includes bleeding from injuries to the retrohepatic vena cava. If explored, vascular disruption from the kidney parenchyma or hilum is managed like that encountered with splenic injuries. For small, low-grade kidney injuries, one should use manual compression, electrocautery, and topical hemostatic agents to stop the bleeding and preserve the organ. High-grade parenchymal injuries and those associated with significant penetrating injury will likely require nephrectomy. Bleeding from the main or a branch renal artery should be repaired to preserve all or a portion of the kidney. However, if the main renal artery has major damage or has been occluded for more than 1 hour, attempts at repair and renal preservation are futile, and nephrectomy is the best option.

Zone III hematomas should also be observed unless expanding or associated with a major penetrating component. Because they are most associated with pelvic fracture and venous bleeding, zone III hematomas are amenable to preperitoneal packing and tamponade, either before or after external fixation of the fracture. Arterial bleeding from a pelvic fracture may not be controlled with packing and instead requires open ligation of an internal iliac artery or its branches or, more commonly, endovascular control with the use of selective embolization tools such as coils or plugs.

OTHER CONSIDERATIONS FOR VASCULAR INJURY MANAGEMENT

Vascular Conduits

Repair or reconstruction of more severe forms of vascular injury requires some form of material with which to perform the patch, interposition graft, or bypass. Vascular prostheses or conduits can be considered as autologous (i.e., from the patient), synthetic, xenografts, or those taken as cadaveric or regenerative allografts. The surgeon should be familiar with the different types of vascular prostheses and conduits as each one has material properties that affect its safety and efficacy for different forms of vascular injury.

The ideal conduit resembles the size of the injured vessel, is readily available, is easy to handle and sew, and resists infection and thrombosis. The most used autologous conduit is a superficial vein from one of the patient's extremities (e.g., saphenous, cephalic). For most cases of extremity vascular injury, the great saphenous vein from the uninjured limb is used as a conduit or repair material. If there is no concomitant deep venous injury, a superficial vein from the injured limb can be used as a matter of practicality. Short segments of superficial vein from the extremities can also be opened and used for patch angioplasty. Deep-extremity vein conduits are more appropriate for repair of large junctional or torso vessels; however, harvesting the deep femoral vein requires larger incisions and has a

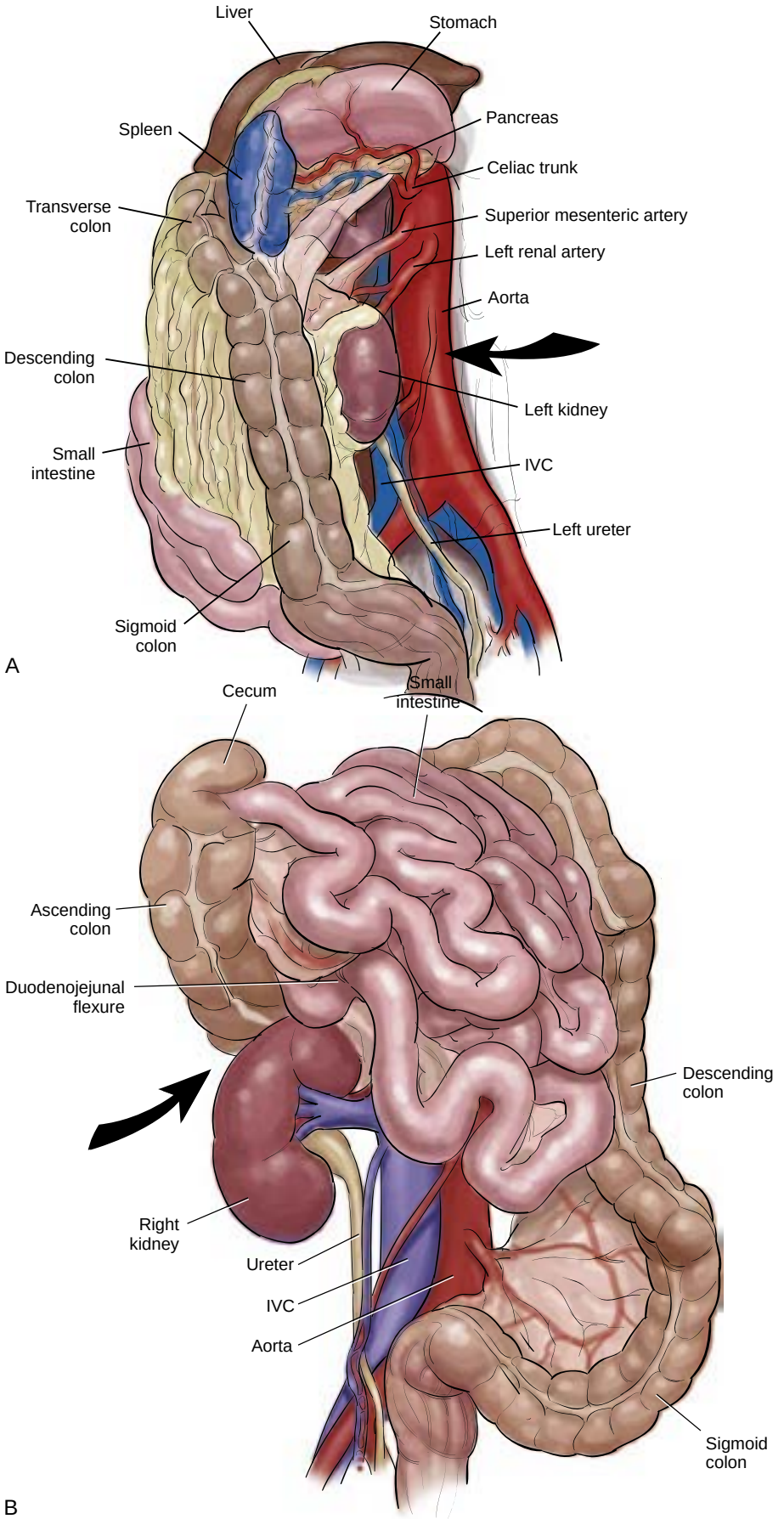


FIG. 9 **(A)** Left medial visceral rotation to expose zone I and left-sided zones II and III vascular structures (Mattox maneuver). **(B)** Right medial visceral rotation to expose right-sided zone II and zone III vascular structures. Includes the Kocher and Cattell-Braasch maneuvers. *IVC,* Inferior vena cava. *(From Rasmussen TE, Tai NR.* Rich's Vascular Trauma. *3rd ed. Philadelphia: Elsevier; 2016.)*

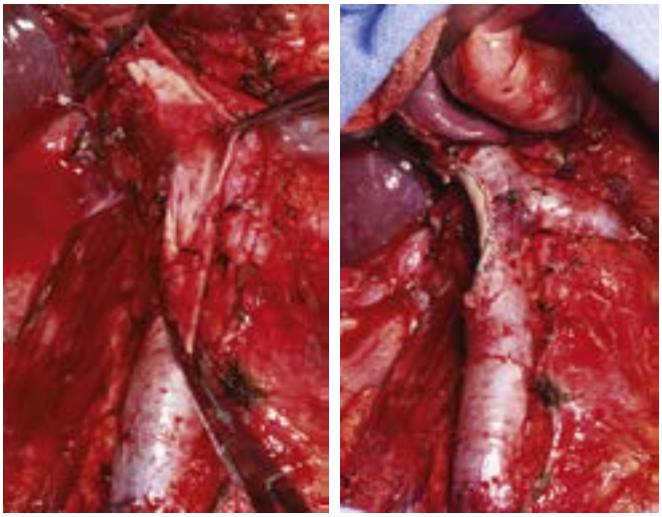


FIG. 10 Large inferior vena cava defect after right nephrectomy repaired with bovine carotid patch angioplasty.

higher rate of associated morbidity such as venous hypertension and associated compartment syndrome.

Prosthetics such as Dacron (e.g., woven polyester) and ePTFE have been used as vascular conduits since the 1950s and 1970s, respectively. Dacron, which is readily available "off the shelf" is supplied in different and precise diameters, lengths, and configurations. Similarly, ePTFE grafts are readily available and avoid the time and incisional comorbidities associated with harvest and use of an autologous vein. Prosthetic conduits are most commonly used for the repair of larger junctional and/or central vascular injuries such as the aorta and side branch vessels. The main drawback of synthetics is their relative propensity to become infected when used in the setting of contaminated wounds.

Cryopreserved cadaveric allograft such as the CryoArtery (CryoLife) and xenografts such as bovine carotid or Artegraft (Artegraft) have shown effectiveness as biologic conduits in the management of vascular infections and contaminated vascular injures for several decades. Xenograft material such as bovine pericardium is also widely utilized for patch angioplasty repairs. The Human Acellular Vessel (HAV) (Humacyte) is a new bioengineered conduit consisting of decellularized (non-antigenic) extracellular matrix originating from arterial smooth muscle cells. This product is manufactured using regenerative medicine techniques and results in an "off-the-shelf" conduit of uniform caliber that can be implanted as an interposition or bypass graft. Because the conduit is a nonantigenic biologic, evidence suggests that it becomes populated by endothelial cells from the recipient patient. The HAV is not yet cleared by the US Food and Drug Administration, but pivotal clinical trials designed to show the safety, efficacy, and durability of the conduit for dialysis access, peripheral arterial disease, and vascular trauma are underway in the United States and Europe.

Anticoagulation and Antiplatelet Use

Systemic anticoagulation is useful to prevent extension of thrombus that formed as part of the initial injury and formation of new clot as the vessels are isolated, controlled, and repaired. Although ideal to use, systemic anticoagulation is likely to be contraindicated in severely injured patients in whom it may exacerbate bleeding from concomitant injuries (e.g., long bone fracture, traumatic brain injury, and solid organ injury). Regardless of systemic heparin use, one should proceed with isolation and control of the vascular injury. As previously noted, thrombus at the injury site should be removed with forceps and saline flush and a Fogarty thromboembolectomy catheter passed proximal and distal to remove more remote clot from the inflow and outflow vessels. Heparinized saline (1000 units heparin per liter of normal saline) should be flushed onto the surface of the newly debrided, healthy vessel wall and infused into the inflow and outflow circulations (i.e., local, and regional heparin).

Patients in whom a vascular repair or reconstruction was performed should be treated with some combination of antiplatelet and or anticoagulation therapy in the postoperative period. The exact type and dose will depend on patient factors, overall injury severity, and type of vascular repair. Nearly all patients can begin treatment with an aspirin and a prophylactic dose of Lovenox or subcutaneous heparin in the immediate postoperative period. For more complicated vascular reconstructions or patients prone to thrombosis, this regimen can be escalated to include intravenous heparin with or without a transition to a direct oral anticoagulant or warfarin.

Soft Tissue Coverage

As a final but crucial step in the management of vascular injury, the surgeon must ensure that the repair sutures, patch angioplasty, or graft is covered with viable, well-perfused soft tissue. This step is a requirement to prevent desiccation and or infection of the repair, which will result in anastomotic disruption and bleeding. Adjacent muscle, subcutaneous fat, and skin are most used in the extremities and cervical region, whereas the retroperitoneum and omentum are used to cover vascular repairs in the abdomen and pelvis. If the muscle and soft tissue adjacent to the repair or graft is injured, grossly contaminated, or nonviable, a more extensive transfer or rotational muscle flap (e.g., sartorius or rectus femoral flap) should be used to move healthy tissue as coverage. If needed, these and even more complex myocutaneous free flaps can be performed with plastic surgery colleagues who offer a wider range of expertise with this aspect of care. If soft tissue coverage is not possible during the initial operation, one should cover the repair or graft with a Vaseline or antibiotic-impregnated gauze and a semimoist dressing, pack and approximate the wound, and closely monitor the patient as plans are made to return to the operating room within 1 or 2 days. Waiting more than 1 or 2 days to establish definitive, viable soft tissue coverage of an arterial reconstruction is ill advised and prone to result in anastomotic disruption and life-threatening hemorrhage.

Extremity Fasciotomy

As noted previously, fasciotomy should be considered following the repair of extremity vascular injury. A lower extremity fasciotomy is performed through two generous longitudinal incisions, one on the medial side of the leg and the other on the lateral side. The medial incision allows for exposure and release of the posterior superficial and posterior deep compartments, while the lateral incision is used to decompress the anterior and lateral compartments. To ensure a complete fasciotomy, one should clearly identify and divide (i.e., "take down") the fascia attached to the medial edge of the tibia that covers the posterior deep compartment (medial incision) and visualize the intermuscular septum that divides the anterior from the lateral compartments through the lateral exposure.

Reperfusion-related compartment syndrome in the upper extremity is rare because of the forearm's relatively small muscle mass and a robust collateral circulation around the shoulder and elbow. However, one should be mindful of compartment syndrome in the forearm and be able to expose and release its three compartments (the dorsal, volar, and mobile wad), which are separated by fascia and an interosseous septum. The dorsal and volar compartments are divided into superficial and deep subcompartments.

The superficial and deep volar compartments are exposed through a gentle *S*-shaped incision on the volar side starting 1 cm proximal to the medial condyle and coursing slightly lateral, reaching the midline at the junction of the middle and distal third of the forearm. The distal incision can be extended onto the hand; however,

doing so may cause difficulty with wound closure, which can subsequently expose the median nerve. If the incision is extended onto the hand, it should be on the ulnar side of the palmaris longus tendon to avoid the palmar cutaneous branch of the median nerve. The dorsal compartments are exposed and opened through a shorter longitudinal incision on the dorsal side beginning 3 to 4 cm distal to the lateral epicondyle. The mobile wad can also be exposed and opened in the proximalmost aspect of this dorsal incision.

Prophylactic extremity fasciotomy is recommended in younger patients and those with greater than 3 to 4 hours of ischemia or concomitant crush injury or fracture. A preemptive fasciotomy should also be considered in patients who will remain intubated or sedated and thus unable to respond to serial physical examinations of the arm or leg. Surgeons should also have a low threshold to perform a fasciotomy if the patient will be transferred out of their care to a different surgical team, treatment facility, or echelon following the initial operation.

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Endovascular Management of Vascular Injuries

Joseph V. Lombardi, MD, Mikael A. Fadoul, MD, and Marissa Famularo, DO

With a rise in the use of endovascular techniques, both in surgical training and in practice, the extension of this technology to the treatment of traumatic vascular injuries is not surprising. Endovascular techniques are now often the first-line treatment for some of the most dangerous traumatic vascular injuries encountered. This technology assists with quick control of difficult injuries and has led to improved outcomes in trauma patients, especially when used in combination with traditional open techniques. In an analysis of the National Trauma Data Bank, the use of endovascular procedures to treat traumatic vascular injuries increased from 0.3% in 2002 to 9.0% in 2010, with thoracic aortic and iliac artery injuries responsible for the majority of this increase.

Endovascular options promise a quick, minimally invasive approach to injuries that otherwise may require large, morbid exposures. Additionally, the prospect of using a familiar endovascular approach to an arterial site and avoiding a difficult or rarely encountered open exposure is an attractive option to many surgeons, especially those with limited trauma experience. Although it may be enticing to use a familiar elective approach in a trauma situation, it is important to remember that trauma alters normal anatomy in unpredictable ways. Often, the best approach to a traumatic vascular injury is a combination of endovascular and open techniques, and any surgeon treating these complex injuries should be prepared to use a combination that best suits each patient.

PREPAREDNESS

Successful endovascular repair of a traumatic injury starts long before the injury itself occurs, with the creation and stocking of a hybrid suite. As previously stated, the best approach to most vascular trauma includes a combination of open and endovascular techniques allowing for greater flexibility in the management of these challenging patients. Although some of the following techniques can be performed in any operating suite with a traditional C-arm, a true hybrid operating suite, capable of both endovascular and open repairs, is invaluable.

Inventory including a wide variety of wires, catheters, stents, and stent-grafts provides necessary options in challenging cases with variable anatomy. As many trauma patients are younger than the average vascular patients, artery size is often smaller as well. This requires stents and stent-grafts in smaller diameter sizes than what is routinely used in a standard vascular practice. For that reason, a well-stocked endovascular trauma suite may have a much different inventory than that which we use for the average vascular patient.

In addition to a hybrid suite and a well-stocked trauma inventory, having properly trained staff available at all times is important for any program that wishes to successfully treat traumatic vascular injuries in a hybrid manner. Nurses and technicians familiar with endovascular products and techniques are an essential part of any vascular trauma team. With a combination of the appropriate staff, inventory, and operating suite, all manners of vascular injuries can be treated successfully.

MANAGEMENT OF BLUNT THORACIC AORTIC INJURIES

Blunt thoracic aortic injury (BTAI) is one of the most common and most deadly injuries documented in trauma patients. Identification requires a high grade of clinical suspicion, as many patients with BTAI present insidiously without hemodynamic instability. Plain films of the chest are used to assess for gross aortic abnormalities during the initial trauma evaluation. Traditionally, abnormalities, including changes in the contour of the aortic knob or widening of the mediastinum, prompted further investigation with invasive aortography. Today, however, computed tomographic angiography (CTA) is used to evaluate any patients with a high suspicion for injury.

Grading of injuries is useful to guide future management. The most widely used classification scheme, first proposed by Azizzadeh et al., includes four grades of BTAI: grade I (intimal tear), grade II (intramural hematoma), grade III (pseudoaneurysm), and grade IV (rupture) (Fig. 1). These grades can help surgeons make decisions regarding treatment strategies and timing to optimize results.

Most grade I injuries heal spontaneously. Serial imaging with impulse control is, therefore, a reasonable treatment plan. Imaging on or near the third post-trauma day confirms stability or regression of the lesion in the majority of patients. Nonoperative management is supported by the Society for Vascular Surgery (SVS) guidelines. Grade IV injuries, which rarely survive initial injury and transport to the hospital, have a similarly simple treatment algorithm. These patients should all proceed to the operating room for emergent repair.

Grade II and III patients, however, present more challenging management decisions. For each patient, two main questions must be answered: (1) Is repair required? (2) If so, what is the optimal timing of intervention? Although the 2011 SVS guidelines recommend intervention for all grade II and III patients, recent evidence is challenging this recommendation and deserves special review.

Several studies have reported the relative safety of nonoperative management in patients with grade II injuries. The infrequency of a true grade II injury has led several authors to group these patients together with grade I patients, reporting combined outcomes and further complicating the data. Other proposed classification schemes even group these two grades together initially. The true nature of disease of these intramural hematomas, however, remains unclear. Although it is likely that observing grade II injuries is safe, it is unclear and currently unsupported by official societal guidelines. Any observation mandates close follow-up and careful impulse control.

Nonoperative management of aortic pseudoaneurysms (grade III BTAI) is also controversial. One review of 18 patients with grade III BTAI reported a 6% early aortic-related mortality in patients treated with nonoperative management. A large systematic review of published reports revealed a less than 5% aortic-specific mortality in patients treated nonoperatively, but follow-up was poor and results reporting was not standardized. All reports suggesting feasibility of nonoperative management document the need to perform this strategy only in "select patients." Unfortunately, predictors of failure have not been identified, and therefore choosing the correct patients, at this time, is impossible. In addition, continued follow-up, an absolute necessity in patients with higher-grade injuries managed nonoperatively, is famously impossible to achieve routinely, especially in trauma patients. A 10% risk of need for surgical repair in grade III patients has been reported, proving the importance of continued, reliable follow-up. With an early risk of potentially preventable fatality and a high risk of failure to follow-up, the danger in observing grade III injuries is unacceptably high.

The previous data suggest, however, that delaying intervention on grade II and III injuries while polytrauma patients are optimized is likely a safe option. A delay before thoracic endovascular aortic repair (TEVAR) has become increasingly common nationwide and is associated with improving national outcomes for BTAI patients. A recent query of the National Trauma Data Bank performed by Alarhayem et al. evaluated outcomes after TEVAR performed for BTAI based on timing of repair. Those undergoing repair within the first 24 hours had a more than twofold increase in mortality, 9.8% compared with 4.4% in the delayed repair group. This mortality benefit persisted when these groups were stratified by injury severity score. Close observation with impulse control and serial imaging is necessary. One important caveat is that of the traumatic brain–injured patient. When purposeful hypertension is necessary to maximize cerebral perfusion, the principles of care are often at odds with the impulse control necessary to safely observe a BTAI. In these specific and not infrequent cases, we often elect to proceed with early TEVAR, allowing for permissive hypertension and the optimal treatment of any concomitant neurologic injuries.

Once intervention is deemed necessary, a surgical approach must be chosen. Traditional open repair has been compared with endovascular repair in several studies. Open repair of BTAI is a notoriously morbid procedure. TEVAR has been shown to decrease both mortality and morbidity, including spinal cord ischemia and renal failure, in patients with BTAI. Reduction of these morbid complications has made endovascular repair the treatment of choice. Endovascular repair is recommended over open repair whenever anatomically feasible, including in pediatric patients. National trends reflect these recommendations, with a sharp decrease in the number of patients with BTAI treated with open surgery being reported over time.

Several devices have been proven to be safe and effective in the endovascular treatment of BTAI. Percutaneous femoral access is the preferred method of access when suitable, although femoral cutdown or iliac conduit may be required in patients with diseased access

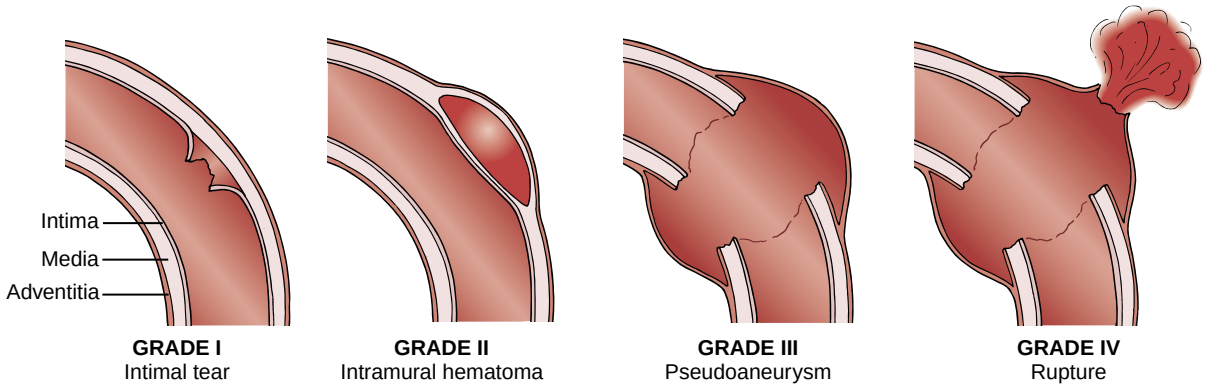


FIG. 1 Classification of traumatic aortic injury. *(From J Cronenwett, KW Johnston.* Rutherford's Vascular Surgery, *8th ed. Philadelphia: Elsevier; 2014.)*

vessels. Crossing the area of injury with a wire can be challenging, especially in the setting of transection. In these cases, careful use of a glide wire is often the best way to cross a lesion. Access into the true lumen of the healthy, proximal aorta can be confirmed with intravascular ultrasound or transesophageal echocardiogram, although in practice often a good angiogram is sufficient.

Landing in healthy aorta with at least 20 mm of neck proximal and distal to the aortic injury is an important tenet of endovascular repair. This often requires coverage of the left subclavian artery (LSA). In most patients, routine revascularization of the LSA is unnecessary and not recommended. However, in patients with an atretic or absent right vertebral artery or prior left internal mammary artery cardiac bypass, early revascularization should be performed. Otherwise, careful monitoring of the postoperative neurovascular exam can be used to direct revascularization in select patients. A smaller amount of thoracic aortic coverage is usually necessary in BTAI than in aneurysmal disease. As such, the risk of spinal cord ischemia in BTAI patients is low, and routine use of spinal fluid drainage is not recommended, although close postoperative evaluation of neurologic exam is important.

The ideal surveillance schedule after TEVAR for BTAI is unclear. Multiple studies have reported extremely low rates of reintervention following TEVAR for BTAI, suggesting low utility in frequent reimaging. Problems leading to reintervention predominantly occur early, usually within 3 months. For these reasons, several authors have suggested a decreased frequency of surveillance after stable scans at 1 year. Patient compliance is historically low in all trauma patients, and clear discussions with the patient and family are necessary to ensure that any surveillance program is followed.

PENETRATING AXILLOSUBCLAVIAN INJURIES

Penetrating injuries to the axillary or subclavian artery are rare but carry a high mortality. Open surgical repair is difficult, and exposure is often time-consuming, as proximal control often requires a sternotomy or anterolateral thoracotomy. Endovascular therapy is gaining popularity as a fast therapeutic treatment option for these unstable patients. Small studies have demonstrated superiority of endovascular repair in penetrating axillosubclavian injuries, with lower morbidity and mortality when compared with open surgical repair; however, patient selection is key. A larger review of contemporary data from 11 large centers demonstrated that endovascular repair is often used in more stable patients with less severe injuries. Endovascular repair is certainly an important tool that can assist in both control and repair of these challenging injuries.

In addition to penetrating axillosubclavian injuries, iatrogenic injuries are becoming increasingly relevant in the era of interventional cardiology procedures requiring large sheath access. Kawsara et al. analyzed temporal trends in pacemaker implantation after transcatheter aortic valve replacement (TAVR) procedures utilizing the National Readmission Database. During the study period, the number of TAVR procedures drastically increased, with 8463 TAVRs performed during the 2012–2013 period compared with 47,418 during 2016–2017. With the increasing volume of TAVRs being performed, the number of associated axillosubclavian access is also increasing. Frequency of axillosubclavian access for TAVR procedures has been reported with rates in the 3% to 7% range. In a propensity-matched analysis comparing femoral versus subclavian access, Petronio et al. reported a life-threatening bleeding event rate of 7.8% and a major bleeding event rate of 36.2%.

Brachial access is often the quickest way to cross an axillosubclavian injury. This method can be performed percutaneously, although in practice a brachial cutdown is often the preferred method. Brachial access avoids traversing the aortic arch before crossing the injury, a step that can be time consuming in patients with difficult arch anatomy. This approach also minimizes arch manipulation in those patients with a heavy atherosclerotic disease burden. A combination of femoral and brachial access may be necessary for patients with difficult lesions, transections, or small brachial arteries. Covered self-expanding stents or balloon-expandable stents can be used, and oversizing by 10% to 20% is recommended.

Close postoperative evaluation with frequent physical exams is necessary, as this patient population is at particularly high risk for stent thrombosis. When appropriate, antiplatelet therapy should be initiated.

ENDOVASCULAR REPAIR OF TRACHEOINNOMINATE ARTERY FISTULA

Tracheoinnominate fistula (TIAF) is a rare but feared complication of tracheostomy, which is caused by pressure from the tracheostomy tube tip or cuff within the trachea against the overlying crossing innominate artery. TIAF is thought to be more common in patients where the cuff or edge of the tube reaches this area. This may be secondary to a low tracheostomy, a long tracheostomy tube, or patient anatomy. TIAF has a reported incidence of 0.7%, with the majority of fistulas (72%) occurring within the first 3 weeks after tracheostomy placement.

Diagnosis is the first important step in treating a TIAF. Although some patients initially present with overt hemorrhage, a herald bleed that stops spontaneously often precedes this event. TIAF should be suspected in any patient with a new episode of bleeding from their tracheostomy, especially if the tracheostomy was placed more than 3 days before the episode. Bronchoscopy remains the diagnostic test of choice, as CTA is rarely diagnostic. A lesion on the anterior tracheal wall adjacent to the pulsation of the crossing innominate artery is highly suggestive of fistula and should prompt repair. The interval between a herald bleed and overt hemorrhage is unpredictable, and evaluation should be obtained emergently after any episode of bleeding.

Patients who present in extremis with active bleeding present a unique challenge. The first maneuver attempted should be overinflation of the tracheostomy balloon. If this is ineffective, digital compression of the innominate artery against the manubrium (the Utley maneuver) can be attempted by placing a digit into the pretracheal plane, usually through the tracheostomy after orotracheal intubation. Throughout all attempts at control, the operating room (OR), preferably a hybrid suite, should be readied for emergent use.

An endovascular first approach has been adopted in the management of these difficult lesions, as open repair of TIAF is plagued by high mortality. Although TIAF is considered a contaminated lesion, postoperative infectious complications occur in a minority of cases. It is therefore reasonable to attempt endovascular repair, with close postoperative follow-up and lifelong antibiotic therapy. It should also be noted that the patient population experiencing TIAF is often fraught with comorbidities, and the documented survival after these events, even after successful repair, is low. This has led many authors to compare endovascular TIAF repair to a palliative procedure.

While coil embolization of the innominate has been suggested, stent-graft placement across the lesion is usually considered first-line therapy. Wire access across the lesion can be obtained via femoral approach, although carotid cutdown is often preferred as it allows for protection against distal embolization and easy access across the lesion without navigating the arch. The length and size of the innominate artery often makes graft selection for this area difficult, with iliac limbs often being the most appropriate choice. Type II endoleak from a patent subclavian artery can be problematic (Figs. 2 and 3). In this case, a supraclavicular approach to the right subclavian allows for proximal ligation of the artery and subsequent carotid-subclavian bypass (Fig. 4).

RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA

Noncompressible vascular injuries causing hemorrhage from a vessel in the abdomen or pelvis is notoriously difficult to control quickly



FIG. 2 Retrograde angiogram of innominate artery pseudoaneurysm. *(From Troutman DA, Dougherty MJ, Spivack AI, Calligaro KD. Stent graft placement for a tracheoinnominate artery fistula.* Ann Vasc Surg. *2014;28:1037.e21–4.)*



FIG. 3 Large type II endoleak from right subclavian artery after stent-graft placement. *(From Troutman DA, Dougherty MJ, Spivack AI, Calligaro KD. Stent graft placement for a tracheoinnominate artery fistula.* Ann Vasc Surg. *2014;28:1037.e21–4.)*

and can lead to significant morbidity and mortality in trauma patients. In the past, noncompressible torso hemorrhage leading to hemodynamic collapse was treated with resuscitative thoracotomy (RT) and cross-clamping of the descending thoracic aorta. An effort to improve upon this maximally invasive approach led to the development of resuscitative endovascular balloon occlusion of the aorta (REBOA).



FIG. 4 Computed tomographic angiography after stentgraft exclusion of innominate artery pseudoaneurysm with carotid to subclavian bypass. *(From Troutman DA, Dougherty MJ, Spivack AI, Calligaro KD. Stent graft placement for a tracheoinnominate artery fistula.* Ann Vasc Surg. *2014;28:1037.e21–4.)*

BOX 1 Stepwise Approach to Implementation of Resuscitative Endovascular Balloon Occlusion of the Aorta

Step 1: Arterial access
Step 2: Positioning of the balloon
Step 3: Balloon inflation
Step 4: Management of hemorrhage
Step 5: Balloon deflation
Step 6: Device and sheath removal

In REBOA, a balloon inserted through the common femoral artery is used to occlude the aorta either above the celiac artery or below the renal arteries, depending on the suspected location of bleeding. Aortic occlusion not only assists with control of hemorrhage but also aims to increase cardiac and cerebral perfusion.

Insertion and use of REBOA requires several steps (Box 1). Each step has several guidelines, which, when followed, can help prevent complications. Step 1 requires accessing the common femoral artery. Traditionally, a femoral cutdown was required for safe cannulation; however, more recently, percutaneous access has been used with increasing frequency. The location of arterial access is important in the prevention of complications. A high stick can lead to retroperitoneal hemorrhage, while a low stick can lead to occlusion of the vessel by the device sheath and thrombosis. Accidental venipuncture

can cause iatrogenic arteriovenous fistulas. The risk of arteriovenous fistula development increases with concomitant arterial and venous access. The precise location for safe arterial access can be difficult to find, especially in a hypotensive, vasoconstricted patient in the high-stress environment of the trauma bay. Fortunately, ultrasound, a familiar tool readily available in the trauma bay, has been shown to significantly decrease the incidence of access complications after percutaneous arterial cannulation. In the hands of a skilled user, ultrasound decreases the time to cannulation and should be used in all cases of REBOA placement.

Once the common femoral artery is safely accessed, the Seldinger technique is used to place an appropriately sized sheath. Although historically a number of different balloons and devices have been used, there is currently one Food and Drug Administration–approved device, the ER-REBOA (Prytime Medical). This device is inserted through a 7Fr sheath.

In step 2, the ER-REBOA device is advanced blindly into position with no fluoroscopic guidance or guidewire. This should occur without resistance. Preexisting arterial pathology or malpositioning may prevent easy, safe passage of the device, and resistance should prompt abandonment of the technique. Other devices and balloons use a guidewire for positioning. Fluoroscopy or radiography is used to confirm zone positioning of the balloon, after which it is inflated. Many catastrophic complications have been documented secondary to poor balloon positioning. Therefore, it is important for practitioners to be familiar with the device they are using and the proper placement of any radiopaque markers on that specific device.

After balloon inflation, all efforts should be made to quickly repair the patient's source of hemorrhage and subsequently deflate the balloon. Longer aortic occlusion times portend poor outcomes. There is some evidence that the hemodynamic stability provided by ER-REBOA and the minimally invasive nature of the femoral sheath create a decreased sense of urgency among providers, with some reports even documenting patients who have had CTAs performed with a ER-REBOA in place. Patients with an inflated balloon should be considered unstable and should be treated just as a patient after RT and aortic cross-clamping.

Once a patient has been stabilized, the balloon can be deflated. This maneuver should always be performed with the full awareness of the entire team, including anesthesia, as this can generate profound physiologic changes. Volume shift and metabolic abnormalities can lead to hypotension after balloon deflation. Temporary partial or complete reinflation of the balloon can be helpful to augment blood pressure. If no drop in blood pressure occurs after deflation of the balloon, distal embolization or thrombosis should be suspected. After balloon deflation, the device is removed through the sheath. Again, any resistance should raise high suspicion for complications.

Finally, removal of the sheath can occur. In a patient with normal coagulation, the 7Fr sheath used for the ER-REBOA can be removed safely with manual pressure held for approximately 30 minutes. Basic postcatheterization care will assist in the prevention and identification of complications, including 4 hours of bed rest after sheath removal and close evaluation of the groin and distal pulses for at least 24 hours. Larger sheaths or any sheath in a coagulopathic patient may be unsafe for basic manual removal. In these cases, and any case when the location of initial puncture is unknown or erroneous, femoral cutdown with direct arterial repair is the safest option.

Reports in the literature regarding complications and outcomes of ER-REBOA have become more prevalent with the device's increased utilization in the care of the trauma patient. Recently published literature has drawn critical attention to the use of this technology. Anecdotal reports from high-volume centers suggest that a multitude of vascular complications can, and do, occur. In our institutional experience, an ER-REBOA positioned in a dissection plane was advanced into the infrarenal aorta and inflated, leading to bilateral lower extremity ischemia requiring amputation and inferior mesenteric artery occlusion requiring colectomy (Fig. 5). Like any surgical procedure, understanding and evaluating for possible complications of ER-REBOA are paramount to its safe and effective use. Notification of the vascular surgical team is included by some groups as an important early step in the ER-REBOA process, helping to prevent, identify, and correct complications. This step is highly recommended.

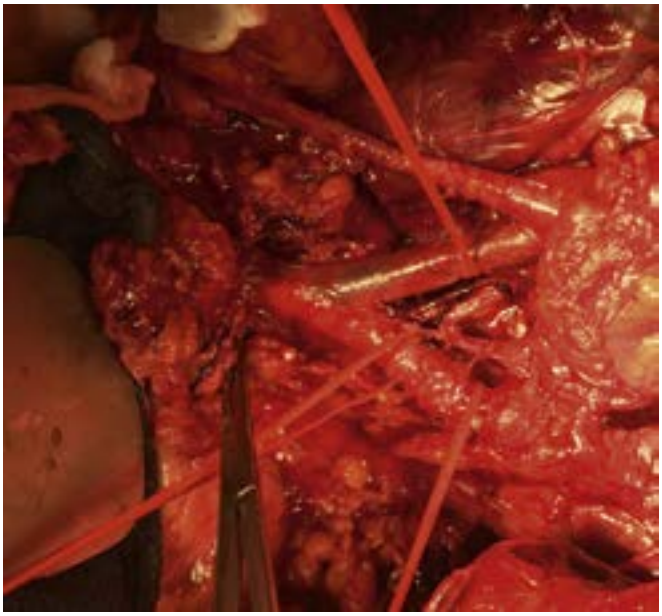


FIG. 5 Bilateral lower extremity ischemia requiring amputation and inferior mesenteric artery occlusion requiring colectomy.

Some small studies and the AORTA registry have documented improved outcomes after ER-REBOA use when compared with RT. ER-REBOA has also been shown to be an effective bridge to definitive hemostasis after severe pelvic trauma. However, questions remain regarding the safety and utility of this newly adopted technology. A retrospective review of the ACS-TQIP Database by Joseph et al. analyzed outcomes in patients undergoing ER-REBOA with a propensity score matched group. ER-REBOA use was associated with an increased rate of mortality, acute kidney injury, and lower extremity amputation. Despite the theoretical advantage of quickly achieving hemostasis, the use of ER-REBOA did not translate to a decrease in transfusion requirement. There was also an increase in the time to laparotomy and angioembolization in the ER-REBOA group. While Levin et al. found that the majority of amputation in patients receiving ER-REBOA were associated with preadmission trauma, 10% of amputations in their cohort were unrelated to this. While attempting a new or unproven technique in a dying patient may be justified, the literature currently does not support the safe extension of this technology to stable patients. The paucity of literature, along with the association of major complications in those receiving ER-REBOA, further call this technology into question, highlighting the importance of identifying the appropriate indications and patient cohort that would benefit from such an intervention. This technique, therefore, should never be used as a replacement for traditional proximal control in open trauma or vascular cases.

ENDOVASCULAR MANAGEMENT OF INADVERTENT ARTERIAL PLACEMENT OF VENOUS CATHETERS

Inadvertent arterial catheterization is an infrequent complication of a common procedure. Although in the femoral artery catheters can often be removed safely with manual pressure applied, accidental cannulation of the carotid or subclavian artery proves more difficult to manage. The subclavian artery is impossible to compress manually

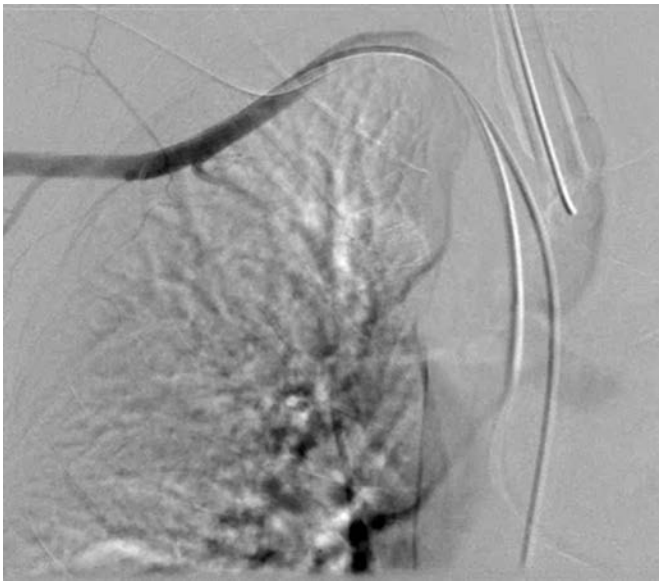


FIG. 6 Femoral approach to vessel.



FIG. 7 Balloon placement.



FIG. 8 Completion angiogram.

due to its anatomic location. For accidental carotid cannulations, there is an added risk of stroke due to thrombus formation on the catheter that may be dislodged upon removal. Also, as most internal jugular (IJ) venous cannulations are now performed under ultrasound guidance, accidental carotid cannulations frequently involve through-and-through IJ injuries that are not amenable to percutaneous closure.

Using a percutaneous closure device after accidental sheath placement has been evaluated and noted to be safe, even for carotid artery cannulations. If the accidental cannulation is identified early, before thrombus can form on the catheter tip, this is likely a reasonable approach and provides a quick, minimally invasive solution. To prevent thrombus formation, it is wise to heparinize any patient with a subclavian or carotid line as soon as it is identified. For additional safety, it is recommended that closure be performed in an OR or hybrid suite. It is our practice to obtain access to the vessel in question via a femoral approach (Fig. 6). For inadvertent subclavian cannulation, the same approach can be taken as in penetrating injuries. For lesions difficult to cross from a femoral approach, or those with difficult arch anatomy, percutaneous or surgical access of the brachial artery may be performed. A balloon can then be placed proximal to the injury in case proximal control is necessary (Fig. 7). The catheter is then removed, and the closure device is deployed. After placement of the closure device is complete, a completion angiogram is performed to rule out any extravasation (Fig. 8). This is especially important for subclavian injuries, as manual compression is not possible in this location.

If a pseudoaneurysm or arteriovenous fistula is present at the cannulation site, placement of a covered stent over the area may be the best approach. Both self-expanding and balloon-expandable stents have been successfully used in this manner. In cases of accidental carotid puncture, the high likelihood of concomitant venous injury makes use of a covered stent superior to closure device as a treatment strategy. It is important to remember, however, that embolization during stent deployment in the carotid circulation is a risk. Each case must be individualized, and open operative repair is often the safest approach for carotid injuries for this reason.

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Extremity Compartment Syndrome

Charles E. Lucas, MD, and Anna M. Ledgerwood, MD

During the London Blitz in 1941, Bywaters and Beal reported the disastrous consequences of compartment syndrome when not recognized or treated. Alert citizens with limbs crushed by collapsed buildings were extracted by civil defense neighbors and conveyed by horse-drawn ambulances to nearby hospitals. Within 48 hours, friends and neighbors were dead due to muscle necrosis within crushed limbs, thus releasing systemic products of muscle death, such as creatinine phosphokinase (CPK), which caused renal shutdown. Fascial decompression and hemodialysis were not yet available. Prevention of this lethal sequence requires recognition of compartment syndrome causes, pathophysiology, and treatment.

CAUSES OF COMPARTMENT SYNDROME

Compartment syndrome is caused by external compression as was seen during the London Blitz, tissue expansion due to ischemia from vascular disruption, or a combination of both (Box 1). External compression occurs when a plaster cast or wrap is applied soon after a long bone fracture before soft tissue swelling has maximized, thus increasing tissue pressure and obstructing capillary flow. Any patient complaining of pain in this setting must have the cast bivalved or the wrap removed to prevent impaired capillary flow leading to necrosis. Masking the pain of tissue ischemia with narcotics is hazardous.

The classic example of internal compartment hypertension follows the ischemia/reperfusion injury (Box 1). Arterial occlusion from injury thrombosis or external compression causes cellular ischemia. Reperfusion promotes cellular repair, which is associated with obligatory interstitial and intracellular hypervolemia, which in turn increases tissue pressure. Patients with injury to the femoral artery trifurcation or the popliteal artery are especially prone to distal ischemia due to a reduced collateral flow when vascular reconstruction is delayed beyond 6 hours. The likelihood for compartment syndrome increases when the interstitial and intracellular hypervolemia is combined with soft tissue injury from long bone fractures and/or venous injury requiring ligation.

The tissue ischemia/reperfusion syndrome occurs in patients undergoing urgent abdominal aortic aneurysmectomy, especially when technical difficulties delay successful restoration of flow. Patients with delayed reconstruction, especially to the popliteal artery after severe injury, are likely to develop compartment syndrome (Fig. 1). Extensive combined injuries of bone, vessels, and soft tissues are seen after pedestrian/motor vehicle collisions, high velocity rifle wounds, and close-range shotgun wounds (Fig. 2). Arterial shunting, external fixation of fractures, rapid vascular reconstruction, and extensive fascial decompression are often needed to salvage the involved limb. When such patients present to a nontrauma center or a frontline military facility, a temporary vascular shunt should be placed as the patient is prepared for transfer to a higherlevel care facility for definitive repair. The patient who has had such a shunt placed does not need to be heparinized, and the definitive repair should be performed within 6 hours. When the definitive repair does occur, routine fascial decompression should be performed.

The combination of both external compression and internal expansion occurs after crush injury, most commonly seen with industrial accidents, severe circumferential burns of the extremity requiring extensive volume expansion, excessive direct soft tissue injury from a high-voltage electrical current, or a constrictive wound eschar. Burns without eschar, without circumferential swelling, and generalized sepsis rarely increase tissue pressure beyond capillary hydrostatic pressure.

Venous occlusion due to iliofemoral thrombosis or impaired venous return from external pressure may lead to compartment

BOX 1 Etiology of Compartment Syndrome

External Compression

Cast/ACE wrap
Military antishock garments
Burn eschar

Internal Compartment Expansion

Ischemia and reperfusion
Arterial injury, thrombosis, tourniquet
Burns, frostbite
Cellular insult and swelling
Crush injury
Exercise/exertion/anterior leg compartment
Electrical injury/high voltage
Blood accumulation and edema
Fractures
Hemophilia
Anticoagulants
Venous occlusion
Miscellaneous
Intravenous infiltration
Drug injection/soft tissue

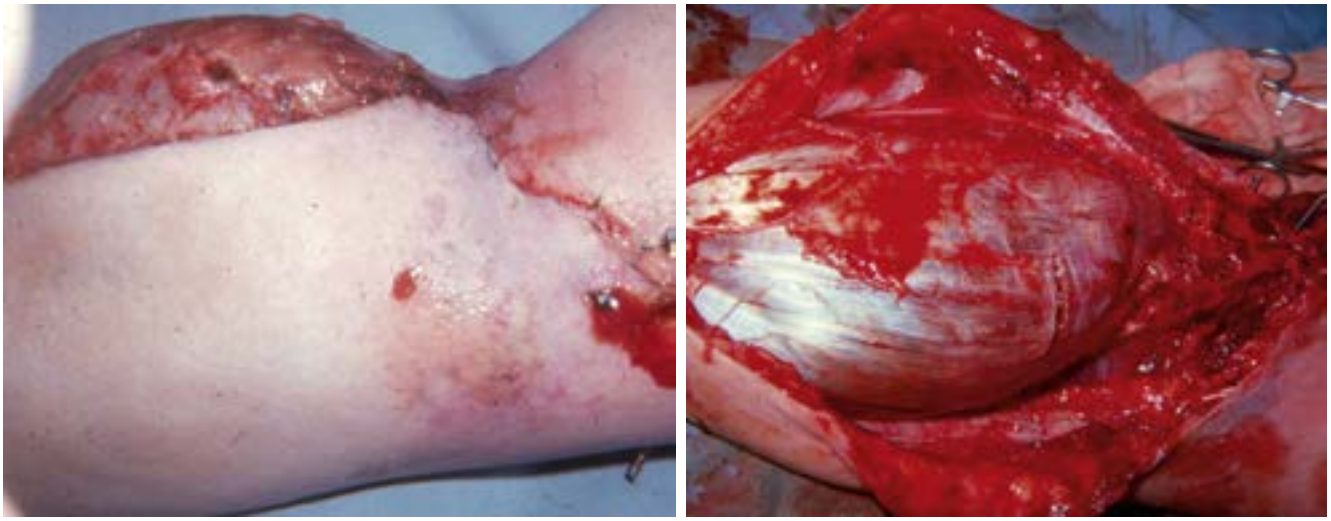


FIG. 1 A delay in fasciotomy after repair of a popliteal artery injury and ligation of the adjacent vein without fasciotomy led to compartment syndrome, which reveals superficial muscle necrosis. These areas of superficial muscle death were minimally debrided, and complete fascial decompression was added. The underlying muscle gradually improved with frequent dry dressing changes over the next three weeks. Aggressive muscle debridement should be avoided in this setting.

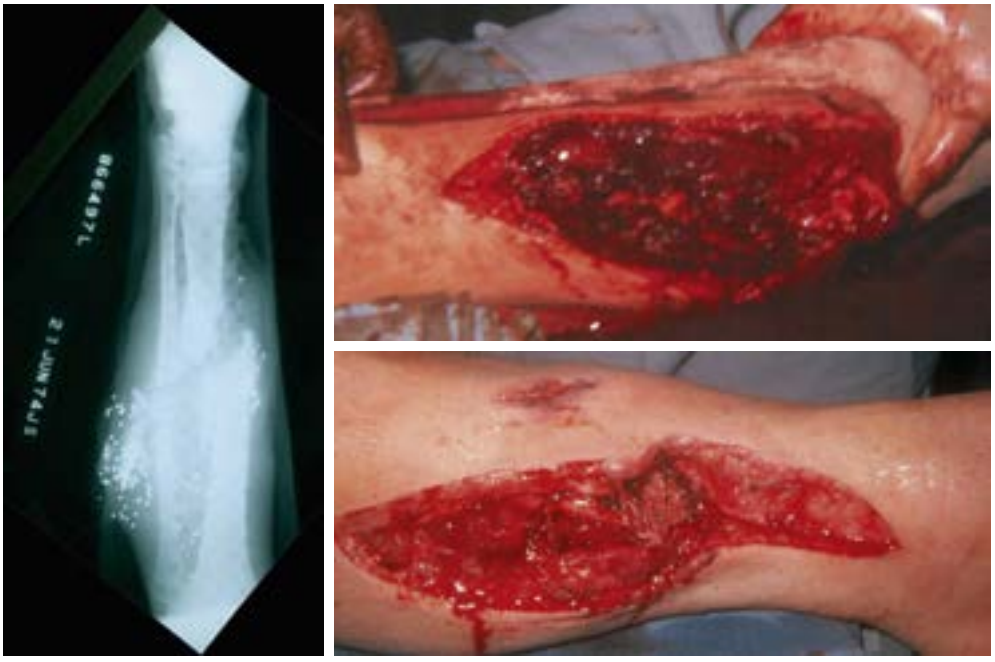


FIG. 2 This 14-year-old boy had a close-range shotgun blast to the calf, causing tibial and fibular fractures and extensive soft tissue injury with disruption of the peroneal and posterior tibial arteries. An interposition vein graft was rerouted through the anterior compartment and extensions of both the entrance and exit wounds provided good compartment decompression. The wound was allowed to heal by second intent and, by 3 weeks, had good granulation tissue; he was later skin grafted and had a good long-term result.

syndrome (Fig. 3). The latter may occur when an intoxicated or overnarcotized patient lies on the extremity for a prolonged period; myoglobinemia with renal failure often accompanies this insult. Unusual causes of compartment syndrome include intramuscular or subcutaneous injection of illicit drugs causing abscess formation with extensive cellulitis and tissue ischemia. This is commonly seen with soft tissue injection of "mixed jive" heroin when attempted venipuncture fails. Extensive debridement may be indicated (Fig. 4).

DIAGNOSIS

A thorough history and complete physical examination directs the examiner to the diagnosis of compartment syndrome. The alert and cooperative patient should be assessed for the six "Ps," namely pressure, increased pain with passive extension, paresis, paralysis, and pulselessness. Pain is typically throbbing and unrelenting. Pressure, an early objective finding, reflects the swollen, hard, and tender muscle. Passive stretch of the involved muscles increases the pain. Paresis,



FIG. 3 This patient, admitted for a drug overdose, was seen in the critical care unit for a swollen right thigh, which was hard and tense, and was associated with myoglobinuria. Medial and lateral thigh fasciotomies revealed pale muscles, which rapidly pinked up after compartment decompression. He went on to develop acute renal shutdown and required dialysis for 3 weeks, but all muscle groups survived, and he had good long-term function following split-thickness skin grafting.

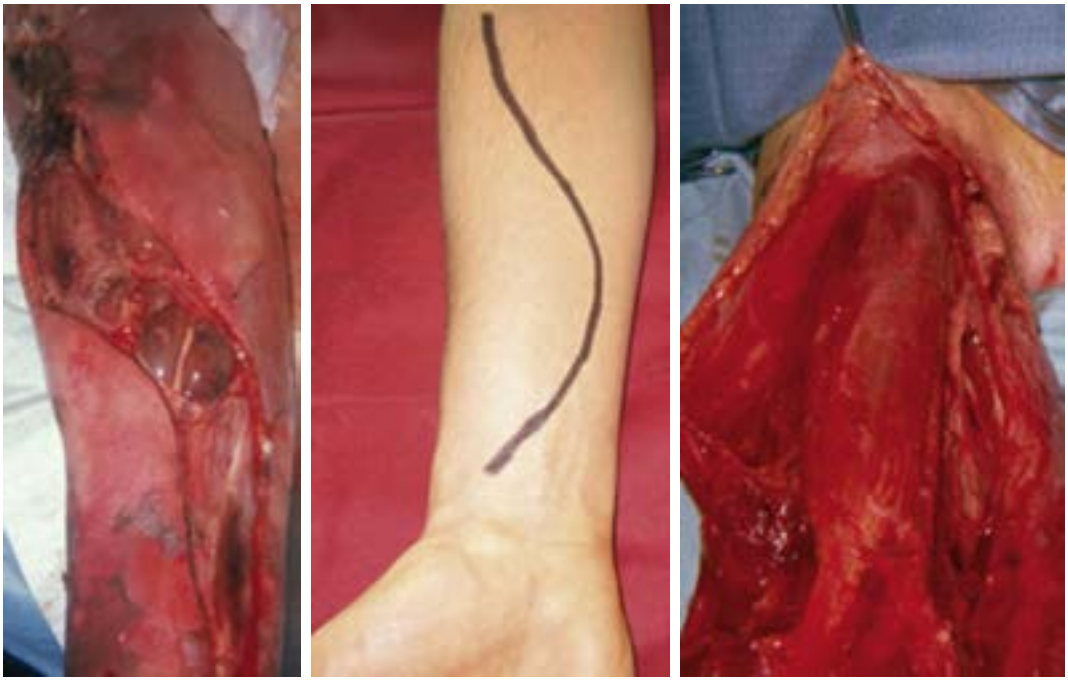


FIG. 4 Injection of contaminated "mixed jive" heroin into the forearm subcutaneous tissues led to extensive soft tissue necrosis involving the forearm and distal arm with associated compartment syndrome. Extensive soft tissue debridement and extension of the forearm fasciotomy incision proximal to include the anterior compartment of the arm resulted in limb salvage and a good long-term result. The classic incision for a fasciotomy of the anterior arm is shown.

or muscle weakness, is due to nerve compression and is a reliable finding in patients with anterior compartment syndrome of the leg. The deep peroneal nerve in the anterior compartment innervates the web space of the great toe; paresis in this area suggests an anterior compartment syndrome. Paralysis appears late. Pulselessness occurs later when the tissue pressure exceeds capillary pressure; the pulse often is present during the early phases of compartment syndrome.

Objective confirmation of compartment hypertension in the impaired patient requires direct pressure monitoring. Therapeutic fasciotomy, therefore, is usually performed on the basis of clinical examination. The impaired or anesthetized patient can have compartment pressure monitoring by the direct insertion of a needle attached to a handheld, solid-state transducer device (STIC catheter; Stryker Surgical, Kalamazoo, Michigan) that facilitates repeated



FIG. 5 The Stryker pressure manometer is a handheld, solid-state transducer device that can be used to directly measure muscle tissue pressure. The syringe and manometer are contained in a special chamber, and the directions for use are engraved on the back of that chamber.

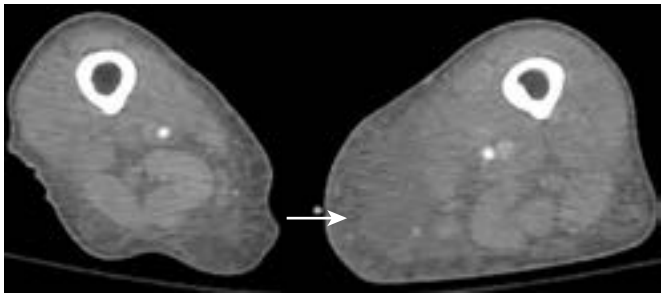


FIG. 6 This patient with severe sepsis developed myositis of the gracilis and adductor muscles. The left gracilis *(right)* is much smaller than the right gracilis *(left)*. A long medial fasciotomy provided immediate relief of symptoms and allowed the underlying ischemic muscles to recover.

measurements before and after compartment decompression (Fig. 5). Alternatively, a venous pressure manometer filled with sterile saline and attached to an extension tube and an 18-gauge needle can be inserted into the muscle. The manometer is filled to 40 cm H_2O and placed at the level of the muscle when the stopcock is opened. The saline column will either rise or fall. When the column rises, fasciotomy is needed; if the column falls, observation can be continued. A water column pressure of 40 cm H_2O is the same as 30 mm Hg.

ARM COMPARTMENT DECOMPRESSION

The arm has two compartments, namely the anterior compartment containing the deltoid and biceps brachii and the posterior compartment containing the triceps. Anterior compartment hypertension may occur after the inadvertent subcutaneous injection of intravenous fluids or blood products. When street drugs are injected, rapid and extensive cellulitis may result. Decompression is provided through a long curving linear incision, beginning just distal to the deltoid and extending over the biceps to the antecubital fossa. Compartment hypertension in both the anterior and posterior compartments more likely occurs when an intoxicated patient sleeps with the arm positioned under the trunk. The posterior compartment incision extends directly over the triceps muscle to about 3 cm proximal to the elbow. If necessary, decompression of the deltoid muscle can be achieved by extending the anterior incision to the rotator cuff.

FOREARM COMPARTMENT SYNDROME

The forearm has three muscular components. The volar compartment contains the pronator teres, flexor carpi radialis longus, palmaris longus, flexor carpi ulnaris, and flexor digitorum superficialis. These muscles originate from the medial epicondyle of the humerus. The posterior or dorsal compartment is composed of the supinator, abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus, and extensor indicis. These extensor muscles arise from the lateral humeral condyle. The lateral compartment consists of the brachial radialis, which also arises from the lateral humeral condyle.

Isolated anterior compartment syndrome occurs after the extravasation of intravenous fluids, street drug injection, or unusual insect bites. Decompression of this compartment is achieved through an incision that begins at the lateral humoral condyle near the elbow, descends medially in a curved manner for the proximal half of the forearm, and then laterally down to the area just above the wrist (see Fig. 4). This incision also decompresses the lateral compartment. When all three compartments are compromised after severe burns or extensive trauma with long bone fractures and ischemia requiring vascular reconstruction, a posterior decompression incision should be added.

THIGH COMPARTMENT SYNDROME

Compartment hypertension of the thigh or upper leg is rare but may occur from crush injury, venous outflow obstruction, or extensive bone and soft tissue disruptions from explosions or high-velocity firearm wounds (Fig. 6). The thigh has three compartments, with the anterior compartment containing the Sartorius and the quadriceps femoris, the medial compartment containing the gracilis and adductor muscles, and the posterior compartment containing the biceps femoris, semitendinosus, and semimembranosus. Compartment syndrome of the thigh often involves all three compartments, requiring total decompression. Fasciotomy of the anterior and posterior compartments can be achieved through one excision, extending from the greater trochanter posterior laterally to just above the knee. The fascia overlying the vastus lateralis is identified so that the anterior compartment can be decompressed through an incision just anterior to the intramuscular septum and the posterior compartment decompressed through another incision, just posterior to this septum. Decompression of the medial compartment is achieved by a medial incision, which stays posterior to Hunter's canal and opens the fascia overlying the gracilis and adductor muscles (see Fig. 6).

LEG COMPARTMENT DECOMPRESSION

Bilateral incisions are recommended for decompressing the four calf compartments (Figs. 7–9). The medial incision is made just distal to the medial tibial condyle and extends inferiorly to about 1 cm posterior to the posterior edge of the tibia, thus decompressing the superficial posterior compartment. After dividing the fascia overlying the gastrocnemius, the anterior superficial fibers of the gastrocnemius and soleus are separated from the posterior periosteum of the tibia, thus facilitating access to the deep posterior compartment (Fig. 10). The lateral and anterior compartments are decompressed by a lateral incision along an anterior margin of the fibula between the muscle fibers separating the lateral compartment from the anterior compartment (Fig. 1). The skin must be mobilized anteriorly to expose the fascia overlying the anterior compartment muscles and then posteriorly to expose the fascia overlying the lateral compartment; both fascial planes are incised the full length of the incision (Fig. 11).

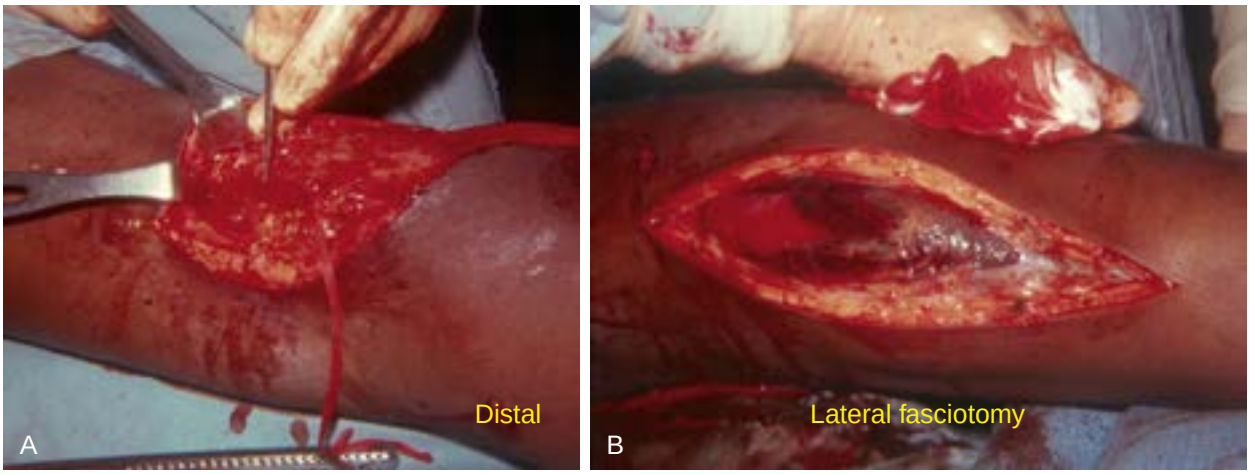


FIG. 7 This patient had a car bumper injury of the popliteal artery, which was repaired through a posterior approach. Decompression of the superficial posterior compartment was achieved by extending the distal portion of the incision inferiorly, whereas decompression of the anterior and lateral compartments was achieved through a lateral fasciotomy incision.



FIG. 8 This patient had primary repair of the popliteal vein and vein graft interposition of the popliteal artery following a crush injury. The skin was closed primarily, leading to compartment hypertension, which caused marked bulging of the gastrocnemius (**A**) with superficial necrosis (**B**) necessitating resectional debridement of about half of the gastrocnemius. Following combined injury to the popliteal artery and vein, routine prophylactic compartment decompression is recommended.

SELECTIVE COMPARTMENT DECOMPRESSION

Occasionally, decompression of three of the four lower leg compartments will lower the pressure in the deep posterior compartment. For example, one patient who had pressures of 78 cm H_2O in the anterior, lateral, and superficial posterior compartments had three compartment decompressions through medial and lateral incisions, which reduced the three compartment pressures to 18 cm H_2O. The deep posterior compartment pressure was then measured and was also 18 cm H_2O. When deep posterior compartment pressures are obtained after three compartment decompressions and are below 20 mm Hg, no further decompression is needed. Selective compartment decompression is often the best approach to low-velocity injuries to the popliteal or femoral arteries (Fig. 12).

ANTERIOR COMPARTMENT SYNDROME

The anterior compartment syndrome is an unusual single compartment syndrome of the calf. The patient typically gives a history of increased physical activity and exercise for an extended period. The anterior compartment muscles become firm and are extremely painful; massage will not help. The severe, constant pain is localized to the anterior compartment. Plantar flexion will exacerbate the pain. This is a surgical emergency and requires immediate anterior compartment decompression by an incision from the tibial tuberosity to just above the ankle in the midpoint of the anterior compartment muscle mass. Delay in operation due to imaging may lead to muscle necrosis.

CHRONIC EXERTIONAL COMPARTMENT SYNDROME

Rarely, acute exertional stress may lead to a recurrent compartment-like syndrome. This tends to occur after unusually excessive exercise of specific muscle groups and may require early compartment decompression. This chronic form of exertional compartment syndrome may occur in the arms in competitive rowers or in the legs in competitive runners. Cessation of the offending activity often provides relief so that compartment decompression is usually not required. Careful monitoring, however, is required.

HAND AND FOOT COMPARTMENT DECOMPRESSION

Decompression of the muscle compartments of the hands and feet is rarely needed. Injuries that may necessitate decompression

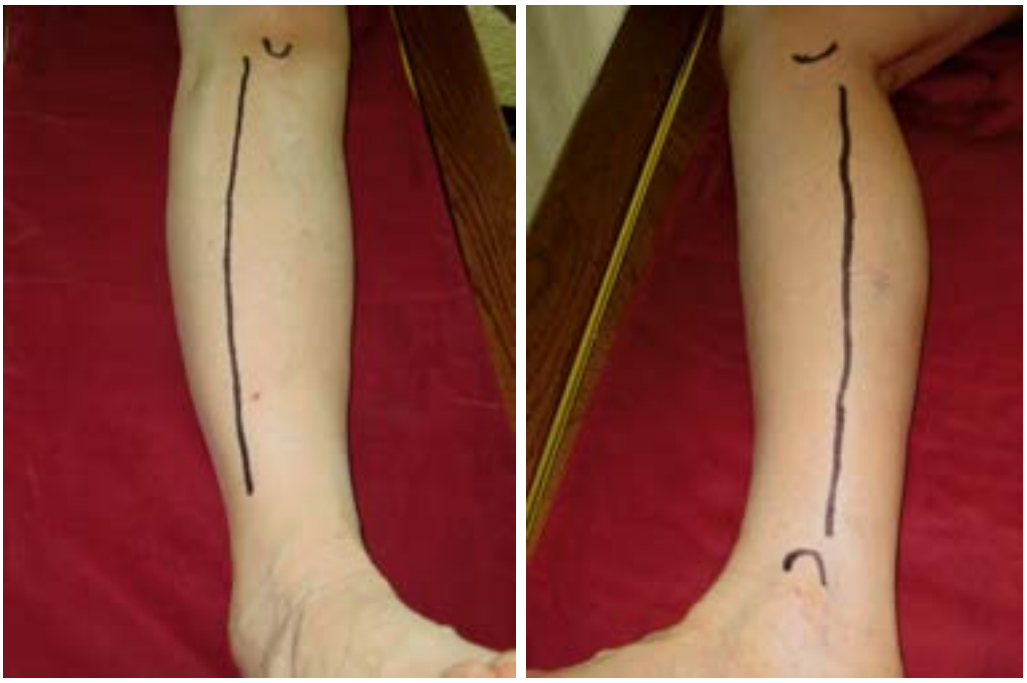


FIG. 9 Four compartment fasciotomy of the calf is achieved by making a lateral incision along the anterior margin of the fibula over the intramuscular groove separating the anterior and lateral compartments *(left)*. The medial incision is made just distal to the tibial condyle and extends between the superficial posterior muscle group and the tibia *(right)*.

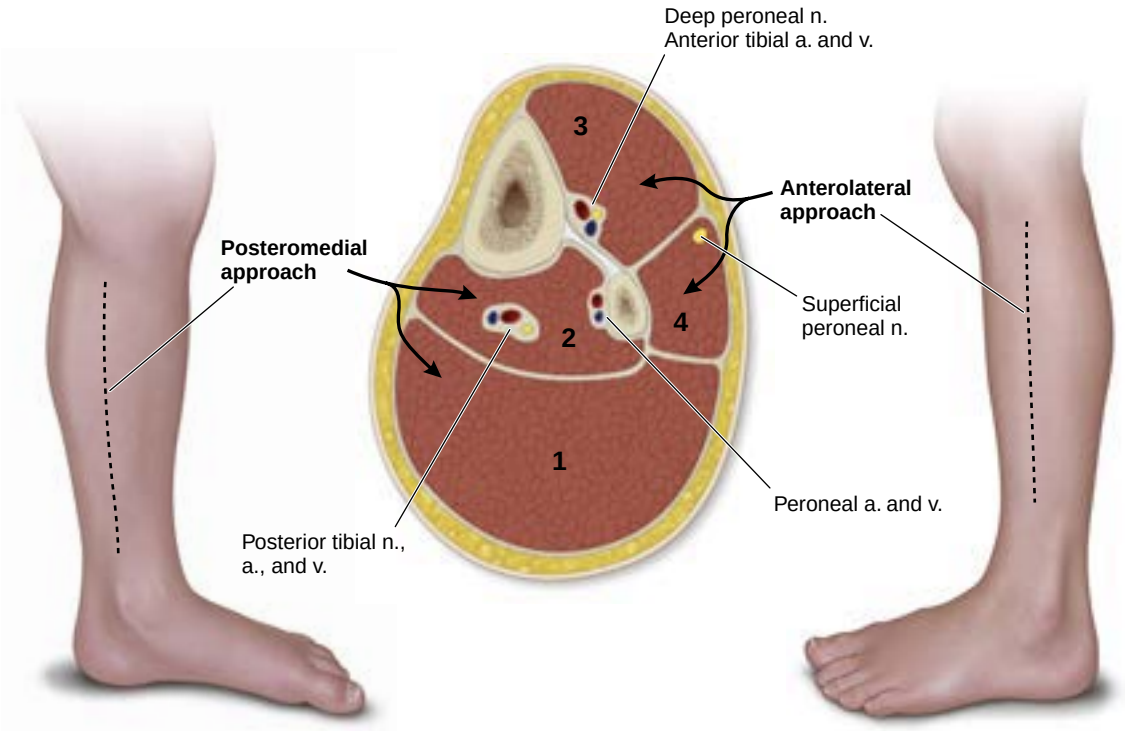


FIG. 10 Decompression of the anterior and lateral lower leg compartments is best provided through a lateral incision at the intramuscular groove followed by skin retraction, which exposes both the anterior compartment and lateral compartment muscles. Decompression of the deep posterior compartment through a medial incision exposes the gastrocnemius muscle, which is retracted medially and posteriorly along with the soleus muscle away from the tibia, providing access to the deep posterior compartment. Unless the soleus muscle is detached from the tibia, only a three-compartment fasciotomy has been performed. *(From Herring JA.* Tachdjian's Pediatric Orthopaedics: From the Texas Scottish Rite Hospital for Children. *5th ed. Philadelphia: Elsevier; 2013.)*

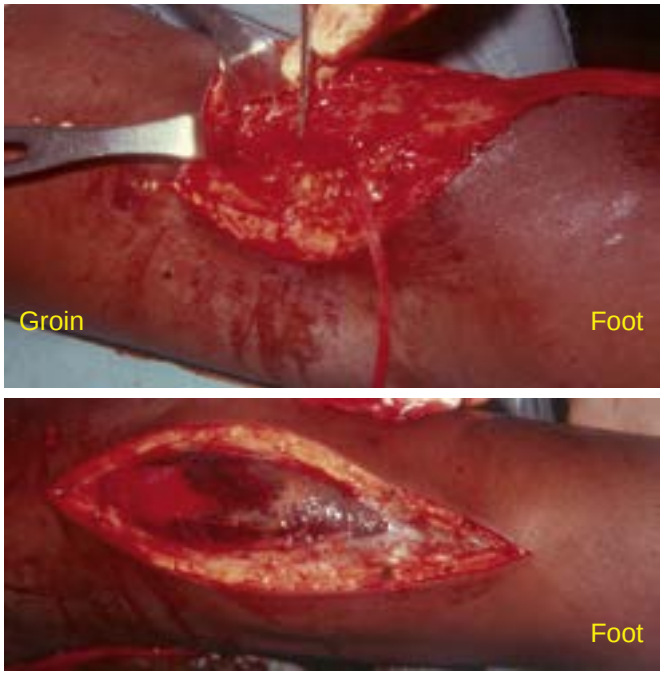


FIG. 11 This patient had a bumper/crash injury of the popliteal artery, which was repaired through a posterior approach. Decompression of the superficial posterior compartment was achieved by extending the distal portion of the operative incision inferiorly, whereas the lateral and anterior compartments were decompressed through a lateral fasciotomy.

include extensive burn, severe cellulitis, and industrial crush injuries. Whenever possible, incisions on the plantar surface of the foot or the volar surface of the hand should be avoided as they impair function. Decompression of the hand compartments can be made by dorsal incisions over the second and fourth metacarpals, allowing for fasciotomy over the interosseous muscles on each side of the metacarpals (Fig. 13). Decompression of the muscle compartments of the foot is, likewise, made by dorsal incisions over the second and four metatarsals, with a third incision made along the medial aspect of the arch muscles (see Fig. 13). When performing these dorsal incisions, one must recognize that both the dorsal and volar lymphatics of the hands and feet ascend dorsally, so patients requiring compartment decompression will likely have extensive lymphedema, making hemostasis quite tedious.

POSTOPERATIVE MANAGEMENT

Extremities with open fasciotomy wounds can be dressed with dry gauze and a soft wrap while being treated with elevation. A vacuum-assisted closure device is seldom needed but can be applied if there is extensive soft tissue damage. A posterior splint of the lower extremity is strongly recommended to prevent foot drop. Some fasciotomy incisions can be closed in 5 to 7 days with closure of the skin. One should avoid closing the fasciotomy incision too soon, as this may lead to recurrent compartment hypertension. If there is extensive muscle bulging precluding skin approximation, full-thickness skin grafts can be applied when the edema has subsided. Sometimes there is a delay in compartment decompression, which leads to superficial muscle necrosis. Excisional debridement should be conservative; the underlying ischemic muscle that is compromised will usually survive and regain function. A superficial layer of necrotic muscle that persists can be debrided at 2 to 3 days after compartment decompression (see Fig. 1). The patient must be monitored for myoglobinuremia and, if present, treated aggressively with hydration, urine alkalinization, and dialysis if renal failure develops.

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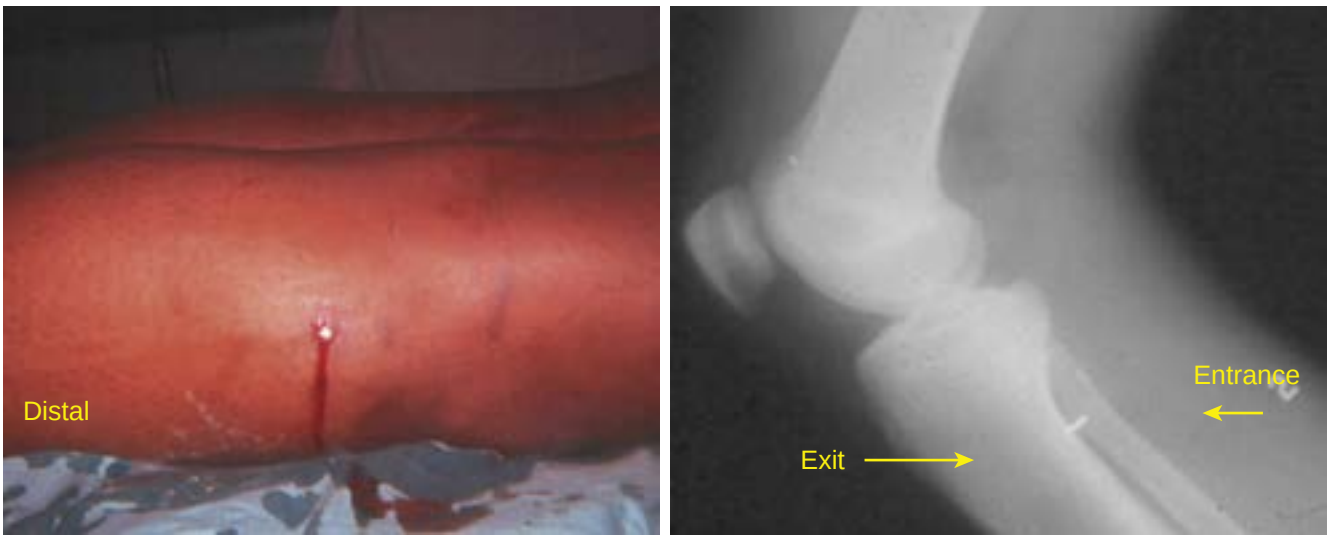


FIG. 12 This patient presented with a through-and-through gunshot wound to the proximal calf, as identified by the two radio opaque markers; he had injury to the tibial perineal artery trunk with a tight calf, necessitating bilateral fasciotomy in conjunction with resection and primary repair of the tibial peroneal trunk. Three-compartment fasciotomy provided optimal decompression.



FIG. 13 Decompression of the hand muscles can be achieved through dorsal incisions over the second and fourth metacarpals, thus exposing the fascia of the interosseous muscles. Decompression of the foot compartments is best made by dorsal incisions made over the second and fourth metatarsals, with a third incision made along the medial aspect of the arch muscles. When possible, incisions made on the plantar surface of the foot or the volar surface of the hand should be avoided since these incisions compromise function.

Burn Wound Management

Christina Lee, MD, Philip S. Barie, MD, MBA, and Abraham P. Houng, MD, MSE

Burn injury varies in magnitude and importance: size and depth of injury are indicative of severity. The topic of this chapter is a broad area of damaged or lost skin from burn injury, resulting in a wound without the capacity to heal itself. Burn injury is commonplace, but the principles of care also apply to wounds of other etiologies. Scar from burn injury is different from surgical incision scar, which can often be hidden in a natural crease, beneath hair, or in the umbilicus, in that burn scar is often extensive and visible. Considering that mechanisms of injury vary, understanding the unique characteristics of flame, scald, cold, chemical exposure, radiation, crush, and conductive electrical current injuries provides guidance to achieve the best care and outcomes.

Surgical excellence is facilitated by an appreciation of the goals of surgical burn care, which are closure, function, and cosmesis. These goals are individual yet interdependent and should not be compromised; maximization of each simultaneously is the path to the best result. Whether and when to operate, meshing of skin grafts, and positioning of graft seams and donor sites are some of the considerations that, when approached thoughtfully, improve the long-term result. Poor cosmetic or functional outcomes must not be accepted as an unavoidable result of injury and reconstruction.

Following wound closure, subsequent weeks and months often bring dramatic changes. Knowledge of scar behavior and indications for interventions, from compression to early surgical intervention, are important for optimal results. Untreated scar can lead to deterioration of appearance, loss of range of motion, and skin breakdown, forming new wounds. The behavior of scar during maturation is multifactorial but strongly influenced by early care. Surgeon follow-up and coordination with the rehabilitation therapy team (physiatrists, physical and occupational therapists, wound care nurses, behavioral health therapists, pain management specialists, and nutritionists) are needed for all major burns and those involving face/neck, hands, and perineum.

The goals of long-term burn care are to close the wound, maintain or restore function, and achieve acceptable cosmesis; in essence, to return the patient to the preinjury state. The degree to which the patient reintegrates into society is a measure of success. Possible long-term problems associated with the care of the burn patient are best avoided through close and complete follow-up with the multidisciplinary team. This chapter will focus on the unique problems associated with the evaluation and treatment of burn wounds and is aimed at the surgeon whose practice is not burn-focused.

EVALUATION

Assessing the Patient and the Burn

The relative infrequency of burn injury when compared with other traumatic injuries may distract from a thorough and complete evaluation. The systematic approach to acute trauma care outlined by the Advanced Trauma Life Support course (American College of Surgeons Committee on Trauma, Chicago, IL) should also be applied in the care of the burn patient. The patient should undergo primary and secondary surveys to identify all injuries (burns and other injuries may coexist). Early in the evaluation and treatment of a burn patient, whether to provide care locally or to transfer the patient to a specialized burn center must be considered. This decision is facilitated by the American Burn Association transfer criteria, which were developed specifically to aid physicians in identifying patients who need the specialized multidisciplinary care available at burn centers.

The estimation of burn size and depth is foundational to care of the patient. All subsequent decisions about patient treatment are impacted by these estimates. The percentage calculation of total body surface area (TBSA) burned is facilitated by standard, separate nomograms for adults and children but is best done with the assistance of an experienced practitioner. The *rule of nines* (Fig. 1) is a commonly used way of estimating burn size. In children, especially toddlers, the standard rule of nines does not work well, because children's heads are proportionately larger and the lower extremities are smaller compared with adults. Another helpful gauge is that the patient's palm represents approximately 1% of the body surface area in patients of all ages. It is often helpful with larger or scattered burns to write down each of the body area estimates and sum them when complete.

No proven, widely accepted diagnostic tool is currently available to guide the clinician in assessing the depth of the burn (Box 1). Several commercial ultrasound and infrared camera devices have been studied for burn wound depth assessment. However, clinical examination of burn depth by an experienced clinician remains the standard for determining the need for surgery.

The ability of the wound to heal versus the need for surgery is an important determinant of the outcome of burn care. Accurate assessment, mature decision making, and insightful treatment planning by an experienced surgeon achieve the best results. The benefit of early wound excision and grafting is scientifically proven, including increased survival for large burns and better cosmesis for smaller burns. Allowing a wound to declare its healing potential before operating (which may take several weeks) leads to several substantive problems. Painful daily dressing changes lead to high analgesic requirements, narcotic-related complications including dependency, and psychological pain syndrome and posttraumatic stress. A wound that remains incompletely healed for more than 21 days is at greater risk of hypertrophic scarring and contracture formation. Conversely, an inexperienced surgeon who performs excision and grafting on a burn wound that has healing potential removes viable tissue and sacrifices natural regenerative capacity had it been left in place. Therefore, the surgeon must find a balance in individual cases between aggressive and nonaggressive care with respect to decision making regarding wound care and surgical treatment. Wounds estimated to heal within 17 days should be left to do so in most patients, considering comorbidities, age, and body area involved.

Burn wound evaluation should be done after light cleaning and before any topical treatment is applied (see Box 1). Application of a topical treatment may preclude subsequent use of dressings designed to adhere to wounds. If burn center transfer is indicated, contact the burn center immediately after initial assessment for instructions about wound care for the patient. Typically, receiving burn centers will prefer smaller wounds to be kept in a clean, moist dressing, whereas larger wounds are kept in dry dressings to prevent excessive heat loss during transfer. Mixed-depth wounds may require observation for a time to arrive at a treatment plan; the burn center is in the best position to do so. Burns with greater than 15% to 20%

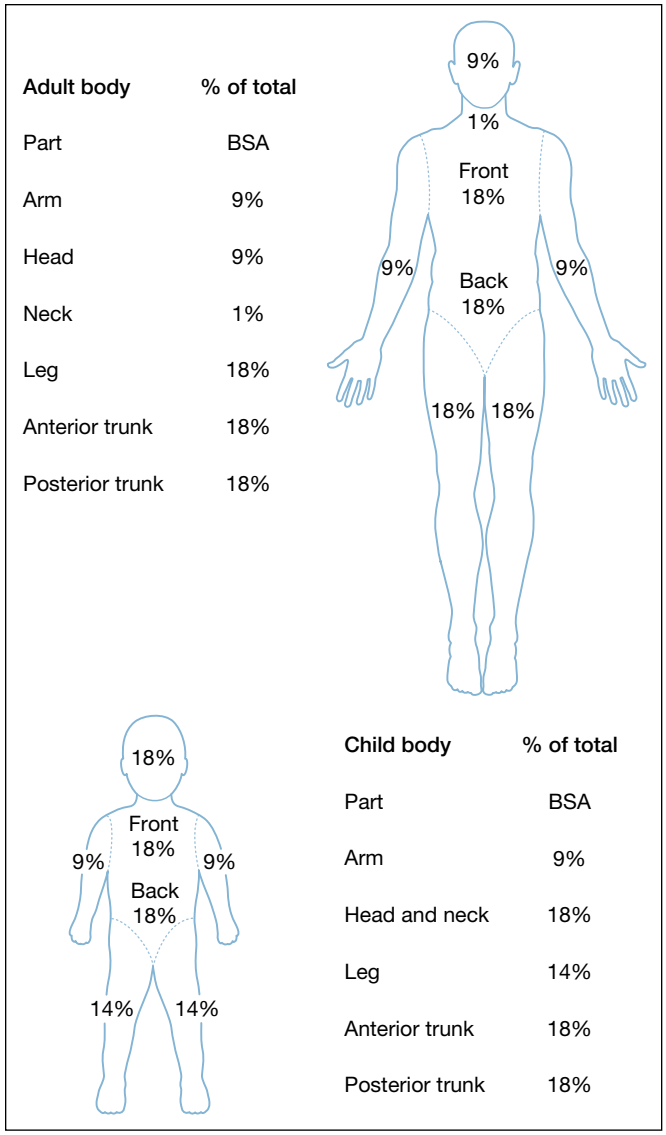


FIG. 1 Diagram of the rule of nines. *BSA*, body surface area. *(From Herndon D. Total Burn Care. 4th ed. Philadelphia: Saunders; 2012.)*

BOX 1 Useful Points for Estimating Burn Size

It is possible to estimate burn size before thorough cleaning of wounds.

- It is challenging to assess burn depth before thorough debridement of wounds, especially intact blisters.
- Do not include first-degree burns in the estimate.
- Second-degree burns blister and have sloughing of the epidermis.
- Superficial second-degree burns are moist, with blanching redness and are painful.
- Deeper second-degree burns remain sensate but less so than superficial burns; they may be red but will not blanch with digital pressure.
- Dryness and wounds with a whitish base are signs of a deep wound.
- Third-degree burns are dry, leathery, and insensate.

TBSA stimulate a systemic inflammatory response and need formal burn resuscitation with intravenous fluids to prevent hypovolemia, hypoperfusion, and the sequelae of tissue ischemia from shock. Inadequate fluid resuscitation may lead to cardiovascular collapse and conversion of burns to deeper wounds. Burns of lesser depth but still substantial area may need increased fluid as a result of evaporative fluid loss, particularly in children. Burn fluid resuscitation formulas are designed to guide resuscitation volume from inception, usually for the first few hours. Actual fluid requirements should be titrated according to standard endpoints of resuscitation and the overall condition of the patient. Patients with smoke inhalation injury often have fluid requirements in excess of calculated volumes.

Large burns have an absolute need for nutritional supplementation, preferably with enteral (tube) feedings. The rate of epithelialization, formation of granulation tissue, and immunocompetence depend on adequate nutrition. Depending upon burn size and preinjury nutritional status, large burns may require nutritional supplementation of 50% to 100% of basal caloric requirements (25 kcal/kg, 1.2 g protein/kg). Small- and medium-sized burns' nutritional needs are best guided by admission status, clear caloric goals, and an accounting of intake.

Assessing the Need for Decompression

Following burn injury, the early identification and treatment of elevated tissue pressure, similar to that of extremity compartment syndrome, can avoid the loss of viable tissue and eliminate a cause of profound morbidity. Thermally injured tissue forms edema due to the loss of microvascular integrity and transvascular fluid movement to the interstitial space of injured tissue. The larger the burn, the greater the edema, which also forms in unburned tissues, but there is seldom morbidity from edema of unburned areas. However, burned skin is less compliant than normal; thus, edema combined with decreased skin compliance can result in high levels of tissue pressure, especially in a circumferential burn. Releasing increased tissue pressure can be achieved by escharotomy. In burn injury, the restriction is at the level of the skin. Full-thickness incision of the burned skin or eschar to an edge of normal skin results in resolution of the increased pressure. Decompression of the deep fascial compartments is normally not required. Figures 2 and 3 demonstrate the recommended locations of decompressive escharotomies on the hands and body. Performance of escharotomy with an electrosurgery device until subcutaneous fat protrudes facilitates speed and hemostasis.

Circumferential burns are often considered for decompression; however, the presence of a circumferential burn is not an automatic indication. Incisions for decompression can cause substantial dyscoimesis in the future. For a cooperative patient with a small-to-medium size partial-thickness burn, careful fluid administration with limb elevation, coupled with serial examinations for increased tissue pressure, is an option. Subeschar and deep fascial compartment pressure monitoring is useful and encouraged. By contrast, larger or deeper circumferential extremity burns require decompression almost universally.

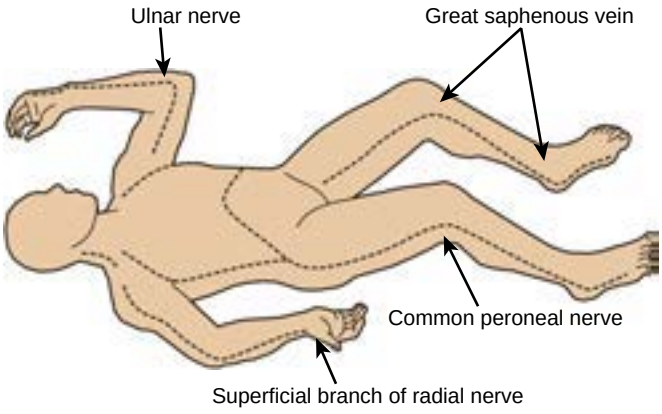


FIG. 2 Locations for escharotomy placement on the body. *(From Wolfe S, et al.* Green's Operative Hand Surgery. *7th ed. Philadelphia: Elsevier; 2016.)*

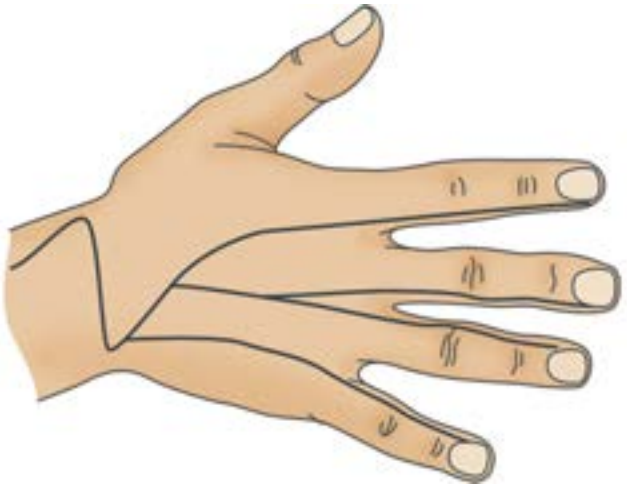


FIG. 3 Locations for escharotomy placement on the hands.

Electrical Injury

Burn injury from a true conductive electrical source is a particularly difficult clinical problem that requires a rapid, aggressive surgical approach. The external appearance of the wound on physical examination can be misleading, as entrance and exit wounds can be small while the amount of tissue damage to deep structures can be severe but hidden by intact overlying skin. Compartment syndromes from myonecrosis pose a risk of further tissue loss. In addition, myoglobin release from necrotic muscle can produce acute kidney injury, which increases mortality depending on its severity. Moreover, necrotic muscle is an excellent medium for bacterial colonization and invasion. Numerous long-term sequelae of conductive electrical injury and the complexity of the care required dictate that such patients should be transferred promptly to a burn center.

Child Abuse

The surgeon caring for a burned child must remain vigilant to the possibility of intentional inflicted harm and obtain an absolutely clear understanding of the circumstances surrounding the injury. Intentional burn injury is a common manifestation of direct abuse or to obscure other forms of child abuse. In addition to assessment of the patient (Box 2), multiple practitioners should interview the involved adults and child separately, then discuss as a group the circumstances reported by the adults and the child before the injury

BOX 2 Warning Signs for Child Abuse

- Lack of splash marks in purported scald injury
- Linear distribution of skin injury with purported immersion injury
- Contact burns that are evenly injured
- Wounds in various stages of healing
- A halo of scaled buttocks skin around unburned area, indicating the child was held down with force during immersion
- Unburned adults
- A previous history of burn injury

is attributed to an accidental cause. The input of the child protective services team can be an integral part of patient safety.

OPERATIVE CARE OF THE BURN WOUND

Meticulous preoperative planning dictates the steps of the procedure, as well as plans for further staged procedures, decreasing operative delays and optimizing results. Intraoperative patient positioning and draping is based on the locations of the wound and the proposed donor site. To address the entire wound adequately, one must identify any areas that are expected to heal spontaneously with wound care versus those that will require operative wound closure. Regardless, all wounds are cleaned and dressed as part of the procedure including those not planned for surgery, so as to afford the opportunity to clean and examine wounds thoroughly, under anesthesia, that might not be possible otherwise. In burns of TBSA greater than 40%, rapid closure is the prime directive as a life saving maneuver, representing the best defense against sepsis, catabolism, and death. During the early period of care for major burns, the main focus is necessarily on closure, but some consideration of the two remaining goals, function and cosmesis, must also be borne in mind. The operative discussion that follows will focus on less-extensive burns.

Preparing the Wound Bed

The tenets of burn surgery are the efficient removal of all dead tissue without damaging or sacrificing living tissue, while minimizing blood loss. Small wounds may be excised completely and either closed primarily or with a local tissue flap. Extremity burns that require grafting can be excised safely under tourniquet, minimizing blood loss associated with debridement. The determination of viable-versus-dead tissue is best made by exsanguination of the extremity, followed by inflation of the tourniquet. Red-to-purple staining after exsanguination is a reliable marker of nonviability, whereas healthy dermis is characterized by a pearly white appearance. Fat that is compromised is a dull yellow-to-orange/brown color; healthy fat is bright yellow. However, in a chronic burn wound and in lower extremities with clinical evidence of venous stasis, dermal discoloration may be misleading and lead to overaggressive surgery; thus, care must be taken when using this assessment, and experience is required.

Tangential excision is the most common method for removal of dead tissue. Special-purpose instruments are used, including the dermatome, which may be used for partial-thickness debridement. It is important to complete the excision to the surgeon's satisfaction in one stage and then to achieve hemostasis, as this will shorten the procedure and limit blood loss. Large areas can be excised compartmentally. To achieve hemostasis after tangential excision of a large surface area, arterial forceps or cautery may be used to control pulsatile blood flow. Application of a moist dressing with topical epinephrine or thrombin and mild compression can facilitate hemostasis of large surface areas, although the latter can be costly. The majority of bleeding points do not require direct attention, and compressive dressings may be left in place for 10 to 15 minutes before removal.

On the trunk, excision under tourniquet is not possible, and blood loss can be substantial. The bleeding pattern and tissue appearance is used to determine tissue viability and completeness of excision. Partial-thickness tangential excision of dermis is characterized by diffuse, punctate bleeding from the entire cut surface, whereas full-thickness skin debridement often results in pulsatile bleeding from perforating vessels. Tumescent fluid injection beneath the wound will limit blood loss. Burn wounds of great depth over a large area may require excision to the level of the fascia; this can limit blood loss greatly and increases efficiency, but the resulting marked functional and cosmetic impact must be considered when undertaking this approach. Small trunk wounds may also be excised completely and closed primarily or by tissue flap.

Special Considerations

Exposed vital structures such as bone, periosteum, tendon, peritoneum, major blood vessels, and nerve require additional consideration. These structures are often poor beds for a skin graft to "take" on, which may lead to graft failure. Worse still, the resulting wound will leave these delicate structures at risk of further compromise. Consider the use of homograft skin or moist dressings until granulation tissue has formed. Dermal templates have been used to temporize wound closure as well. However, there is little evidence that they can bridge gaps in the wound bed at the site of avascular structures such as the peritoneum. The dermal template provides a tissue layer between the skin graft and the vulnerable structure beneath, to allow smooth and separate movements of each until a viable bed for grafting is achieved. Dermal templates are also used more broadly to close large/deep burn wounds. Disadvantages of dermal templates include 2 weeks or more for templates to mature, requirement for a second procedure for skin grafting over the matured template, and careful handling required to prevent infection. The putative long-term benefits of decreased scarring and improved function are unproven.

Placing the Skin Graft

Several technical points to skin grafting must be considered. Place the skin under mild tension, aided by attaching one edge, then pulling/stretching the skin toward the opposite edge of the defect. Trim the skin to fit to the wound, leaving an ideal 1- to 2-mm gap from wound edge to the graft. The skin graft should contact the wound bed completely. This can be difficult with deep contours and can be aided by dressings under gentle positive or negative pressure. Avoid meshing skin whenever possible, particularly on exposed areas such as the hands and face. Anticipate that seams between strips of donor skin comprising larger grafts will become visible scars and areas of more intense contraction. Plan orientation appropriately. Staples, sutures, glues, and other modes of fixation can all be used, depending on the need. For children, consider fixation that is absorbable or sutures that are easily removed to facilitate aftercare.

Donor Sites

The creation of a donor site wound is necessary whenever skin autografting is required. The donor site(s) selection should be of a location that minimizes the impact of the harvest. Factors to consider in choosing a donor site are cosmesis, healing potential, intraoperative positioning and draping, pain, and practical postoperative positioning. It is important to counsel the patient that the donor site will create an additional permanent scar. When preparing to harvest the donor site, remember never to trust the dermatome calibration; inspect the gap created by the chosen setting visually. It is customary to set the dermatome to cut 6/1000 to 12/1000 of an inch deep. It can be useful to confirm the dermatome setting mechanically by passing a #15 scalpel blade tip into the gap. The knife should enter partially and glide the length of the dermatome blade without dropping in entirely. This technique will ensure that the width of the gap is less than 10 to 12/1000 of an inch. Activate the dermatome before contact with the skin and continue with gentle but persistent pressure and forward motion until it is lifted off the skin. Lubrication of the donor site with mineral oil makes it easier to control the passage of the dermatome. Good positioning of the patient and the surgeon will yield the best harvest. Watch the skin as it comes out of the dermatome. Do not rush; if the skin emerging from the dermatome is not satisfactory, keep the dermatome running and communicate with your assistants to try to improve the harvest. If there is no improvement, lift off and abort the attempt and reassess. An attempt that yields poor skin will lengthen the procedure, harm the cosmetic result, and increase morbidity.

Scalp as a Donor Site

Large, flat surfaces with good tissue turgor (anterior thighs, back) are suitable for harvesting large, uniform strips of skin for engraftment. The scalp is a possible donor site, as the skin obtained is a good color match for face, neck, and upper chest, and it can be a reliable donor site in patients with poor healing potential as a result of other chronic disease. When done properly in a hair-bearing individual, the donor site is invisible just weeks after the procedure. Scalp skin typically yields 3% to 4% TBSA before meshing. Late pain is usually less with the scalp donor site than with other donor sites. When the skin is taken carefully with standard harvest depth, healing is rapid and reliable with minimal risk of postoperative alopecia. Harvesting a graft from the scalp should always be undertaken after appropriate preparatory tumescent skin infiltration with bupivacaine and epinephrine in a balanced salt solution. Attempting harvest of scalp skin without tumescent fluid instillation will result in excessive blood loss, which can be difficult to control. Approximately 500 mL of tumescent fluid is routine for a complete adult scalp harvest.

To harvest a scalp graft, remove the hair from the area with clippers before entering the operating room; shave the scalp with a razor after the patient is under anesthesia, and instill the tumescent fluid with a 14-gauge spinal needle moving about the area. The appropriate depth can be ascertained by the relative ease of infiltration. Tending to the burn wound debridement at this point will allow sufficient time (10–15 min) for the epinephrine to take effect without adding to operative time. When recipient wound bed preparation is complete, return to the head and harvest the scalp skin as needed. The general principle of wound bed preparation followed by skin harvest is broadly applicable to minimize excessive harvesting and decrease operative time.

Dressings

A grafted wound bed requires a period free of shear forces so that adherence of the skin graft to the wound bed can take place. Additionally, the skin graft requires a moist environment that is free from bacterial contamination. The creation of a dressing to address these goals is as crucial to success as the other aspects of burn surgical care. Postoperative positioning, nursing care, and patient compliance (especially for children), can be major issues. A grafted extremity is dressed easily with a petrolatum gel-based fine gauze, clean dressing, and a splint; however, the task becomes more challenging with grafting that involves uneven surfaces subject to constant motion (e.g., anterior shoulder and lateral neck). Options include a tie-on bolster dressing in conjunction with a neck collar and axillary splint. A negative-pressure dressing can be considered if a good circumferential seal can be obtained with or without splinting, depending on the mobility of the wound.

Special problems are encountered with small children and their ability to work their way free of a dressing, so consider this as the procedure is planned. When the grafted areas require a complex dressing, it is good practice to discuss postoperative plans with nursing, rehabilitation staff, and the patient—or in the case of a child, with the patient's parent(s) or guardian—to increase the likelihood of success. For example, postoperative prone positioning may be an excellent choice for a graft placed on the back; however, such a plan is unlikely to succeed if it is not discussed and agreed upon beforehand. An unusual position can be tried with the patient before surgery, and bed modifications can be made to prepare for the patient after surgery. Innovative dressings are possible if the goals are understood and open communication takes place with everyone involved. A dressing failure may lead to graft loss, a return to the operating room for repeat grafting, more pain, and greater disfigurement.

SUMMARY

This chapter is offered with the surgeon in mind whose practice is not burn-focused. An effort has been made to offer advice to avoid problems and treat burns that do not require a burn center in the judgment of the treating physician. For a more complete discussion of burn care, the reader is directed to the Suggested Readings list. Burn centers can be contacted for advice on burns not thought to need the burn center. Utilization of a burn center as a source of education on best practice is to be encouraged, as well as for tertiary referral for specialty burn care.

Suggested Readings

Barie PS, Gupta A, Narayan M. Medical management of the burn patient. In: Cameron JL, Cameron AM, eds. *Current Surgical Therapy*. 13th edition Philadelphia: Elsevier; 2020:1295–1306.

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Medical Management of the Burn Patient

Robert Sheridan, MD, and Jeremy Goverman, MD

INTRODUCTION

Burn Care System

Over the past 30 years, burn care has evolved as a cohesive multidisciplinary specialty with a mature burn center verification process overseen by the American College of Surgeons Committee on Trauma and the American Burn Association. These organizational developments have contributed very significantly to improved outcomes allowing surgical teams to focus on burn management integrating disparate patient needs toward the overarching goal of successful rehabilitation and reintegration.

Burn Center Referral

The American Burn Association has promulgated a list of criteria that recommend transfer of more complex patients to burn centers, which reflect common sense opinion (Box 1). Those receiving burn patients should consider their personal and institutional capabilities as they evaluate and make transfer decisions. Discussion with regional supporting burn programs is never inappropriate.

BOX 1 The American Burn Association Criteria for Transfer to Burn Center

1. Partial-thickness burns (second-degree, superficial, and deep thickness) >10% TBSA
2. Burns involving face, hands, feet, genitalia, perineum, or crossing major joints
3. Full-thickness burns (third-degree) of any age group
4. Electrical burn injuries
5. Chemical burn injuries
6. Inhalation injury
7. Burn injury with preexisting medical comorbidities that may impact mortality or prolong recovery
8. Burn injury with concomitant trauma where burn poses greatest risk to morbidity and mortality
9. Burned children in hospitals where there is no qualified personnel and equipment for pediatric care
10. Burn injury requiring specialized social, emotional, or rehabilitative intervention

PHYSIOLOGIC CHANGES

Early Physiology

Burns over 20% of the body surface are often associated with a hypodynamic circulatory state in the first hours, with reduced blood pressure and peripheral perfusion. Unless shock is profound, usually associated with inadequate resuscitation, the changes are not generally caused by infection but are felt to be driven by hypovolemia, hypothermia, and the neurohormonal milieu immediately following a burn. Support of this physiology involves maintenance of body temperature, provision of added volume (guided by resuscitation formula), and judicious use of vasopressors.

Late Physiology

Over the subsequent 24 hours, a hyperdynamic state usually evolves in successfully resuscitated patients. This is characterized by tachycardia, enhanced peripheral flow with afterload reduction, increased body temperature, and muscle catabolism. It is driven primarily by a changing neurohormonal milieu and mimics septic physiology. Distinguishing these changes from those driven by infection is an important consideration in daily care. These changes will generally persist until well after definitive wound closure. The physiology is best managed with nutritional support. Efforts to tamp down the changes pharmacologically (NSAIDs, β-blockers, anabolic agents) have a mixed track record at best.

INITIAL EVALUATION

Evaluation of the Patient

Even with large burns, the cutaneous wound can generally wait until the patient is completely evaluated. It is easy to miss major coexisting injuries or to not adequately appreciate major comorbid conditions if the initial evaluation is hasty. Be thorough. Using imaging if injury mechanism indicates. The Advanced Trauma Life Support (ATLS) structure is an excellent evaluative template to apply routinely.

Evaluation of the Wound

The wound should be evaluated for size, pattern, depth, and circumferential components. Burn size can be estimated by "the rule of nines," patient's entire palm being 1% of the body surface, and by anthropometric chart (Fig. 1). Burn depth is often underestimated on initial examination and is best reevaluated serially by experienced examiners. Burn depth varies from very superficial epithelial first-degree, superficial and deep-dermal second-degree burns, full-thickness skin third-degree burns, and deep-tissue fourth-degree burns. Circumferential components should be noted for immediate decompression or monitoring for evolving status of perfusion over time.

INITIAL WOUND CARE

Decompression

Opportunities for effective decompression should not be missed. Edema beneath circumferential deep burns of the torso and extremities can compromise ventilation and perfusion, respectively. Simple escharotomies performed with coagulating electrocautery should be done as this evolves (Fig. 2). Retro-orbital edema in the setting of deep facial burns can compromise retinal blood flow. Lateral canthotomy will address this when intraocular pressures are excessive (Fig. 3). Deep thermal burns, high-voltage electrical injuries, and crush injuries are associated with compartment syndromes that respond to fasciotomy, which can be done through the bed of well-placed escharotomy incisions (Fig. 4).

Topical Care

Initially, burn wounds are sterile or nearly so, but subsequent rapid bacterial proliferation can be expected. The objectives of topical care are to reduce colonization, minimize desiccation, and reduce pain. There are many effective options that tend to be program-specific. Familiarity with specific agents is useful (Table 1). Increasingly, a variety of silver-releasing membrane dressings are used to good effect, again being highly program-specific. Vigilance for submembrane infection is important. For superficial burns, petroleum-based antibiotic topical agents are useful and contribute to good pain control. Weak enzyme-containing ointments are currently available for burns with thin amounts of overlying eschar. Available in Europe and likely coming to the United States are very strong enzyme preparations that may significantly speed eschar separation, reducing periods of uncertainty as to burn depth and potentially shortening the time to definitive closure.

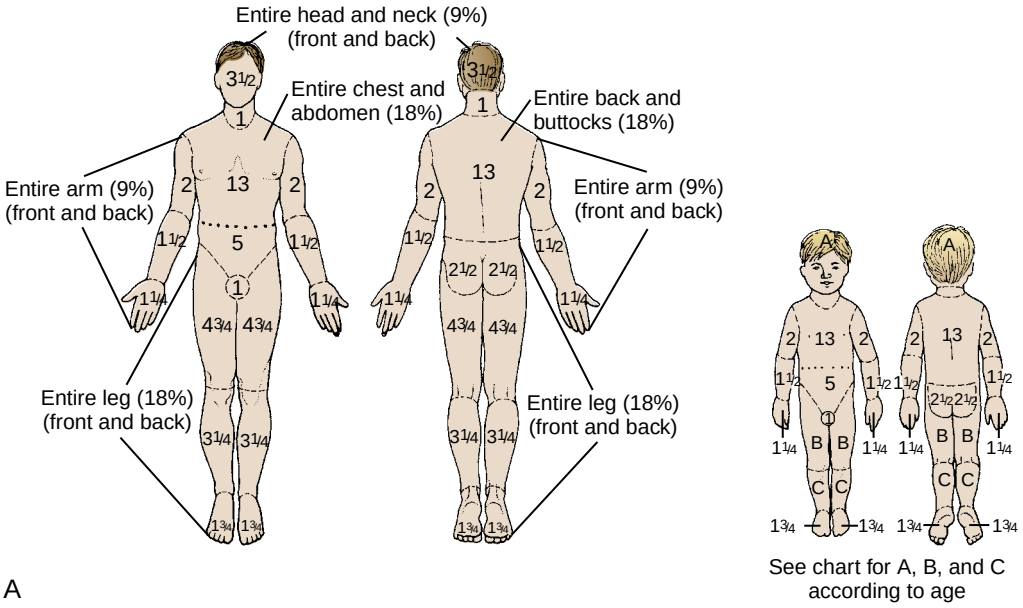
BURN EXCISION

Excision Philosophy and Basic Strategy

Data around the benefit of "early" excision (variably defined but generally meaning surgical removal of eschar within the first week of injury) are less robust than is widely assumed. However, it is generally believed that in patients with unequivocal full-thickness injury, early excision and definitive closure hastens recovery in patients with small unequivocal full-thickness burns and enhances survival in those with mid-size and larger unequivocal full-thickness burns. Data do not seem to support early excision of partial thickness burns or mixed-depth burns with a small full-thickness component. When considering this approach to burns, it is essential to clearly decide what to excise, when to excise, and how to cover resulting wounds. Multiple wound and nonwound factors must be considered including patient age and fragility, extent of unequivocal full-thickness wound, patient preference, distance from patient home, wound location, initial unclarity of wound depth, and available resources. Some frail patients with small deep burns are better served by protracted topical care and contraction than by hasty stressful excision with donor sites. These questions should be thoughtfully addressed on a case-by-case basis.

Excision Basic Technique

Historically, burn excisions have been described (rightfully) as bloody and physiologically stressful. However, that is no longer true



A

AGE	Birth–1 yr	1–4 yr	5–9 yr	10–14 yr	15 yr	Adult
Head	19	17	13	11	9	7
Neck	2	.....	.....	.....	.....	.....
Ant trunk	13	.....	.....	.....	.....	.....
Post trunk	13	.....	.....	.....	.....	.....
R buttock	2½	.....	.....	.....	.....	.....
L buttock	2½	.....	.....	.....	.....	.....
Genitalia	1	.....	.....	.....	.....	.....
R U arm	4	.....	.....	.....	.....	.....
L U arm	4	.....	.....	.....	.....	.....
R L arm	3	.....	.....	.....	.....	.....
L L arm	3	.....	.....	.....	.....	.....
R hand	2½	6½	8	8½	9	9½
L hand	2½	6½	8	8½	9	9½
R thigh	5½	5	5½	6	6½	7
L thigh	5½	5	5½	6	6½	7
R leg	5	.....	.....	.....	.....	.....
L leg	5					
R foot	3½					
L foot	3½					

B BODY AREA

FIG. 1 Burn size.



FIG. 2 Torso escharotomy.

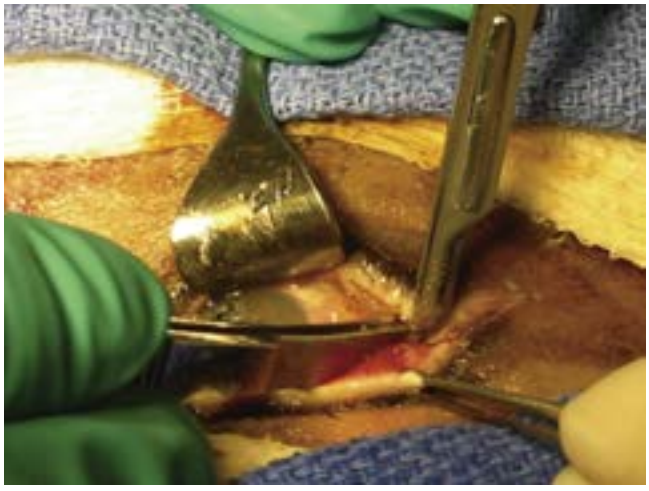


FIG. 3 Lateral canthotomy.



FIG. 4 Escharotomy with fasciotomy.

TABLE 1 Topical Agents

Agent	Characteristics
Silver sulfadiazine	Painless on application, fair to poor eschar penetration, no metabolic side effects, broad antibacterial spectrum
Mafenide acetate	Painful on application, excellent eschar penetration, carbonic anhydrase inhibitor, broad antibacterial spectrum
0.5% Silver nitrate	Painless on application, poor eschar penetration, leaches electrolytes, broad spectrum (including fungi)
Vache	Solution of hypochlorous acid with broad spectrum of antisepsis
Cerium nitrate	Felt to decrease inflammatory mediator release from viable areas of wounds

and having that expectation is a disservice to patients and operating room staff and providers. Very simple techniques exist to minimize operative blood loss and should be part of every excision, beginning with careful preoperative planning so that intraoperative indecision does not lead to longer operative time and enhanced blood loss. Although extremity tourniquet excision is useful, the most valuable technique is dilute epinephrine clysis, which is safe and extremely effective (Table 2).

TABLE 2 Hemostatic Techniques of Burn Excision

Technique	Characteristics
Dilute epinephrine clysis	Epinephrine clysis with 0.5 mcg/cc is well tolerated and effective in wound excision and split-thickness donor sites.
Extremity tourniquet	Exsanguinate and use pneumatic or broad elastic wrap tourniquet for extremity excisions.
Maintenance of euthermia	Hypothermic patients bleed more. Maintain euthermia with room heating and patient warmers. Truncate case if unable to maintain body temperature.
Avoidance of "excision indecision"	Decisions are ideally made before surgery so OR time can be minimized.
Staging excisions	Oftentimes multiple smaller sessions are better tolerated than single massive excisions.
TxA	Not standard of care but has been used with variable effect topically and intravenously.

RESUSCITATION

General Strategy

All the myriad different resuscitation formulas share the overarching goal of maintaining acceptable organ perfusion during an early postinjury period of hemodynamic uncertainty and capillary leak. Exactly how this is best done and monitored is the source of endless debate. The authors' personal practice, based on extensive practical experience in adults and children, is detailed in Table 3.

Fluid Choice

For historic reasons, early burn resuscitation formulas emphasized avoidance of colloid, despite this being the more physiologic replacement. This resulted in predictable anasarca with its attendant morbidity. In recent years, colloid fluids (especially 5% albumin) have become a routine part of burn resuscitation with reduced incidence of anasarca-driven morbidity.

End points and Monitoring

Age-specific resuscitation endpoints should drive regular titration of fluid infusions during resuscitation. Commonly accepted endpoints are listed in Table 4.

Management of Anasarca (ACS, Escharotomy Monitoring)

Although seen less frequently today, morbid events related to anasarca remain fairly common and should be addressed in a timely fashion. These include extremity ischemia treated with escharotomy (see Fig. 2), retrobulbar edema treated with lateral canthotomy (see Fig. 3), intracompartmental edema treated with fasciotomy (see Fig. 4), and abdominal compartment syndrome managed with torso escharotomy and occasionally abdominal decompression.

CRITICAL CARE

Practice of Burn Critical Care

Burn critical care has evolved in parallel with surgical critical care in general. Common practice and developments will not be repeated here. From a systems perspective, critical care must be an embedded component of any burn program. Exactly how this is done will vary from program to program, from stand-alone burn intensive care units staffed by burn surgeon intensivists to collaborative practices with a multispecialty intensive care unit with processes to ensure smooth continuous coordination between the surgical and medical teams. From a system perspective, there are a few issues that are somewhat unique to the burn patient, including those itemized in Box 2.

TABLE 3 Personal Burn Resuscitation Practice

Overall Burn Size	Lactated Ringers Solution	5% Albumin Solution
1–20	1.5 M	None
20–50	P–1 M	1 M
50–100	P–2 M	2 M

M = calculated maintenance IV fluid rate

P = total hourly fluid calculation using Parkland Formula

Other relevant points:

If patient is child less than 20 kg, 1M of calculated LR is replaced with D5LR to prevent hypoglycemia.

During first 24 hours, infusions rates are adjusted hourly to endpoint targets. For first 24 hours, LR is primary titration target. After 24 hours LR and 5% Albumin are titrated in tandem. Usually, at 24 hours patients are requiring 1.5 M overall.

Overall goal is to "just on the dry side of euvolemia."

In hemodynamically stable patients, tube feeds can be started and advanced during first 24 hours. This volume should be subtracted from LR rates.

Resuscitation efficacy should be frequently assessed and reassessed and quantity and type of resuscitation fluid appropriately adjusted.

TABLE 4 Resuscitation Endpoints

Endpoint	Target
Physical Exam	Full peripheral pulses; warm distal extremities
Mean Arterial Pressure (MAP)	MAP >65 mm Hg; HR <100 bpm, SBP >100 mm Hg
Urine Output	Adults: >0.5 cc/kg/h Young Children: 1 cc/kg/h
Venous O_2 Saturation (SvO_2)	SvO_2 >65–75
Hemoglobin (Hgb) Hematocrit (Hct)	Men: 13.5–17.5 g/dL, 41%–50% Women: 12.0–15.5 g/dL, 36%–48%
Acid-Base	pH 7.35–7.45
Base Deficit	(-)2 mEq - (+)2 mEq
Central Venous Pressure	2–10 cm H_2O

LONG-TERM FOLLOW-UP

Most burn programs now have an embedded capacity to meet the long-term recovery needs of their patients. This important component of care can be addressed through dedicated burn aftercare programs or coordinated collaborative relationships with rehabilitation and reconstruction resources that should include emotional support.

Reconstruction Philosophy

The current paradigm of burn care represents an integrated and multidisciplinary approach to injury where acute care, rehabilitation, and reconstruction are all considered from the moment the burn patient arrives to the burn unit. Prediction, prevention, and treatment of potential functional and aesthetic morbidity now starts at the time of initial resuscitation with attention to judicious use of fluids during resuscitation, consideration of early splinting of joints, and early excision and grafting. The primary goals of burn reconstruction are restoration of function and form via the prevention and treatment of contractures and hypertrophic scarring (Box 3).

An important principle to consider is that most burn injury results in skin loss. Even for burns that undergo early excision and grafting, the visible scar is often the result of significant contracture of surrounding skin, which results in scar contractures and wounds under tension. The right time to perform burn reconstruction after the acute phase differs from patient to patient. Typical prevention measures include splinting, physical and occupational therapy, silicone gel sheeting, compression, and massage. Treatments include surgical releases and scar lengthening procedures with local or distant tissue flaps, split thickness, or full-thickness skin grafting. Nonsurgical treatment options include intralesional steroid injections and laser therapy.

Laser Therapy

Lasers have gained in popularity for scar management over the past decade. For the treatment of hypertrophic burn scar, fractionated photothermolysis is most commonly used with CO_2 or erbium. Fractional technologies can be divided into two main categories: ablative and nonablative. Histologically, with nonablative lasers, the treatment results in a column of denatured epidermis and dermis and an intact stratum corneum. With ablative lasers, the column of tissue is vaporized, the stratum corneum is removed, and the microcolumns demonstrate a thin layer of eschar lining the cavity. Around these cavities are concentric zones of coagulation, comprised of denatured collagen. Reepithelialization of the coagulation zones occurs rapidly, within 48 hours. The combined thermal and physical damage induced by the laser ultimately results in collagen induction, regeneration, and realignment resulting in improvements in the thickness, pliability, and tightness of the hypertrophic scar, as well as improvements in scar-related symptoms such as neuropathic pain and pruritus.

BOX 2 Unique Burn-Specific Critical Care Issues

Cardiovascular

- Endocarditis and suppurative thrombophlebitis may be the cause of persistent bacteremia.
- Hypertension can be seen in up to 20% of children and can be managed with β-adrenergic blockers.
- Central line sites may be wound-limited and needed for prolonged periods—treat with care and use minimum line diameter in children.

Pulmonary

- Carbon monoxide intoxication can be managed with 6 hours of 100% normobaric oxygen especially when burns preclude safe use of hyperbaric oxygen.
- Inhalation injury is associated with small airway occlusion and pneumonia after several days as endobronchial lining sloughs.

Neurologic

- Transient delirium is common and generally resolves with supportive therapy. Anoxia, metabolic disturbance, and structural lesions should be considered using history, exam, and indicated imaging.
- Seizures can result from hyponatremia or abrupt benzodiazepine withdrawal.
- Peripheral nerve injuries can occur from direct thermal injury, compression from compartment syndrome or overlying inelastic eschar, major metabolic disturbances, or suboptimal splinting techniques in sedated patients.
- Delayed peripheral nerve and spinal cord deficits can rarely develop weeks or months after high-voltage injury secondary caused by small-vessel injury and demyelination.

Hematologic

- Neutropenia and thrombocytopenia can be markers of impending sepsis.

Renal

- Early acute renal failure may follow inadequate resuscitation or myoglobinuria.
- Late renal failure may follow sepsis and multiorgan failure or the use of nephrotoxic agents.

Adrenal

- Acute adrenal insufficiency may be caused by early burn shock and present later as hypotension, fever, hyponatremia, and hyperkalemia.

Otolaryngologic

- Bacterial invasive chondritis of the burned ear can cause rapid loss of potentially viable ear cartilage and may be prevented by topical mafenide acetate that penetrates the wound.

Gastrointestinal

- Hepatic transaminase elevations secondary to transient hepatic blood flow deficits during resuscitation from large burns generally resolves with volume restitution.
- Late hepatic failure, beginning with elevations of cholestatic chemistries and progressing through coagulopathy and frank failure, complicates sepsis and multiorgan failure.
- Early and late pancreatitis is generally coincident with splanchnic flow deficits early and sepsis-induced organ failures later in the hospital course.
- An ulcer diathesis can be seen in burn patients generally caused by early splanchnic perfusion compromise. Complications of bleeding and perforation are best prevented pharmacologically.
- Intestinal ischemia, which can progress to infarction, may occur due to inadequate perfusion with late or inadequate resuscitation.

Ophthalmologic

- After resolution of edema of the burned face, ectropia from progressive contraction of burned ocular adnexa results in exposure of the globe, which is ideally managed with acute eyelid release. Tarsorrhaphy is rarely helpful as the same contraction forces pull out tarsorrhaphy sutures.
- Corneal ulceration that develops after corneal burn or from exposure can progress to full-thickness corneal ulceration if secondary infection occurs. This can be minimized by diligent globe lubrication and acute lid release where necessary.

Genitourinary

- Neither bladder catheterization nor fecal diversion is usually required for management of perineal and genital burns.

Musculoskeletal

- Ranging, splinting, and antideformity positioning are ideally continued throughout the period of critical illness to facilitate later rehabilitation efforts.

BOX 3 Risk Factors for Burn Scar Formation

Injury-Related

Depth of burn
Microbiologic burden
Location of burn

Patient-Related

Genetics
Race/skin color/age

Treatment-Related

Type of wound closure
Time to healing (~21 days)
Tension

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Cold-Induced Injuries and Hypothermia

Sean Hickey, MD, and Colleen M. Ryan, MD

INTRODUCTION

Cold-induced injury is classified into three broad categories: (1) nonlocalized cold-induced injury (systemic hypothermia), (2) localized nonfreezing cold-induced injury, and (3) localized freezing cold-induced injury.

SYSTEMIC HYPOTHERMIA: NONLOCALIZED COLD-INDUCED INJURY

In the United States, 1500 deaths per year are related to hypothermia. Approximately 50% of all deaths due to hypothermia in the United States are in persons ≥65 years of age. Systemic hypothermia is defined as a core body temperature less than 35°C. Systemic hypothermia occurs when heat is lost to the environment at a greater rate than the body can produce via cellular metabolism. Primary hypothermia is caused by exposure to cold environments, whereas secondary hypothermia is an inability of the body to adequately produce heat. Systemic hypothermia is most often related to immersion in cold water and is associated with significant morbidity and mortality, especially in pediatric and elderly populations. Hypothermia is often associated with environmental exposure during military campaigns and winter-related recreational activities. Traumatic injuries are associated with hypothermia, especially in those presenting with traumatic brain injuries, traumatic injuries occurring at night or during the winter season, patients admitted following motorcycle or bicycle accidents, trauma patients requiring prolonged extraction or extended preclinical time, and in trauma patients receiving preclinical nonwarmed intravenous fluids. Poorer outcomes are often demonstrated in the homeless due to lack of shelter or appropriate cold-weather clothing and those with poor social support or comorbid psychiatric conditions such as schizophrenia or bipolar disorder. Populations afflicted with drug and alcohol use disorders also demonstrate worse outcomes.

Heat lost to the environment under normal, nonfreezing conditions occurs through four mechanisms: radiation, evaporation, conduction, and convection. Radiative heat loss becomes more pronounced at ambient temperatures less than 20°C and is responsible for 60% of heat lost to the environment. Radiant heat loss is proportional to the area of exposed body surface area (BSA) and ambient temperature. Radiation is the major source of heat loss in most surgical patients. Twenty-five percent of the heat lost to the environment is due to evaporation of water from the skin and respiratory tract. During strenuous activities, the body can lose 85% of its heat to the environment due to evaporation of water from increased sweating and minute ventilation. The remainder of heat lost to the environment is due to conduction (15%) and convection (2%). Conduction and convection are the dominant mechanisms leading to systemic hypothermia. Immersion in cold water leads to rapid decrements in core body temperature due to the intrinsic properties of water that conduct heat away from the body 25 to 30 times faster than cold air.

There are efferent physiologic and behavioral responses to facilitate increased heat production and prevention of heat loss to regain normothermia. It is important to note that behavioral response to hypothermia is by far the most effective. Behavioral responses to hypothermia are interventions such as self-extrication from a cold, wet, and/or damp environment; obtaining access to dry and/or warm shelter; removal of wet or damp clothing; and obtaining dry cloth coverings to decrease radiant and convective heat loss. The physiologic responses to hypothermia are discussed later in this chapter.

Signs and Symptoms

Generalized exposure to cold temperatures (whether near or below freezing) can lead to systemic hypothermia, which is classified into four categories: mild (32°C–35°C), moderate (28°C–32°C), severe (20°C–28°C), and profound (<20°C). These broad temperature categories guide treatment algorithms in hypothermic patients. It is important to recognize that moderate to severe hypothermia is associated with an approximate 40% in-hospital mortality rate. Of note, the lowest adult accidental hypothermia survival without neurologic sequelae was reported with a core temperature of 13.7°C.

Mild hypothermia is defined as a temperature of 32°C to 35°C. Patients demonstrate minimal alterations in other vital signs such as heart rate or blood pressure. The patient tends to be alert and oriented, although they may have altered sensorium, ataxia, lethargy, and dysarthria. The body's response to mild hypothermia is to institute shivering until the thermal setpoint is achieved or until glycogen stores are depleted. Of note, the presence or absence of shivering may be unreliable, especially if the patient is intoxicated, hypoglycemic, demonstrates altered mental status, or has concomitant injuries.

Moderate hypothermia is defined as a temperature of 28°C to 32°C. The patient develops central nervous system depression demonstrated by altered mental status to complete loss of consciousness. Vital signs are deranged. Hypotension, bradycardia, cardiac arrhythmias, hypoventilation, hyporeflexia, decreased pupillary constriction and dilation to stimuli, and eventual loss of the shivering mechanism are common.

Severe hypothermia is defined as a temperature less than 28°C, with profound hypothermia being defined as below 20°C. Symptoms include coma with dilated pupils, severe hypotension, bradycardia, complete loss of muscular tone, life-threatening cardiac arrhythmias including ventricular fibrillation, decreased cardiac output, and severely depressed or absent respirations.

It is important to remember that hypothermic patients often present with associated traumatic injuries. Care of the patient should start with the standard Airway, Breathing, Circulation, Disability, and Exposure (ABCDE) guidelines as set forth by the American College of Surgeons: The Committee on Trauma.

Physiologic Responses to Generate Heat and Conserve Core Body Temperature

The nude human body prefers an ambient temperature between 20°C and 25°C. Intrinsic thermoregulatory mechanisms governed by the hypothalamus allow the unstressed human adult to tolerate a wide variation in environmental temperatures. The hypothalamus is responsible for regulating the body's core temperature in the thermoneutral setpoint of 37±0.5°C. Any deviation above or below this set point leads to thermoregulatory efferent responses to maintain the core body temperature within the thermoneutral zone. The body's physiologic response to systemic hypothermia is twofold: (1) increase heat production by increasing cellular metabolism and (2) reduce heat loss by shunting blood via peripheral vasoconstriction.

The response to systemic hypothermia in children, adolescents, and adults is due to increased release of thyroid hormone and catecholamine, which increases the basal metabolic rate in addition to increased shivering. Involuntary shivering by striated muscle cells is known to increase basal metabolic rate three to fivefold. Involuntary shivering will continue until the body's glycogen stores are depleted. Interestingly, newborns are unable to activate involuntary shivering of striated muscle in response to hypothermia and must rely on

nonshivering thermogenesis from brown fat deposits immediately after birth.

In a normothermic individual, a 2°C to 4°C gradient exists between the superficial skin and the core tissue compartments. Peripheral vasodilation and vasoconstriction of cutaneous arterioles is mediated by two competing sympathetic neuronal branches and allows for a brisk thermoregulatory reflex to maintain normothermia. Blood flow to the superficial skin can raise as high as 8 L/min (or 60% of cardiac output) in patients with severe heat exposure to essentially 0 L/min in patients with immersion hypothermia. Thus, cutaneous vasoconstriction is the primary mechanism of heat conservation in the hypothermic individual by rapidly diverting warm blood away from the skin to decrease conductive and convective heat lost to the environment.

Diagnosis and Treatment

Given the association between traumatic injuries and hypothermia, all patients in the prehospital setting are placed in full spine precautions with a rigid cervical collar in place. Immediate establishment of intravenous access is performed given the potential for ventricular fibrillation in moderate to severe hypothermia. The diagnosis of hypothermia can be made based on a history of cold exposure, physical exam, electrocardiogram (ECG) evaluation, and determination of the patient's core body temperature utilizing an appropriate thermometer. Concerning findings on ECG include prolongation of the QRS interval and the presence of J waves (also known as Osborne waves), which characteristically are defined as a positive deflection at the J point (negative in aVR and V1) and most prominent in the precordial leads.

The Swiss Staging Model can be used in the prehospital setting or in austere environments as a guide to determine severity of hypothermia when an appropriate low temperature thermometer is not available. The Swiss Staging Model classifies degree of hypothermia based on symptoms: HT-I, conscious and shivering; HT-II, impaired consciousness and no shivering; HT-III, unconscious, not shivering, but vital signs present; and HT-IV, no vital signs (Table 1).

Standard clinical thermometers read to a minimum temperature of 34°C and lack the ability to accurately determine core body temperature due to alterations in peripheral vasoconstriction. Historically, the Swan-Ganz catheter was considered the gold standard for measuring core body temperature. However, caution should be taken placing pulmonary artery catheters during the management of accidental hypothermia due to complications associated with inducing unstable arrhythmias. In clinical practice, core body temperature is best measured via an esophageal probe inserted into the lower third of the esophagus and is considered standard of care for patients requiring endotracheal intubation. In hypothermic patients who do not require endotracheal intubation, a continuous rectal thermometer can be used in place of an esophageal thermometer. Care must be taken to insert the thermometer at least 10 to 15 cm into the rectum and avoid placing the probe directly into cold feces. Bladder temperature if appropriately insulated may also be used in awake patients.

In moderate to severe hypothermia, a broad laboratory workup is initiated including lactate, creatine kinase, lipase, arterial blood gas, and toxicology screen. While reviewing the laboratory workup, it is important recognize that hematocrit will rise 2% for every 1°C drop in temperature. White blood cell count and platelet counts are often decreased due to splenic sequestration, and prothrombin and partial thromboplastin times are often increased due to coagulopathy. Lipase is often elevated in hypothermia, and clinically significant pancreatitis is common. Insulin is ineffective at temperatures below 30°C; thus, treatment of elevated blood glucose in the hypothermic patient begins with rewarming.

Initial management of a hypothermic patient begins with removal of wet or damp clothing with scissors. Aggressive movements during physical exams may precipitate ventricular fibrillation. Rubbing and massaging of the patient's extremities should be avoided. Intravenous antibiotics should be given if hypothermia is associated with cold-water immersion.

For mild hypothermia (or HT-I), patients are often treated with passive external rewarming. Dry, warm blankets or clothing are applied, and active movement is encouraged. Warmed, sugar-containing beverages are recommended. In an austere environment, skin-to-skin contact with a warm body can facilitate rewarming.

Moderate hypothermia (or HT-II) is treated with active external rewarming with forced warmed air, warmed humidified oxygen, thermal packs, heating pads, radiant heat, and/or warm water immersion at 37°C to 42°C. Rewarming the trunk should occur before the extremities. For moderate to severe hypothermia (HT-II and HT-III), both active external rewarming and active internal rewarming is instituted simultaneously. Active internal rewarming includes warmed IV fluids, in addition to pleural, peritoneal and/or bladder irrigation with warmed 42°C isotonic saline. Pleural rewarming with a left thoracostomy tube should be avoided as it may contribute to cardiac arrhythmias. Extracorporeal rewarming is the most effective method for active internal rewarming and can increase core temperature by 1°C to 2°C every 3 to 5 minutes. In moderate to severe hypothermia, initiation of rewarming should take precedence over treatment of any frostbite related injuries.

Patients in cardiopulmonary arrest (HT-IV) should undergo resuscitation per advanced cardiac life support guidelines until rewarmed to 32°C. Fixed and dilated pupils are not a contraindication for beginning cardiopulmonary resuscitation. Exceptions to cardiopulmonary resuscitation in the hypothermic patient include a frozen chest wall, potassium of greater than 12 mEq/L on presentation, and lethal associated injuries.

Outcomes After Hypothermia

Outcomes are worst for the very young and elderly. The young are more susceptible to hypothermia due to decreased glycogen stores and decreased ability to maintain the shivering response to

TABLE 1 Swiss Staging Model: Degree of Hypothermia Based on Symptoms and Therapies

Stage	Clinical Symptoms	Estimated Core Temperature	Therapy
HT-1	Conscious, shivering	35°C to 32°C	Warm room and clothing; administer warm liquids
HT-2	Impaired consciousness, not shivering	32°C to 28°C	Telemetry, passive, and active external rewarming
HT-3	Unconscious, no shivering, vital signs present	28°C to 24°C	HT-2 therapies, plus active internal rewarming, consider ECMO if available
HT-4	No vital signs, apparent death	24°C to 13.7°C	ACLS algorithm, HT-3 therapies, ECMO if available
HT-5	Death due to irreversible hypothermia		

hypothermia. The young have a relative increase in their BSA, which facilitates an increased rate of heat lost to the environment with respect to adults. Infants and the young are at greater risk of complications given decreased cognition related to age and difficulties in communication, and they are unlikely to implement behavioral interventions to treat immersion hypothermia without help from adults.

Older adults are more susceptible to hypothermia than healthy middle-aged adults. The cause is multifactorial. Recovery from hypothermia requires a brisk vasomotor response that is blunted with increasing age. Thus, older individuals are unable to conserve heat lost to the environment. It is essential to recognize that comorbid conditions, especially related to cardiac function, limit an elderly patient's recovery from accidental hypothermia. In contrast, nearly all young patients who present with accidental hypothermia in the absence of shock survive neurologically intact. Increased in-hospital mortality is associated with age greater than 75, frailty, prehospital cardiac arrest, need for endotracheal intubation, hemodynamic instability, and hyperkalemia. Outcomes are unrelated to the severity of hypothermia on presentation.

LOCALIZED NONFREEZING AND FREEZING COLD-INDUCED INJURY

Localized cold-induced tissue injury is an array of soft tissue injury related to continued exposure to nonfreezing temperatures, or due to exposure temperatures below freezing. Exposure to nonfreezing and freezing temperatures can lead to localized disruptions in vascular flow to affected tissues. Continued exposure to nonfreezing temperature potentiated by a wet or damp environment can lead to localized conditions such as chilblains, immersion foot/trench foot, and immersion hand. Exposure to freezing temperatures causes frostbite, the most severe form of cold-induced injury to soft tissues. Cold-induced tissue injury often occurs in patients presenting without hypothermia. Areas most affected by frostbite are the extremities, digits, and other often exposed areas such as the ears, chin, and cheeks. Initially, the skin takes on a grey and waxy appearance, and is insensate before rewarming. Patients will often report paresthesia of affected tissues and may report neurologic deficits.

Chilblains

Chilblains (also known as *pernio* or *perniosis*) is most common in the civilian setting due to continued exposure to above-freezing temperatures and damp environments. The diagnosis is based upon the patient's history of recent cold exposure and clinical exam. The dorsal fingers and toes are most affected and often demonstrate violaceous skin lesions, macules, and/or nodules at the sites of cold exposure. Associated symptoms include tenderness, pruritis, pain, and burning. Complications associated with chilblains are blistering, ulceration, and wound infection but not tissue loss. Chilblains can be acute or chronic. Acute chilblains present within 12 to 24 hours of cold exposure with associated skin lesions and symptoms resolving within 2 to 3 weeks. Chronic chilblains are characterized by recurrent lesions, chronic pain, and paresthesia lasting longer than several weeks. The primary treatment for acute and chronic chilblains is to prevent further exposure of the tissue to the cold and to perform local wound care if lesions become blistered, hemorrhagic, or ulcerate. Any evidence of infection should lead to prompt antibiotic therapy for cellulitis.

Immersion Foot and Hand and Trench Foot

Immersion foot and hand and trench foot are clinically and pathologically identical; however, they are associated with different etiologies. Trench foot is well described during World War I and was due to continued exposure to nonfreezing temperatures and damp or wet socks or boots. Immersion foot and hand was well described in World War II and due to continued exposure to cold water following shipwrecks. Both injuries occur when the tissues are exposed to a damp environment in temperatures ranging from 1°C to 15°C over a prolonged period. Affected extremities initially demonstrate tense edema and severely tender violaceous skin lesions. In severe presentations, this is followed by microvascular thrombosis, ulcers, tissue loss, and dry or wet gangrene. Nerve damage can occur within 14 to 22 hours and can lead to chronic vasospastic symptoms, severe hyperalgesia to light touch, and burning sensations. Sensory deficits usually diminish; however, paresthesia often continues. In severe cases or chronic exposure to nonfreezing cold temperatures, paralysis can ensue.

FROSTBITE

Frostbite is a cold-induced, thermal injury related to tissues freezing and thawing when exposed to temperatures at or below their freezing point. The hands and feet account for the most affected areas of injury in greater than 90% of frostbite cases. Frostbite can occur with variable exposure time (minutes to hours) to freezing temperatures due to environmental conditions leading to conductive or convective heat losses and types of clothing and/or boots/gloves worn at the time of exposure. Early diagnosis and treatment of frostbite is essential to maximize tissue salvage. Frostbite has been characterized by severity much like burn injuries in a first- through fourth-degree classification system based on the depth of injury. Often, a single extremity will have several differing degrees of frostbite depth.

The traditional classification of burn injury can loosely guide general practitioners as to the degree of severity for cold-induced injury; however, one must be cognizant that this is a generalized association between frostbite and thermal injury, with the underlying mechanisms and treatment algorithm being vastly different.

First-Degree Frostbite

First-degree frostbite, also known as "frostnip," refers to superficial cooling of the skin without cellular damage (Fig. 1). The injury is not associated with blistering, ulcers, or hemorrhagic lesions; however, superficial desquamation can occur and typically resolves within 1 to 2 weeks. Symptoms of frostnip are itching, pain, paresthesia, and numbness associated with white, yellow, and or erythematous appearance of the affected skin. Occasionally, long-term sensitivity to hot and cold temperatures can occur following a first-degree frostbite injury.



FIG. 1 First-degree and second-degree frostbite. Epidermal skin loss and peeling are seen.

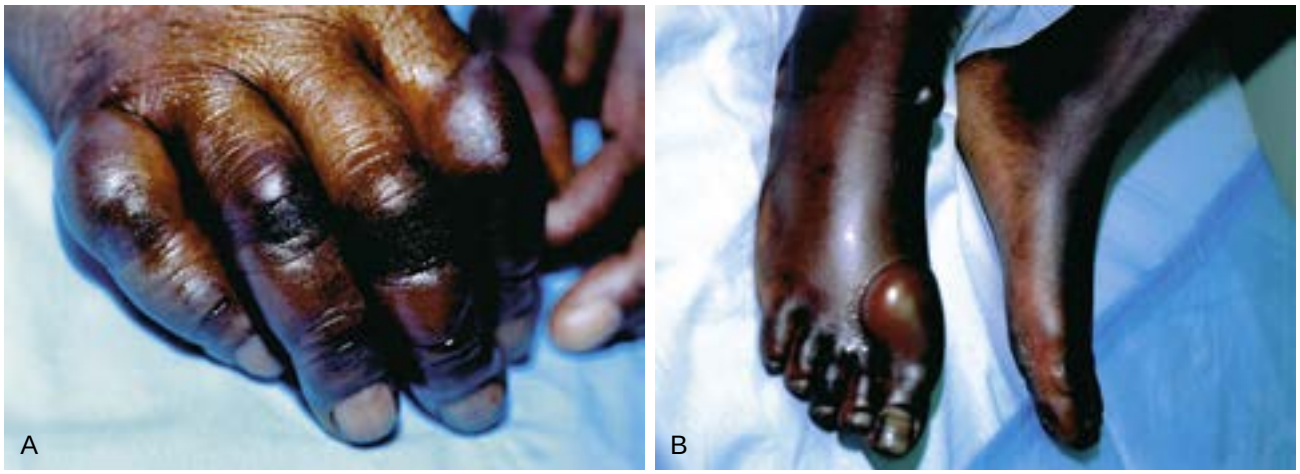


FIG. 2 **(A)** Second-degree frostbite in the fingers. Vesicles and swelling are seen. **(B)** Second-degree frostbite in the feet. Vesicles and swelling are seen.

Second-Degree Frostbite

As freezing continues, the superficial skin and dermis are injured, leading to blister formation 24 to 48 hours after exposure to freezing temperatures (Figs. 1 and 2). Patients present with pain, numbness, paresthesia with associated edema, and erythema of involved tissues. Blisters may be filled with serous fluid and often harden and turn purple to black following rewarming. The severity of the injury often appears worse as dermal appendages and deeper tissues are spared. The blisters form an overlying eschar, which sloughs off several weeks later, revealing healthy granulation tissue and or dermis/epidermis. There is no long-term tissue loss with second-degree frostbite. The affected tissues are often permanently sensitive to both heat and cold.

Third- and Fourth-Degree Frostbite

Third- and fourth-degree frostbite are most severe and involve both the superficial and deep tissue (Fig. 3). Third- and fourth-degree frostbite tend to cause hemorrhagic blisters and full-thickness injuries down beyond dermal appendages and into the adipose tissue. Patients with third-degree frostbite present with edema and hyperemia within 24 to 72 hours of injury, which then develops into a thick black eschar several days later. The overlying eschar will typically lift after 4 to 12 weeks. Fourth-degree injuries extend down to and/or involve bone, muscle, and nerves. The affected tissue often hardens and mummifies within 1 to 2 weeks following the injury, sooner if infection occurs. Neurologic symptoms for third- and fourth-degree frostbite are like those experienced by patients affected by first- and second-degree frostbite.

Epidemiology

Cold temperatures remain a credible threat to those not prepared to weather the elements in both the military and civilian setting. At the present time, in both the military and civilian settings, frostbite is an injury of morbidity rather than mortality and is associated with loss of digits and extremities. In the military setting, trench foot and frostbite contributed to over 1 million United States casualties in World Wars I and II, and the Korean War. Although there is no formal reporting of cold-induced injury in the military or civilian setting, a general trend indicates that modern frostbite injury is now more common within the civilian rather than military setting in both the developed and underdeveloped world.



FIG. 3 Third-degree and fourth-degree frostbite with tissue death; note demarcation beyond the interphalangeal joint.

In the modern era, trench foot and immersion foot and hand tend to happen in the military setting, whereas chilblains and frostbite are most seen in the civilian setting. In the civilian population, cold-induced injury is associated with winter recreational activities (such as skiing, hiking, and climbing), poor socioeconomic status such as with homeless populations or those afflicted with mental health issues, and those suffering from alcohol or substance abuse. Severe winter storms occurring in normally dry, warm, and arid regions are associated with both frostbite and hypothermia. Populations acclimated to warm environments are often inadequately prepared for cold-weather natural disasters in terms of access to adequate shelter and clothing, and are often left without access to power to generate heat. Thus, disaster preparedness at a national level is paramount to prevent hypothermia and frostbite during severe cold weather-related emergencies by supporting regional, local, and state responses.

Pathophysiology

Tissue injury from frostbite is the result of two separate processes: immediate cellular injury from cold exposure and a prolonged inflammatory reaction during reperfusion, creating further tissue injury. Cellular damage from cold exposure can additionally be delineated to (1) direct cellular injury from freezing temperatures,

(2) direct cellular injury from formation of intracellular ice crystals, (3) indirect cellular injury due to formation of intravascular and extracellular ice crystals, and (4) thrombosis and ischemia from endothelial damage and vascular stasis, ultimately resulting in progressive ischemia due to microvascular thrombosis, which continues to evolve in a delayed fashion.

Diagnosis and Adjunct Imaging Studies

In patients with the signs and symptoms of cold-induced injury, diagnosis is clinical and dependent on history of recent cold exposure, in addition to physical exam and imaging.

Plain radiographs are not indicated for acute frostbite injury unless there is concern for underlying fracture. Chronic bone changes can occur following frostbite injury and include bony destruction and, in children, damage to growth plates. Of note, these findings are rarely encountered in the thumbs, as patients often curl the first digit into their palm to protect it from continued exposure.

Diagnostic digital subtraction angiography should be performed before administration of thrombolytics and has been demonstrated to be an essential first-line investigation to determine the extent of microvascular thrombosis, as well as to monitor response to therapy if thrombolytics are instituted.

Technetium (Tc)-99m scintigraphy (also, known as *bone scan*) has been shown to be useful in identifying patients as candidates for systemic thrombolysis and/or catheter-directed thrombolytic therapy to affected extremities. Tc-99m scintigraphy has been shown to predict the severity of frostbite injury, while also distinguishing viable versus non-viable bone. For patients who have contraindications to thrombolysis, interval Tc-99m scintigraphy may be useful in determining the demarcation of necrosis in affected extremities. Thus, scintigraphy may allow the clinician to offer debridement of non-viable tissues without the traditional several weeks "watch and wait" method to determine demarcation.

Single-photon emission computed tomography (SPECT) is a nuclear bone scan combined with conventional computed tomography (CT) imaging. SPECT has been shown to determine the severity of frostbite injury, as well as the transition zone between viable and non-viable bone, while providing greater accuracy than what is provided with Tc-99m scintigraphy. Thus, both Tc-99m imaging as well as SPECT imaging may facilitate earlier debridement of nonviable tissue.

Magnetic resonance imaging (MRI) combined with **magnetic resonance angiography (MRA)** may be an adjunct to bone scans (Tc-99m or SPECT) to determine extent of tissue ischemia and microvascular thrombosis; however, there is limited experience in the literature with this imaging modality.

Medical Management of Frostbite

Patients must be managed with the standard Airway, Breathing, Circulation, Disability, and Exposure (ABCDE) guidelines as set forth by the American College of Surgeons. Because frostbite injury itself will not cause significant mortality, it is important to first recognize if coexisting hypothermia and/or associated trauma is present and treated accordingly. In addition, tetanus prophylaxis is recommended.

Rapid rewarming is the single most important therapy to promote tissue salvage of frostbitten tissues. Rapid rewarming is accomplished with an immersive warm water while providing adequate opioid analgesia. Lower temperature rewarming at 37°C to 39°C rather than at 42°C does not substantially increase the time to rewarming and decreases associated pain. Thawing typically occurs within 30 minutes. Treated areas demonstrate a flushed or erythematous appearance.

Thrombolytic therapy in frostbite addresses the underlying mechanism of microvascular thrombosis as a cause for tissue ischemia. Determination of cyanosis and vascular examination of the extremity must be performed after rewarming. Although there are no high-quality data or established protocols, thrombolytics can be offered within 24 hours of thawing. Systemic or catheter-directed tissue plasminogen activator (tPA) is offered to patients who are at risk for requiring multiple digital or limb amputations in the absence of contraindications. Angiography should be obtained before and following thrombolytic administration to monitor the response to treatment. Systemic anticoagulation with intravenous heparin or treatment dose low-molecular-weight heparin are often given in conjunction with tPA. Patients are reimaged following therapy. It is reasonable to offer thrombolysis for cyanosis proximal to the distal phalanx and demonstrated loss of perfusion at or proximal to the middle phalanx. Patients demonstrating cyanosis proximal to the interphalangeal joints should obtain a CT angiography or Tc-99m scintigraphy and if circulation is absent thrombolysis administered. Thrombolysis should not be delayed for transfer to a tertiary center; however, consultation is advised.

There is no consensus on the management of frostbite-related blisters. It is reasonable to aspirate and/or debride large nonhemorrhagic blisters overlying joints to improve mobility, or nonhemorrhagic blisters that are tense or those that become infected. Hemorrhagic bullae are often treated with aspiration. Debridement of hemorrhagic blisters is avoided as this signifies deeper tissue injury due to evolving microvascular thrombosis. Minor blisters should be left intact.

Frostbitten tissue and/or bullae are covered with sterile nonadherent, petroleum-type layer followed by a bulky gauze dressing utilizing an aseptic technique. Fingers and toes should be wrapped independently or separated with bulky gauze dressings to prevent compressive trauma. Padding or splinting affected extremities may prevent further trauma during extraction from an austere environment. Occlusive dressings should be avoided. The evidence for applying topical aloe vera cream and oral ibuprofen with dressing changes to decrease inflammation is limited; however, it is reasonable to administer. Prophylactic antibiotics are not indicated for the treatment of frostbite unless there is evidence of infection.

Surgical Management of Frostbite

Patients with frostbite injury are at risk for reperfusion injury and compartment syndrome and early surgical consultation is advised. Neurovascular exams of the affected limbs should be performed and documented. Compartment pressures should be obtained if there is concern for compartment syndrome and prompt decompression performed if elevated. Complete demarcation of tissue necrosis occurs 1 to 3 months following frostbite injury. Debridement and/or amputation should be delayed until the necrotic tissue is fully demarcated. CT angiography and/or Tc-99m scintigraphy can assist in determining surgical margins. Patients requiring interval debridement and/or amputation should be referred to a surgeon with experience in treating frostbite injury.

OUTCOMES IN FROSTBITE

Frostbite injuries are rare in the North American civilian population. Mortality from frostbite is rare; however, approximately half of all patients admitted with frostbite will be admitted to the intensive care unit and approximately 20% will require surgical intervention. Long-term sequelae related to paresthesias, hyperhidrosis, and chronic pain is common even in low-grade frostbite in healthy individuals.

Due to the rarity of frostbite in the civilian population, optimization of the treatment/outcomes of frostbite will require large

multicenter trials. Wide adoption of common data elements, such as the Hennepin score, a worksheet that enables uniform quantitative description of the location and amount of tissue threatened, impacted and/or amputation (from which treatment salvage rates can be calculated) will support this goal.

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Electrical and Lightning Injury

Leigh Ann Price, MD, and Laurie Anne Loiacono, MD

Electrical injury is an unusually devastating form of mechanical trauma and one of the most destructive and disfiguring traumatic events a human can sustain. Associated with significant morbidity and mortality and a wide range of acute and long-term physical, psychological, and social disabilities, this complex injury is typically a combination of electrical shock, thermal injury, and blunt trauma that can potentially involve overwhelming multisystem damage. Understanding of the physics and pathophysiology of electrical injury promotes an understanding for the treatment plan(s) aiming to mitigate the morbidity and mortality caused by accidents involving electricity. The overall incidence of these injuries is low compared with other multisystem trauma injuries in the United States. Because of this, most healthcare teams have limited experience with this mechanism of injury, adding to the complexity of developing an effective medical and surgical care plan. This chapter illustrates the specific aspects of this injury that are relevant or additive to standard trauma and critical care protocols.

Optimal management of electrical and lightning injury necessitates: (1) a basic understanding of electrical injury mechanisms and their associated patterns of disease, (2) timely and appropriate resuscitation, (3) aggressive surgical and critical care medical management, and (4) implementation of coordinated multidisciplinary care for these patients from onset of injury through injury recovery, rehabilitation, and reintegration.

EPIDEMIOLOGY

The term *electrocution,* originally defined as death caused by the passage of electrical current through the body, was derived from the combination of *electro* and *execution*, coined in the late nineteenth century after implementation of the first electric chair in 1890. With the implementation and advancement of commercial applications for electricity throughout the nineteenth and twentieth centuries, the word *electrocution* commonly has been applied to circumstances of accidental death after exposure to electrical current. The first recorded nonjudicial fatality from accidental exposure to electricity (other than lightning strikes) occurred in France in 1879.

Nearly 1000 deaths per year in the United States are attributed to electrical injuries, and the most frequent cause of death is related to cardiac issues. Approximately 400 electrical injury–related deaths are caused by high-voltage electrical sources, whereas lightning causes an additional 50 to 300 deaths per year. Adulthood injuries occur mostly in occupational settings and are the fourth leading cause of workplace-related traumatic death, whereas in children, electrical injuries occur most often at home. According to the National Burn Registry, patients with electrical injuries accounted for just less than 4% of burn center admissions. Of these, more than one-half were work-related accidents, 3% were attributed to lightning, and 11% were in children. Fifty percent of the electrical injuries reported in the National Burn Registry required operation.

The majority of electrical injuries in construction and utility workers are related to brief, high-voltage (>600–1000 volts) exposure with upwards to 40% of serious electrical injuries being fatal (56% of these deaths occur in the workplace). Electrocution represents 5% to 6% of all work-related traumatic mortality, accounting for an excess of 500 deaths per year and making it the second-leading cause of occupation-related deaths in the United States. Short- and long-term morbidity in many electrical injury survivors is typically related to significant musculoskeletal and neurologic disability.

Electrical injuries account for 2% to 3% of all burns in children, and the majority of electrical injuries in children are associated with transient, low-voltage exposure to household electrical and extension cords and wall outlets. Older children are exposed to life-threatening high-voltage injury through climbing activities. More than 200 household-related electrocutions (i.e., death by electricity) occur annually and are typically associated with consumer product misuse or malfunction.

PHYSICS (AND PATHOPHYSIOLOGY) OF ELECTRICAL INJURY

Direct Injury (Electrical and Lightning)

The severity of direct electrical injury is determined by several critical factors:

1. Voltage (high or low)
2. Type of current (alternating or direct)
3. Intensity of current (amperage)
4. Pathway of the current through the body (vertical, horizontal, peripheral)
5. Duration of current exposure
6. Area of contact on the body
7. Resistance of the body tissues involved

Understanding the basic physics of electricity provides the knowledge and insight into just how powerful electrical energy can be, how damaging it can be to the tissues, and the thorough consideration of necessary treatment.

ELECTRICITY BASICS

Current

Electricity is defined as the flow of electrons through a conductor. *Electrical current* (I) is the rate of flow of electrons in a conductor and is measured in *amperes* (A). Injuries result from current in several forms: *alternating current* (AC), *direct current* (DC), or pulse-type shocks such as lightning. High-voltage utility power lines may be either AC (most common, commercial) or DC.

Alternating Current

Alternating current (AC) is the directional flow of current in a circuit constantly being reversed back and forth in a repetitive sinusoidal pattern and is a more efficient way of generating and distributing electricity than DC. Standard household current is AC at a rate of 60 Hz (cycles per second) and is supported by 100 to 250 amps (A). AC can be much more dangerous than DC in certain circumstances because it causes tetanic muscle contractions that prevent a victim from releasing the electrical source, also known as the "let-go" threshold. The "let-go" reaction occurs when the current through a hand and arm may cause the hand to involuntarily close and remain closed so that the energized conductor cannot be released. The bidirectional flow of AC produces cutaneous burns known as *contact points* in contrast with the entrance and exit wounds from DC. The "let-go" current intensity varies from 3 to 9 mA depending on body size (tetany occurs at 16–20 mA). Though AC is generally lower voltage and produces less direct tissue injury, prolonged contact can alter the cardiac cycle, causing arrhythmias and cardiac arrest. Ventricular fibrillation occurs at 50 to 100 mA, and asystole occurs at >2 A. Keep in mind that although most providers speak about voltage, it is the amperage that kills.

Direct Current

Direct current (DC) means that the direction of electrical current remains constant. It is found in automobile electrical systems, railway tracks, batteries, and lightning. DC provides a vector directionality to the electrical current exposure, hence the typical "entrance and exit" point cutaneous wounds that identify potential current pathway. High-voltage DC injury often produces smaller, cutaneous "entrance and exit" wounds, but much more significant deep tissue injury in addition to the electrical current tissue effects. DC does not produce the same contraction of the muscles that is found with AC. Although low-voltage DC is not as dangerous as the corresponding AC, contact with high-voltage DC is more apt to be fatal than contact with AC of the same voltage.

Voltage and Resistance

Voltage

The force that drives current (I) across the potential difference is the voltage (V) and contributes critically to the intensity of the electrical injury. Medically speaking, electrical injuries are classified as either *high-voltage* (>1000 V) or *low-voltage* (<1000 V). (Note: The US National Electrical Code defines the difference between low-voltage and high-voltage injury at 600 V.) Typical voltage delivered to homes in the United States and Canada is 120/240 V, providing 240 V for appliances requiring high power and 120 V for general use. Low-voltage injuries tend to occur indoors and are almost exclusively AC. In the United States, the AC power system operates at 60 Hz, causing the current to reverse polarity 120 times a second. Based on this fact, the terms *entrance* and *exit* should be abandoned, and the resultant wounds from AC should be referred to as *contact points*. Voltage in high-tension power lines tends to exceed 100,000 V and is most commonly AC in developed areas. High-voltage mortality and amputation rates typically exceed low-voltage rates twofold to threefold.

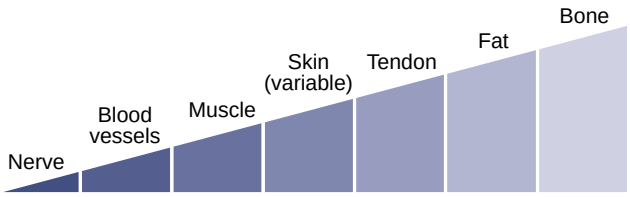


FIG. 1 The magnitude of average electrical resistance across body tissues.

Voltage at a point must always be measured with respect to another point. The voltage difference between the two points is a factor in determining the current that will be in a given electrical path between them.

Resistance

Resistance (R) is the hindrance to current flow and is measured in *ohms*. Resistance creates heat based on Joule's law. *Joule heating* is energy transfer that occurs when charged particles meet resistance and lose energy to tissues in the form of heat.

Joule's Law

$$\text{Power (J)} = I^2 \text{ (current)} \times R \text{ (resistance)}$$

Materials that are the best conductors (meaning they facilitate current flow) have the least resistance. With increasing resistance, more energy is expended in the form of heat and results in thermal tissue damage.

Different tissues have innately different resistances (Fig. 1), and resistances will vary under different conditions. Overall resistance of a tissue depends on the surface area of contact, the tissues in the current's pathway, pressure applied, duration of exposure, magnitude of current flow, and absence or presence of moisture. For example, dry skin has a much greater resistance (approximately 100,000 ohms) than moist skin (less than 2500 ohms).

The relationship between the above forces is described by *Ohm's law:*

$$I = V/R,$$

where the current (I) is directly proportional to the voltage (V) and inversely proportional to resistance (R).

PHYSICS AND PATHOPHYSIOLOGY OF ELECTRICAL INJURY

All electrical injury involves both direct and indirect mechanisms. The direct damage is caused by the actual effect of electrical current on the body tissues or organs (e.g., brain or heart) or by the conversion of electrical to thermal energy resulting in burns. Indirect injuries are the result of associated tissue injury from severe muscle contraction, blunt trauma from falls or ejection, or associated multiorgan system dysfunction (e.g., renal failure from rhabdomyolysis).

Injury to the affected tissue predominantly depends on the intensity and duration of electrical exposure. For example, brief exposure to current will conduct rapidly across low resistance tissues (Ohm's law) with less heat production and structural tissue damage, but more electrophysiologic derailment of end organs (i.e., heart, CNS, and muscle). Hence lightning causes little, if any, direct tissue injury.

If contact time is brief, nonthermal direct electrical damage to tissue occurs as the current disrupts the microelectrical gradient across cell membranes via electroporation and conformational changes in membrane proteins. Electroporation results in a significant increase in the electrical conductivity and cell membrane permeability leading to tissue edema and possible cell injury**.** Muscle fibers and nerves are the most susceptible. It can either induce cell necrosis or permanently, partially, or reversibly affect cell membrane function in the absence of joule heating. Damage will be relatively localized to the involved tissue cell membranes and result in functional disruption of end organs that are dependent on coordinated electrical activity, such as the heart, brain, spinal cord, and muscle (Table 1). These cell membrane effects may progress over time and partially explain some of the delayed clinical symptoms observed following electrical injury, such as vascular thrombosis and rupture, cognitive dysfunction, and late-appearing spinal cord deficits (Table 2).

Lightning primarily is thought to be a form of DC, but it can be both positively and negatively charged, taking on the form of DC or AC depending on the circumstance (Table 3). Positively charged lightning is considered more dangerous because its electrical field is stronger, flash duration is longer, and the peak charge can be much greater than a negative strike. The most important difference between lightning AC and electrical AC is that lightning does not cause the muscle tetany seen with AC of other electrical injuries. Lightning remains one of the most dramatic examples of high-voltage direct electrical injury. Its injuries are a small subset of electrical injuries, but lightning is responsible for an average of 400 injuries and approximately 50 deaths per year in the United States. The odds of being struck by lightning has a lifetime prevalence of 1 in 3000 (estimated 80 years). Estimated fatality from lightning is 30%, and 70% to 80% of survivors may have permanent disabilities.

Occasionally, lightning can move along a horizontal pathway and strike "out of the blue sky" 10 miles or farther away from its generation point. In the United States, the Gulf Coast and Rocky Mountain states, particularly Florida and Colorado, have the highest strike densities and report the highest number of lightning-related injuries and deaths.

In addition to tissue injury related to direct contact with an electricity source, injuries noted from the aforementioned lightning strike patterns include thermal burns through clothing or other heated material; shock wave from a thermoacoustic phenomenon (e.g., thunder) leading to ruptured tympanic membranes; concussive or blast-type injuries secondary to the rapidly expanding air near a lightning strike; and injury caused by a subsequent fall.

Lightning injury can be minor, moderate or severe.

- **Minor**: often awake and alert, may have confusion or amnesia, dysesthesia, hearing or vision changes. Physical findings may be temporary, and complete recovery can occur.
- **Moderate**: disoriented, combative, unconscious, paralysis, skin mottling, hypotension, respiratory failure, secondary cardiac arrest. Physical symptoms may resolve over time. Long-term sequelae such as cognitive and sleep disorders, weakness, dysesthesias, and peripheral neuropathy can develop.
- **Severe**: Serious injury or death occurs in 30% of victims; blunt trauma, contusion from shock wave, cardiac dysrhythmias, cardiac arrest (primary or secondary), CNS dysfunction. Asystole may be transient, and spontaneous rhythm may recover as a result of cardiac automaticity. Hypoxia related to central apnea may lead to secondary cardiac arrest. Long-term sequelae such as cognitive and sleep disorders, weakness, dysesthesias, and peripheral neuropathy can develop without direct evidence of initial direct anatomic brain injury.

Keraunoparalysis is transient paralysis that can occur following a lightning strike and is characterized by signs and symptoms of motor and sensory loss (affecting lower limbs more than upper limbs), pulselessness, and pallor associated with vasospasm. Keraunoparalysis typically resolves within several hours following the injury but can mimic spinal cord injury and temporarily mask underlying musculoskeletal injury. Unlike high-voltage electrical

TABLE 1 Examples of Acute, Direct Electrical Organ Tissue Dysfunction

Tissue	Acute Effect
Heart	Asystole, arrhythmia, cardiac tissue necrosis (myocardium, nodal tissue, conduction pathways, coronary arteries)
Central nervous system	Brainstem dysfunction: central apnea, loss of consciousness, seizure, confusion, amnesia, cranial nerve deficits, spine fracture, paralysis or keraunoparalysis, spinal cord transection, visual and hearing disturbances, tympanic membrane rupture
Muscle	Tetany: rhabdomyolysis, lactic acidosis, bone stress fracture, "locking-on" phenomenon

TABLE 2 Examples of Late Electrical Injury Organ Tissue Dysfunction

Tissue	Late Effect
Heart	Patchy cardiac tissue necrosis (myocardium, nodal tissue, conduction pathways, coronary arteries); late arrhythmias are rare
Central nervous system	Cognitive deficits, spinal cord and peripheral nerve dysfunction, cataracts
Muscle	Weakness, arthropathy, nonspecific myopathy and fibrosis, limitation of joint function
Vascular	Venous thrombosis, arterial rupture

TABLE 3 Patterns of Lightning Strikes

Direct strike	Lightning directly strikes victim
Splash strike	Lightning hits another object and "splashes" onto the victim
Side flash	Victim is inside a building, and exposure to current occurs through a conductive source within the structure (e.g., a metal object or landline telephone)
Step voltage	Lightning strikes the ground, and the current is conducted along the ground to an adjacent victim

injuries in which massive internal tissue damage may occur, lightning seldom causes substantial burns. Historically, most of the burns are caused by other objects (moisture, metal on a belt, jewelry or coins in the pocket) being heated up and causing a contact burn rather than caused by the lightning itself. The transformation of the electrical energy to heat can generate temperatures as high as 50,000°F. However, the duration of this transmission is only 1 to 2 milliseconds, and as a result, the insulating property of the skin does not have time to break down. The two most common causes of death related to lightning injury are (1) cardiopulmonary arrest caused by interruption of the cardiac cycle by the DC and resulting in asystole and (2) apnea from the DC's interference with the brain's respiratory center, which will result in hypoxia, arrhythmia, and secondary cardiac arrest if left untreated. The estimated morbidity is 5 to 10 times higher than the casualties of non–lightning-related electrical injury (Table 4). A pathognomonic fernlike pattern called *keraunographic* markings or Lichtenberg figure may appear on the skin of lightning strike victims (Fig. 2). This is not a burn and often disappears within 24 hours.



FIG. 2 **Lichtenberg figure.** (Courtesy A.R. Doben, MD.)

Direct Injury (Thermal)

When contact time is prolonged, heat damage will dominate as the whole cell in the pathway is compromised. Thermal burn injury caused by electricity may be classified into three categories:

1. Joule heat: Direct effect of electrical current on tissue resistance causing heating of tissue, resulting in deep and superficial burns. Extent of specific tissue injury depends on current path, Joule's law, and duration of exposure.
2. Arc: Direct thermal injury from arcing is caused by high-voltage current passing through the air. These injuries are most commonly seen in electricians working with metal objects close to an electrical source. These injuries occur without actual current flowing *through* tissue. Electricity arcs at a temperature up to 4000° to 5000°C, generating a "flash"-type injury.
3. Flame: Thermal burns result from ignited clothes or surroundings and are managed as conventional flame burns.

Most direct injuries are a combination of both electrical current conduction and heat transfer to tissues (Fig. 3). Both mechanisms should be expected and fully explored in the course of the electrically injured patient's evaluation.

Importance of Current Pathways

Identification of *contact points* often helps establish the path the current has taken. A path parallel or vertical to the axis of the body (craniocaudal) is most dangerous because it may affect all of the vital organs. A horizontal path (e.g., from hand to hand) may spare the

TABLE 4 Comparison Between Lightning, High-Voltage, and Low-Voltage Electrical Injury

	Lightning	High Voltage	Low Voltage
Voltage (V)	$>100 \times 10^6$	>1000	<1000
Current (A)	>200,000	Variable	240
Duration	Instantaneous	Brief	Prolonged
Type of current	Mostly DC	DC or AC	Mostly AC
Cardiac effect	Arrest: asystole	Arrest: Ventricular fibrillation	Arrest: ventricular fibrillation
Respiratory effect	Respiratory arrest: direct CNS injury	Respiratory arrest: indirect trauma or tetanic contractions of respiratory muscles	Respiratory arrest: tetanic contractions of respiratory muscles
Muscle effect	Single	Contraction: DC—single AC—tetanic	Contraction: Tetanic
CNS effect	Early and delayed brain injury, coma, seizures, blindness, deafness, aphasia, cerebral vein thrombosis, late spinal cord deficits, cataracts	Early and delayed brain injury, coma, seizures, blindness, deafness, aphasia, cerebral vein thrombosis, late spinal cord deficits, cataracts	Paresthesias, transient neuropathy
Burns	Rare: superficial ("flashover" diverts current around the body)	Common: superficial (less) and deep (most)	Usually superficial, can be full-thickness
Rhabdomyolysis	Uncommon	Very common	Common
Blunt injury	Blast effect, shock wave	Muscle contraction, fall	Fall (uncommon)
Mortality (early)	Very high (about 30%)	Moderate (about 5%–15%)	Low

brain but still be fatal from its effect on the heart and respiratory muscles. A path with contact points confined to a single extremity may cause extensive local damage but not be fatal (Fig. 4).

Immediate cardiac arrest and life-threatening arrhythmias may occur with the conduction of current across the heart. AC tends to cause ventricular fibrillation, whereas DC tends to cause asystole. Actual injury to the heart or the metabolic effects from injury elsewhere in the body (e.g., hyperkalemia and rhabdomyolysis) may result in delayed cardiac arrhythmias and acute renal failure.



FIG. 3 High-voltage electrical injury.

Paralysis of the muscles of respiration can result in apnea. Effects on the spinal cord and brain can lead to immediate death or long-term neurologic abnormalities.

Indirect Injury

Additional tissue and organ injury not directly caused by but clearly related to the electrical insult is a significant contribution to morbidity and mortality of these patients. Many electrically injured patients fall from a height or are thrown or ejected following a blast or arc. These patients should receive a full multitrauma assessment on initial evaluation, including full spine and airway stabilization.

Respiratory failure can result from direct, blunt, or electrical lung injury; smoke or chemical inhalation; pulmonary edema; or acute lung injury. Many victims who develop muscle injury from tetany, direct electrical injury, or blunt trauma develop early acute kidney injury secondary to rhabdomyolysis or shock. CNS abnormalities can be transient, permanent, or delayed based on gross and histologic anatomic structure injury.

MANAGEMENT

The development of guidelines and outcome-based benchmarks requires established standards of practice; however, no specific guidelines exist at this time for electrical injuries. Because of the traumatic, multisystem nature of electrical injury (including



FIG. 4 **(A, B)** A farmer working in the field came in direct contact with a low hanging wire (7000 V). **(C)** An electrician grabbed a cable (270 V, alternating current) overhead to avoid falling into a ditch. **(D, E)** A lineman touched a power line (7620 V, alternating current).

potential associated blunt or penetrating trauma injuries), these patients should be managed according to both trauma and burn reconstruction guidelines for care. These guidelines include the following:

- Establish safe access to the electrically injured patient.
- Rapidly assess the patient's airway, breathing, circulation, and disability (rapid neurologic assessment), and provide in-line immobilization of the entire spine (primary survey).
- Treat life-threatening findings immediately. Control threatened airway and/or ventilation, decompress tension pneumothorax or pericardial tamponade, control external hemorrhage, expose the patient, and manage potential core temperature heat loss (hypothermia).
- Establish intravenous (IV) access (interosseous access if in the field), and continuously monitor vital signs (including temperature), neurologic status, pulse oximetry, respiratory function, ECG, and urine output (urinary catheter); consider central venous pressure monitoring.
- Expose and cover thermal burn sites with clean, dry sheets or towels and then an appropriate topical dressing when at the hospital. Keep in mind the need for escharotomy or fasciotomy.
- Initiate fluid resuscitation with warmed, isotonic crystalloid IV fluids to a target urine output (UO) of 0.5 cc/kg/hour if low risk for rhabdomyolysis (greater than1.0 cc/kg/hour if high risk for rhabdomyolysis). Monitor for the development of hyperkalemia and hyperchloremia.
- Continuously closely assess physiologic response to multisystem support.
- Provide aggressive surgical and critical care support in an appropriate burn or critical care setting.
- Implement coordinated multidisciplinary care for these patients from onset of injury through injury recovery and rehabilitation.

PREHOSPITAL MANAGEMENT/SPECIAL CONSIDERATIONS

The scene of an electrical injury is unique compared with other trauma sites. The rescuer can easily become another victim and should be aware of the following:

- Victim's existing contact with the current source: DO NOT TOUCH; specialized nonconductive equipment is necessary to safely recover these victims.
- Active live electric sources: confirm disconnection
- Environment conductors to avoid (i.e., puddles of liquid, exposed metals and wires)

Victims of lightning injury may be treated immediately.

Critical Care Management

Early, goal-directed resuscitation; targeted multi-organ system assessment and support; and aggressive surgical management are critical in the first hour following injury and are cornerstones for optimal patient outcome (Table 5).

Optimal surgical treatment will vary with the severity and etiology of electrical injury and the specific location of the injury site.

Multidisciplinary, System-Based Critical Care Management of the Electrical Injury Patient

Neurologic

Serial global and focal neurologic assessments are necessary. A full spine assessment should be completed within the first 24 hours. Attention to aggressive pain management is important to optimize respiratory mechanics and clinical response to therapy. Emphasize early mobilization, aggressive physical therapy/occupational therapy, and cognitive/vision/hearing assessments, and develop a comprehensive rehabilitation plan.

Complications

Neurologic complications are common sequelae of electrical injuries and can affect both the central and peripheral nervous systems. Early manifestations include varying levels of unconsciousness (including coma), sensory dysfunction, memory disturbances, autonomic dysfunction, respiratory paralysis, and motor dysfunction. Victims of lightning strikes can present with fixed and dilated pupils as the result of focal neuromuscular effects of the electrical injury rather than permanent brain injury. Deficits may be "patchy" with sensory deficits not coinciding to the motor findings. Clinical manifestations of neurologic injury may be delayed for days or even months and are not consistent with the size or location of the injury.

Cardiac

After severe electrical current exposure, cardiac arrest (asystole or ventricular fibrillation) and respiratory arrest can occur simultaneously as the result of synchronous depolarization of all myocardial cells and medullary CNS paralysis. Spontaneous recovery of cardiac automaticity may facilitate return of spontaneous circulation before recovery of respiratory dysfunction, predisposing the patient to development of severe respiratory acidosis with secondary cardiac arrest. Electrocution victims without gross clinical signs of life may have occult cardiac activity, so Basic Life Support, Advanced Cardiac Life Support and possibly Advanced Trauma Life Support guidelines should be the standard of care for all victims of electrical injury.

Monitoring

Continuous EKG monitoring should be performed for the first 24 hours. If no acute cardiac issues or arrhythmia are identified, continuous monitoring can be discontinued. Avoid hypotension and tachycardia. Check the echocardiogram if hypotension occurs or if cardiac enzymes suggest acute myocardial injury.

Complications

Ventricular fibrillation is the most common fatal arrhythmia, occurring in up to 60% of patients in whom the current has taken a horizontal pathway. However, virtually any cardiac dysrhythmia can be precipitated by any electrical injury. The overall estimate of arrhythmia following electrical injury is up to 15%; most of these are benign and occur within the first few hours of hospital admission. Recent studies have shown that new-onset atrial fibrillation is the most common dysrhythmia seen in survivors; it can be easily managed with medical treatment. An ECG should be performed in all patients who sustain electrical injuries, whether low or high voltage. The duration of cardiac monitoring needed is generally between 24 and 48 hours but should continue further if any underlying cardiac injury has not been completely ruled out.

Direct myocardial injury is uncommon but can present as a traumatic cardiac contusion. Myocardial infarction is rare.

Respiratory

For extubated patients, respiratory management includes using incentive spirometry, cough and deep breathing, early mobilization, and oxygen as needed to maintain oxygen saturation (SaO_2) greater than 92%. For intubated patients, respiratory management includes using a *lung-protective ventilator strategy* in the presence of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), developing a weaning plan, considering the value of early tracheostomy, maintaining the head of the bed at ≥30 degrees, providing venous thromboembolism (VTE) and ulcer prophylaxis, and performing a daily sedation holiday and ventilator weaning assessment.

TABLE 5 Critical Care Management of the Electric Injury Patient (First Hour)

Concern	Action	Goal
Airway (PRIORITY) Assess for • Airway patency • Altered mental status • Facial injuries • Airway obstruction • Aspiration	1. Manual airway support as needed (i.e., clear airway, bag valve mask) 2. Intubate EARLY. Diffuse edema and multisystem organ dysfunction may progress quickly (surgical airway may be necessary) 3. Clinically confirm placement with examination and end-tidal CO_2 monitor (radiologic confirmation of endotracheal tube placement ASAP); well-secure endotracheal tube in place. 4. Immediate C/T/L/S Spine immobilization 5. Initiate pulse oximetry	• Secure airway
Breathing Assess for • Spontaneous effort • Pneumothorax • Hemothorax • Chest wall compromise (musculoskeletal or burn) • Smoke inhalation (if associated material ignition)	1. Treat pneumothorax immediately 2. Initiate mechanical ventilation if needed 3. Correct hypoxia with supplemental O_2 (start with 100% FiO_2) 4. Check ABG 5. Chest x-ray (confirm tube placement, identify injury) 6. Consider early bronchoscopy to assess for inhalation injury if flame exposure is involved 7. Early escharotomy if needed	• AVOID Hypoxia • SaO_2 >92% • PCO_2 35–45 mm Hg • Plateau pressure <30 mm Hg
Circulation Assess for • Shock • Distended neck veins • Cardiac tamponade • Cardiac arrhythmia • Cardiac dysfunction • Hemorrhage • Peripheral pulses	1. BLS/ACLS/ATLS algorithms 2. Treat cardiac tamponade immediately 3. Establish adequate IV access. Edema and multisystem organ dysfunction will progress quickly 4. Infuse Isotonic IV fluids toward target goals 5. Continuous ECG and blood pressure monitoring 6. Place urinary catheter 7. FAST exam +/– focused CT to assess for hemorrhage 8. Consider central venous access for resuscitation monitoring 9. Early fasciotomy 10. Complete blood count, type, and crossmatch; cardiac enzymes; lactate	• MAP ≥60–65 mm Hg • UO ≥0.5 cc/kg/hour *(if suspect rhabdomyolysis: UO >1.0 cc/kg/hour)* • SVO_2 60–65 mm Hg • Lactic acid <2.0 • Closely monitor for development of pulmonary edema
Disability Assess for • Acute brain injury • Acute spine injury • Musculoskeletal deformity	1. Assess consciousness, pupillary size and response, lateralizing signs, level of spinal cord injury 2. Assess Glasgow Coma Scale (GCS) score 3. Assess spine pain and gross function 4. Full neurologic examination when possible 5. CT Head/Spine as needed	
Exposure Assess for • Core temperature • Cutaneous injury	1. Warm IV fluids 2. Warm room 3. Insulating covers (if needed) 4. Perform burn wound area assessment 5. Cover burn sites with dry, clean linen (pending definitive burn care) 6. Splint unstable fracture sites to avoid neurovascular compromise 7. Serial, focused neurovascular checks	• AVOID hypothermia • Core temp 98.6°F (37°C)
Comprehensive Evaluation Assess for • Efficacy of current treatment • Identify and treat additional/missed injuries	1. Secondary and tertiary surveys per ACS trauma protocol 2. Pertinent additional studies and laboratory tests such as UA, CK/MB, troponin, ECG 3. Focused radiologic studies 4. Consider transfer to burn center	

Gastrointestinal

Gastrointestinal management includes early enteral feeds and a daily bowel assessment and regimen.

Renal

The goal UO is 0.5 cc/kg/hour. The adjusted goal for rhabdomyolysis is UO >1.0 cc/kg/hour.

Complications

Rhabdomyolysis-induced acute renal failure is a feared complication that results from massive tissue necrosis and can be complicated by pigment-induced kidney injury. Myoglobin plays a dominant role in the pathogenesis of rhabdomyolysis-induced acute renal failure. These mechanisms involve: (1) renal constriction and ischemia from hypovolemia caused by extravascular extravasation of fluid, (2) direct cytotoxic action of myoglobin on the proximal convoluted tubules caused by tissue and muscle breakdown, and (3) myoglobin cast formation in the distal convoluted tubules.

The most essential component to avoid and potentially treat these complications is adequate fluid resuscitation and increased urine output by maintaining a UO of approximately 100 mL/hour until the urine visibly appears clear. Osmotic diuresis with mannitol and alkalization of urine has been proposed as adjunct strategies but are not currently supported by Level 1 evidence.

Infectious Disease

Tetanus administration should be considered when appropriate. System inflammatory response syndrome (SIRS) criteria should be monitored closely for needed sepsis workup.

Musculoskeletal

Radiologic studies of suspicious areas should be obtained as necessary to evaluate for fractures, and frequent neurovascular checks to affected extremities are necessary to monitor for evolving tissue injury. Early fasciotomy is required for compartment syndrome. Early carpal tunnel release may be necessary for clinical signs of tissue entrapment. Early aggressive debridement of nonviable tissue should include splinting the affected extremity in the position of function.

Complications

Bone has the highest resistance of any body tissue, thus generating the greatest amount of heat when exposed to an electrical current. This causes the greatest amount of thermal damage to tissue adjacent to long bone structures and manifests as periosteal burns and possible osteonecrosis. Tetanic muscular contractions induced by AC may result in fractures or dislocation of a bone or joint.

In addition, traumatic injuries resulting in fractures from blast injuries, falls, or repetitive forceful muscle contractions have also been reported. Patients with significant electrical injuries or altered mental status should have imaging studies of their cervical spine to rule out any evolving pathology.

Unfortunately, escharotomy is not of much use in electrical burn patients because of the depth of the injury. Fasciotomies and/or carpal tunnel releases should be performed in the operating room immediately when the circulation is presumed to be impaired. Initial fasciotomy should be performed in the areas of contact and conduction; for instance, the carpal tunnel may be released if the injury occurs in the wrist. The injury may be confined to the digits and/or hand, but if the patient has a considerable amount of pain, it may be advisable to complete a carpal tunnel release as the canal may become narrow with the recent trauma, and deep tissue injury at this location may cause swelling and lead to early signs of compression. Fasciotomy plays a major role in the early management of electrical burns and can dramatically improve the salvage of tissue including the limb. Splinting extremities in positions of function must be accomplished for preservation of joint use in the extremities.

Skin Complications

By far, the most common manifestations of electrical injuries can be attributed to the thermal damage caused to exposed skin. As mentioned earlier, though we often refer to *entry* (more tissue damage) and *exit* wounds, with AC there is no such thing as current entering or leaving. Instead, injuries are labeled as *contact points*.

Superficial, partial-thickness, and full-thickness burns can occur from any electrical injury. Estimates have shown that exposure to only 20 to 35 mA per mm^2 of skin surface for 20 seconds increases the skin temperature to 50°C, causing denaturing of protein, which leads to blistering and swelling. A crucial point to remember is that the degree of external injury cannot be used to determine the extent of the internal damage, regardless of voltage. Minor superficial burns may coexist with massive muscle coagulation and necrosis.

Of note, the incidence of superficial surface burns is high in victims of lightning injury, but deep burns are uncommon.

SURGICAL MANAGEMENT

Low-Voltage Injury Management

Low-voltage injuries (<1000 V; see Fig. 4C) are less devastating but can remain just as debilitating. These injuries often require close monitoring for the first few hours of admission to rule out evolving vascular sequelae to the limb or potential complications of myoglobin clearance. The first elective operative procedure is sharp excision of the eschar, often completed using a tourniquet, followed by initial placement of meshed allograft. The allograft is placed during the first excision, even if the wound bed appears healthy and completely viable; this allows metabolic changes to alter the tissue beneath. In general, after the second debridement, sheet (non-meshed) autograft is then applied to those wounds on the face, neck, and hands; otherwise, meshed autograft can be utilized at the surgeon's discretion. Again, splinting the extremity in its position of function must be accomplished for preservation of joint(s) use in the extremity. Early intervention by a rehabilitation therapist (physical therapy and occupational therapy) will optimize patient outcome and advance function with better range of motion and strengthening. It is considered good practice to educate patients that in the distant future they may require additional surgical therapy for burn contracture release that may include placement of a full-thickness skin graft.

High-Voltage Injury Management

Most electrical injuries cause damage to limb tissue by generation of heat causing thermal insult and by endothelial damage with progressive tissue necrosis. These injuries are often associated with limb loss via amputation at various levels and carry a high rate of morbidity. Limb salvage and appropriate, aggressive initial resuscitation is challenging from the moment these injuries are first encountered. The American Burn Association referral criteria recommend that patients with high-voltage electrical trauma to the upper extremity should be referred to specialized burn centers experienced with these injuries.

Most high-voltage (>1000 V) injuries are associated with deep tissue injury that is often underappreciated and more extensive than initially apparent. The initial management of the limb involves immediate (first 6–8 hours postinjury) surgical exploration and decompressive fasciotomies. Fasciotomy plays a major role in the early management of electrical burns and can dramatically improve the salvage of tissue including the limb. Escharotomy alone (incision is made into the subcutaneous fat just beyond the eschar) is of limited benefit. Although escharotomies may often be performed at the bedside, fasciotomies and/or carpal tunnel release should be performed in the operating room.

Indications for surgical decompression include progressive neurologic dysfunction, vascular compromise, increased compartment pressure, and systemic clinical deterioration from suspected ongoing myonecrosis. Decompression includes forearm fasciotomy and assessment of muscle compartment integrity. The decision to include a carpal tunnel release should be made on a case-by-case basis. Initial fasciotomy should be performed in the areas of contact and conduction; for instance, the carpal tunnel may be released if the injury occurs in the wrist. However, if the injury is confined to the digits and/or hand and the patient has a considerable amount of pain, it may be advisable to complete a carpal tunnel release as the recent trauma and deep tissue injury can cause the canal to become narrow, which may result in swelling and lead to early signs of compression. Delayed exploration and decompression in the compromised extremity may result in increased amputation rates along with increased organ failure and mortality. To date, no definitive data exist to illustrate that immediate surgical decompression reduces the need for amputation in any series.

As shown in Figure 3, lack of opportunity for limb salvage may be obvious early regardless of the number of surgical debridements because of the extent of devitalized tissue noted on presentation. However, one important consideration regarding amputation is the length of tissue able to be retained and the remaining length required to fit a prosthesis. It is important to not confuse nonviable tissue with minimally bleeding tissue. As a general surgical principle, we are not trained to "leave behind" nonviable tissue because there is an increased risk for infection; however, there is evidence to suggest that keeping some (minimally bleeding) tissue in question with multiple serial debridements, under a watchful eye, may improve the overall outcome. It is advisable to always start with debridement of devitalized tissue and continue every 48 hours until sustainably viable tissue is apparent and the source is controlled. Superficial muscle may be found viable and even appear uninjured by color and electrical stimulation with cautery. However, the muscle located deeply along the bone may be severely injured. Any questionably viable tissue is not debrided at the first exploration. Leaving a tendon that lacks its peritenon intact may be of use in long-term limb salvage as there may be regeneration along the intact, viable tissue. Open wounds remaining at the end of the initial and subsequent debridements are closed with sheet (unmeshed) skin allograft to provide the most optimal environment for the marginally viable tissues and to prevent bacterial contamination in the sterile wounds. Serial debridements and reexploration of the wounds should be performed and continued until no further necrotic tissue is present and the wound has stabilized (6–8 days), making the final preparations for definitive reconstruction or formal amputation possible. Splinting the extremity in a position of function must be accomplished for preservation of joint use in the extremity, and this should be commenced even before the first surgery.

Significant advances in extremity reconstruction have been made through the development of high-quality, functional prostheses and new advances in tissue engineering such as vascularized composite allotransplantation (VCA). VCA is an option held in reserve after all other attempts have been exhausted and the patient has survived the initial injury, as the immunosuppression necessary for graft survival can harm the patient in the acute phase as we continue to await chimerism.

In addition to the basic general surgical principles such as debridement of nonviable tissue, protection of tissue perfusion, nutritional optimization, and control of infection, reconstructive surgery follows basic principles of the reconstructive ladder: healing by secondary intention, primary closure, delayed primary closure, grafts (split-thickness, full-thickness), tissue expansion, and flaps (random, axial, and free). This provides a systematic approach to wound closure by the emphasis of simple to complex techniques based on local wound requirements and complexity.

In burn surgery, rarely are the first few rungs of the ladder helpful because of the nature of the injury; we often jump to the rung of grafting secondary to tissue loss. There must be a healthy, vascularized wound bed for a split-thickness graft to take (i.e., if the peritenon or periosteum is lacking, the graft will not take). Allografting versus autografting is a very important tissue choice and ultimately the decision of the surgeon (keep in mind that if the allograft does not adhere, neither will the autograft). Use of allografting preserves the patient's tissue until the wound bed is ready and allows the surgeon to return to the operating room for redebridement of areas where microscopic changes at the cellular level are noted.

Full-thickness skin grafting is often susceptible to infection if nonviable tissue is left behind because of the lack of adequate vascular blood supply. Rarely is tissue expansion even considered in an acute burn injury. Random and axial flaps are used when appropriate and often are the preferred method of reconstruction, especially in the acutely injured. However, the operating surgeon must keep in mind that during an electrical injury, significant vessel damage may occur to the media or endothelium of the vessel in which the flap is based.

Other vascular abnormalities such as vascular occlusions; arteritis and aneurysm formation; thrombosis and segmental narrowing of major extremity vessels; and a marked decrease in the density of small nutrient vessels have all been described after electrical injuries. As a rule of thumb, the ideal tissue to be used is outside of the zone of injury; this principle should also be respected and strongly adhered to during free tissue transfer. Although free flap reconstruction is rarely indicated in an acute burn injury, as the versatility and variability of the free flaps have evolved, so has the applicability to tissue reconstruction. Timing of the reconstructive procedure in relation to the injury, the age of the patient, existing medical comorbidities, the length of the operative procedure and extent of the zone of injury all have a significant impact on the success rate of a free flap reconstruction. The importance of these issues should not be minimized as free flap coverage may be necessary for coverage of exposed joint, bone, vessels, or tendons. The failure rate of postinjury free tissue transplantation is well-documented to range from postoperative day 5 up to 6 weeks. Therefore, it is critical to optimize the burn patient's treatment from its onset, and the outcomes of these types of injuries will be life-altering.

Scalp and Cranial Defects

Deep electrical burns to the scalp are often some of the most challenging reconstructive cases in surgery and may appear as a small burn wound with a much larger unforeseen injury hidden beneath the surface. Necrotomy, decompression, aggressive debridement, and attempts at skin grafting are often insufficient to adequately close the wounds because of an underpredicted zone of injury. Often, areas of nonviable bone and surrounding tissues complicate these wounds. Early involvement of plastic reconstruction services for consideration of major rotation flap and/or free flap planning is warranted.

Commissure Injuries (Pediatric)

The American College of Surgeons has recommended that all facial burns be triaged to an American Burn Association burn center. Commissure burns typically occur in the young patient and commonly result from biting or teething on a household appliance cord. Although considered a relatively low-voltage (120–240 V) injury, this soft tissue injury can be devastating and lead to significant tissue loss (Fig. 5). The burn is a result of the saliva permitting the local conduction and arcing of electricity. The electrical energy is generally concentrated to the oral commissure and the anterior tongue. As with any trauma, the initial management, according to the Advanced Trauma Life Support guidelines, involves a thorough assessment from head to toe. Rarely do these isolated injuries require intubation.

The contact burn wound, often a grayish-white eschar, should be gently cleansed and dressed with an ointment of choice. On examination of the vestibule of the mouth, digital palpation may



FIG. 5 Oral commissure burns caused by contact with a household electrical wire. Associated complications include labial artery rupture, which may occur 7 days postburn.

reveal a "woody," indurated buccal mucosa as far posterior as the tonsillar pillars. Early surgical intervention can lead to loss of potentially salvageable tissue that may be necessary for the reconstructive surgery and thus should be avoided. The goal of early treatment is to maintain a clean, moist environment that allows the tissue to heal. The child should be encouraged to continue to eat and drink. Involvement of a speech pathologist can be of significant help from the onset. The use of a custom-made splint can help reduce scar/contracture formation and should be initiated between 10 and 14 days postinjury. The eschar will continue to demarcate and slough within 7 to 21 days. Based on the proximity of the labial artery to the oral commissure, vessel rupture can be expected to occur in approximately 10% of patients. Parents and caregivers should be educated that if labial artery rupture bleeding occurs, compression of the site between the index finger and thumb should be performed to minimize the hemorrhage, and the patient should immediately return to the hospital. Seldom do these need surgical intervention for ligation.

The continued healing from the burn can result in tissue scarring and contracture. Contracture can interfere with normal vocalization, facial expression, eating, oral hygiene (including dental care), not to mention the psychological sequelae of the trauma. Long-term burns to the mouth can be associated with microstomia. Contracture of the angle of the mouth is generally treated approximately 1 year post–burn injury as it takes at least 1 year for the burn to become stable because of the sphincter action of the orbicularis oris muscle. Late effects of burn reconstructive surgery may include Z-plasty, V-Y flaps (commissuroplasty), ventral tongue advancement flaps, or trapezoid flaps. Of note, the tongue advancement flap, often the only choice based on initial injury, may give a less aesthetically pleasing appearance as the tongue papilla are transferred to the external orifice.

Late Complications

A multitude of late complications from electrical injuries include cataracts, increased cholelithiasis causing cholecystitis, delayed hemorrhage from blood vessel rupture, skeletal complications of fibrosis, and limitation of joint function.

Although there have been significant advances in both burn and the critical care management of these very specialized patients, prevention and safety remain the best way to avoid or minimize the occurrence and severity of electrical injury. With the exception of lightning, electrical injuries are almost always preventable.

Suggested Readings

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ERAS Protocols for General Surgery

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INTRODUCTION

Enhanced recovery after surgery (ERAS) pathways, introduced more than 25 years ago, represent a paradigm shift in perioperative care that involves integration of evidence-based, multimodal, multidisciplinary interventions that mitigate the undesirable effects of the surgical stress response. Traditional perioperative care has been fragmented with surgeons and anesthesiologists practicing in silos with significant variability in care. Implementation of ERAS pathways have the potential to limit this variability and improve patient safety. In addition, perioperative care pathways reduce postoperative complications and shorten hospital length of stay without increasing postdischarge readmission rates. With reduction in hospital length of stay, ERAS pathways have allowed migration of some surgical procedures from the inpatient setting to the outpatient setting. The ultimate aim of ERAS pathways is to improve patient-reported outcomes, including return to activities of daily living, and to address psychosocial issues (e.g., anxiety, depression, cognitive dysfunction) and enhance patient satisfaction.

Recognition of the generalizability of the ERAS interventions and transferable improvements in postoperative outcomes led them to becoming the standard of care for several surgical procedures. Although initially the ERAS pathways were implemented in relatively healthy patients undergoing elective surgical procedures, there is evidence of potential benefits in high-risk patients (e.g., older and sicker patients with low functional reserve) and those undergoing emergency surgery. Thus, ERAS principles should be applied for all surgical patients.

ERAS PATHWAY COMPONENTS

Typically, an ERAS pathway includes approximately 15 to 20 interventions (also referred to as *elements* or *components*) divided into three distinct phases: preoperative, intraoperative, and postoperative periods (Table 1). Several studies have reported correlation between the overall compliance with ERAS elements and reduced postoperative complications and hospital length of stay. Several elements have now become the standard of care (e.g., preoperative optimization of comorbid conditions, minimal preoperative fasting duration, maintenance of normothermia, intraoperative antibiotic prophylaxis, and venous thromboembolism [VTE] prophylaxis). Also, some of the initially recommended elements (e.g., avoidance of preoperative mechanical bowel preparation, preoperative complex carbohydrate loading, and use of epidural analgesia in minimally invasive procedures) lack definitive evidence and may not be valid in the current rapidly changing perioperative care practices.

Although the relative contribution of individual interventions is not clear, the use of a minimally invasive surgical approach is one of the core elements as it is associated with a reduced surgical stress response. In addition, avoidance of drains, nasogastric tubes, and urinary catheters is also critical. Furthermore, postoperative elements such as early oral intake and mobilization appear to influence outcomes the most. Thus, interventions that facilitate oral intake and mobilization such as absence of nausea and vomiting, optimal pain control using an opioid-sparing strategy, and avoidance of fluid overload play a major role in enhancing recovery. For the ambulatory setting, procedure and patient selection is one of the key elements that influence perioperative outcome.

Overall, compliance with ERAS pathways may be improved through strong clinical leadership with the desire and ability to change and employment of updated evidence-based pathways.

PREOPERATIVE CONSIDERATIONS

Preoperative Optimization of Comorbid Conditions

Because a patient's preexisting comorbidities can influence postoperative outcomes and quality of recovery, preoperative identification and optimization of comorbid conditions has become the standard of care. Risk stratification can be used to identify patients at high risk for developing postoperative complications and implement specific preoperative interventions to modify perioperative care. For example, assessment and treatment of preoperative anemia, malnutrition, and frailty have been shown to influence postoperative outcomes and hospital length of stay, particularly in high-risk patients undergoing major invasive surgical procedures. Modern preoperative clinics promote global optimization through patient engagement and interdisciplinary collaboration between preoperative anesthesia and surgical teams to achieve shared decision making and better compliance with ERAS components. Ideally, upon scheduling the surgery, the surgeon's office should refer the patient to this multidisciplinary preoperative clinic.

Prehabilitation

Prehabilitation is a paradigm shift in preoperative care, which includes cardiopulmonary conditioning, muscle strengthening, and malnutrition correction. Prehabilitation has been reported to reduce frailty and improve postoperative functional status, and consequently shorten hospital length of stay. Prehabilitation allows patients to become engaged in their care. Optimal patient- and procedure-specific approaches are being developed, but their practical application remains challenging because of the need for delaying surgery and cost implications.

TABLE 1 Elements of the ERAS Pathway

Preoperative	• Risk assessment and optimization of comorbid conditions as well as risk stratification • Prehabilitation • Patient and family education and counseling • Minimal preoperative fasting and adequate hydration during the fasting period

Intraoperative	• Use of the fast-track anesthesia technique
	  • Avoidance of preoperative midazolam
	  • Avoidance of deep anesthesia
	  • Minimal intraoperative opioid dose
	  • Minimal muscle relaxant dose and reverse residual paralysis at the end of surgery
	  • Minimal number of drug combinations and short-acting anesthetic agents at the lowest possible doses
	• Goal-directed hemodynamic management (optimization of intravascular volume and rational use of vasoactive [vasoconstrictor or vasodilator] drugs)
	• Lung-protective ventilation
	• Multimodal antiemetic prophylaxis
	• Procedure-specific multimodal opioid-sparing pain management
	• Maintenance of normothermia
	• Antibiotic prophylaxis
	• Glycemic control
	• Venous thromboembolism prophylaxis

Postoperative	• Early oral intake and avoidance of fluid overload • Early mobilization

Patient and Family Education and Counseling

Patient and family education and counseling is arguably one of the critical elements. Involving the patient in preoperative decision making, preferably using decision aids, improves transparency, reduces patient anxiety, and can help provide patient-centered care. Psychological preparation and feeling of partnership in perioperative care can optimize patients' behavioral recovery and has been shown to positively influence postoperative pain levels, early mobilization, and hospital length of stay. Importantly, patient education should include not only the information on the perioperative course and what the patient can expect, but also postoperative goals that must be achieved and factors that must be met for enhanced recovery. It is necessary to emphasize the need for patient participation and instill a sense of responsibility by clearly stating what is expected from the patient. Development of realistic expectations and increased co-operation on the part of the patient facilitates the recovery process.

Avoidance of Prolonged Preoperative Fasting

Prolonged preoperative fasting is frequently associated with hypovolemia, electrolyte imbalance, and hypoglycemia. Fasting can induce a metabolic response that can cause insulin resistance. Although avoidance of prolonged fasting has been emphasized, there is evidence that patients fast for longer than the recommended duration. Current guidelines recommend clear liquids until 2 hours before surgery; however, patients do not even consume water after the evening meal. Thus, patients should be given clear instructions to consume water during the fasting period. For example, patients could be encouraged to drink water before going to bed and just before leaving home on the day of surgery. In fact, recent evidence suggests that the fasting guidelines for clear liquids (i.e., water intake) must be liberalized, and patients should be allowed to drink water if they are thirsty in the preoperative period.

Carbohydrate Loading

Surgical stress response can cause insulin resistance resulting in hyperglycemia, poor glucose uptake, and muscle degradation, which can delay recovery. Basic science and low-quality clinical evidence suggest that carbohydrate loading (at least 45 g of a complex carbohydrate drink) 2 hours before surgery reduces insulin resistance and is associated with a small reduction in hospital length of stay. However, recent meta-analyses conclude that there are no benefits from preoperative carbohydrate loading compared with placebo in terms of postoperative complication rate and hospital length of stay. Furthermore, there is concern for hyperglycemia and associated adverse outcomes in diabetic patients. Overall, preoperative carbohydrate administration adds unnecessary healthcare costs. Nevertheless, administration of simple cheaper sports drinks with carbohydrates and electrolytes 2 hours before surgery may improve patient satisfaction by reducing preoperative thirst and hunger, although evidence for this is currently lacking.

Bowel Preparation

Avoidance of mechanical bowel preparation in patients undergoing colonic surgery has been recommended for enhanced recovery after surgery. However, meta-analyses of randomized controlled trials and observational trials in elective colorectal surgery found no differences in postoperative complications (e.g., anastomotic leak, surgical site infection, intraabdominal collection, mortality, reoperation, and hospital length of stay) between mechanical bowel preparation and no preparation. Oral antibiotic preparation, either in combination with mechanical bowel preparation or alone, has been reported to reduce postoperative complications in elective colorectal surgery. Overall, the routine use of preoperative mechanical bowel preparation is not recommended in colonic surgery except, based on limited evidence, for patients undergoing an anterior resection with diverting stoma.

Shortening the Duration of Ileus

Several enhanced recovery pathways recommend the use of alvimopan, a peripheral opioid antagonist, as it has been reported to accelerate gastrointestinal recovery, reduce postoperative ileus, and shorten hospital length of stay. However, the studies reporting such benefits have several limitations including significant heterogeneity with regard to the surgical type and approach as well as perioperative care. Importantly, all of the studies reporting benefits of alvimopan used very high opioid doses in the perioperative period. Thus, the role of alvimopan in current clinical practice that involves an opioid-sparing approach remains controversial.

Patient Selection for Ambulatory Surgery

For ambulatory surgery to be safe and efficient, careful selection of procedures and patients is crucial. Patient selection is a dynamic process that depends on the interaction among the surgical procedure, the patient's comorbid conditions, and anesthetic technique as well as social factors and the ambulatory setting (i.e., hospital-based ambulatory center, short-stay [23-hour] facility, or free-standing ambulatory surgery center). It is generally accepted that patients with a high burden of comorbid conditions, specifically those with poorly

stabilized medical conditions (i.e., American Society of Anesthesiologists [ASA] physical status >3) are not suitable for ambulatory surgery, particularly if the surgical procedure requires administration of general anesthesia. Examples of patients considered ineligible (i.e., ASA physical status 4) include recent (<3 months) new-onset, unstable, or severe angina, myocardial infarction, coronary stents, new-onset or decompensated heart failure, severe valve dysfunction, high-grade atrioventricular block, cerebrovascular disease (transient ischemic attacks/cerebrovascular accident), acute respiratory disease, and end-stage renal disease not undergoing regular dialysis. Other factors that influence decision making include bleeding disorders and use of antiplatelet and anticoagulant drugs. Factors such as age, weight, and presence of sleep-disordered breathing (e.g., obstructive sleep apnea) should not be considered in isolation to determine suitability for ambulatory surgery. The best approach is for the entire perioperative team to develop procedure-specific inclusion/exclusion criteria. This will avoid unnecessary cancellations on the day of surgery.

INTRAOPERATIVE CONSIDERATIONS

Fast-Track Anesthetic Technique

Although anesthesia-related mortality is extremely low, intraoperative care can influence short-term and long-term morbidity. The residual effects of drugs used to provide general anesthesia (i.e., hypnotic-sedatives, neuromuscular blocking agents, and opioids) can influence 30-day readmission rates. Because the drugs used during general anesthesia have additive or synergistic effects, a minimal number of drug combinations should be used. Also, when possible, drugs should be short-acting and should be administered at the lowest possible doses. The superiority of choice of inhalation anesthesia versus total intravenous (IV) anesthesia is unclear, even in high-risk populations (e.g., cancer surgery patients). Similarly, the role of opioid-free anesthesia (i.e., complete avoidance of intraoperative opioids) remains controversial. In fact, there is concern that the analgesic adjuncts (e.g., ketamine, dexmedetomidine, lidocaine, magnesium infusions) used in an opioid-free anesthesia technique may be detrimental to recovery.

Mechanical Ventilation

The use of lung protective ventilation strategies (i.e., tidal volumes 6–8 mL/kg, ideal body weight with positive end expiratory pressure [PEEP] 5–10 cm H_2O) have been shown to reduce postoperative pulmonary complications and thus have become the standard of care. In addition, end-tidal carbon dioxide ($ETCO_2$) values should be maintained around 40 mm Hg, rather than the traditional 30 to 35 mm Hg, as they improve tissue and organ perfusion.

Goal-Directed Fluid Therapy and Hemodynamic Management

Goal-directed hemodynamic management, which aims to maintain adequate perfusion pressure and oxygen delivery, is imperative in maintaining organ function. Hemodynamic management includes optimizing intravascular volume (fluid and blood management) and rational use of vasoactive drugs such as vasopressors and inotropes. This approach uses both static (e.g., mean arterial pressure) and dynamic (e.g., stroke volume variation and pulse pressure variation) hemodynamic variables.

Although the target mean arterial pressure remains controversial, most accept a value of 65 mm Hg. Although goal-directed fluid therapy guided by cardiac output monitoring was considered an important element of ERAS for all surgical patients, recent evidence has demonstrated that it does not confer benefits in the setting of an ERAS pathway (versus traditional care). Fluid imbalance is reduced within the ERAS pathway because the minimally invasive surgical approach is associated with a lower propensity for intraoperative fluid and blood loss, and patients are encouraged to hydrate during the fasting period as well as resume oral intake immediately after surgery. The goal of intraoperative fluid management is to achieve a "zero" fluid balance. Intraoperative administration of 3 to 5 mL/kg/h balanced crystalloid solution is recommended as a baseline. In addition, blood loss should be replaced with balanced crystalloid solution in the ratio of 1:1.5. The use of goal-directed fluid therapy guided by cardiac output monitoring is appropriate in high-risk patients undergoing major surgical procedures in whom the expected blood loss is greater than 1000 mL.

Nausea and Vomiting Prophylaxis

It is well documented that postoperative nausea and vomiting (PONV) adversely impacts outcomes. PONV reduces the patient's ability to comply with the critical goals of an ERAS pathway such as early oral intake and mobilization. All patients should receive at least 2 to 3 antiemetics from different classes, either preoperatively or intraoperatively (Box 1). Patients at very high risk (e.g., history of motion sickness, history of previous PONV, high opioid requirements after surgery) should receive 3 to 4 antiemetics.

Preoperative PONV prophylaxis could include a scopolamine transdermal patch or aprepitant 40 mg orally, both administered 1 to 3 hours before surgery. Intraoperative options include dexamethasone 8 to 10 mg IV at induction of anesthesia and a serotonin 5-HT3 antagonist (ondansetron 4 mg IV or palonosetron 0.75 mg IV) at the end of surgery. In addition to antiemetic effects, dexamethasone has analgesic and antiinflammatory effects that can facilitate recovery

BOX 1 Recommendations for Postoperative Nausea and Vomiting Prophylaxis and Treatment

General Principles

All patients should receive two to three antiemetics from different classes either preoperatively or intraoperatively.
Patients at very high risk (i.e., history of motion sickness, previous postoperative nausea and vomiting) should receive three to four antiemetics as well as total intravenous anesthesia.
All patients should receive a procedure-specific opioid-sparing analgesic regimen.

Options for Antiemetic Prophylaxis

Scopolamine transdermal patch (1–3 hours before surgery)
Aprepitant 40 mg PO (1–3 hours before surgery)
Dexamethasone 8–10 mg IV at induction of anesthesia
Dopamine D_2 antagonist (droperidol 0.625–1.25 mg IV or haloperidol 0.5–1 mg IV) at the end of surgery
Serotonin 5-HT3 antagonist (ondansetron 4 mg IV or palonosetron 0.75 mg IV) at the end of surgery

Options for Rescue in the Postanesthesia Care Unit

Antiemetic of a class not administered preoperatively or intraoperatively
Promethazine 6.25 mg IV

Options for Treatment on the Ward

Ondansetron (4 mg IV or 8 mg orally disintegrating tablet [ODT])
Promethazine 6.25–12.5 mg IV
Prochlorperazine 2.5–5 mg IV
Dimenhydrinate 25–50 mg IV

Postdischarge Treatment

Ondansetron 8 mg ODT
Over-the-counter antiemetics (e.g., meclizine, dimenhydrinate)

and thus have been increasingly included in ERAS pathways. Of note, a single IV dose of dexamethasone 8 to 10 mg does not seem to influence wound infection and healing.

Rescue treatment options for PONV in the recovery room include antiemetics of a class not administered preoperatively or intraoperatively (see Box 1). Options for treatment on the wards include ondansetron 4 mg IV or 8 mg orally disintegrating tablet [ODT], promethazine 6.25 to 12.5 mg IV, prochlorperazine 2.5 to 5 mg IV, or dimenhydrinate 25 to 50 mg IV. Postdischarge nausea and vomiting may be treated with ondansetron 8 mg ODT or over-the-counter antiemetics such as meclizine and dimenhydrinate.

Procedure-Specific Pain Management

Pain management is a critical component of an ERAS pathway. The primary aim should be to facilitate ambulation rather than achieve a certain pain score. Optimal perioperative pain management includes preoperative identification of patients at high risk of postoperative pain. Opioid-sparing multimodal analgesia improves outcomes by reducing the risks of opioid-related adverse events such as nausea, ileus, respiratory depression, and sedation. The number and choice of analgesics used would depend on the balance between the invasiveness of the analgesic technique and consequences of pain as well as the adverse event profile of the intervention (Table 2).

Unless there are contraindications, acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) or a cyclo-oxygenase (COX-2)–specific inhibitor should be administered preoperatively or intraoperatively. In addition, a single intraoperative dose of dexamethasone 8 to 10 mg, IV is recommended. Regional/local analgesic techniques are the core of an optimal multimodal analgesic strategy and thus should be used when possible. However, the role of neuraxial blocks (e.g., epidural analgesia) in the ERAS setting is decreasing because of concerns of delayed ambulation and the availability of alternative analgesic techniques that can provide similar pain relief

TABLE 2 Analgesic Options for Procedure-Specific Multimodal, Opioid-Sparing Analgesic Strategy

Analgesic Technique	Indications	Comments
Acetaminophen	All patients, if no contraindications	Oral administration is preferred Maximum 24-hour dose should be 4 g
NSAIDs	All patients, if no contraindications	*Contraindications* Risk of kidney injury: preexisting renal insufficiency, hypovolemia, major blood loss, hypotension, use of nephrotoxic agents Bleeding and coagulation disorders Hypersensitivity to aspirin or NSAID-exacerbated respiratory disease H/O gastrointestinal bleeding
Dexamethasone	All patients, if no contraindications	Primarily for PONV prophylaxis Avoid in patients with HbA1c >10%
Ketamine infusion	Opioid-tolerant patients undergoing major painful surgery if non-opioid approaches (e.g., regional analgesia, acetaminophen, NSAIDs) are not possible	No role for single bolus doses Dosing: 0.25 mg/kg IBW bolus followed by 0.1 mg/kg/h infusion
Lidocaine infusion	Major open abdominal surgery, if nonopioid approaches (e.g., regional analgesia, acetaminophen, NSAIDs) are not possible	Dosing: 1.5 mg/kg IBW bolus followed by 2 mg/kg/h infusion
Dexmedetomidine infusion	No role in pain management	Lack of benefits and concerns of prolonged hypotension and sedation
REGIONAL ANALGESIA		
Epidural analgesia	Major open thoracic and abdominal surgery	Concerns in patients receiving VTE prophylaxis Postural hypotension and delayed mobilization
Interfascial plane blocks	Open truncal surgery	Breast surgery: erector spinae plane or pectoralis II blocks or serratus plane block Thoracotomy: erector spinae plane Upper and lower abdominal surgery: erector spinae plane blocks or four-quadrant TAP blocks Lower abdominal surgery: erector spinae plane blocks or TAP blocks
Peripheral nerve blocks	Limb surgery	
Surgical site infiltration	Most surgical procedures	± Other regional analgesic techniques

IBW, Ideal body weight; *NSAID,* nonsteroidal antiinflammatory drug; *PONV,* postoperative nausea and vomiting; *TAP,* transverse abdominis plane; *VTE,* venous thromboembolism.

and recovery outcomes. Patients undergoing major limb surgery benefit from peripheral nerve blocks (e.g., brachial plexus blocks for major upper limb surgery and popliteal-sciatic nerve blocks for major foot and ankle surgery). Patients undergoing torso surgery benefit from interfascial plane blocks (e.g., transversus abdominis plane blocks and erector spinae plane blocks). Surgical site infiltration provides excellent analgesia; however, it is necessary that all layers of the surgical incision are infiltrated meticulously under direct vision immediately before tissue/skin closure. For example, in patients undergoing open abdominal surgery, the peritoneal, musculofascial, and subdermal planes should be infiltrated. The injection solution includes the maximum dose of local anesthetic based on body weight (e.g., for average adults, bupivacaine ~150 mg or ropivacaine ~300 mg) diluted with normal saline to a total volume depending upon the incision size, typically 60 to 100 mL.

IV lidocaine infusions have been shown to reduce pain and opioid requirements as well as hasten gastrointestinal recovery after abdominal surgery. The role of a single dose of ketamine (25–100 mg) remains controversial because the benefits over other analgesics (i.e., acetaminophen and NSAIDs or COX-2–specific inhibitors) and regional analgesia is unclear. There are also concerns of adverse effects such as nightmares and sleep disturbances. Nevertheless, a ketamine infusion may be used for opioid-tolerant patients undergoing major surgical procedures. The role of gabapentinoids (i.e., gabapentin and pregabalin) is controversial because of limited benefits and the potential for adverse effects such as sedation, dizziness, visual disturbances, and orthostatic hypotension. When gabapentinoids are used (e.g., surgical procedures with a high propensity of persistent postoperative pain), they should be used with great caution and at the lowest possible dose.

After discharge home, acetaminophen and NSAIDs or COX-2–specific inhibitors should be used on a regular "round-the-clock" or "scheduled" basis. Opioids should be used as "rescue" analgesics on an "as-needed" basis. Using opioids that are not combined with acetaminophen (e.g., oxycodone and tramadol) should alleviate the concerns of acetaminophen toxicity. Patients should also be educated about concerns with opioid use and be familiarized with alternative nonpharmacologic analgesic treatments such as the application of ice, elevation of the operated extremity, music, and cognitive behavioral modalities.

Venous Thromboembolism Prophylaxis

Prophylaxis for VTE has been emphasized because it is one of the common causes of morbidity and mortality. Several professional societies have published guidelines for VTE prophylaxis. The choice of agent is dependent on other aspects of the patient's overall health such as surgery type, presence of kidney disease, bleeding risk, and analgesic modality (i.e., neuraxial procedures). Mechanical prophylaxis alone may be appropriate in patients with high bleeding risk, while a combination of mechanical and pharmacologic prophylaxis is preferable in patients with high VTE risk. Also, for patients undergoing a major surgical procedure, extended (i.e., more than 3 weeks after surgery) prophylaxis may be necessary. Of note, the guidelines for VTE prophylaxis have been based on evidence from outside ERAS pathways. Early mobilization within the ERAS pathway should reduce the risk of VTE; however, the type and duration of VTE prophylaxis within the ERAS pathway is not well studied.

POSTOPERATIVE CONSIDERATIONS

Early Oral Nutrition and Avoidance of Fluid Overload

Because of the increased metabolic demands in the perioperative period and the catabolism associated with surgery, early postoperative oral nutrition is an indispensable component for enhanced recovery. Most patients, except for those with delayed gastric emptying, tolerate early oral intake. PONV, high opioid dose, and fluid overload detrimentally affect oral intake. Thus, early resumption of oral nutrition is the logical continuation of previously stated ERAS components. Surgical factors including the presence of nasogastric tubes, ileus, severe shock, intestinal ischemia, or a high-output fistula may preclude oral nutrition and necessitate other forms of support (i.e., parenteral supplementation).

Early Mobilization

Early mobilization is considered one of the most important elements as it improves pulmonary and gastrointestinal function, reduces VTE, and avoids loss of muscle mass and function. Furthermore, unimpaired muscle function is essential for hospital discharge and return to activities of daily living. Patient co-operation and early consultation with physical therapists are imperative for effective implementation of this component of the ERAS pathway. The inability to mobilize may be a reflection of poor postoperative pain control, nausea and vomiting, orthostatic intolerance, postoperative morbidity, dependence on IV fluids, lack of facility ancillary support services, or poor patient motivation.

Nursing/Ancillary Support Considerations

The nursing team plays a crucial role in the successful implementation of ERAS pathways, and they must undergo significant training and education in pathway components to ensure higher compliance rates among patients. Even though important pathway components (e.g., mobilization, diet, pain, education) are prescribed, application for day-to-day practice depends on the nurses. Hospitals can ensure compliance by having continuing education for support staff, adequate staffing, and positive feedback for the nursing teams. Active participation in this type of patient-centered care plan should be tracked and audited by hospital systems.

POSTDISCHARGE CONSIDERATIONS

Postsurgical recovery is measured differently within a hospital organization and by patients. Compliance within the ERAS program has been shown to reduce postsurgical discharge complications and readmission rates. However, because of the positive impact of ERAS pathways on hospital discharge times, the majority of the recovery phase occurs after discharge home, leaving patients and their families feeling vulnerable and unprepared. Patients may see this late recovery phase as taking weeks to months before they return to a physical, emotional, and financial (i.e., return to work) baseline. Challenges remain in accurately measuring functional recovery after surgery and in providing adequate education via digital aids so patients can make informed decisions regarding identification of potential complications and when to seek help or visit the emergency department. Such education would reduce unnecessary visits to the acute care facility. In addition, utilizing digital technology will provide novel ways to track mobility, nutritional status, and mental health, thus promoting positive self-management in the recovery phase.

SUMMARY

Given the significant clinical benefits, ERAS pathways are increasingly being implemented worldwide (Table 3). A multidisciplinary approach (i.e., collaboration among surgeons, anesthesiologists, nurses, and physical therapists) is necessary to ensure high compliance rates and achieve maximum benefits. It is clear that several elements are interconnected and collectively influence postoperative outcomes. Fast-track general anesthetic techniques involving opioid sparing and goal-directed hemodynamic management combined with prevention of pain, nausea, and vomiting influence postoperative outcomes.

Conflicting recommendations and inconsistent education of ancillary staff may be a major factor for the lack of implementation or patchy implementation of ERAS pathways. Although evidence for ERAS elements continues to evolve, some are accepted as dogma without

TABLE 3 A Sample ERAS Pathway

Preoperative considerations	Initial Visit (Weeks Before Surgery)
	• Patient evaluation: identify and optimize comorbid conditions (identify high-risk patients)
	  • Optimize chronic cardiovascular, respiratory, and endocrine diseases as well as renal dysfunction
	  • Assess and treat anemia
	  • Assess and treat malnutrition
	  • Assess functional capacity (frailty)
	  • Assess and manage psychiatric issues
	  • Manage chronic medications
	• Minimal preoperative laboratory testing: only for specific comorbid conditions and surgery
	• Prehabilitation: cardiopulmonary conditioning, muscle strengthening, and malnutrition correction
	• Patient and family education and counseling as well as discharge planning
	Day Before Surgery
	• Avoid mechanical bowel preparation; however, if planned, combine it with oral antibiotics
	  • No role for mu-opioid receptor antagonist (alvimopan)
	• Minimize the preoperative fasting period, *and* encourage oral hydration during fasting (1–2 glasses of water before going to bed preferred)
	• Avoid oral sedatives
	Day of Surgery
	• Hydrate well on the morning of surgery. Drink 1–2 glasses of water before leaving home
	• No role for complex carbohydrates; if desired may consume Gatorade/Powerade up to 20 oz
	• Pain prophylaxis
	  • Acetaminophen 1–1.5 g, PO, ~2 h preoperatively
	  • Celecoxib 400 mg, PO, ~2 h preoperatively (OPTIONAL)
	• Venous thromboembolism prophylaxis
	  • Heparin /LMWH 5000 units SC, 30–60 min before surgery
	  • Bilateral sequential compression devices (SCDs) placed in the preoperative area, start before induction of anesthesia
	• PONV prophylaxis: Scopolamine patch in patients at high risk of PONV, caution in patients older than 65 years of age because of potential for confusion and urinary retention
	• Premedication: None (avoid routine use of midazolam before moving the patient to the operating room)

Intraoperative considerations	Surgical Considerations
	• Minimally invasive surgical approach
	• Avoidance of drains and nasogastric tube (prophylactic drainage for pelvic anastomosis): reduce anastomotic dehiscence, SSI, reoperation
	Anesthetic Considerations
	• Use of fast-track anesthesia technique
	  • Avoid deep anesthesia
	  • Minimize intraoperative opioid use
	• No role for opioid-free anesthesia (lidocaine, ketamine, dexmedetomidine, magnesium infusions)
	  • Avoid residual muscle paralysis
	• Minimize neuromuscular-blocking drugs, and reverse appropriately
	• Hemodynamic management: maintain MAP ~65 mm Hg, systolic pressure > 90 mm Hg
	• Avoidance of fluid underload/overload
	  • Baseline lactated Ringer's ~3–5 mL/kg/h
	  • Fluid bolus ~100 mL urine output <0.5 mL/kg/h and/or if systolic pressure variation >15% (if a line present)
	• Blood management
	• Lung protective mechanical ventilation: tidal volume 6–8 mL/kg, PEEP 5 cmH_2O, $ETCO_2$ ~40 mm Hg
	• Maintenance of normothermia (core body temperature of 36°–38°C)
	• Glycemic control: maintain blood glucose level <200 g/dL
	• Antibiotic prophylaxis
	• Antiemetic prophylaxis
	• Procedure- and patient-specific multimodal opioid-sparing pain management

TABLE 3 A Sample ERAS Pathway—cont'd

Postoperative considerations	• Control comorbid conditions: hydration, hemodynamics
	• Glycemic control
	• Pain management
	• VTE prophylaxis: SCDs +POD # 0-Heparin/LMWH 5000 units sq 6–8 h, POD # 1-Enoxaparin 40 mg, SC q
	• PONV treatment
	• Bowel regimen: Docusate 100 mg PO bid or senna 1 tab PO bid
	• Fluid management until full oral intake
	  • POD 0: Lactated Ringer's 50 mL/h, bolus 100–200 mL if urine output <0.5 mL/kg/h unless hemodynamic instability
	• D/C urinary catheter as soon as possible
	  • Abdominal surgery POD 1, except for pelvic operations (proctectomy, LAR, APR), on POD 3
	• Early oral intake (factors that influence oral intake)
	  • Gum chewing encouraged
	  • On POD 0: Water ~800 mL + liquid nutritional support (Boost, 1 can) ~2 h after surgery
	  • On POD 1 until discharge: soft diet
	• Early postoperative mobilization (factors that influence mobilization)
	  • On POD 0: out of bed more than 2 h, including sitting in chair and walks, if appropriate
	  • On POD 1 until discharge: out of bed more than 6–8 h including walks for more than 4 h
	  • Patient up in chair for all meals
	• Physical therapy
	• Hospital-associated disability: No in-room entertainment (TV); communal area for meals; emphasize sleep and activity; gender, age, and level of education influence postoperative pain

adequate evidence of their efficacy, and others are not beneficial at all or even deleterious to outcomes. However, this is lost in daily practice as originally proposed elements often are regarded as compulsory, irrespective of the evidence for their use. Therefore, it is imperative to identify interventions that are beneficial in improving postoperative outcomes while other interventions may be followed based on local circumstances. This concept of "partial ERAS" should increase implementation and contribute to improved patient outcomes.

Finally, it is essential to institute an audit program to evaluate the success of ERAS pathways and the need for modification. Although hospital length of stay and readmission rates are commonly used to define success of an ERAS pathway, they do not reflect true recovery of a patient; thus patient-reported outcome measures must be emphasized. Furthermore, it is necessary to address early identification and management of complications in the hospital (i.e., failure to rescue) as well as after discharge from the hospital (i.e., days alive and out of hospital).

Suggested Readings

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Fluid and Electrolyte Therapy

S. James El Haddi, MD, MS, Jane Stevens, MSN, MD, and Albert Chi, MD

An essential component of patient care is the appropriate management of fluid and electrolytes. From the molecular to organ level, a patient's physiology is dependent on their electrolyte and fluid balance. Surgical patients have unique needs that are directly affected by maintenance and resuscitative fluids. The mismanagement of resuscitation and fluids can have disastrous results, as the complex systems in the human body heavily depend on precise homeostasis. The purpose of this chapter is to discuss normal fluid and electrolyte distribution and corrective therapies for pathologies encountered in the surgical patient.

FLUID COMPARTMENTS, DYNAMICS, AND OSMOLALITY

The overall percentage of water to the total body weight is defined as total body water (TBW). Depending on their level of body fat, a patient's TBW is 50% to 60%. Fat tissue has a higher water content

than muscle, and thus obesity and physiologic gender will affect this proportion, with males having around 60% and females 50% to 55%. This water is distributed in the intracellular and extracellular space and is further subdivided as shown in Figure 1. These proportions may change in the setting of disease; however, in an otherwise healthy 70-kg male, their TBW would be 42L with 28L intracellular and 14L extracellular (two-thirds and one-third TBW, respectively).

This balance of extracellular and intracellular water content is maintained by the cellular plasma membrane and solutes. The membrane is permeable to water so that the osmolality, or concentration of solutes, is equal between the intracellular, interstation (between cells), and intravascular components.

Although the overall concentration of solutes is equal throughout the body, the membrane and its associated protein channels regulate the permeability of selected solutes, which creates a transmembrane differential. The nonpermeable solutes are referred to as effective osmoles that drive the osmotic forces, which direct water movement across the cell membranes. Lipid-rich membranes allow for simple diffusion across membranes while protein-based water channels, known as aquaporins, allow for direct movement.

Membranes in the capillaries are permeable to smaller solutes such as sodium, potassium, glucose, and low-molecular-weight proteins that are less than 50,000 kDA. These small solutes have no role in effective osmoles to facilitate capillary fluid movement, and instead this is directed by Starling's law. In contrast to the Frank-Starling curve cardiac contractility, Starling's Law states that transcapillary water movement results from the balance between oncotic pressure of effective osmoles and hydrostatic pressure from blood flow. This is shown in the following equation:

$$J_v \propto K\left[\left(P_c - P_i\right) - \sigma\left(\pi_c - \pi_i\right)\right]$$

Here, the efflux of fluid J_v is directly proportional to the membrane coefficient and the difference between the capillary hydrostatic pressure P_c and interstitial hydrostatic pressure P_i. It is inversely related to the reflection coefficient σ and the difference between the capillary oncotic pressure π_c and the interstitial oncotic pressure π_i. The oncotic pressures are generated by plasma proteins too large to cross the capillary wall, and net movement is created by an imbalance between the hydrostatic forces and water concentration gradients. In the average physiologic state, the hydrostatic pressure will force fluid into the interstitial space while plasma proteins will provide oncotic pressure to draw fluid into the intravascular space. Due to the higher hydrostatic forces in the arteriolar end of the capillary bed, there is a net efflux of fluid. Along the length of the capillary bed there is a sharp drop-off in the hydrostatic pressure resulting in a reversal of the direction of flow in the venous end of the capillary.

Although small solutes do not generally contribute to water movement across capillary membranes, they will function as effective osmoles that direct fluid between the intracellular and extracellular spaces. Given their relative abundance, sodium (Na^{+}) and potassium (K^{+}) are the primary determinants of osmolality in the extracellular and intracellular spaces, respectively. Due to their charge, they are unable to pass across the lipid-rich membrane, and thus this concentration gradient is maintained by the Na^{+}/K^{+} adenosine triphosphatase (ATPase) pump. This well-described protein will transport three sodium extracellularly in exchange for two potassium molecules intracellularly. This net efflux of positively charged ions creates a net negative cell membrane potential that can be utilized for work. In addition, the manipulation of these ions results in water movement down its relative concentration gradient from the low osmolality compartment to the high osmolality compartment.

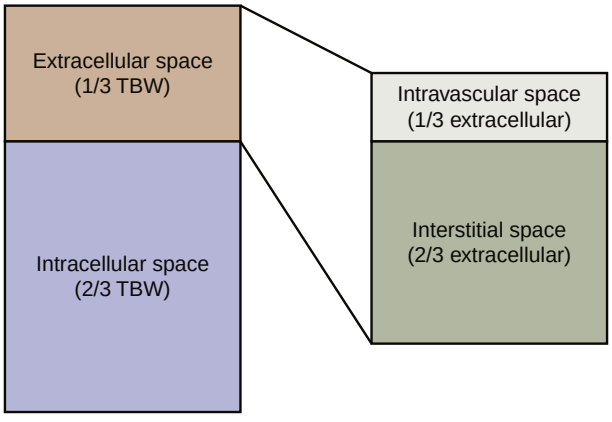


FIG. 1 Body fluid distribution. *TBW*, Total body water.

Conceptually, osmolality is the inverse of the concentration of water, and thus a higher concentration of solutes and osmolality is fundamentally a lower concentration of water creating a gradient that is inevitably equilibrated. It is because of this that administration of a hypotonic solution will result in decreased extracellular osmolality, so the water will move intracellularly creating swelling. Hypertonic solutions will increase extracellular osmolarity driving water intracellularly and creating cellular shrinking as water moves down its relative concentration gradient. Serum osmolality is maintained in a narrow therapeutic range through osmoregulation. It can be estimated using the following equation:

$$\text{Serum osmolality} = 2\left([\text{Na}] + [\text{K}]\right) + \frac{[\text{BUN}]}{2.8} + \frac{[\text{glucose}]}{18}$$

In this equation, BUN is blood urea nitrogen and the resultant units are mOsm/kg. Normal serum osmolality ranges from 275 to 290 mOsm/kg with a physiologic 1% to 2% variation. Variations beyond this are detected by osmoreceptors in the hypothalamus. Hyperosmolality, or a relative decrease in the concentration of water, drives thirst along with secretion of antidiuretic hormone (ADH) from the posterior pituitary gland. This peptide-based hormone has a myriad of receptors throughout the body with differing effects including the upregulation and fusion of vesicles containing aquaporin channels in the basolateral membrane of the distal collecting tubules. These channels facilitate diffusion of water promoting resorption and increasing urine osmolality. Depending on the serum osmolality and renal function, urine concentration can increase up to 1200 mOsm/kg. ADH release is also stimulated by central baroreceptors in the setting of decreased plasma volume, resulting in increased water reabsorption to restore plasma volume and osmolality homeostasis.

Osmoregulation and volume regulation are regulated processes, with sodium serving not only as the primary regulator of extracellular osmolality but also of volume status. Hormone systems such as the renin-angiotensin-aldosterone (RAA) axis promote volume expansion. Renal hypoperfusion is detected in the juxtaglomerular apparatus by the macula densa within the distal convoluted tubule. The juxtaglomerular cells will secrete renin in response to low sodium in addition to hypoperfusion, which promotes the formation of angiotensin from angiotensinogen. The ultimate result is increased aldosterone production to promote sodium reabsorption in the distal convoluted tubule. The competing axis in sodium regulation is partially enacted through atrial natriuretic peptide (ANP). This hormone is secreted by the cardiac atria in response to increased atrial stretch to increase sodium and volume loss. ANP will promote dilation of the afferent glomerular arteriole, thus increasing renal perfusion in addition to inhibiting sodium resorption and thus water excretion.

FLUID STATUS AND THE MANAGEMENT OF VOLUME THERAPY

Assessment of Fluid Status

Patients can undergo large volume shifts due to preoperative, intraoperative, and perioperative fluid losses and shifts. A healthy normothermic adult with a normal metabolic rate loses approximately

1.5 mL/kg/hr of fluid, while animal models have estimated that evaporative intraoperative fluid loss ranges from 1 mL/hr to 1 L/hr depending on the amount of exposed viscera and type of surgical procedure. Many surgical patients may also arrive to the operative theater dehydrated, whether due to the associated condition that necessitated surgical intervention or potentially due to administration of a preoperative bowel prep and prolonged *nil per os* status. The components of the various gastroenteric fluids are important to note (Table 1). Furthermore, hemorrhage, ongoing enteric losses, and use of crystalloid in the operative field can all have a role in the volume status changes within the surgical population. While nearly all patients require replacement of these fluids, selecting the appropriate amount, rate, and type of volume replacement is critical to prevent iatrogenic sequelae.

The postoperative inflammatory state will often result in a low effective intravascular volume due to cytokine-induced permeability, which results in fluid shifting to the extravascular space. Excessive thirst, dry mucous membranes, oliguria, poor skin turgor, tachycardia, hypotension, orthostasis, and abnormal mentation are all signs that a patient has moderate to severe low effective circulatory volume. Several clinical tools exist to assist with assessing volume status including urine and serum electrolyte levels, acid-base balance, and invasive monitoring equipment.

Urine output remains a mainstay for assessing volume status in an otherwise healthy adult; however, recent studies have shown that morbidity and mortality are not improved when using it for goal-directed therapy. Although a healthy adult should produce at least 0.5 mL/kg/hr and children should produce 1 to 2 mL/kg/hr, the expanded non–water-storing tissue in obese patients may overestimate goal urine outputs. Furthermore, some literature have suggested that, in adults, a perioperative urine output goal of 0.2 mL/kg/hr is tolerated well without significant increased risk of acute renal failure. In addition, patients with renal insufficiency, those receiving diuretics, and those with hyperglycemia and other osmotic diuretics may further alter the accuracy of urine output as a surrogate marker of volume status.

Other markers of intravascular volume depletion include elevated hematocrit, low serum bicarbonate level, elevated base deficit, prerenal azotemia (classically defined as BUN/creatinine ratio greater than 20:1), a fractional excretion of sodium (FENa) of less than 1%, elevated urine osmolality, and a fractional excretion of urea less than 35%. Fractional excretion of urine remains a useful tool in the surgeon's armamentarium; however, renal insufficiency and use of loop diuretics can interfere with the test's accuracy. The FENa is as follows:

$$\text{FENa} = 100 \times \frac{(P_{Cr} \times U_{Na})}{(U_{Cr} \times P_{Na})}$$

While the fractional excretion of urea is:

$$\text{FEUrea} = 100 \times \frac{(P_{Cr} \times U_{Urea})}{(U_{Cr} \times P_{Urea})}$$

Classes of IV Fluid Therapy

Fluid therapy is generally considered to be divided into two categories based on composition and goal. Maintenance fluids are used to replace normal and insensible fluid losses. These typically contain dextrose to maintain plasma osmolality and mitigate glycogen depletion. In contrast, resuscitative or replacement fluids replace abnormal and excessive losses and correct for water or electrolyte deficits. Patients with large fluid deficits in the immediate postoperative period, injury, or dehydration are usually treated with resuscitative fluids. Common parenteral fluids are shown in Table 2.

Maintenance Fluids and Daily Electrolyte Requirements

Sensible losses, by definition, can be quantified and occur primarily in urine (~800–1500 mL daily) and stool (~250 mL daily). Insensible loses include cutaneous losses through exposed skin and upper respiratory tract. Intraoperatively, insensible losses occur through exposed body cavities as well. The volume of insensible and sensible losses vary greatly depending on (patho)physiologic states including burns, fever, tachycardia, infection, tachycardia, and other hypermetabolic infections. Cutaneous losses will increase by 10% per day for each degree increase in body temperature above 37.1°C. Thoracotomy and laparotomy sites can increase insensible losses as previously noted.

Maintenance fluid administration in the pediatric and adult populations can be estimated by using the 4-2-1 rule, which is further delineated later. Abnormally high or low percent body fat and renal failure can result in over and underestimation of a patient's maintenance fluid requirements. As noted previously, maintenance fluids will contain dextrose; however, their electrolyte composition is variable and allows for replacement of those lost in both sensible and insensible loss. As with all postoperative cares, monitoring for a patient's response to therapies is advised to avoid iatrogenic injury and failure to rescue. The most common postoperative maintenance fluid for adults is 5% dextrose in one-half normal saline (D5HNS or D5 ½NS) with 20 mEq/L potassium chloride. In children, the standard maintenance fluid is D5HNS or D5 lactated Ringer's (LR) solution. This is to avoid hyponatremia in the pediatric population. Children younger than 2 years of age often receive D5 ¼NS with 20 mEq/L KCl. The reason for the decreased sodium content is that the infant glomerular filtration rate (GFR) is one-quarter the adult level, and the distal nephrons are unable to effectively concentrate the urine, leading to a difficulty in excreting high sodium loads.

When administering maintenance fluids, utilizing the 4-2-1 dosing regimen allows for a quick estimation of a patient's hourly fluid requirements. This equation is 4 mL/kg for the first 10 kg, 2 mL/kg for the second 10 kg, and 1 mL/kg for every remaining kilogram. A quick shorthand for any patient in excess of 20 kg is 60 + n where n is the patient's weight in kg minus 20. For a 70-kg patient, this would be 60 + (70 − 20) = 60 + (50) = 110 mL/hr. When administering D5HNS, this would equate to 203 mEq/day, which is greater than

TABLE 1 Electrolyte Composition (mEq) of Gastrointestinal Fluids

Fluid	Daily Production (mL)	Na^+	K^+	Cl^-	HCO_3^-
Saliva	1000	30–80	15	70	30
Gastric	1000–2000	60–80	–10	100	0
Pancreas	1000	140	20	60–90	40–100
Bile	1000	140	75	100	40
Small bowel	2000–5000	140	20	100	25–50
Large bowel	200–1500	75	30	30	0

Electrolyte composition (mEq) of gastrointestinal fluids: *Cl^-*, Chloride; *HCO_3^-*, bicarbonate; *K^+*, potassium; *mL*, milliliter; *Na^+*, sodium.

TABLE 2 Electrolyte Composition (mEq) of Parenteral Fluids

Fluid	Na^+ mEq/L	K^+ mEq/L	Cl^- mEq/L	Ca^{2+} mg/L	HCO_3^- mEq/L	Dextrose mg/L	pH	Osmolality (mOsm)
Extracellular Fluid	142	4	103	5	27	0	7.4	280
LR	130	4	109	2.7	28	0	6.5	275
NS (0.9% NaCl)	154	0	154	0	0	0	4.5	308
½NS (0.45% NaCl)	77	0	77	0	0	0	4.5	308
¼NS (0.22% NaCl)	34	0	34	0	0	0	4.5	77
Hypertonic Saline (3% NaCl)	513	0	513	0	0	0	4.5	1026
5% Dextrose in Water	0	0	0	0	0	50	5	278
5% Albumin	145	0	145	0	0	0	7.4	310
25% Albumin	145	1	145	0	0	0	7.4	312
6% Hetastarch in Lactated Solution	143	3	124	5	28	990	5.9	307
Normosol	140	5	98	0	0	0	6.6	294
Plasma-lyte	140	5	98	0	0	0	7.4	294

Components of various fluid compositions as reported by manufacturers.

the required 1 or 2 mEq/kg/day by 45%. Patients with normal kidney function can excrete the excess sodium load; however, patients with renal or cardiac dysfunction may have resultant hypernatremia.

Resuscitative Fluids

Resuscitative fluids are commonly used in the immediate postoperative period and in the setting of hypovolemia. The rate of fluid administration is determined by the severity of deficit, ongoing losses, and the patient's underlying comorbidities. Normal saline, Plasma-Lyte, Normosol, and LR closely approximate the composition of extracellular fluids; however' NS and LR are the most commonly used resuscitative fluids. As shown in Table 2, LR has a pH of 6.5 and provides 28 mEq of bicarbonate (HCO_3^-) per liter, making it preferential in the setting of acidosis. NS has a pH of 4.5 and does not contain bicarbonate but instead a higher concentration of Na^+ and Cl^- (154 mEq), making it preferential in patients with a metabolic alkalosis. This does mean it can create hyperchloremic metabolic acidosis in the setting of high-volume resuscitation. Large-volume resuscitation should be carried out with isotonic fluid such as NS or LR with cautious monitoring of desired clinical endpoints. Although many have posited that colloid solutions such as albumin, hydroxyethyl starch, and even fresh-frozen plasma (FFP) can provide a theoretical benefit over crystalloid through application of oncotic pressure, there has yet to be a clearly demonstrated benefit in patient outcomes in prospective randomized trials.

Enhanced Recovery After Surgery (ERAS) Protocols and Fluid Management

Enhanced recovery after surgery (ERAS) programs are evidence-based multidisciplinary pathways designed to accelerate postoperative recovery and shorten time to discharge without compromising safety. ERAS protocols are evidence-based, standardized, utilize preoperative teaching, and have clear goal-directed therapies. Traditionally, colorectal ERAS programs focus on minimizing intraoperative and postoperative IV fluids. Balanced fluid administration is provided intraoperatively through goal-directed therapy that uses vasopressors in addition to fluids and closely monitors hemodynamic parameters. Excessive IV fluid in the perioperative period has been linked to a myriad of complications including delayed return of bowel function and urinary retention.

Although the preponderance of studies in the current literature do clearly suggest that a fluid restrictive strategy can be utilized for major abdominal surgical interventions including colorectal and hepatobiliary operations, there is significant heterogeneity as to which method of goal-directed therapy is optimal. Notable tools under investigation include estimated stroke volume variance, tissue oxygen tension, uncalibrated pulse contour, stroke volume augmentation, and even automated closed-loop systems. Although many of these techniques for providing individualized and optimized fluid resuscitation to patients intraoperatively and in the postoperative period may each focus on different components of complex volume homeostatic regulators, there has been no clear superior technique. Furthermore, with the creation of automated closed-loop systems demonstrating immediate perioperative benefits, the psychology of providers could be a factor in interpreting patient volume status that can in turn impact patient outcomes. Regardless of whichever technique is employed, the main trend in the recent literature of ERAS protocols and goal-directed therapy is to avoid overresuscitation of the patient and to focus on targeted physiologic markers of hypovolemia.

DIAGNOSIS AND TREATMENT OF ELECTROLYTE DISORDERS

Sodium

Homeostasis and Clinical Significance

As stated previously in this chapter, sodium is the principal determinant of serum osmolality and free water balance. The normal physiologic range is 135 to 145 mEq/L, and it is predominantly located in the extracellular space. Cell membranes are relatively impermeable to sodium compared with water, making it an effective osmole. Because of the close relationship between water balance and sodium levels, it is vital to recognize a patient's underlying volume status and overall osmolarity when treatment sodium abnormalities.

Hypernatremia

Hypernatremia is defined as sodium concentrations in excess of 145 mEq/L and can be subdivided into mild, moderate, or severe. Symptoms of severe hypernatremia are related to central nervous depression due to cellular dehydration. This includes muscle

weakness, restlessness, insomnia, lethargy, and coma. Hypernatremia is almost always associated with a hypertonic state but can be related to hypervolemic, euvolemic, and hypovolemic states. Assessment of volume status is an important first step in the recognition of the underlying etiology and its proper management.

Hypovolemic hypernatremia is seen in patients with dehydration and uncontrolled fluid losses. Patients at extremes of age and those with end-stage liver disease are particularly vulnerable. Patients with ongoing sensible loss through nasogastric suction, vomiting, diarrhea, and even those with lactulose administration are at risk. In contrast, euvolemic hypernatremia occurs commonly due to disruption of the renal and neurohypophyseal axis. Any patient who has underlying traumatic brain injury, cerebral hemorrhage, or pituitary surgery with euvolemic hypernatremia should undergo prompt workup for neurogenic diabetes insipidus (DI). In general, any patient with hypernatremia and a urine osmolality less than 600 mOsmol/kg should receive desmopressin (DDAVP). An increase in urine osmolarity of 50% is suggestive of neurogenic DI. Because nephrogenic DI is by definition an inappropriate response to DDAVP, this makes treatment more difficult. In the setting of nephrogenic DI, there are a myriad of possible causes, with management largely depending on the underlying pathophysiology.

Hypervolemic hypernatremia is largely iatrogenic in nature due to fluid resuscitation with hypertonic solutions or mineralocorticoid excess. Treatment of hypernatremia begins with calculation of the free water deficit and estimation of chronicity. The free water deficit in liters (H_2O) is dependent on the patient's weight in kg (w) and serum sodium concentration [Na].

$$H_2O = 0.6 \times w \times \left(\frac{[Na]}{140} - 1 \right)$$

Patients with severe hypernatremia, defined as a serum sodium concentration >160 mEq/L or symptomatic hyponatremia should undergo treatment with a 5% dextrose solution in water, or D5W. Those with mild hypernatremia can be corrected gradually with NS. Adults with acute development (<24 hr) should be corrected rapidly, whereas those with chronic hypernatremia (≥48 hr) should have more cautious replacement. Acute hypernatremia in adults can be corrected to near normal levels within 24 hours without significant risk of osmotic demyelination. Chronic hypernatremia should not exceed 0.5 mEq/L/hr with a total change of 10 mEq/L/day, although correcting at rates up to 12 mEq/L/day has been reported without significant sequelae in adults. Furthermore, it is not recommended to correct less than 6 mEq/L/day as this has been associated with increased mortality. It is recommended to obtain serial serum sodium measurements throughout correction until the patient has normalized and has stable serum sodium.

Hyponatremia

Hyponatremia is subdivided into mild ([Na] 130–135 mEq/L), moderate ([Na] 120–130 mEq/L), and severe ([Na] <120 mEq/L). Use of LR solution perioperatively has been associated with mild transient hyponatremia, which generally does not require intervention. Moderate to severe hyponatremia occurs in approximately 1% of postoperative patients, with 20% of these cases becoming clinically significant. Due to the relative decrease in extracellular solute and osmotic gradient in hyponatremia, severe cases can cause cellular edema. Cerebral swelling can then lead to headaches, lethargy, seizures, and coma. The rate of development of hyponatremia is often related to the clinical manifestations. Severe hyponatremia can be asymptomatic in chronic etiologies such as cirrhosis and heart failure. Furthermore, female physiologic gender, young age, and hypoxia are associated with more severe symptoms of hyponatremia.

The sodium deficit estimation is similar to the calculation of free water deficit using the estimated TBW estimate, which again depends on the patient's sex (approximately 60% for males and 55% for females).

$$\text{Na deficit} = \text{TBW}\left(140 - [\text{Na}]_{\text{Serum}}\right)$$

As with management of hypernatremia, the rate of correction should be closely monitored. Rapid correction of hyponatremia can cause central pontine myelinolysis with permanent spastic quadriparesis and pseudobulbar palsy. Patients with liver disease appear to be particularly susceptible. In this population, there is no reported safe rate of correction. Again, with acute onset severe symptomatic hyponatremia, the sodium should be corrected as quickly as possible. These patients with evidence of neurologic compromise (active seizures, respiratory failure, etc.) should have the sodium corrected by 2 to 6 mEq/L via a 100 mL bolus of 3% hypertonic saline solution over 10 minutes. This can be repeated if clinical improvement is not noted; however, the patient should not exceed a correction of 6 mEq/L over the initial 24 hours. Patients with mild to moderate encephalopathy can undergo infusion of 3% saline at a rate of 1 mL/kg/hr. In general, this will increase the sodium by 1 mEq/L/hr. Patients who are asymptomatic can utilize hypertonic saline and/or furosemide diuresis to facilitate gradual correction.

As with hypernatremia, assessment of osmolality and volume status is a crucial step in the workup and treatment of asymptomatic hyponatremia. In the perioperative period, abnormalities in volume status are relatively common.

Hypovolemic hypotonic hyponatremia is the most common form of hyponatremia in the postoperative setting. Urine sodium levels <20 mmol/L suggests sequestration of isotonic fluids in the extravascular space, loss from the gastrointestinal (GI) tract, or loss from skin. In this unique setting, fluid restriction will worsen the clinical picture, and thus mild to moderate cases are treated with isotonic saline.

Hypervolemic hyponatremia is the least common subtype in the postoperative period. This is most commonly the iatrogenic result of hypotonic fluid administration. It is for this reason that hypotonic fluid resuscitation should only be used for hypernatremia. Treatment for hypervolemic hyponatremia can be accomplished with water restriction and gradual diuresis.

Euvolemic hyponatremia is uncommon postoperatively as it is often the result of inappropriate ADH secretion (SIADH), hypothyroidism, or psychogenic polydipsia. In the postoperative period, there are noted transient increases in ADH due to pain, stress, narcotics, and volume depletion. This transient state is often not sufficient to create hyponatremia. SIADH occurs with traumatic brain injuries, carcinoid and small cell pulmonary lung malignancies, and lung infection. SIADH is often associated with urine osmolality >150 mmol/kg and urine sodium >25 mmol/L. The absence of hypokalemia differentiates it from adrenal insufficiency. Due to the sodium filtration and water resorption in SIADH, isotonic saline will worsen the hyponatremia. Instead, SIADH is treated with fluid restriction (~1 L/day) and gradual correction of sodium levels.

Hypertonic hyponatremia suggests that another major solute is out of the normal range such as the BUN or glucose. These solutes will create a concentration gradient of water (via oncotic pressure differential) that will then equilibrate extracellularly. It is important to note that in the setting of elevation of another solute that the measured sodium levels can be artifactually decreased due to decreased water concentration in the sample, with nonionic solutes increasing the total extracellular volume. This will decrease the sodium concentration relative to plasma but not relative to plasma water volume, which is the clinically significant concentration resulting in isotonic hyponatremia. Direct ion-selective electrodes used in blood gas analyzers are not as susceptible to this artifact.

Isotonic hyponatremia, or pseudohyponatremia, is associated with hypertriglyceridemia, hypercholesterolemia, hyperproteinemia, and hyperglycemia. Elevations in serum glucose will create a pseudohyponatremia where every 100 mg/dL increase in glucose over 100 mg/dL will artificially decrease the sodium by 2 mEq/L.

$$[\text{Na}]_{\text{Corrected}} = [\text{Na}]_{\text{Measured}} + 2\left[\frac{\text{glucose} - 100}{100}\right]$$

Hypotonic hyponatremia occurs in the setting of hypervolemia due to expanded extracellular and interstitial volumes. The relative intravascular depletion results in ADH promoting salt and water retention. This is commonly seen in nephrotic syndrome, cirrhosis potentially with hepatorenal syndrome and hypoalbuminemia, congestive heart failure, and chronic renal insufficiency. Hypotonic hyponatremia is often treated with sodium (1500–2000 mg/day) and fluid (approximately 1 L/day) restriction.

Potassium

Homeostasis and Clinical Significance

Serum potassium levels are maintained in a narrow range of 3.5 to 5 mmol/L by the kidney. This is regulated via the RAA system. Aldosterone promotes secretion of potassium in the distal tubule. Most of the body's potassium exists in the intracellular space, and thus transcellular shifts are the primary culprit for development of potassium abnormalities. Metabolic acidosis results in the efflux of potassium into the extracellular space in exchange for intracellular movement of hydrogen to buffer serum pH. Insulin and β_2 receptor stimulation will shift potassium intracellularly.

Hyperkalemia

Hyperkalemia is defined as $[K^+]$ above 5.5 mEq/L either due to translocation of intracellular potassium or total body excess. Due to the dependence on the potassium concentration gradient in maintaining the transmembrane potential, hyperkalemia can cause ventricular arrythmias and death. Electrocardiographic (ECG/EKG) findings in progressing order of hyperkalemia severity are peaked T waves, QRS widening, shortened QT interval, and ventricular ectopy. Acute rises in potassium are not well tolerated, but chronic hyperkalemia, such as those in renal failure, may be asymptomatic. Acidosis promoting transmembrane shifting, rhabdomyolysis, cell lysis, and insulin deficiency are common causes. In the surgical population, ischemia reperfusion injuries especially in the setting of revascularization after 4 to 6 hours of ischemia can cause acute severe systemic hyperkalemia. Other important populations include burns and crush injuries. Spironolactone and succinylcholine can also cause hyperkalemia, and succinylcholine in the setting of burns and crush injuries is to be avoided. Although there exists some debate as to whether LR can exacerbate or promote hyperkalemia, the relative alkalinity and possible dilutional effects may actually assist in the treatment of extracellular potassium.

There are multiple possible treatment modalities of hyperkalemia, with more aggressive measures depending on symptoms. The general strategies include stabilization of the transmembrane potential, shifting of the potassium intracellularly, and elimination of excess total body potassium. Any patients with EKG changes should receive 1 or 2 g of calcium gluconate intravenously over 2 to 3 minutes with continuous cardiac monitoring as the first step of treatment. Due to the relative abundance of extracellular calcium, the supplementation of this double-charged ion will serve to assist in the restoration of the transmembrane potential and mitigates the risk of fatal arrythmias without treatment of the underlying pathophysiology. Repeat doses can be administered as needed to eliminate EKG changes associated with hyperkalemia. To shift the potassium intracellularly, the serum can be alkalinized via bicarbonate, β_2 agonists such as albuterol, and a combination of insulin and dextrose that can be administered. Again, as with the calcium supplementation, these measures may mitigate the potentially fatal effects of hyperkalemia but do not treat total body potassium excess. This can be managed via use of loop diuretics, hemodialysis, and cation exchange resins such as Kayexalate. These exchange resins are to be used with caution in the surgery patient as oral agents are contraindicated in the obstructed patient and rectal administration is contraindicated in immunosuppression. Furthermore, the sorbitol used in Kayexalate suspensions carries its own risk of bowel ischemia.

Hypokalemia

Hypokalemia is a serum $[K^+]$ below 3.5 mEq/L and is frequently encountered postoperatively due to nasogastric suctioning and enteric losses. Loop diuretics can also cause hypokalemia. Symptoms of hypokalemia include fatigue, weakness, ileus, and arrhythmias. EKGs can show flattening of T waves and prominent U waves. Given that 98% of the total body potassium is intracellular, small changes in serum concentrations may reflect large changes in total body potassium stores. Hypokalemia is often associated with hypomagnesemia and acidemia, and thus magnesium must be replenished before K^+ to facilitate adequate serum concentrations. In the setting of acidemia, correction of the pH will exacerbate the issue as hydrogen ions are exchanged for potassium in the functioning nephron. Although enteric and IV replacement of potassium is possible, oral potassium supplements are often poorly tolerated and peripheral IV replacement is associated with allodynia. IV administration should be reserved for moderate to severe hypokalemia and in patients who cannot tolerate oral replacement. Severe hypokalemia can be replaced through central access, although rates should not exceed 20 mEq/hr given the possible risk of arrythmia with concentrated potassium exposure to cardiac tissue. Given the large total body deficit associated with serum abnormalities, serial replacements are often necessary.

Calcium

Homeostasis and Clinical Significance

Calcium is one of the most abundant electrolytes in the body due to storage in mineralized bone tissue. Serum calcium ranges from 8.5 to 10.5 mg/dL, and this is tightly maintained by bone demineralization, interstitial absorption, urinary excretion, and bone formation. The majority of this homeostatic regulation is controlled by parathyroid hormone and calcitriol. Serum calcium is largely bound by albumin, and thus the active, or ionized portion, must be adjusted to serum albumin levels accordingly.

$$\text{Calcium} = 0.8\ (\text{Normal Albumin} - \text{Patient's Albumin}) + [\text{Ca}]_{\text{serum}}$$

Although this correction can be useful for a quick estimate of a patient's ionized calcium, the actual measurement is necessary for patient care and is generally available in most clinical laboratories.

Hypercalcemia

Hypercalcemia is a total serum calcium greater than 10.4 mg/dL or ionized calcium greater than 5.6 mg/dL. This is most often seen in malignancy (such as breast cancer) or in hyperparathyroidism. Other common causes include thiazide diuretics, lithium, familial hypocalciuric hypercalcemia, vitamin A and D overdose, and immobilization. Symptoms include headache, nausea, emesis, altered mental status, lethargy, myalgias, arthralgias, polyuria, and nephrolithiasis. Treatment is indicated in symptomatic and asymptomatic patients with serum concentrations exceeding 14 mg/dL. Treatment begins with normal saline at a rate of 200 to 300 mL/hr to dilute circulating calcium and promote renal excretion. Next, nonthiazide diuretics such as furosemide are given IV to further promote renal excretion and mitigate fluid overload. Calcitonin (4 IU/kg) will inhibit bone and renal reabsorption of calcium. Bisphosphonates are best for long-term calcium control in the setting of enhanced bone resorption.

Hypocalcemia

Hypocalcemia is a serum calcium below 8.4 mg/dL or ionized levels below 4.5 mg/dL. It can be due to increased efflux or decreased influx to the extracellular space. Efflux causes include alkalosis through albumin binding, citrate binding in the setting of massive blood product transfusion, and severe pancreatitis resulting in saponification. Decreased influx is due to hypoparathyroidism and vitamin D deficiency. Hyperphosphatemia and hypomagnesemia also alter calcium homeostasis. Postoperative blood product administration and large volume crystalloid resuscitation can also result in hypocalcemia.

Classically patients with hypocalcemia will first experience perioral numbness and tingling. Patients may also experience hyperreflexia upon facial nerve stimulation (Chvostek's sign), muscle spasm of the hand with inflation of a blood pressure cuff (Trousseau's sign), and prolonged QT on EKG. Indications for treatment include symptomatic hypocalcemia, corrected serum calcium below 7.0 mg/dL, or ionized calcium lower than 3.0 mg/dL. Oral replacement for chronic hypocalcemia can be done through calcium carbonate or calcium gluconate at 1 to 1.2 g of calcium per day. Resistant or severe hypocalcemia may require vitamin D supplementation. IV calcium gluconate and calcium chloride are reserved for severe hypocalcemia with tetany, laryngospasm, and seizures. Calcium chloride has three times as much elemental calcium as calcium gluconate and requires central IV access. Magnesium should be replaced concurrently when replacing calcium as in hypokalemia.

Magnesium

Homeostasis and Clinical Significance

Magnesium has a number of roles throughout the body including homeostasis of calcium and potassium in addition to energy metabolism and protein synthesis. Less than 1% of the total body magnesium is stored extracellularly, and serum levels range from 1.4 to 2.0 mEq/L.

Hypermagnesemia

Hypermagnesemia is a rare clinical entity and symptoms (such as lethargy) are even less common. Long-term hemodialysis, burns, and trauma are the more common risk factors. In the event that noniatrogenic hypermagnesemia is encountered, it can be managed with saline expansion of the plasma volume and loop diuresis to promote renal excretion. Severe cases can be treated with 1 g of IV calcium gluconate over 5 minutes, with repeat and faster boluses being an option in the setting of cardiac arrest (e.g., 1 g over 2 minutes repeated after 5 minutes). It is worth noting that survival benefits of calcium boluses have not been demonstrated in this setting.

Hypomagnesemia

Hypomagnesemia is often seen postoperatively due to dilution. Alcoholics and critically ill patients are at elevated risk. Poor intake and GI losses including diarrhea and biliary/enteric fistulas are other risk factors. Symptomatic hypomagnesemia is rare and often does not occur until levels are below 1.0 mEq/dL. Ventricular arrhythmias including torsades de pointes can occur making monitoring for postoperative hypomagnesemia critical.

Phosphorus

Homeostasis and Clinical Significance

Serum phosphate levels range from 2.2 to 4.7 mg/dL and remain critical for many essential cellular processes in the body. Given that phosphorus remains an essential factor in the production of ATP, levels are often altered in critically ill and postoperative patients. Patients with poor nutritional status may also experience deficient phosphate levels. Eighty percent of the total body phosphate resides in bone and less than 1% is intravascular. Thyroid hormone and insulin promote resorption mostly in the proximal tubule, whereas parathyroid hormone promotes excretion.

Hyperphosphatemia

Hyperphosphatemia occurs when serum phosphate exceed 5.0 mg/dL but is rare in the postoperative period. Patients with renal insufficiency often have a deficiency in 1,25-dihydroxyvitamin D causing both hyperphosphatemia and hypocalcemia. These patients may also experience symptoms from the hypocalcemia. Treatment of hyperphosphatemia includes volume expansion and stimulation of renal excretion via acetazolamide. In severe cases or in the setting of profound renal failure, hemodialysis may assist. Often patients with chronic failure and associated chronic hyperphosphatemia may undergo treatment with phosphate binders such as aluminum hydroxide. Other causes include tumor lysis syndrome, rhabdomyolysis, laxative use, and hypoparathyroidism. Pseudohyperphosphatemia is also described in the setting of multiple myeloma, with immunoglobulins interfering with laboratory evaluation of phosphate levels.

Hypophosphatemia

Hypophosphatemia is defined as a serum phosphate level less than 2.5 mg/dL with associated arrhythmias, platelet dysfunction, abnormal glucose metabolism, and cardiopulmonary arrest. Causes include internal redistribution, deficient intake, and excessive loss. Redistribution can occur with increased insulin secretion, epinephrine, acute respiratory alkalosis, or bone hunger. Deficient intake can occur with malabsorption due to GI tract surgery, short gut syndrome, steatosis, vitamin D deficiency, phosphate-binding medications, and chronic diarrhea. Excretion is associated with acetazolamide, hyperparathyroidism, and major hepatic resection.

A life-threatening cause of hypophosphatemia is refeeding syndrome, in which chronically nutritionally depleted individuals receive a carbohydrate load, prompting an insulin surge. This in turn will promote redistribution of phosphate intracellularly, exacerbating hypophosphatemia and depletion of adenosine triphosphate, which can promote cardiopulmonary collapse and death. Any patient at risk of chronic malnutrition must have their phosphate levels monitored closely when they receive nutrition.

Large hepatic resections can also promote hypophosphatemia. Traditionally it was thought that this was due to increased consumption of adenosine triphosphate with liver regeneration; however, emerging evidence exists that the hypophosphatemia of hepatic resections and pancreatic surgery may instead be due to alterations in renal function and the hepatorenal axis. Regardless of the etiology, postoperative phosphate levels should be monitored and cautiously corrected.

Hypophosphatemia treatment begins with the assessment of the etiology. Symptomatic and severe (<1.0 mg/dL) hypophosphatemia is treated with IV phosphate until serum levels exceed 1.5 mg/dL followed by oral therapy; 31 mg of phosphate is equivalent to 1 mmol of phosphate. IV dosing varies, but in general 0.08 to 0.64 mmol/kg can be given at a maximum rate of 7 mmol phosphate/hr. Oral therapy, either as sodium or potassium salt, has variable oral bioavailability and can induce diarrhea that may limit efficacy. The formation can be tailored depending on availability and the patient's underlying renal function. When serum phosphate is between 1.0 to 1.9 mg/dL, oral therapy is often sufficient. Continuous therapy over 5 to 7 days is often necessary due to the large proportion of extravascular phosphate in total body phosphate levels. Again, due to the inability of patients with renal failure to clear serum phosphate, caution is advised in replacement due to the risk of hyperphosphatemia.

TABLE 3 Signs, Symptoms, and Treatment of Electrolyte Disorders

Disorder	Neurologic	Cardiovascular	Gastrointestinal	Renal	Treatment
Hyponatremia	Confusion, seizures, coma	Hypotension, hypertension	Salivation	Oliguria	Fluid resuscitation 0.9% NaCl Hypertonic saline + diuretic
Hypernatremia	Confusion, seizures, coma	Fluid overload	Thirst		Free water 0.45% NaCl
Hypokalemia	Fatigue, weakness	Atrial arrhythmias, flat T waves or U waves	Ileus	Nephrotoxicity	Oral/IV potassium Magnesium repletion
Hyperkalemia	Confusion, paralysis, areflexia	Ventricular arrhythmias, peaked T waves, prolonged QT, wide QRS	Nausea, vomiting, abdominal pain		Insulin + 50% dextrose 10% calcium gluconate Dial
Hypocalcemia	Paresthesia, perioral tingling, carpopedal spasms, Chvostek's sign	Ventricular arrhythmias, prolonged QT			IV calcium gluconate 1,25 Dihydroxy-vitamin D
Hypercalcemia	Confusion, fatigue, coma	Shortened QT	Abdominal pain	Stones, nephrogenic DI (long-term)	0.9% NaCl Furosemide
Hypomagnesemia	Weakness, cramping, hyperreflexia	Atrial ventricular arrhythmias (torsades de pointes)	Dysphagia		IV Magnesium sulfate
Hypermagnesemia	Sedation, paralysis, areflexia	Ventricular arrhythmias	Diarrhea		0.9% NaCl Furosemide
Hypophosphatemia	Confusion, seizures, weakness	Heart failure, respiratory failure			Sodium or potassium phosphate
Hyperphosphatemia	Muscle cramps, perioral tingling, paresthesias	Ventricular arrhythmias			0.9% NaCl, phosphate binders

DI, Diabetes insipidus; *IV*, intravenous; *NaCl*, sodium chloride.

SUMMARY

Fluid and electrolyte disorders (Table 3) require prompt assessment and correction in critically ill patients. While IV therapies and electrolyte management have the potential for great benefit in the surgical patient, inappropriate or inaccurate treatment can result in serious harm.

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Common Pediatric Surgical Emergencies

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INTRODUCTION

Pediatric surgery falls within the purview of general surgery. Accordingly, it is the intent of this chapter to discuss many of the more common pediatric surgical emergencies from birth to adolescence that are relevant to practicing general surgeons in the community as well as general surgery trainees preparing for board exams. The key management steps for each condition are emphasized. This chapter is not meant to be a comprehensive text of all pediatric surgical emergencies, and we do not focus on complex neonatal congenital anomalies because this group of children is almost exclusively referred to board-certified pediatric surgeons based at major tertiary care referral centers.

PHYSIOLOGY AND ANESTHESIA IN CHILDREN

As the saying in pediatric surgery goes, "children are not small adults." Certainly, as children approach the teenage years, they are more like adults than neonates, toddlers, and school-aged children, but there are many important differences in the physiology and anesthesia of children that are worth noting. First, the normal vital signs in newborns are vastly different than those in adolescents and adults, and the normal ranges change with age (e.g., heart rate 120–180 beats per minute in term infants compared with 60–100 beats per minute in teenagers, blood pressure 70s/40s mm Hg in term infants compared with 100s/60s mm Hg in teenagers). Second, there are important airway issues that are different in children than they are in adults. Besides the obvious smaller size of the airway, orotracheal intubation in children is more challenging in general because of a more prominent occiput, a larger tongue, and a floppier epiglottis. In children younger than 12 years of age, an emergent surgical cricothyroidotomy with placement of either an endotracheal tube or tracheostomy tube is contraindicated because the pediatric airway is less rigid, the glottis is smaller, and there is a nontrivial risk of injury to these structures or to the posterior wall of the trachea. Therefore, needle cricothyroidotomy with jet oxygenation is the emergency airway procedure of choice in young children until they are stable enough for transport to the operating room for conversion to a surgical tracheostomy. Third, there is emerging data that general anesthesia may be detrimental to the developing pediatric brain. Thus, pediatric surgical problems that require general anesthetics but are more elective in nature (e.g., lumps and bumps) in infants should be delayed if possible.

Appendicitis

Pediatric appendicitis is the most common acute surgical problem in children. In many ways, it is managed similarly to adults; however, pediatric patients, especially younger age children (2–6 years of age) frequently present perforated. In contrast with adults, ultrasound and MRI have become the preferred imaging modalities in many pediatric emergency departments because they provide comparable diagnostic accuracy while avoiding the potential long-term malignancy risks associated with ionizing radiation (Fig. 1).

As in adults, laparoscopic appendectomy in children is now the standard of care in the operative management of most cases of acute appendicitis. Despite a smaller working space, conversion of laparoscopy to an open procedure is rarely necessary, even in smaller children. There are now several recent studies that support nonoperative management of acute, simple appendicitis with broad-spectrum antibiotics as a viable treatment alterative in children, demonstrating symptom resolution in 24 to 48 hours in 80% to 90% of cases. Those with a concomitant infection with COVID-19 are usually managed nonoperatively. However, not all children qualify for nonoperative management, such as those with a fecalith, and there is medium-term follow-up data suggesting that overall recurrence rates after discharge may be as high as 40%. As a result, operative management within 12 to 24 hours of diagnosis continues to be the preferred management approach among many pediatric surgeons. Same-day discharge is possible in many children with early disease after appendectomy. In addition, given concerns about recurrent appendicitis, most surgeons view nonoperative management as a bridge to elective outpatient interval appendectomy. In children with known perforated appendicitis who present with symptoms for 5 days or more, patients can often be managed

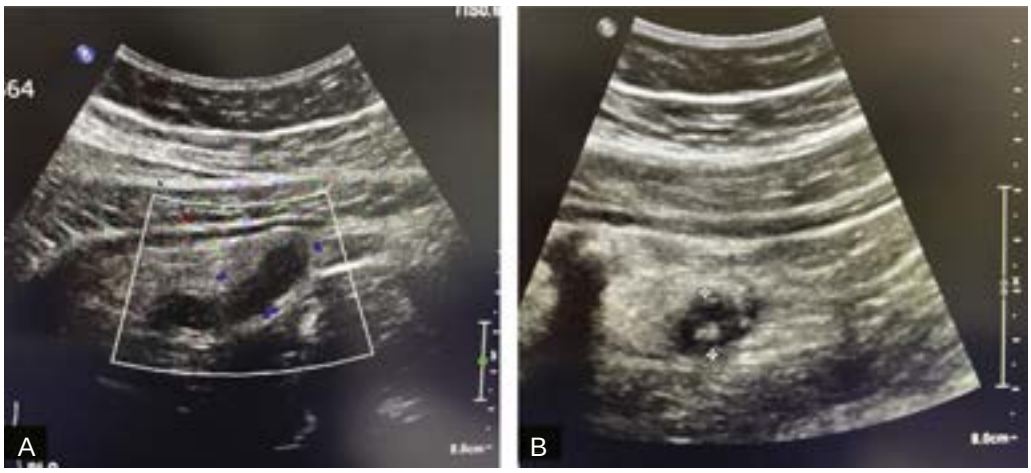


FIG. 1 Selected right lower quadrant ultrasound images in a 10-year-old boy with abdominal pain shows a dilated fluid-filled tubular structure in increased vascularity **(A)** and an echogenic focus consistent with an appendicolith **(B)**. These findings are consistent with acute appendicitis.

nonoperatively with interventional radiology drain placement (if there is an amenable abscess) followed by an interval appendectomy in 6 to 8 weeks. There is no consensus on the optimal duration of antibiotics for perforated disease, with or without appendectomy, because of the wide spectrum of clinical disease. Antibiotic duration is often based on institution-specific protocols with longer courses used for patients who are febrile, have leukocytosis, are without source control, and/or have a prolonged ileus.

Pediatric Trauma

Trauma is the leading cause of mortality and morbidity in children 1 to 14 years of age in the United States. It accounts for more death and disability than all other childhood diseases combined. Unfortunately, there must be increased awareness of nonaccidental trauma (NAT), particularly in younger pediatric patients. Any injury pattern that does not fit the history or a history that keeps changing should alert suspicion for possible NAT (Fig. 2). Injuries or rib fractures in different stages of healing or a delay in seeking medical attention should also alert the surgeon to abuse. Another concerning injury is a scald burn in a stocking distribution without splash marks. In all these cases, the mechanisms for evaluating for child abuse providers in your hospital should be activated. Typically, this usually involves consultation with social work and the child protection team. If there is sufficient concern, then a skeletal survey should be performed to look for evidence of other acute and healed fractures. If there is intracranial hemorrhage demonstrated by cross-sectional imaging of the brain in the setting of NAT, then an exam for retinal hemorrhages by ophthalmology is needed. Once NAT is confirmed, then local government agencies (i.e., child protection services) should be notified to ensure the safety of the injured child following recovery.

Pediatric trauma assessment follows Advanced Trauma Life Support (ATLS) protocols in a similar manner to adult trauma. The one major exception, however, is that chest, abdomen, and pelvis CT scans should be minimized in children, whenever possible, based on evidence-based guidelines. If a child is critically ill, then a CT scan is obviously appropriate. However, imaging in the clinically stable child is approached in a more stepwise fashion starting with trauma radiographs (e.g., cervical spine, chest, and pelvic x-rays) and serum blood work (e.g., CBC, CMP, lipase, PT/INR, PTT, and microscopic urinalysis). If the laboratory studies suggest a concern for bleeding, the lipase is elevated, the AST or ALT is greater than 200 U/L, or urinalysis shows more than 20 red blood cells per high power field, then a CT scan of the abdomen and pelvis are performed. If no abnormalities are identified by clinical exam, radiographs, and blood work in the clinically stable child, continued observation with serial abdominal exams is appropriate.



FIG. 2 Transverse head CT image in a 2-month-old boy showing an acute right posterior subdural hematoma secondary to non-accidental trauma.

The use of head CTs in pediatric blunt trauma follows guidelines established by the Pediatric Emergency Care Applied Research Network (PECARN). Depending on the clinical presentation, these guidelines help the surgeon decide whether children with a normal or near-normal mental status based on the Glasgow Coma Scale (GCS) should be imaged by head CT versus close observation for several hours in the emergency department. If repeat imaging is needed after an abdominal initial CT or changing clinical exam, a trauma protocol ultrafast MRI can be helpful to monitor the evolution of intracranial hemorrhage.

The treatment of most pediatric traumatic injuries is similar to those in adults. However, one notable exception in younger children is a stronger preference toward nonoperative management of splenic injuries, regardless of grade of injury by CT. The threshold for splenectomy in non-teenage children is quite high because of the increased risk of overwhelming post-splenectomy sepsis, an infection associated with high mortality. Obviously, if a child is unstable or has ongoing transfusion requirements, then splenic embolectomy or splenectomy may be indicated. An ethical dilemma that may arise in the management of solid-organ injury in children is parental refusal of blood transfusions for religious or other reasons. In these cases, the surgeon is ethically and legally allowed to override the parents in order to save the child's life.

Pediatric Inguinal Hernias

Inguinal hernias in children are common, especially in the premature neonatal population. They are almost universally indirect hernias resulting from failure of closure of the processus vaginalis during the third trimester of fetal life. Because these hernias tend to increase in size and neonates are not able to communicate symptoms, these hernias should be surgically repaired when safe for the child to undergo anesthesia. If the neonate is in the neonatal intensive care unit, these hernias are often repaired before discharge home. Premature infants who undergo hernia repair under general anesthesia who are younger than 60 weeks corrected gestational age as well as term infants who are younger than 48 to 52 weeks gestational age are required to stay overnight postoperatively for apnea monitoring before discharge.

Inguinal hernias in young children can be repaired using a variety of techniques and approaches. In neonates and infants, many pediatric surgeons now favor repair by laparoscopic-assisted ligation of the internal inguinal ring using a permanent suture. Open inguinal hernia repairs with a high ligation of the hernia sac are also commonly performed, especially in patients older than 1 to 2 years of age and in those with a large hydrocele component to the hernia. Regardless of operative approach, mesh repair is rarely necessary before adolescence because there is almost never a direct inguinal or femoral hernia present in younger children, and the mesh does not grow with the child.

Incarcerated inguinal hernias are much more common in infants than they are in older children and adults. If an infant presents with an incarcerated inguinal hernia without overlying erythema or peritonitis, an attempt at manual reduction of the hernia at the bedside should be performed by an experienced provider. Administering an opioid and placing the child in the Trendelenburg and frog-leg positions can be helpful maneuvers before applying manual pressure. If the hernia cannot be reduced, then an urgent surgical repair should be performed given concerns for strangulation. Successful reductions should be followed with open or laparoscopic inguinal hernia repair before discharge given the high rate of recurrence (Fig. 3). The laparoscopic approach has the additional benefit of being able to fully evaluate for intestinal injury at the time of repair. However, if an

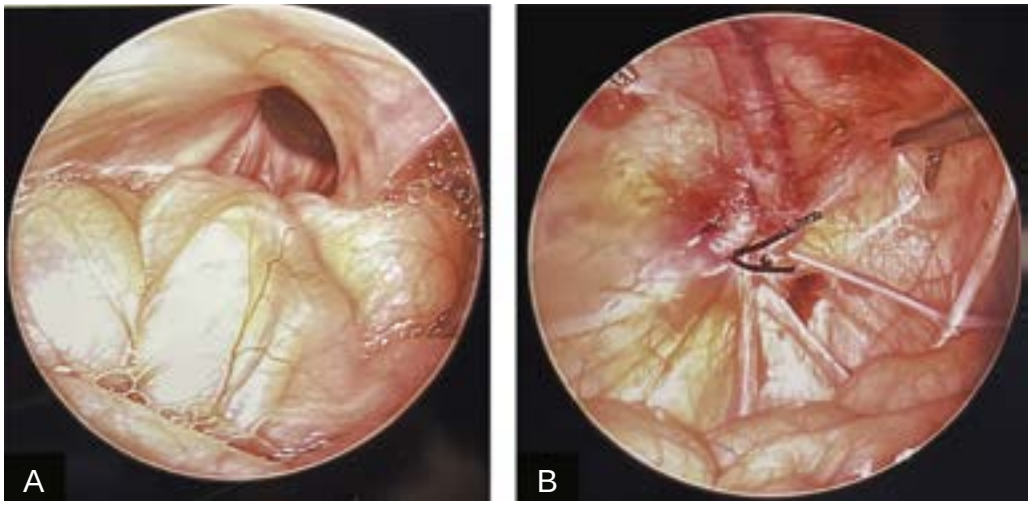


FIG. 3 Intraoperative photographs before **(A)** and after **(B)** laparoscopic inguinal hernia repair by ligation of the left internal inguinal ring in an infant.

open hernia repair is planned, it may be wise to wait 24 to 48 hours to allow for inguinal soft tissue edema to resolve.

Bilious Emesis and Malrotation

Bilious emesis in newborns and young infants is the major symptom of malrotation with midgut volvulus and therefore should always be considered a diagnostic surgical emergency until the condition has been ruled out. Malrotation anomalies of the gut, which are surprisingly common with an incidence estimated to be 1 in 200, are associated with midgut volvulus because of the presence of abnormal right upper quadrant adhesions in conjunction with a narrowed mesenteric base. Seventy percent of children with symptomatic malrotation will present in the first year of life, and of those, 70% occur in the first month (i.e., 49% of all patients with malrotation will develop symptoms in the first month). If an infant presents with bilious emesis and is clinically ill, this alone may be an indication for emergent operative exploration without contrast imaging to save the child's life.

It is important to understand that a "normal bowel gas pattern" shown on plain radiographs can never be used to exclude malrotation in an infant with bilious emesis under any circumstance. An expeditious workup for bilious emesis always requires an emergent upper gastrointestinal contrast (UGI) study. A positive UGI study warrants emergent laparotomy for presumed volvulus of the entire midgut. A small bowel follow-through study to fully delineate the presence of a small bowel obstruction is not necessary if malrotation is present. Although abdominal CT scans may identify malrotation as an incidental finding in older children and adults with abdominal pain, there is no role for CT as the initial study in symptomatic infants who present with bilious emesis.

There are three key features of the duodenum that are used to exclude malrotation based on a UGI study: (1) crosses to the left of midline (using the spine as the landmark on anteroposterior views, Fig. 4), (2) C-loop shape such that the fourth part of the duodenum rises to the level of the pylorus (anteroposterior views), and (3) retroperitoneal course toward the spine (as demonstrated on lateral

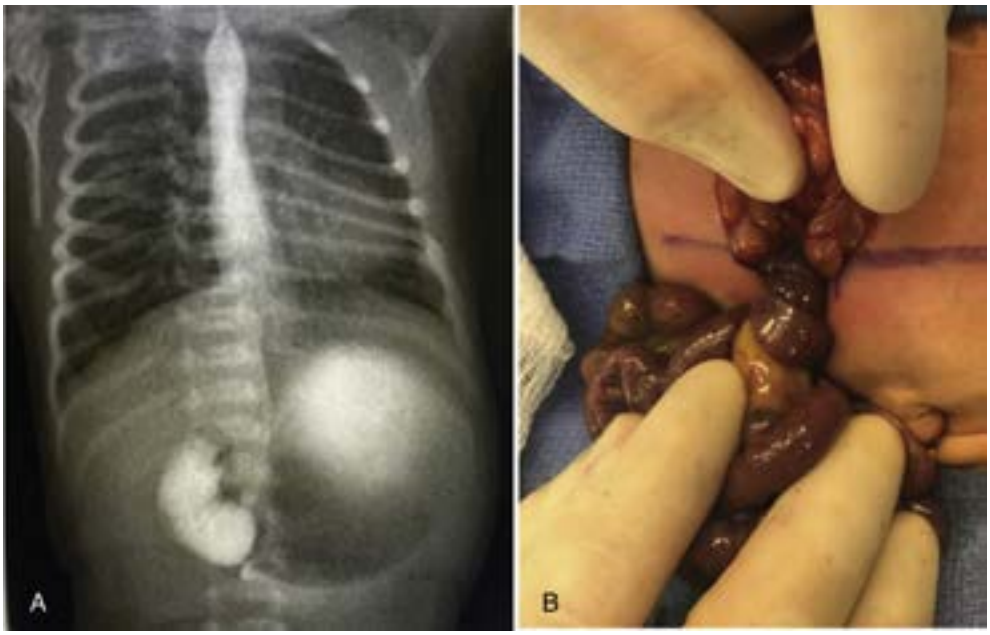


FIG. 4 Bilious emesis in a newborn identified malrotation based on an anteroposterior plain radiograph **(A)** showing failure of contrast progression past the midline in a dilated duodenum. **(B)** Intraoperative photograph at emergent laparotomy confirms malrotation with midgut volvulus.

view). Absence of any one of these components is considered an abnormal UGI and warrants exploration in the symptomatic child. If a UGI series for bilious emesis has ruled out malrotation, a surgical condition distal to the ampulla of Vater may still be present, but there is usually less urgency in the diagnostic workup.

In all cases of symptomatic malrotation with midgut volvulus, an emergency supraumbilical transverse laparotomy is performed because the volvulus must be detorsed as soon as possible before total midgut necrosis ensues. The operation, known as the *Ladd procedure,* consists of six main steps: (1) detorsing the volvulus by rotating the gut counterclockwise (i.e., "turning back the hands of time") usually with a 180- to 360-degree twist; (2) lysing Ladd's bands (bands from the cecum across the duodenum to the right lower quadrant peritoneum); (3) straightening the duodenum, which is often kinked and folded by adhesions; (4) widening the mesentery by opening it like a book and lysing any mesenteric adhesions; (5) performing an appendectomy; and (6) placing the bowel in a position of nonrotation, meaning the colon is on the left side of the abdomen and the small bowel is on the right side. The position of nonrotation serves to keep the small bowel mesentery as wide as possible to minimize the risk of future volvulus. The risk of recurrent volvulus after an open Ladd procedure is less than 2% but is never reduced to that of the normally rotated patient.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a severe inflammatory disease that affects the small and large intestine and occurs in approximately 1 in 1000 live births. NEC is a disease primarily of premature infants and rarely occurs in term infants in the absence of sepsis, congenital heart disease, or respiratory illness. The risk of NEC is highest in premature infants who weigh less than 1500 g and are fed enterally. The overall mortality secondary to NEC is approximately 30%, with a higher mortality in infants requiring surgery (approaching 50%).

The classic presentation of NEC is abdominal distention, bloody nasogastric tube output, and bloody stools. In the history, one will often find that these clinical changes coincided with a change from breast milk to formula or fortification of breast milk to higher caloric density. The workup for NEC includes laboratory evaluation with CBC, electrolytes, and blood gas. Metabolic acidosis and thrombocytopenia should raise increased suspicion for NEC. Radiologic evaluation with abdominal films should be obtained (both an anteroposterior and left lateral decubitus film if the infant will tolerate it). Radiographs will demonstrate pneumatosis, and in severe cases, portal venous gas and/or pneumoperitoneum. Ultrasound is more sensitive than plain films for detecting pneumatosis and portal venous gas, but its role as an aid in surgical decision making remains undefined.

The management of NEC depends on the severity. Historically the severity of NEC was classified using the Bell grading system (Table 1). Those with stage I and IIA disease can be treated primarily with nasogastric tube decompression, bowel rest, and broad-spectrum antibiotics (e.g., piperacillin/tazobactam) provided that the clinical status, serial laboratory tests, and x-rays are closely followed and do not worsen over time. The antibiotic course is typically 7 days from resolution of pneumatosis on plain radiographs, although the exact length of treatment is often individualized.

The decision to operate for NEC (20%–40% of cases) can be difficult. The only absolute indication for operative management is pneumoperitoneum. However, many children will undergo a laparotomy in the absence of pneumoperitoneum because of deteriorating clinical status or worsening imaging findings despite medical management. In these cases, there is a high suspicion for bowel necrosis. Relative indications to operative management include abdominal wall erythema/cellulitis and radiographic evidence of portal venous gas and/or a persistent fixed loop of dilated bowel. Surgery for NEC consists of a transverse superumbilical laparotomy, exploration of the intestine and colon, and removal of all necrotic bowel while salvaging all healthy or questionable bowel. If there is a lot of ischemic bowel without frank necrosis, a spring-loaded silo should be placed with plans for a second look operation in 24 to 48 hours. If the area of pathology is well demarcated, most pediatric surgeons would create a proximal ostomy and distal mucous fistula before abdominal wall closure. The ostomies can be reversed after 6 weeks or more have passed if the child weights at least 3 kg. It is essential that the infant tolerate feeds before surgery (to ensure no proximal stricture from NEC), otherwise a small bowel follow-through should be performed before reversal of the ostomies. A contrast enema and/or mucous fistula study should also be performed as well to rule out distal strictures before placing the bowel back into continuity.

It is important to distinguish NEC from spontaneous intestinal perforation (SIP), another intestinal disease that affects low-birthweight premature infants. SIP has been associated with indomethacin administration and/or early postnatal steroids and presents as pneumoperitoneum secondary to a focal area of terminal ileal perforation. In contrast, babies with NEC have more widespread, patchy intestinal ischemia and necrosis with perforation as later stages. Accordingly, neonates with SIP will often lack the signs of shock initially that are almost universally observed in neonates with ischemic bowel secondary to NEC. Surgical management of SIP and NEC are similar in that necrotic intestine should be resected and ostomies created. However, in very-low-birthweight neonates (<1000 g) in whom SIP is highly suspected, placement of a bedside lower quadrant peritoneal drain (using a vessel loop or ¼-inch Penrose drain) is considered appropriate first-line therapy. After the

TABLE 1 Modified Bell Classification for Necrotizing Enterocolitis

	Clinical Findings	Radiographic Findings	Gastrointestinal Findings
Stage I	Apnea, bradycardia, and temperature instability	Normal gas pattern or mild ileus	Mild abdominal distention, stool occult blood, gastric residuals
Stage IIA	Apnea, bradycardia, and temperature instability	Ileus with dilated bowel loops and focal pneumatosis	Moderate abdominal distention, hematochezia, absent bowel sounds
Stage IIB	Metabolic acidosis and thrombocytopenia	Widespread pneumatosis, portal venous gas, ascites	Abdominal tenderness and edema
Stage IIIA	Mixed acidosis, coagulopathy, hypotension, oliguria	Moderate to severely dilated bowel loops, ascites, no free air	Abdominal wall edema, erythema, and induration
Stage IIIB	Shock, worsening vital signs and laboratory values	Pneumoperitoneum	Bowel perforation

From Holcomb GW, Murphy JP, St. Peter SD. *Holcomb and Ashcraft's Pediatric Surgery.* 7th ed. Philadelphia: Elsevier; 2020.

intestinal perforation heals spontaneously and the clinical condition of the neonate improves, the peritoneal drains and antibiotics can be discontinued after 7 to 10 days. For those managed with a drain, the surgeon should be prepared to do a laparotomy if there is no clinical improvement in 24 to 48 hours.

Pyloric Stenosis

Hypertrophic pyloric stenosis is relatively common, occurring in approximately 1 in 300 live births. The male-to-female ratio is 4 to 1. Pyloric stenosis is not a congenital disease. Instead, it typically presents in infants between 3 and 6 weeks of age (range, 2–10 weeks) with progressively worsening, nonbilious emesis that ultimately becomes projectile in nature. Because of the proximal obstruction and emesis, they often present severely dehydrated as evidenced by sunken fontanelles and dry mucous membranes. On physical exam, one may be able to feel an epigastric, olive-shaped mass, but this usually requires decompressing the stomach with a nasogastric tube and pain medications to be successful.

Ultrasound has become the gold standard for diagnosis of hypertrophic pyloric stenosis (Fig. 5). Pyloric stenosis is confirmed when the pyloric muscle thickness is 4 mm or more and the pyloric channel length is at least 16 mm. Typically, the sonographer will also observe the inability of fluid to pass through the pylorus during the entire exam. On occasion, a UGI is performed when serial ultrasound exams show equivocal findings with gastroesophageal reflux disease and pylorospasm still in the differential diagnosis. All infants with hypertrophic pyloric stenosis should have a complete metabolic panel obtained. The metabolic panel will often demonstrate a hypochloremic, hypokalemic, metabolic alkalosis.

Surgery for hypertrophic pyloric stenosis is never a true emergency. These infants must first be resuscitated to address the dehydration and electrolyte abnormalities. These infants should receive one or two 20 mL/kg boluses of normal saline in addition to 1.5 × maintenance rate of D5/NS with electrolytes checked every 6 to 12 hours until normal. Infants with bicarbonate greater than 30 mEq/L have a diminished respiratory drive and are at risk for postoperative apnea and possible respiratory arrest. Therefore, they should not undergo anesthesia until the metabolic alkalosis is corrected. The endpoints suggestive of a successful preoperative resuscitation include wet diapers, a chloride level of 90 to 100 mEq/L, and a bicarbonate level of 30 mEq/L or lower.

Once all electrolyte abnormalities have been corrected, laparoscopic pyloromyotomy has become the operation of choice among many pediatric surgeons (although a right upper quadrant or periumbilical pyloromyotomy can also be performed). The laparoscopic approach is conducted through three laparoscopic incisions: one with a port at the umbilicus and two 3-mm stab incisions without ports on either side of the abdomen. The pylorus is carefully stabilized with a grasper, and the muscular layer is incised and split from the stomach to where the muscle softens on the duodenal side. One should see bulging mucosa underneath the myotomy, which indicates a complete myotomy. A leak test is then performed by injecting 30 to 60 mL of air through an orogastric tube to demonstrate that air passes through the pylorus and that no air escapes through the exposed mucosa. Although there have been numerous published studies on the optimal feeding protocol for these infants following pyloromyotomy, ad lib feeding with a 60-mL limit may be the easiest and best approach. Most children can be discharged from the hospital within 36 hours after tolerating at least two consecutive feeds.

The two most infamous complications of pyloromyotomy are an incomplete myotomy and a mucosal perforation. An incomplete myotomy occurs when the myotomy is not carried far enough on to the stomach side and presents as ongoing projectile emesis. This requires a return to the operating room for revision. A mucosal perforation can be managed with either closure of the perforation and buttressing with omentum or, more commonly, repair of the mucosal perforation, closure of the myotomy, and then rotation of the pylorus to perform a repeat myotomy 180 degrees from the first. If not identified intraoperatively, these infants can become septic and must undergo emergency operation with peritoneal washout.

Ileocolic Intussusception

Ileocolic intussusception is a condition in which the terminal ileum slides distally and telescopes into the adjacent right colon, leading to obstruction and impaired blood flow to the affected segment. Although rare in adults, it is a common cause of abdominal pain in

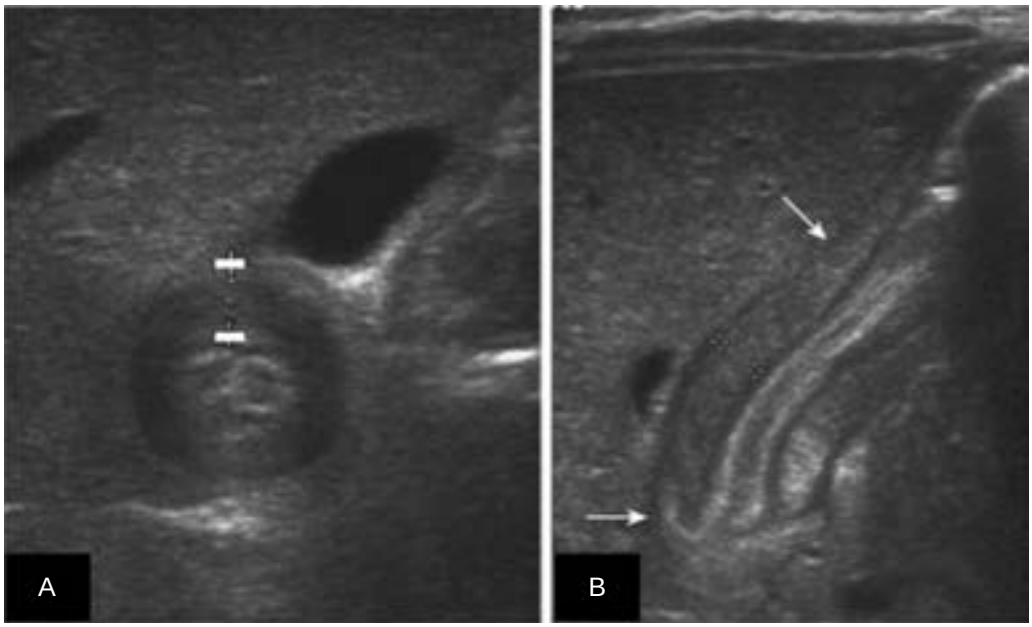


FIG. 5 Ultrasound images of an infant with hypertrophic pyloric stenosis demonstrating transverse view **(A)** of a thickened pyloric wall to 4 mm and longitudinal view **(B)** of an elongated and closed pyloric channel to 17 mm adjacent to a dilated stomach. Arrows delineate the length of the pylorus and point to the outside of the pyloric muscle. *(From Holcomb GW, Murphy JP, St. Peter SD.* Holcomb and Ashcraft's Pediatric Surgery. *7th ed. Philadelphia: Elsevier; 2020.)*



FIG. 6 Abdominal ultrasound image in pediatric patient demonstrating a target sign consistent with ileocolic intussusception. *(From Holcomb GW, Murphy JP, St. Peter SD.* Holcomb and Ashcraft's Pediatric Surgery. *7th ed. Philadelphia: Elsevier; 2020.)*

older infants and toddlers. Most children present with intermittent abdominal pain and vomiting, while others may be inconsolable or lethargic. The history often describes distinct periods in which the child may keep his or her legs curled up followed by periods of relatively normal activity and minimal pain. Some patients may also have "currant jelly" stools as a result of sloughing of intestinal mucosa at the site of the intussusception. Because most intussusceptions in children are caused by viral-mediated mesenteric lymphadenopathy serving as the lead point, there may also a history of a recent viral illness (either respiratory or gastrointestinal). Physical exam findings may reveal abdominal tenderness and possibly a palpable abdominal mass.

The workup for possible intussusception often starts with an abdominal plain film to look for evidence of a small bowel obstruction. However, if there is increased suspicion, an abdominal ultrasound exam should be ordered to look for the obstructing mass. CT scans can be performed but are rarely required to establish the diagnosis and expose the child to unnecessary ionizing radiation. The ultrasound exam will demonstrate a classic target sign (Fig. 6), which represents the terminal ileum intussuscepting into the cecum. If the ultrasound exam is positive or equivocal, then proceeding with an air-contrast enema can be both diagnostic and therapeutic. The only contraindications to performing an air-contrast enema for suspected intussusception are peritonitis, free air, and hemodynamic instability.

An air-contrast enema performed by a pediatric radiologist is the first-line treatment of choice in younger children in stable condition and is associated with a 70% to 90% success rate. The colonic pressure should never exceed 120 cmH_2O pressure during the study, and the surgeon should be immediately available in the rare event (1%–2%) that a perforation occurs. Successful reduction is suggested by resolution of the obstructing mass followed by reflux of air into the terminal ileum. Once reduced, children are observed for a short period (range, 4–24 hours) based on institutional protocols and then discharged once tolerating a regular diet. Family should be warned that the overall recurrence rate is 5% to 10%, with most recurrences evident in the first 2 to 3 days postreduction. If the intussusception recurs after successful reduction, the air-contrast enema can be repeated. However, if it recurs after three reductions, then most surgeons would proceed to the operating room for definitive reduction and to determine whether a pathologic lead point may be the etiology. Pathologic lead points, which may include a Meckel diverticulum, duplication cysts, colonic polyps, colonic lipomas, and lymphoma, are more common in children older than 4 years of age.

If radiologic reduction fails or the patient has peritonitis, surgical reduction should be performed. This can be done by laparoscopy or laparotomy (Fig. 7). In the open approach, the classic teaching is that the surgeon should carefully milk or push the intussuscepted ileum out of the cecum as opposed to pulling it out, which is thought to pose a higher risk of perforation. If the bowel is necrotic or cannot be reduced, it should be resected. During the operation, one should confirm whether there are any pathologic lead points that would require resection. In cases of lymphoma, the disease should be treated medically.

SUMMARY

This chapter discusses the contemporary diagnostic workup and management of children presenting with common surgical emergencies. All general surgeons and trainees preparing for board exams must be familiar and comfortable with handling these pediatric surgical problems and the various nuances in their care when compared with those present in their adult counterparts. Although many of these surgical emergencies are now managed by full-time, board-certified pediatric surgeons, adult general surgeons in the community setting will inevitably encounter many of these cases

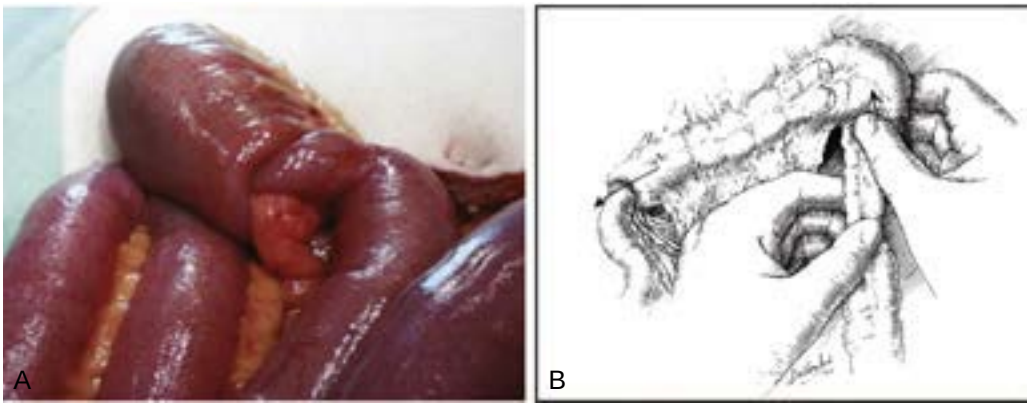


FIG. 7 Ileocolic intussusception as viewed by laparotomy **(A)** with schematic depiction **(B)** demonstrating technique used for successful reduction.

over their careers, and if appropriately managed, can make a substantial impact on minimizing morbidity and can potentially save a young child's life.

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A Practical Approach to Surgery in the Frail Elderly

Rachel G. Khadaroo, MD, PhD, FRCSC, and Michael E. Zenilman, MD

As the Western population ages, surgeons are operating more frequently on older and frailer patients. At least one-third of all operations performed in North America are on patients aged 65 and older. Frail older adults are at a higher risk for postoperative complications, readmission, and death. Consequently, frailty is associated with increased healthcare costs. Studies have shown that frailty—not age—is the important factor in patient outcomes. This chapter will provide surgeons with a practical approach to modifying the preoperative, operative, and postoperative care of older adults with the goal of patients returning home and maintaining their function (Fig. 1). This chapter will focus on defining frailty and providing tools to modifying outcomes, including the role of prehabilitation, for frail patients. At the same time, any care that helps older patients helps all patients.

PREOPERATIVE ASSESSMENT

As well as the normal medical and risk assessment conducted for any patient, the older patient requires a preoperative frailty assessment, consideration of prehabilitation, and a discussion about the goals of care.

Frailty Assessment

Frailty is a state of increased vulnerability to diverse stressors that is more prevalent in later life. A surgeon cannot "eyeball" frailty because even the vulnerable/prefrail population is at increased risk of poor outcomes. Frailty assessment is truly a missed opportunity for the surgical team. We recommend using any well-validated frailty scale (see examples later). Ideally, this should be performed preoperatively and address at least the physical, psychological, and social domains. The assessment allows for improved risk prognostication, patient and family discussions, and targeted preventive measures to optimize surgical outcome.

There are two ways to measure frailty: (1) as a biologic-driven model (Table 1) or (2) a deficits-driven model. There are many well-validated frailty assessments, and we will share some that we have used.

In our experience, a deficit-driven model is easier to apply in surgical practice. We will describe three commonly used and diverse surgical frailty assessments.

The Edmonton Frail Scale

The Edmonton Frail Scale (EFS) was developed at the University of Alberta in 1999 and is used worldwide. Notably, in the UK, which started one of the first proactive geriatric surgical care services, this scale was used in preoperative assessment. Its nine objective questions provoke a comprehensive assessment addressing cognition, general health, functional independence, social support, medication use, nutrition, mood, continence, and functional performance. It generates a score from which the patient is deemed as fit, vulnerable, or mild/moderate/severe frail (Fig. 2).



FIG. 1 Pathway and interventions to modify outcome in older patients.

TABLE 1 Biologic Model of Frailty (abbreviated)

Abnormalities	Frailty Scale
Involuntary weight loss of 10 lb/4.5 kg or more in the past 6 months	Fit (no abnormalities) Prefrail (2 abnormalities or less) Frail (3 or more abnormalities)
Reduced grip strength	
Difficulty initiating movements	
Reduced walking speed	
Fatigue	

Developed by Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. *2001;56:M146-56.*



FIG. 2 Components of Edmonton Frail Scale questionnaire. *(See website for full questionnaire; adapted from* https://edmontonfrailscale.org/*.)*

Clinical Frail Scale

In our Acute Care Surgical Service and Critical Care unit at the University of Alberta Hospital, we use the Canadian Study of Health and Aging Clinical Frail Scale (CFS) created in 2005. It is not a questionnaire but a simple way to summarize information from a clinical encounter. It is a useful, well-validated tool in acute care and surgical settings (Fig. 3). Our work done in the Acute Care Surgery population demonstrated the degree of frailty independently and dose-dependently predicted readmission or death. Importantly, the vulnerable population was at similar risk to the frail. A systematic review by Lin and colleagues in 2016 on frailty and postoperative outcomes also demonstrated that frailty was associated with mortality, complications, and prolonged length of stay.

The FRAIL Questionnaire

Another easy-to-use assessment for the older trauma population is the FRAIL Questionnaire, which has only five questions that categorizes patients as nonfrail, prefrail, and frail (Table 2).

Prehabilitation

Prehabilitation is the process of optimizing physical function preoperatively to allow patients to return to their normal function postoperatively. The analogy is: The operation is like running a marathon, so would you do this without preparing? The evidence for prehabilitation is broad, heterogeneous, and inconsistent. There are some studies showing that frail patients have greater benefit and that at least 2 to 4 weeks of prehabilitation is necessary. The PREPARE Trial (ClinicalTrials.gov NCT04221295) is a randomized controlled trial focused on prehabilitation of frail patients currently being conducted in 11 Canadian hospitals with a planned enrolment of 750 patients to be completed by 2025. It is a misconception that prehab only equals exercise, as it truly includes four components: (1) nutritional assessment, (2) optimizing functional status, (3) lifestyle modifications, and (4) stress management (Fig. 4).

Part of a preoperative assessment for older adults should include a nutritional assessment. At the University of Alberta Hospital, we use the simple two-question Malnutrition Screening Tool (MST) (Fig. 5). A score of 2 or more indicates the patient is at high risk of malnutrition. With this knowledge, you can then consult a dietitian and/or counsel the patient to optimize nutrition. This may mean increasing calories. For older adults, it is often more important to increase their protein intake.

Goals of Care Discussion

All patients should have a goals of care (GOC) discussion. It is important to determine what their wishes are in case of cardiac arrest, need for critical care admission, intubation, and whether they would want to live in an alternative level of care if they became dependent on others. Often, older patients may not be after length of life but *quality* of life.

Areas to discuss with your patients are:

- Overall health goals
- Blood transfusions
- Planned and unplanned admissions to the intensive care unit (including life-sustaining treatment and need for intubation)
- Advance care planning and code status
- Medical proxies or decision makers if the patient cannot make a decision
- Surgical options, nonsurgical options, and outcome if surgery is not chosen

It is important that the code status and their views on life-prolonging treatment are documented clearly before the operation so that the entire team is aware.

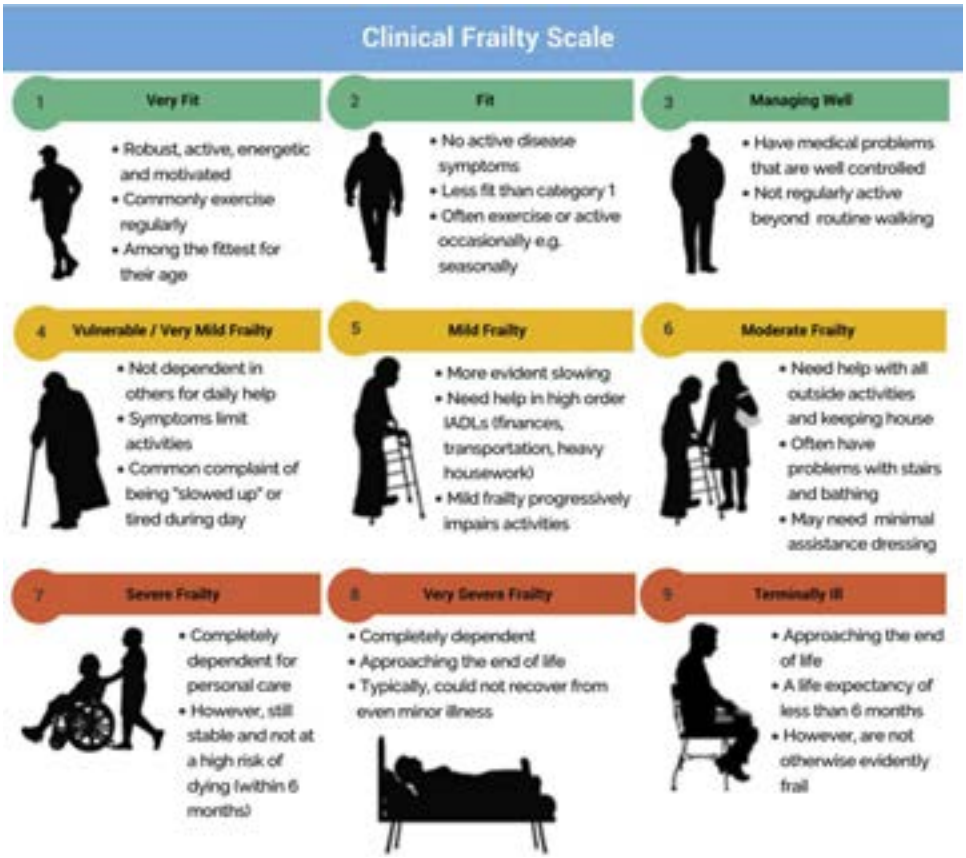


FIG. 3 Adapted Clinical Frail Scale. *(See website for more details; adapted from https://www.dal.ca/sites/gmr.html.)*

TABLE 2 FRAIL Questionnaire

FRAIL Questionnaire Item	Frailty Scale
F (Fatigue): Is the patient easily fatigued?	
R (Resistance): Is the patient unable to walk up one flight of stairs?	Non-frail (Score = 0)
A (Ambulation): Is the patient unable to walk one block?	Pre-frail (Score = 1–2)
I (Illnesses): Does the patient have more than five illnesses?	Frail (Score ≥3 or more abnormalities)
L (Loss of weight): Has the patient lost more than 5% of weight in the past 6 months?	

OPERATIVE MODIFICATIONS FOR THE OLDER PATIENT

Often, surgeries are not modified with the patient's age in mind. However, careful thought must be given to the approach to cause the least physiologic derangement (e.g., laparoscopic versus open) to allow for earlier mobility and less analgesic. Frailty should have a role in operative management, and details have been discussed in previous chapters of this book.

A tailored anesthetic for an older adult should focus on normothermia, careful fluid replacement, and postoperative pain control. The surgeon should also think about pain control at the time of surgery. For example, using preoperative "freezing," blocks, epidural, regional anesthetic, or transverse abdominis plane (TAP) for abdominal surgery can reduce the need for postoperative opioids and, in turn, prevent delirium and improve postoperative mobility.

POSTOPERATIVE CARE

Team-Based/Interdisciplinary Care

Standard hospital care designed to deal expediently with acute illness can be risky for older people. Acute Care for the Elderly models were developed to reduce the preventable functional decline experienced by older patients admitted to acute medical hospital wards, with an emphasis on specialized environment, patient-centered care, medical review, and plans of care. This includes family and caregiver involvement at all stages of care, interdisciplinary assessments, a holistic focus, respect for choices, and an environment supportive of discharge planning and community services. At the University of Alberta Hospital, we conducted the largest study to date applying Elder-friendly Approaches to the Surgical Environment (EASE). It demonstrated a reduction in major complications or death, shorter hospital stays, and more patients returning to their home residence. In addition, a cost analysis on EASE demonstrated 23% cost savings to the healthcare system.

There are key elements in creating an elder-friendly surgical service (Table 3). We started by collaborating with our geriatricians and allied health teams. We also ensured that our health authority and leaders supported the initiative. An important lesson we learned from the EASE study was that not all older patients need a geriatric consult—but the frail patients truly benefit, again emphasizing the

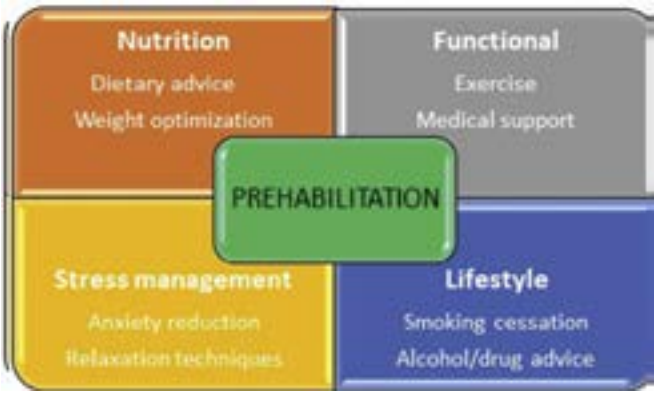


FIG. 4 Components of prehabilitation.

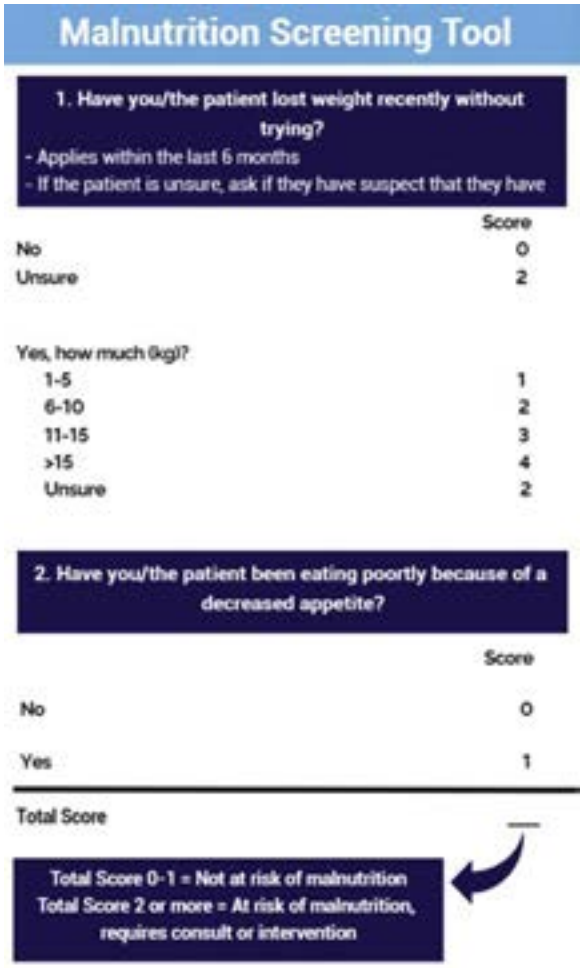


FIG. 5 Malnutrition screening tool. *(From Ferguson M, Capra S, Bauer M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients.* Nutrition. *1999;15:458–464.)*

importance of a frailty assessment. For hospitals that do not have geriatricians, resources such as a geriatric nurse specialist or teaching the team how to conduct comprehensive geriatric assessments may be alternative approaches.

Creating an elder-friendly postoperative order set was very effective in improving care at University of Alberta Hospital. Key elements were:

- Changing medication doses (e.g., opioids small but more frequent doses)
- Removing delirium promoting medications (e.g., no dimenhydrinate/Gravol, meperidine/Demerol, and benzodiazepines)

And proactive orders, such as:

- Removing the Foley catheter postoperative day 1 unless otherwise ordered (this eliminated the surgical team from forgetting to remove it)
- Mobilizing postoperative day 1

We believe it is important to incorporate an elder-friendly patient white board (Fig. 6), which aids in the orientation and care for the patient. The team is aware of the patient's mobility status, sensory devices, and goals, and notes to patient and family can be communicated as well. A key feature that improved clinical care and efficiency was pointing out the "Anticipated Date of Discharge" to the patient and the team.

Delirium Prevention, Detection, and Treatment

Delirium is a major postoperative complication that all surgeons need to recognize. It potentiates postoperative complications and increases mortality. Delirium is an acute, fluctuating disturbance in mental status often associated with confusion, disorientation, altered levels of consciousness, and inattention. It can manifest with either hyper- or hypoactivity. Importantly, 30% to 40% of delirium is preventable. The approach should be to prevent, recognize, and treat the cause.

There are several preventive strategies to prevent delirium:

- A mechanism to ensure safe storage and prompt return of personal sensory equipment postoperatively (e.g., glasses, hearing aids, and dentures).
- Templated order sets with inappropriate medications (e.g., AGS Beers Criteria) removed and alternatives provided.
  - **2.1 Beers Criteria Medications:** Should be avoided if possible; examples used in the perioperative period include barbiturates, benzodiazepines, meperidine, nonbenzodiazepine hypnotics, non-Cox NSAIDs, pentazocine, and skeletal muscle relaxants.
- Opioid-sparing multimodal analgesic.
- Frequent reorientation. A visible clock with the date is very helpful.
- Good sleep hygiene. Changing times of bloodwork to evenings or 7 AM avoids waking patients at 4 AM; using other nonpharmacologic aids (warm milk stimulates melatonin production, hand massage, warm blankets).
- Early mobilization.

Several tools can be used to recognize and detect delirium. Since this is a fluctuating course, the tools often have to be used several times a day. This can correlate with nursing shift change. Our nursing staff uses the Confusion Assessment Method (CAM), which can be done in under 5 minutes with good sensitivity and specificity (Fig. 7). It requires both 1 and 2 and either 3 or 4.

It is then important to have a protocol in place when a positive CAM or delirium score is found so that your healthcare team will be motivated to continue to identify delirium. Once identified, treat the cause. Common causes of delirium include pain, infection, constipation, dehydration, medications, and environment.

Maintaining Function and Preventing Deconditioning

One-third of frail elders develop new functional disabilities in the hospital unrelated to the illness causing their admission, and more than half never regain their previous level of functioning after a prolonged hospital stay. Staying in bed can reduce muscle body loss by up to 5% per day so it is important to have a protocol to allow for

TABLE 3 Key Elements of Creating Elder-Friendly Approaches to the Surgical Environment (EASE)

EASE Interventions	Clinical Care	Important Pathway Elements
Delivery of interdisciplinary care	Daily ward rounds incorporating geriatric specialists in addition to consultation with rehabilitation providers, pharmacists, dieticians, and social workers within 24 h of admission to help develop individual care plans	• Frailty assessment • Comprehensive Geriatric Assessment (CGA)
Implementation of evidence-informed practices	1. Medication review and reconciliation 2. Early mobilization 3. Incorporation of Enhanced Recovery After Surgery 4. Elder-friendly practices, such as comfort rounds (performed every 2 hr by nursing staff to address unmet care needs, mobility, nutrition, pain management, and prevention of falls and delirium) 5. CAM assessment twice daily (to recognize and treat delirium)	1. Creation of standard orders (e.g., d/c Foley POD 1, mobilize out of bed POD 1). 2. Ensure that all sensory devices are provided to patient (e.g., glasses, hearing aids, and dentures). 3. Change bloodwork to 7 AM instead of 5 AM to promote sleep. 4. CAM performed q12h
Early mobilization	Reconditioning Program: a targeted, functional program that patients perform independently at their bedside	1. Early ambulation 2. Early consult to physical therapy if needed
Optimization of transition	The interdisciplinary teams, patient, and caregivers define the optimal blend of patient-specific services required to support safe, quality transitions to discharge with a goal of maximizing functional recovery and returning to baseline health status	1. Early family meeting for discharge planning and addressing care needs 2. Ensure GOC are documented



FIG. 6 Example of an elder-friendly patient white board.

early mobilization to prevent deconditioning. Our group has studied sarcopenia, a loss of skeletal muscle, and found that it is significantly associated with postoperative complications and in-hospital mortality. Although clinical guidelines encourage early mobility, putting it into practice is more challenging.

To counteract the detrimental effects of bedrest, we created a program called, "*BE*dside reconditioning for *F*unctional *I*mprovemen*T*s" (BE-FIT), which consists of a double-sided one-page handout focusing on functional tasks. It is provided to the patient and their family/caregiver to enhance mobility. It does not require a physiotherapist. Instead, healthcare staff (MDs/RNs/LPNs, etc.) encourage patients to complete the exercises more than three times a day immediately postoperation to discharge. This program was able to reduce the time to first mobilization and improved functional outcomes in a subset of patients in the EASE study.

PREPARING FOR DISCHARGE AND RETURNING HOME

The goal of our surgical care is to return a patient to their home with better health than they had when they came to the hospital. Older patients require coordinated care with their family/caregivers and the team to address baseline deficits, rehabilitation needs, and community supports if needed. The interdisciplinary teams, patient, and caregivers define the optimal blend of patient-specific services required

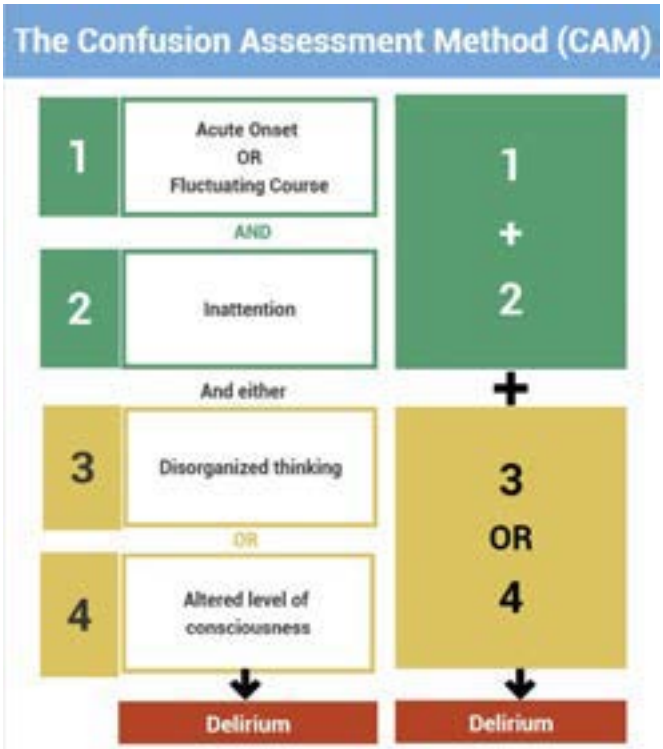


FIG. 7 The Confusion Assessment Method (CAM). *(Adapted from Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium.* Ann Intern Med. *1990;113:941-948.)*

to support safe, quality transitions to discharge with a goal of maximizing functional recovery and returning to baseline health status. Planning this early improves the success of patients returning home.

SUMMARY

Surgeons pride themselves on having a holistic approach to their patients and the ability to care for most of their patients' clinical needs. Given the increase in older patients admitted for surgery, their complex comorbidities and frailty, and the resulting burden to the healthcare system, surgeons need to reassess their approach to caring for older adults. Failure to consider these factors results in poor outcomes and longer hospital stay and increases the need for institutionalization after surgery. These outcomes ultimately increase the use of healthcare resources and cost. The American College of Surgeons has recognized the importance of geriatric surgery and, through a task force, conceived, created, and implemented the Geriatric Verification Program. Several academic and community centers have been verified.

By providing standardized, evidence-informed education and materials to surgical team members, involving a multidisciplinary team that included a geriatrician and/or geriatric nurse specialist early, and following established elder-friendly protocols, pathways, and practices, you will provide comprehensive, effective care for this growing vulnerable population.

Suggested Readings

American College of Surgeons Geriatric Surgery Verification Program. https://www.facs.org/quality-programs/geriatric-surgery

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Perioperative Optimization

Lee A. Goeddel, MD, MPH

The perioperative period—from initial office visit to recovery after surgery—represents a significant period in a patient's life. Perioperative optimization aims to best prepare patients to endure the stress of surgery, to limit complications, and to accelerate recovery. This chapter focuses on five high-yield domains of perioperative care and provides evidence-based recommendations for optimization.

TYPE 2 DIABETES MANAGEMENT: THE GOAL OF PERIOPERATIVE EUGLYCEMIA

Type 2 diabetes mellitus commonly affects the US population. The US Centers for Disease Control and Prevention estimates the prevalence of diagnosed diabetes to be 10.5% in the United States and that an additional 2.8% of the population lives with undiagnosed diabetes. Perioperative hyperglycemia most commonly occurs in people with diabetes but is also common in those without a diagnosis, occurring in up to 40% of general surgery patients and up to 80% of cardiac surgery patients. In patients without a diagnosis of diabetes, this occurrence is considered to be stress hyperglycemia. Perioperative hyperglycemia in both diabetics and nondiabetics is independently associated with complications including wound infection, pneumonia, sepsis, and longer length of stay.

It is critical to clarify baseline endocrine function in the preoperative period and develop a perioperative plan for glucose management in the operating room and in recovery. Hemoglobin A1c (HbA1c) testing remains the mainstay to assess resting glucose metabolism. HbA1c greater than 8% has been independently associated with mortality and wound infection, but even levels greater than 7% have been associated with harm. Before surgery, if the HbA1c is higher than 8%, careful thought should be given to delay surgery in order to achieve more consistent blood glucose control. However, HbA1c will not typically start to decrease for 1 to 3 months. From a surgical perspective it may not be feasible to wait until the HbA1c is below 8%. The optimal time to wait for surgery after treating an elevated HbA1c to improve outcomes is not yet known. An endocrinologist may provide useful consultation.

Perioperative hypoglycemia, while not as common as hyperglycemia, still occurs frequently in this population. Professional societies

differ on suggested glucose targets, which may appropriately differ depending on the location and situation (Table 1). Frequent monitoring and detailed insulin dosing are critical throughout the perioperative period to achieve euglycemia.

While fasting before surgery, a patient's stable insulin dose is often reduced by two-thirds to one-half. New Enhanced Recovery After Surgery (ERAS) programs that focus on carbohydrate drinks up to 2 hours before surgery may prevent catabolic metabolism and hypoglycemia in diabetic patients coming for surgery.

Two recent developments in the perioperative optimization and management of diabetes warrant mention. Insulin pumps have become increasingly used in the United States for both type 2 as well as type 1 diabetes management. These devices continue to evolve in complexity and function. The perioperative team may elect to continue using the device if they are comfortable with manipulating the settings and if they are able to easily access it relative to the surgical field. These devices are often adaptive with closed feedback systems that monitor blood glucose. It is imperative to understand the programmed settings. Usually, the recommended basal rate is maintained unless blood glucose is <110 mg/dL and correctional dosing is set at >180 mg/dL. No less than hourly surveillance blood glucose testing in the operating room is recommended for these patients as well.

A new class of oral hypoglycemic agents approved for treating diabetes, the sodium-glucose cotransporter-2 inhibitors (SGLT2i), are now commonly prescribed. These agents have been linked to postoperative euglycemic diabetic ketoacidosis and thus complicate postoperative recovery. In 2020, the US Food and Drug Administration (FDA) recommended that these agents be stopped before surgery.

RECOMMENDATIONS

1. Referral of surgical patient to primary care physician or endocrinologist for glycemic optimization if preoperative HbA1c greater than 8%.
2. Target perioperative euglycemia has been generally defined as blood glucose level less than 180 mg/dL in the operating room and less than 150 mg/dL in the ICU.
3. Insulin pumps are becoming increasingly common in outpatient diabetes management and may be appropriate to continue perioperatively.

CARDIOVASCULAR DISEASE

The burden of cardiovascular complication after noncardiac surgery remains significant. Out of 200 million major noncardiac surgeries performed in the United States, it is estimated that 5% to 8% of patients suffer a major cardiac complication within 30 days of surgery. The preoperative period is a crucial time to assess a patient's baseline cardiac status, project their risk of major adverse cardiac event, and develop a management plan.

The American College of Cardiology and the American Heart Association (ACC/AHA) have published extensive clinical practice guidelines regarding the perioperative workup and management of cardiac disease. The complete guidelines can be found in published documents from the ACC/AHA (http://my.americanheart.org/professional/StatementsGuidelines/ByTopic).

These guidelines define multiple different populations at risk. A particularly high-risk subset of patients that require additional workup, optimization, and planning before surgery are those with active cardiac conditions (Table 2). For all other patients, the guidelines prescribe the use of an assessment of cardiac risk by available validated risk assessment tools. In particular, the guidelines suggest the Revised Cardiac Risk Index (RCRI) or the National Surgical Quality Improvement Program (NSQUIP) risk calculator. These scales have been validated across populations and are useful guides when starting to plan and treat patients via the rest of the guideline algorithm. However, recent validation studies show that these tools achieve approximately 60% accuracy in predicting adverse cardiac complications after surgery. They should therefore be used with caution.

The most effective predictor of postoperative cardiac complication to date is a protocolized assessment of patient functional capacity. There are multiple assessments of functional capacity and mobility available. Some require patient assessment like the 6-Minute Walk Test or the Time Up and Go Test. Others like the Duke Activity Status Index and the Acute Measure for Post-Acute Care (AMPAC) require no patient interaction. The AMPAC score is also available for repeated measure in the postoperative period to facilitate physical therapy intervention and discharge disposition.

Patients with major cardiac conditions who do not qualify as "active" in Table 2 often require additional perioperative planning. Optimal perioperative medical medication management should consider input from all medical disciplines caring for the patient including primary care, surgery, anesthesiology, and often cardiology. Population trials are ongoing to best direct these decisions regarding perioperative medications for different surgical populations. Based on current available evidence and the 2014 guidelines mentioned earlier, β-adrenergic blocking agents and peripheral dihydropyridine calcium channel blockers are recommended to continue through the perioperative period. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blocking (ARB) agents are usually discontinued before surgery as there appears to be an increase

TABLE 1 Society Guidelines for Treating Perioperative Hyperglycemia

Society	Location	Recommendation
Society of Ambulatory Anesthesia	OR	*Treatment goal:* Intraoperative blood glucose <180 mg/dL
American Diabetes Association	Unspecified	Initiate insulin therapy if blood glucose >180 mg/dL *Treatment goal:* Blood glucose between 140 and 180 mg/dL Goal of 110 to 140 mg/dL may be appropriate for some patients
American College of Physicians	Unspecified	*Treatment goal:* Blood glucose between 140 and 200 mg/dL Recommends against intensive insulin therapy in surgical/medical ICU
Society of Critical Care Medicine	ICU	*Treatment goal:* Maintain glucose <150 mg/dL for most ICU patients
Endocrine Society	Unspecified	*Treatment goal:* Premeal blood glucose between <140 and random <180 mg/dL Higher target glucose <200 mg/dL is acceptable in patients with terminal illness and/or limited life expectancy or at high risk of hypoglycemia
Society of Thoracic Surgeons	OR and ICU	Continuous infusion preferred over SC or intermittent bolus *Treatment goal:* <180 mg/dL during surgery ≤110 in fasting and premeal states

TABLE 2 List of Active Cardiac Conditions Defined in the ACC/AHA Guidelines for Preoperative Cardiac Evaluation In Noncardiac Surgery

Active Cardiac Condition	Additional Information
Unstable coronary artery disease	
Symptomatic heart failure	
Unstable valvular heart disease	Progressive, symptomatic
Unstable arrhythmia	Unstable, acute, symptomatic, or malignant
Unstable pulmonary vascular disease	Symptomatic
Unstable adult congenital heart disease	Symptomatic

in intraoperative hypotension with the induction of anesthesia in the setting of these agents and an associated increase in perioperative mortality. However, this is an active area of research as ACE withdrawal is a well-described poor outcome in multiple populations when these medications are stopped. The significance of ACE/ARB withdrawal in the perioperative period is not yet fully characterized.

Patients with congestive heart failure are at higher risk for perioperative morbidity and mortality that increases with decreasing left ventricular ejection fraction on transthoracic echocardiography. Many of these patients present for surgical treatment on chronic diuretics to assist with fluid management. Typically, these diuretics continue as part of detailed fluid management plan throughout the perioperative period. Perioperative monitoring and management typically focus on optimizing perfusion. Fluid resuscitation remains important in this population, but excess fluid is poorly tolerated. Typical fluid shifts during surgery and recovery place this population at higher risk of arrhythmia, volume overload, wound complications, acute renal failure, and mortality. The goal is to return these patients to their baseline weight, functional status, and perfusion status at discharge.

Recommendations

1. The 2014 AHA/ACC guidelines provide comprehensive guidance for cardiac evaluation and management of noncardiac surgery.
2. Preoperative risk assessment of postoperative cardiac complications is an evolving science with recent evidence supporting the utility of protocolized assessment of functional capacity before surgery.

FRAILTY, MOBILITY, AND PREHABILITATION

Frailty before surgery is defined and assessed broadly. Frailty is an emerging concept used to describe generalized poor functional status and reduced physiologic reserve that results in increased vulnerability to adverse outcomes. Although more prominent in elderly populations, it can also be found in younger patients who suffer from chronic illness, persistent inflammatory states, poor nutrition, or sedentary lifestyle.

Multiple studies have demonstrated an association between preoperative frailty assessment and postoperative outcomes. Frailty predicts postoperative death and increases the likelihood of adverse outcomes after low-risk surgery. It also doubles the odds of new patient-reported disability and impaired quality of life, and frailty increases the odds of nonhome discharge fivefold among older people previously living in the community.

Although these significant associations of frailty to poor postoperative outcomes have been identified, frailty has been assessed heterogeneously and inconsistently, which limits the ability to target successful interventions. Frailty scales are now broadly classified into two scoring system groups: accumulated deficit models and physical frailty phenotypes (Fig. 1). More than 20 frailty scores have been used before surgery.

There is substantial need to mitigate the significant impact of frailty on outcomes in all surgical populations. For high-risk patients, the preoperative phase of care remains a highly desirable time for effective optimization. Frailty assessment identifies a subset of the population at particularly high risk of outcome that may benefit from intervention. Prehabilitation broadly defines interventions targeted before surgery to counter physical frailty and improve outcomes.

Preoperative interventions trialed so far in frail patients have primarily focused on physical function with perioperative exercise routines and have unfortunately shown minimal benefit. These studies have focused on preoperative day programs and both personalized and nonpersonalized exercise routines. A few studies have included nutrition supplementation, cardiology consultation, and haloperidol prophylaxis yielding minimal outcome benefits. Most interventions have targeted the hip fracture population, a population that has a high prevalence of frailty. Comprehensive geriatric assessment and social work interventions have been employed with some hopeful preliminary success. As the mean age of the population in the United States and elsewhere is increasing, the prevalence of frailty is projected to also increase.

Recommendations

1. Frailty screening before surgery should be considered as it identifies a population at higher risk of complication.
2. It is critical to understand the differences between frailty assessment scale types.
3. Prehabilitation is highly desirable, yet evidence-based protocols are not yet available.

NUTRITIONAL STATUS

Nutritional status is an important target of perioperative optimization because it is independently associated with multiple significant outcomes, is straightforward to assess, and in many cases is considered to be modifiable. Malnutrition is a significant predictor of infection, renal and cardiac complications, gastrointestinal fistula formation, poor wound healing, increased hospital length of stay, higher healthcare costs, and death. Yet, there is no consensus on how best to define, to screen, and to treat malnutrition before surgery. NSQUIP defines malnutrition as >10% weight loss during the previous 6 months before presentation for surgery. Only a small segment of the surgical population met this definition with wide variation by surgical presentation.

Multiple validated risk questionnaires exist for malnutrition screening. The perioperative nutrition screen (PONS) is a modified version of the malnutrition universal screening tool that considers body mass index, recent changes in weight, recent decreases in dietary intake, and preoperative albumin level. Historically, certain laboratory values have been used to support a diagnosis of malnutrition (i.e., albumin, prealbumin, or transferrin); however, reliance on these values in isolation is inadequate and can be misleading. While screening for malnutrition, the surgeon must consider the overall clinical presentation. The presence of chronic inflammatory conditions such as diabetes mellitus, rheumatoid arthritis, and Crohn's disease should heighten concern for malnutrition.

Positive screening necessitates a full nutritional assessment, usually with referral to a registered dietitian. A dietitian can assist in developing a detailed and feasible nutrition plan before surgery and for the postoperative period. Seven days of preoperative nutritional support in at-risk patients coming for abdominal surgery decreased postoperative complications by 50%.

Restarting the nutrition plan postoperatively is important in high-risk patients. The postoperative period is a nutritionally catabolic state. In this state, anabolism cannot be achieved when glucose is administered alone without adequate protein delivery. Wound healing and recovery ultimately rely on adequate nutrition.

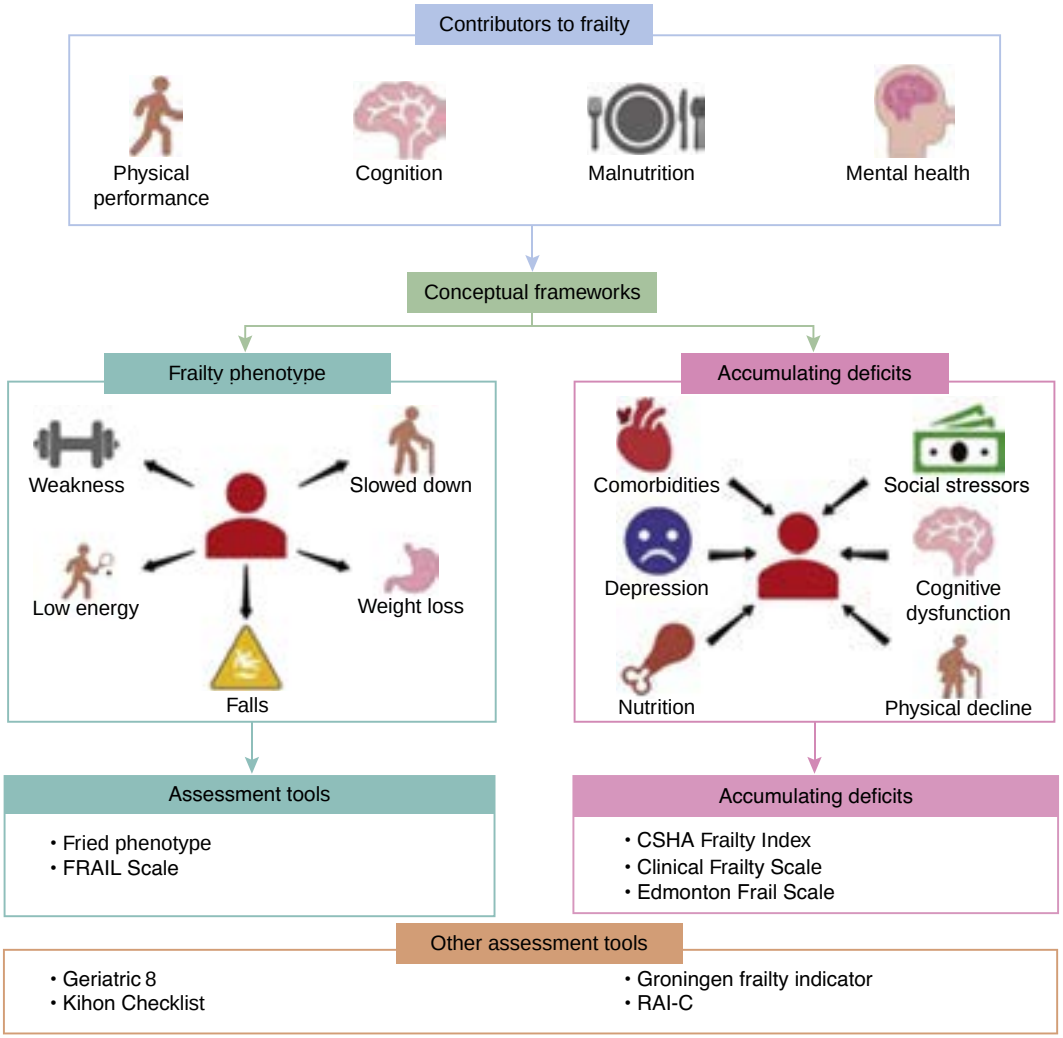


FIG. 1 Relationship between recognized contributors to frailty, conceptual frameworks for frailty, and other assessment tools. *(McIsaac DI, MacDonald DB, Aucoin SD. Frailty for perioperative clinicians: A narrative review. Anesthesia & Analgesia. 2020;130[6]:1450–1460.)*

Recommendations

1. Malnutrition has been independently associated with multiple poor outcomes and is an important target for perioperative optimization.
2. Preoperative screening for malnutrition is important and can allow for referral to a dietitian with immediate intervention if screening is positive.

SARS-COV-2 AND PERIOPERATIVE OPTIMIZATION

The COVID pandemic has brought major challenges to the surgical management of disease. As the virus becomes endemic, some of these challenges are projected to persist. Preoperative viral testing has been common in communities with a high infection rate due to concern for asymptomatic infections. The CDC and state health departments monitor COVID test percent positivity, consecutive days of increased COVID-19 hospitalized patients, regional ICU bed capacity, and med-surg staff capacity to guide policy on elective surgery. There are no defined population cutoffs to mandate preoperative viral testing.

History of infection, exposure to, and active symptoms from SARS-CoV-2 should be assessed in all patients before surgery. Available data suggest that certain surgeries should be delayed until recovery from active infection. Elective and emergency surgery performed in patients with a diagnosis of SARS-CoV-2 infection 7 days before or up to 30 days after surgery observed a pulmonary complication rate of nearly 50% of patients with high associated mortality.

Post–COVID-19 syndrome, or "COVID-19 long hauler" syndrome is a phenomenon that is worth particular mention to perioperative optimization. It is estimated that approximately 10% of patients have persistent symptoms after acute infection, with cough and fatigue as the most common symptoms. These symptoms are noted to be severe in some with significant associated decreases in patient functional capacity. Most patients who report post–COVID-19 syndrome were not hospitalized but had severe symptoms at home. One-third of patients aged 18 to 34 report a significant delay of return to usual state of health, an age cohort that is usually physiologically robust.

Recommendations

1. Surgical outcomes are affected in elective and emergent surgery due to acute SARS-CoV-2 infection.
2. Post–COVID-19 syndrome is common and occurs in many patients not hospitalized from SARS-CoV-2 infection.
3. History of infection, exposure to, and active symptoms from SARS-CoV-2 should be assessed in all patients before surgery.

CONCLUSION

The perioperative period provides an unparalleled opportunity to impact the overall health of the surgical patient. Surgeons must recognize their pivotal role in this process and coordinate multidisciplinary care teams to best manage comorbid conditions throughout the perioperative continuum. The aforementioned domains of care provide five high-yield areas for perioperative optimization; however, this list is not all inclusive and care must be personalized to each individual patient. As the call for precision perioperative medicine grows, these are areas that require detailed evaluation before surgery to employ comprehensive perioperative plans that accelerate recovery.

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Is Nasogastric Intubation Necessary After Alimentary Tract Surgery?

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For much of the twentieth century, surgical dogma taught that a nasogastric tube (NGT) should be used routinely postoperatively in patients undergoing abdominal surgery. Many practical and theoretical reasons were offered as rationale for this approach (Box 1), and NGT insertion became ingrained as part of optimal perioperative care.

HISTORICAL PERSPECTIVE

The first description of the use of a flexible tube to decompress the gastrointestinal (GI) tract after an operation was in 1921 by American gastroenterologist Abraham Louis Levin (Levin tube). In 1926, McIver hypothesized that postoperative abdominal distension was secondary to swallowed air, which would be prevented by suction through an indwelling NGT. Scientific evidence in support for the benefit of routine prophylactic NGT use after GI tract and abdominal surgery was lacking, but this did not prevent its widespread adoption.

BOX 1 Presumed Advantages of NGT Use in the Postoperative Period

1. Bowel rest
2. Prevent intraluminal air and/or fluid accumulation
3. Decrease postoperative nausea and vomiting
4. Prevent or decrease abdominal distension and promote fascial healing
5. Prevent aspiration
6. Assist in anastomotic healing and prevent suture line leaks
7. Promote return of bowel function
8. Decrease hospital length of stay

The prophylactic use of NGT was challenged in 1958 by Gerber and colleagues who showed that patients managed without an NGT had lower morbidity and mortality as well as fewer respiratory tract complications. Although their study was nonrandomized, it led (ironically more than 25 years later) to a randomized trial in a small number of patients with enteric anastomoses that did not demonstrate differences in complication rates.

The use of immediate enteral feeding following abdominal surgery, mainly for trauma, also led to questioning the utility of routine NGT suction. The promulgation of protocols for enhanced recovery after surgery (ERAS) excluded the routine use of NGT following a variety of abdominal operations.

The first meta-analysis in 1995 included 26 clinical trials (3964 patients) comparing selective versus routine use of NGT decompression after elective laparotomy. Routine use was defined as an NGT placed preoperatively or intraoperatively that remained in place until an unspecified point in time (usually return of bowel function, flatus, or decreased output). Selective use was defined as either no NGT used or an NGT placed intraoperatively but removed in the operating room or in the recovery room and replaced only as needed. The analysis demonstrated a significantly lower rate of total complications as well as decreased incidence of postoperative pneumonia, aspiration, and fever with selective use. There was no significant difference between groups in the incidence of anastomotic leak, wound infection, wound dehiscence, or hospital length of stay (LOS).

Since then, numerous randomized controlled trials and meta-analyses have confirmed that prophylactic NGT decompression after elective surgery on the alimentary tract does not afford the benefits ascribed to it by historical surgical dogma. In fact, the majority of studies indicate that the liberal use of an NGT prolongs hospital postoperative LOS and perhaps actually increases the risk of certain complications, especially respiratory complications. A 2010 Cochrane review that examined 37 studies (5711 patients) showed that prophylactic NGT decompression is ineffective in (1) hastening return of bowel function, (2) decreasing risk of aspiration and subsequent pulmonary complications, (3) improving patient comfort by lessening abdominal distension, (4) protecting intestinal anastomoses from leakage, and (5) shortening hospital LOS. The use of NGTs also is associated with significant morbidity related to both placement and prolonged use, not to mention significant patient discomfort.

FOREGUT AND PANCREATIC SURGERY

In spite of a large body of evidence to the contrary, many types of surgical procedures still include widespread usage of NGTs, both intra- and postoperatively. There is often trepidation by surgeons to remove NGTs early and start oral feedings after esophagectomy, gastrectomy, or pancreaticoduodenectomy. For example, following pancreaticoduodenectomy, there is concern over the presence of proximal anastomoses. Furthermore, there are also concerns that early feeding will increase the risk of leaks and fistula formation.

Esophageal operations routinely involve placement of NGTs for gastric decompression, prevention of anastomotic dehiscence, decreased postoperative nausea/vomiting, and decreased aspiration risk. Multiple studies have assessed NGT use in esophageal resections. A meta-analysis comparing seven studies and 608 patients found no difference in rates of anastomotic leak, respiratory complications, and mortality between immediate postoperative NGT removal to early removal (removal by postoperative day 2). Nonrandomized trials have shown that NGT decompression is associated with increased risk of anastomotic and respiratory complications. Randomized studies comparing early (by postoperative day 2) and delayed NGT removal show no differences in outcomes. Therefore, current guidelines strongly suggest NGT use at the time of surgery with consideration for early removal by latest postoperative day 2, when clinically appropriate.

Nine randomized controlled trials and two meta-analyses have studied the use of NGTs after gastrectomies and marshal strong evidence against their routine use. These studies show no difference in time to flatus, rate of anastomotic leaks, respiratory complications, morbidity, or mortality. Indeed, many demonstrate an increased LOS for patients with routine NGT use compared with those without. Similarly, current guidelines for pancreaticoduodenectomy do not recommend routine use of NGTs for decompression. Use after pancreaticoduodenectomy was often considered important in the setting of delayed gastric emptying; however, multiple studies with historical controls demonstrate that rates of delayed gastric emptying are higher with routine NGT use.

COLORECTAL SURGERY AND ERAS

Fast-track surgery, previously described by Kehlet, has been integrated in GI tract surgery but most successfully in elective colorectal procedures. ERAS pathways are the standard of care in colorectal surgery and have been shown to reduce postoperative morbidity, LOS, and healthcare expenditures. A critical component of ERAS is early resumption of oral nutrition immediately after surgery. The most recent meta-analysis of seven randomized controlled trials and 587 patients comparing early feeding to traditional use of NGTs demonstrated significantly reduced LOS and total postoperative complications. This meta-analysis showed no differences in anastomotic dehiscence, pneumonia, infections, rate of NGT reinsertion, vomiting, or mortality. As such, the recommendation for routine use of NGTs during elective colorectal surgery has been restricted to evacuating air intraoperatively with removal before reversal of anesthesia.

EMERGENCY SURGERY AND NASOGASTRIC TUBES

There are limited data available for fast-track protocols and the use of NGTs in emergency surgery on the GI tract. However, in the absence of bowel obstruction or need for immediate post-operative nutritional access, there is no evidence to support their routine use. One randomized controlled trial of emergency abdominal surgery assigned 167 patients to early oral feeding (soft diet given within 24 hours) and 169 to a traditional care pathway (selective NGT use and "nil per mouth" until intestinal function was restored). Patients in the traditional care group were further stratified into high risk (evidence of peritonitis, GI tract obstruction or perforation, or an anastomosis) and low risk (none of the high-risk criteria) and given liquids and then a soft diet once they passed either flatus or stool. This study demonstrated no difference between the early oral feeding and traditional care pathway groups in terms of complication rates, LOS, or need for reoperation. There was a significant increase in postprandial vomiting in the early oral feeding group without any difference in need for NGT reinsertion between either group.

The use of ERAS principles in emergency surgery has been assessed in another randomized controlled trial of patients undergoing laparoscopic surgery for perforated peptic ulcer disease. There were 21 patients assigned to the ERAS group who had their NGT removed in the operating room and given liquids on postoperative day 1. There were 26 patients in the control group who had their NGT removed only after output was less than 300 mL a day. This study demonstrated no difference in morbidity or mortality and a significantly shorter LOS for the ERAS group (3.8 vs 6.9 days). The general applicability of this study is limited by its numerous exclusion criteria. Another randomized study evaluated patients undergoing emergency laparotomy for perforation with peritonitis or intestinal obstruction and compared postoperative NGT use versus no tube usage. No differences in rate of wound complications, gastric upset, respiratory complications, anastomotic leaks, or NGT reinsertions were found. The group without NGT use had a shorter LOS. Although the data in emergency surgery are not conclusive, there is strong evidence that routine NGT use can be omitted in select patients.

COMPLICATIONS OF NASOGASTRIC TUBES

NGT use does not come without the potential for complications, which is one reason to forgo routine use. These complications can occur during placement or after prolonged use. Complications during placement range from mild, such as mucosal irritation or bleeding, to severe, such as intracranial penetration, GI tract perforation, and tension pneumothorax. Patient history and recent surgeries or trauma should be considered before determining whether nasogastric placement is appropriate. Careful consideration of recent upper GI surgery, basilar skull, or maxillofacial fractures is advised. Assessment of NGT position can be confirmed with physical examination and imaging.

Prolonged use of NGTs can result in esophageal strictures, nasal ulcerations, and NGT syndrome, which is ulceration and infection in the posterior cricoid region that causes vocal cord dysfunction and can seriously compromise a patient's airway. Data on other adverse effects, such as patient pain and discomfort, sinusitis, epistaxis, bleeding, middle ear infections, pharyngolaryngitis, pleuritis, hydrothorax, aspiration, esophageal obstruction from tangled NGT tubes, incorporation into a GI tract anastomosis, aortoesophageal fistula, tracheoesophageal fistula, intramural esophageal dissection, cleft nose deformity, and retropharyngeal infected hematoma have been reported. Some of these adverse effects are likely underrecognized and underreported.

WHY ARE SURGEONS STILL ROUTINELY USING NASOGASTRIC TUBES?

Despite the strength and quality of the scientific evidence against routine NGT use after GI tract surgery, it is still common for surgeons to use NGT postoperatively. The reason behind this is likely multifactorial. First, there may be a lack of awareness of the evidence for practicing surgeons. On the other hand, practicing surgeons may be aware of the evidence but do not believe the results can be generalized to their patient populations. Second, practicing surgeons may base their decisions on their own anecdotal experience or that of senior teachers or partners rather than scientific evidence. In either case, all surgeons should be aware of cases of severe and often fatal aspiration occurring during a seemingly smooth postoperative recovery following abdominal and GI tract operations. Although the routine use of NGT does not prevent this occurrence, early recognition of delayed gut electrical activity could lead to selective use of NGT. Most recently, percutaneous assessment of gut electrical activity has been evaluated, and early data indicate possible usefulness in determining readiness for

oral diet. Overall, given the selected findings presented and the guidelines currently available, the routine use of NGTs after GI tract surgery may be unnecessary and potentially detrimental to patient outcomes.

CONCLUSION

Routine use of NGTs after GI tract surgery is not supported by data. Current studies demonstrate that postoperative removal and early oral feeding are safe and efficacious in GI tract surgery. While the NGT is an important tool for the surgeon, it does not come without risks; therefore, its use should be tailored toward therapy for bowel obstructions and postoperative ileus and vomiting or as a means to provide medications and enteral nutrition in appropriate settings. Although we have made great strides in our research on the use of NGTs, much work is still needed to decrease their routine use after GI tract surgery.

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SURGICAL SITE INFECTIONS

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INTRODUCTION

Surgical site infections (SSIs) are defined as infections occurring up to 30 days after surgery (or up to 1 year after surgery in patients receiving implants) and affecting either the incision or deep tissue at the operation site. They are a common postoperative complication, with an annual incidence of approximately 500,000 to 750,000 in the United States alone. It is estimated that $10,000 to $25,000 are spent per SSI, leading to over $2 billion per year being spent on their management. The Centers for Disease Control and Prevention (CDC), the American College of Surgeons (in conjunction with the Surgical Infection Society), and the World Health Organization (WHO) have all published guidelines/recommendations on preventive strategies against SSIs based on evidence-based medicine.

EPIDEMIOLOGY

SSIs occur in approximately 1% to 5% of patients worldwide. However, the incidence is likely underestimated as a large number of SSIs are diagnosed in the outpatient setting. The bacterial pathogens causing SSIs are closely monitored by the CDC via the National Healthcare Safety Network (NHSN), a surveillance system that was created in 2005 to closely track healthcare-associated infections, including antibiotic susceptibility. Interestingly, for SSIs, the percentage of *Staphylococcus aureus* that was oxacillin, methicillin, and/or cefoxitin resistant (i.e., MRSA) was relatively unchanged from 2014 to 2017 (42.6% in 2014 to 41.9% in 2017), while the percentage of vancomycin-resistant *Enterococcus* (VRE) species decreased from 58.4% to 55.6%. The most common bacteria isolated from SSIs from 2006 to 2017 are shown in Table 1.

DEFINITION

The use of standardized definitions is vitally important in the identification of SSI and treatment on an individual level as well as its use on a broader level for surveillance programs (Table 2). SSIs are most commonly defined based on CDC definitions that divide cases into incisional or organ/space. Within the incisional category, they are further divided into those involving skin and subcutaneous tissue and those involving deeper soft tissues.

RISK FACTORS

Risk factors for SSIs have been extensively studied and identified. They include both patient-related factors and non–patient-related factors as seen in Table 3.

CLASSIFICATION

Surgical wounds are assessed based on the classification system listed in Table 4, which was created by the CDC. Data from 1991, when this classification system was created, suggested a much higher risk of SSI with surgical wounds, with Class IV (dirty) wounds having greater than 27% risk of becoming infected. However, more recent data have displayed a much lower risk, with Class IV (dirty) wounds having an SSI rate of 8.5% to 11.8%.

PREVENTION

SSIs are the most common and costly type of hospital-acquired infections, and each SSI is associated with 7 to 11 additional postoperative days. Additionally, patients with an SSI have a 2 to 11 times higher risk of death compared with operative patients whose postoperative courses are not complicated by a SSI. Given that up to 60% of SSIs

TABLE 1 Percentage/Distribution of Most Common Bacteria to Cause Surgical Site Infections Based on National Healthcare Safety Network (NHSN) Data

	2006–2007	2009–2010	2011–2014	2015–2017
Staphylococcus aureus	30%	30.4%	20.7%	17.5%
Escherichia coli	9.6%	9.4%	13.7%	14.1%
Coagulase-negative staphylococci	13.7%	11.7%	7.9%	7.2%
Enterococcus faecalis	11.2%	11.6%	7.5%	8%
Pseudomonas aeruginosa	5.6%	5.5%	5.7%	5.8%
Klebsiella pneumoniae/Klebsiella oxytoca	3%	4%	4.7%	5.1%
Enterobacter species	4.2%	4%	4.4%	4.7%

TABLE 2 Surgical Site Infection Definitions

	Definition
Superficial incisional SSI	Infection that occurs within 30 days of surgery and includes only the skin and subcutaneous tissue of the incision. Plus at least *one* of the following: 1. Purulent drainage, with or without laboratory confirmation, from the surgical incision 2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the surgical incision 3. At least one of the following signs/symptoms of infection *and* superficial incision is deliberately opened by the surgeon (unless incision is culture negative) • Pain, tenderness, localized swelling, redness, or heat 4. Diagnosis made by surgeon or attending physician 5. The following are not considered superficial incisional SSIs: • Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration)) • Infection of an episiotomy or newborn circumcision site • Infected burn
Deep incisional SSI	Infection that occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant* is left in place *and* the infection appears to be related to the operative procedure *and* infection involves deep soft tissues (i.e., fascial and muscle layers) of the incision, *and* at least one of the following is present: 1. Purulent drainage from the deep incision, but not from the organ/space component of the surgical site 2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms • Fever (>38°C), localized pain or tenderness, unless culture of the incision is negative • An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination • Diagnosis made by surgeon or attending physician
Organ space SSI	Infection that occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant* is left in place *and* the infection appears to be related to the operative procedure *and* infection involves any part of the anatomy (e.g., organs or spaces) other than the incision, which was opened or manipulated during the operation *and* at least one of the following is present: 1. Purulent drainage from a drain that is placed through a stab wound into the organ space • If the area around a stab wound becomes infected, it is *not* an SSI. It is considered a skin or soft tissue infection, depending on its depth. 2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the organ space 3. An abscess or other evidence of infection involving the organ/space on direct examination, during reoperation, or by histopathologic or radiologic examination 4. Diagnosis made by surgeon or attending physician

*Implant: a nonhuman-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.

SSI, Surgical site infection.

From Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol.* 1992;13(10):606–608.

TABLE 3 Surgical Site Risk Factors

	Risk Factors
Patient related	Older age, recent radiotherapy, history of skin or soft tissue infection Diabetes, obesity, alcoholism, current smoker, immunosuppression, total bilirubin >1.0 mg/dL, preoperative albumin <3.5 mg/dL
Non–patient related Preoperative	Inadequate antibiotic choice, timing, or dosing. Inadequate skin preparation, gloving, surgical scrub, or hair-removal method
Facility	Inadequate ventilation, increased operating room traffic, nonsterile equipment
Procedure	Emergent procedure, complex procedure, high wound classification, long procedure, blood transfusion, breach in asepsis, poor glycemic control

Data from American College of Surgeons surgical site infection guidelines: Anderson DJ, Podgorny K, Berríos-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35(S2):S66–S88; Norman G, Goh EL, Dumville JC, at al. Negative pressure wound therapy for surgical wounds healing by primary closure. *Cochrane Database Syst Rev*. 2020;6(6):CD009261.

TABLE 4 Surgical Wound Classification

	Definition	Examples	Risk of infection (1991)	Risk of infection (2014)
Class I: clean	Surgical wound in which there is no breach of the respiratory, GI, GU, or genital tracts, and no inflammation is encountered	• Hernia repair (inguinal, femoral, ventral, incisional) • Thyroidectomy • CABG • Mastectomy • Lumpectomy • Total knee replacement • Total hip replacement • Port placement • Axillary lymph node dissection	1%–5%	1.8%–2.6%
Class II: clean-contaminated	Surgical wound in which there is a controlled entrance of the respiratory, GI, GU, or genital tracts without a major break in sterile technique	• Small bowel resection • Lobectomy (lung) • Hysterectomy • Colectomy • Colostomy reversal • Roux-en-Y gastric bypass • Whipple procedure • Laryngectomy • TURP	3%–11%	4.8%–6.7%
Class III: contaminated	Surgical wound that is open, fresh (less than 4 hours old), and/or accidental with a major break in sterile technique and/or uncontrolled/gross spillage from the GI tract. Surgical wound in which acute, nonpurulent inflammation is met	• Cholecystectomy for acute cholecystitis • Appendectomy for nonperforated appendicitis • Nonsterile equipment or debris found on operative field • Small bowel resection for infarcted or necrotic bowel	10%–17%	5.6%–8.6%
Class IV: dirty/infected	Surgical wound that is old (greater than 4 hours old), and/or accidental/traumatic with a major break in sterile technique and/or uncontrolled/gross spillage from the GI tract	• Peritonitis • Appendectomy for perforated appendicitis • Repair of perforated gastric ulcer • Repair of perforated small bowel • Open fracture repair	>27%	8.5%–11.8%

CABG, Coronary artery bypass graft; *GI,* gastrointestinal; *GU,* genitourinary; *TURP,* transurethral resection of prostate.

Data from Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control*. 1999;27(2):97–132; quiz 133–134; discussion 96.

were estimated to be preventable with evidence-based measures, SSI has become a target of quality improvement efforts.

The CDC, the WHO, and the American College of Surgeons (in conjunction with the Surgical Infection Society) have published guidelines on preoperative, intraoperative, and postoperative recommendations for SSI prevention (Tables 5 and 6). The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to evaluate the validity and strength of the CDC and WHO published guidelines. The use of negative-pressure wound therapy (NPWT) for wounds with primary skin closure remains controversial. A recent meta-analysis confirmed a decrease in the rate of SSI for all operations studied. However, it is likely that

TABLE 5 ACS/SIS, CDC, and WHO Guidelines for Surgical Site Infection Prevention

Prehospital Interventions	Recommendations
Preoperative bathing	Full body shower or bath with soap (antimicrobial or nonantimicrobial) is advised on at least the evening before the operative day.
Antibiotics	Preoperative oral antibiotics should be given with a mechanical bowel preparation (MBP) to adult patients undergoing elective colorectal surgery.
Hospital Interventions	**Recommendations**
Intravenous antibiotics	Administer prophylactic IV antibiotics within 120 minutes before the incision, while considering the half-life of the antibiotics. Antibiotics with a shorter half-life such as penicillin and cefazolin should be administered closer to incision time (within 60 minutes). Administer prophylactic IV antibiotics before skin incision in all cesarean sections. Do not administer additional prophylactic IV antibiotics in clean and clean-contaminated cases after the incision has been closed—even in the presence of a drain. Also applies to prosthetic joint arthroplasty.
Topical antibiotics	Do not apply antimicrobial agents (e.g., ointments, solutions, or powders) to the surgical incision for SSI prevention. For orthopedic and cardiothoracic surgery patients, it is recommended that all patients who are known carriers *of Staphylococcus aureus* receive perioperative intranasal applications of mupirocin 2% ointment with or without chlorhexidine gluconate body wash. In addition, do not irrigate surgical wounds intraoperatively with antibiotic solution (can lead to antibiotic resistance [WHO]).
Perioperative glycemic control	Implement perioperative glycemic control protocols in both diabetic and nondiabetic patients. The CDC recommends blood glucose levels <200 mg/dL. The ACS recommends blood glucose levels between 110 and 150 mg/dL, except in cardiac surgery (goal <180 mg/dL)
Normothermia	The use of warming devices to maintain perioperative normal body temperature is recommended for SSI prevention.
Hyperoxia	Patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation for surgical procedures should receive 80% FiO_2 intraoperatively and in the immediate postoperative period (revised from strong to conditional recommendation in the 2018 WHO update).
Intraoperative skin preparation	Perform intraoperative skin preparation with an alcohol-based antiseptic solution unless contraindicated. Patients undergoing any surgical procedure should either not have their hair removed *or* if absolutely necessary the hair should be removed using a clipper. Shaving is *strongly* discouraged at all times, whether preoperatively or in the operating room.
Handwashing	Surgical hand preparation should be done by either scrubbing the hands with antimicrobial soap and water or an alcohol-based hand rub solution before donning sterile gloves. Neither is superior to the other.
Wound care	There is currently no evidence suggesting that timing of dressing removal (<48 hours) affects SSI risk. In class III contaminated wounds closed with interrupted staples, daily wound probing resulted in a decreased rate of SSI without increased patient discomfort. Wound vacuum therapy over closed incisions to decrease SSI in open colorectal surgery, ventral hernia repair, and vascular groin incisions have been shown to be effective.
Post-Hospital Interventions	**Recommendations**
Postoperative showering	No studies have shown a difference in SSI between early showering (12 hours after surgery) and delayed showering (>48 hours).
Postdischarge wound care	Because of the paucity of data, no formal postdischarge wound protocol has been described that decreases the risk of SSI. No reliable postdischarge SSI surveillance methods have been identified as effective, although promising new methods of surveillance are now being explored utilizing smart phone technology (see the Remote Monitoring section in the text).

ACS, American College of Surgeons; *CDC,* Centers for Disease Control and Prevention; *SIS,* Surgical Infection Society; *SSI,* surgical site infection.

TABLE 6 Recommendations for Antibiotic Prophylaxis Based on Surgical Procedure

Surgical Procedure	Recommended Antibiotic	Alternative for Patients with β-Lactam Allergy
Cardiac • Coronary artery bypass • Cardiac device insertion procedures (e.g., pacemaker) • Ventricular assist devices **Thoracic** • Lobectomy, pneumonectomy, thoracotomy • Video-assisted thoracoscopic surgery	Cefazolin or cefuroxime	Clindamycin or vancomycin
Vascular	**Cefazolin**	**Clindamycin or vancomycin**
Gastroduodenal • Procedures involving entry into the GI tract (i.e., bariatric, Whipple procedure) or not involving entry into the GI tract (i.e., Nissen, vagotomy) but in high-risk patients	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Biliary tract • Open surgery	Cefazolin or cefoxitin or cefotetan or ceftriaxone or ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
• Laparoscopic surgery • Elective, low risk	None	
• Elective, high risk	Cefazolin or cefoxitin or cefotetan or ceftriaxone or ampicillin-sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Small bowel • Non-obstructed	Cefazolin	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone
• Obstructed	Cefazolin + metronidazole or cefoxitin or cefotetan	Metronidazole + aminoglycoside or fluoroquinolone
Colorectal	Cefazolin + metronidazole or cefoxitin or cefotetan or ampicillin-sulbactam *or*Ceftriaxone + metronidazole or ertapenem	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone *or*Metronidazole + aminoglycoside or fluoroquinolone
Appendectomy for uncomplicated appendicitis	Cefoxitin or cefotetan or cefazolin + metronidazole	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone *or* Metronidazole + aminoglycoside or fluoroquinolone
Hernia repair	**Cefazolin**	**Clindamycin or vancomycin**
Head and neck • Clean	None	None
• Clean with placement of prosthesis (excludes tympanostomy tubes)	Cefazolin or cefuroxime	Clindamycin
• Clean-contaminated with exception of tonsillectomy and functional endoscopic sinus procedures	Cefazolin + metronidazole *or* Cefuroxime + Metronidazole or ampicillin-sulbactam	Clindamycin
Neurosurgery • Elective craniotomy and CSF-shunting procedures	Cefazolin	Clindamycin or vancomycin
• Intrathecal pump implantation	Cefazolin	Clindamycin or vancomycin
Cesarean section	Cefazolin	Clindamycin + aminoglycoside
Hysterectomy (vaginal or abdominal)	Cefazolin or cefoxitin or cefotetan or ampicillin-sulbactam	Clindamycin *or* vancomycin + aminoglycoside or aztreonam or fluoroquinolone *or* Metronidazole + aminoglycoside or fluoroquinolone

TABLE 6 Recommendations for Antibiotic Prophylaxis Based on Surgical Procedure—cont'd

Surgical Procedure	Recommended Antibiotic	Alternative for Patients with β-Lactam Allergy
Ophthalmic	Topical neomycin-polymyxin B-gramicidin or fourth-generation topical fluoroquinolone	None
Orthopedic • Clean cases of hand, knee, or foot without implantation of foreign materials	None	None
• Spinal procedures with or without instrumentation, hip fracture repair, implantation of internal fixation devices (e.g., nails, plates, screws), total joint replacement	Cefazolin	Clindamycin or vancomycin
Urologic • Lower tract instrumentation with risk factors for infection (includes transrectal prostate biopsy)	Cefazolin or fluoroquinolone orTrimethoprim/sulfamethoxazole	Aminoglycoside +/– clindamycin
• Clean with entry into urinary tract	Cefazolin	Fluoroquinolone or aminoglycoside +/– clindamycin
• Clean without entry into urinary tract	Cefazolin	Clindamycin or vancomycin
• Involving implanted prosthesis	Cefazolin +/– aminoglycoside *or* cefazolin +/– aztreonam or ampicillin-sulbactam	Clindamycin +/– aminoglycoside *or* aztreonam *or* vancomycin +/– aminoglycoside
Clean-contaminated	Cefazolin + metronidazole or cefoxitin	Fluoroquinolone *or* aminoglycoside + metronidazole or clindamycin
Heart transplantation	Cefazolin	Clindamycin or vancomycin
Lung transplantation	Cefazolin	Clindamycin or vancomycin
Liver transplantation	Piperacillin-tazobactam *or* cefotaxime + ampicillin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Pancreas transplantation and pancreas-kidney transplantation	Cefazolin +/– fluconazole (for patients at high risk of fungal infection)	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Plastic surgery—clean with risk factors or clean-contaminated	Cefazolin or ampicillin-sulbactam	Clindamycin or vancomycin

Modified from guidelines developed by the American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), Surgical Infection Society (SIS), and Society for Healthcare Epidemiology of America (SHEA). Data from Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Heal Pharm*. 2013;70(3):195–283.

some surgical wounds benefit from the use of NPWT, while others do not. Whether this is based on the level of contamination in the wound (i.e., clean versus contaminated) or the location of the wound (i.e., abdomen versus extremity) requires further elucidation.

TREATMENT

All surgical wounds with clear evidence of infection (i.e., heat, pain, redness, and/or swelling) should be opened, debrided, cultured, and packed with a wet-to-dry or vacuum-based dressing. The wound should be fully explored for underlying abscesses, fluid collections, necrotizing infection, dehiscence, and enteric content. In addition, all necrotic and infected tissue should be meticulously debrided down to healthy, bleeding tissue, and the wound should be thoroughly irrigated with normal saline.

The use of oral and intravenous antibiotics is recommended based on the United Kingdom's National Institute for Health and Care Excellence (NICE) SSI guidelines. These antibiotics should be tailored based on wound cultures and local/regional antibiograms. Notably, the NICE recommends against the use of topical antibiotics for prevention and treatment of SSIs. The most appropriate duration of antimicrobial use is unclear and is frequently based on the severity of local and systemic inflammation.

The use of NPWT, also known as a *wound vacuum,* is now considered an effective treatment to promote healing in open wounds. NPWT decreases local edema by extracting fluid out of the wound and promotes angiogenesis by promoting blood flow in the region. Within the past 20 years, NPWT has become a popular commodity for the treatment of infected wounds. Previously, NPWT was used mostly after the wound was clean and stabilized; nowadays, however, the use of NPWT with instillation (NPWT-i) of normal saline, sodium hypochlorite, or 0.1% polyhexanide plus 0.1% betaine is commonly used for the acute treatment of open incisional SSI. NPWT-i works by instilling one of these solutions into the wound, allowing the solution to "dwell" in the wound for a certain amount of time (called the *dwell time*), and finally removing the fluid with negative pressure. Much of the published literature on NPWT-i recommends the use of 0.1% polyhexanide plus 0.1% betaine based on its broad-spectrum antibiotic activity. However, Kim et al. recently showed in a prospective, randomized effectiveness study that normal saline can work just as effectively, with a shorter time to a final surgical procedure.

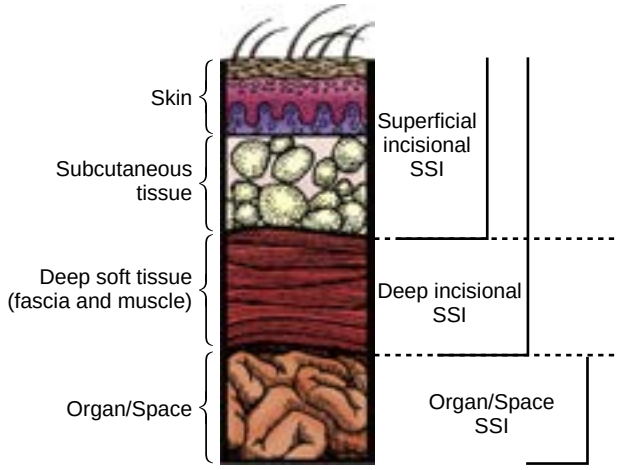


FIG. 1 Surgical site infections. (*From Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention Hospital Infection Control Practices Advisory Committee.* Am J Infect Control. *1999;27:97–132.*)

REMOTE MONITORING

Current estimates suggest that approximately 60 million people in the United States or approximately one in five patients experience barriers in accessing quality surgical care. Several factors are linked to the difficulty of individuals receiving adequate health care including reliable transportation and financial hardship. This results in a delay of care, which in turn leads to increased healthcare-related costs and suboptimal patient outcomes.

In recent years, and particularly during the COVID-19 pandemic, mobile health (mHealth) technology has emerged as a valuable tool. A recent analysis identified 10 applications designed for postdischarge SSI surveillance, 2 of which have been used in the clinical setting. Features included photo documentation of surgical incisions, symptom questionnaires, and in some cases, wound measurements and dressing assessments. These applications have the potential to facilitate convenient and timely communication between the patient and surgeon that would otherwise require a traditional office visit. In practice, this may allow for earlier detection and treatment of SSI in patients who would otherwise be "lost to follow-up" because of socioeconomic barriers. Shortcomings to the successful utilization of mHealth include the need for adequate and reliable Internet access as well as proper implementation by the care team.

Overall, making mHealth services widely available to medically underserved populations has the potential to not only decrease the number of emergency department visits and rehospitalizations but will also allow for early detection and treatment of postoperative SSIs. Ultimately, it will be interesting to see if the use of cell phone technology in postoperative surveillance will have a significant positive effect on patient outcomes and use of healthcare dollars.

SUMMARY

SSIs are the most common postoperative complications and the most expensive healthcare-associated condition in the United States today. Diagnosis is frequently made on clinical grounds, and treatment should be prompt. Because of the importance of SSI, several evidence-based prevention guidelines have been published. Future progress in the prevention and management of this condition will depend on optimizing the host immune response and understanding and controlling the bacterial pathogens that are frequently involved.

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MANAGEMENT OF INTRAABDOMINAL INFECTIONS

Amy V. Gore, MD, and David H. Livingston, MD

Intraabdominal infections (IAIs) are one of the most common reasons for surgical consultation, and a complete understanding of the evaluation and management of these processes is vital. IAIs are implicated in 66% of surgical patients with sepsis, and rates up to 85% are documented in patients following abdominal surgery. The outcomes of patients with IAI vary widely with some cohorts, such as the elderly or critically ill patients, experiencing significant morbidity ranging in severity from surgical site infection and recurrent intraabdominal abscess to organ dysfunction and death. The very broad nature of the diagnoses and the patient population continues to makes the diagnosis and treatment of intraabdominal infections a challenge.

CLASSIFICATION

IAIs result when the sterile abdominal cavity is contaminated, allowing microorganisms to invade and replicate. Classically these infections have been categorized as primary, secondary, and tertiary. Primary IAIs occur as a result of either direct inoculation or distant spread, such as bacterial peritonitis in a patient with cirrhosis and ascites. Secondary IAIs occur as a result of inflammation or perforation

of an intraabdominal organ. Most secondary IAIs require surgical consultation with prompt administration of antibiotics and possible source control. Individual diseases resulting in secondary IAI such as appendicitis or diverticulitis are covered extensively in other chapters and will only be discussed superficially. Other secondary IAIs occur in patients who have sustained intraabdominal trauma or have undergone previous abdominal interventions and are not recovering as expected. Tertiary IAIs are typically a result of persistent or recurrent infections that occur in immunocompromised patients or those who have undergone treatment for a secondary IAI. Tertiary and many secondary IAIs are often polymicrobial, often with resistant organisms, and these groups can tax the surgeon's diagnostic and clinical skills and may require the most complex medical decision making.

The extent of infection can also be useful in classifying IAIs. Localized infections remain confined to a particular organ or anatomic space, such as cholecystitis or appendicitis, whereas diffuse IAIs extend throughout the peritoneal cavity, such as perforated diverticulitis with gross enteric spillage.

The Surgical Infection Society (SIS) recommends differentiating community-acquired IAIs (CA-IAIs) from hospital-acquired IAIs (HA-IAIs), recognizing the different microbiome encountered and greater risk of antibiotic resistance with HA-IAIs. These patients can be further stratified into low- and high-risk according to their age and comorbid conditions including malignancy and immunosuppression.

DIAGNOSIS

Presentation

IAI should be high on the differential in any patient presenting with sepsis and intraabdominal complaints—either gastrointestinal or genitourinary. Evaluation should commence with a detailed history and physical examination. Although symptoms vary, abdominal pain, fever, nausea, vomiting, obstipation, distension, and dysuria are common. Attention to past surgical history, including recent interventions, is important. Although physical examination may be nonspecific, it can provide important clues to underlying pathology. Initially, patients with localized infection may remain hemodynamically normal; however, continued spread, perforation, or those with uncontained infection can quickly progress to sepsis with or without shock and end-organ dysfunction.

Diagnostic Workup

Workup should proceed with laboratory assessment and imaging as dictated by the history and physical exam. Laboratory tests such as a complete blood count (CBC) are useful to determine the degree of leukocytosis or leukopenia. Serum electrolyte levels will provide an assessment of the degree of metabolic derangement and dehydration. Liver function tests, amylase, and lipase are indicated if there is suspicion for hepatobiliary or pancreatic pathology. Serum lactate should be routinely assessed and followed in patients with sepsis and septic shock. Pregnancy tests should be sent on female patients of childbearing age. Cultures should be obtained but should not delay the initiation of antimicrobial therapy.

Patients in the postoperative period can present a diagnostic conundrum as many symptoms, such as pain, fever, intestinal dysmotility, anorexia, and nausea may be more subtle or attributed to the "normal" postoperative state. C-reactive protein has been studied as a potential molecular marker for complications in the post-operative phase. C-reactive protein levels typically peak 48 to 72 hours after surgery, decreasing to baseline by postoperative day 5. Persistent elevation may indicate an infectious complication. Procalcitonin is another molecule that has been extensively investigated as a potential marker of infection, with several large studies demonstrating utility in the intensive care unit (ICU) in predicting sepsis caused by bacterial infection. Procalcitonin has also been shown to be a predictor of mortality. The MOSES study reported a doubling in 28-day mortality when procalcitonin failed to decrease by 80% from baseline by day 4.

In patients presenting with frank peritonitis, operative intervention should not be delayed for imaging studies that will not change management. A plain chest or abdominal radiograph demonstrating free air under the diaphragm is sufficient and should prompt urgent exploration (Fig. 1). In most patients without frank peritonitis or a clear indication to proceed with emergent surgery, computed tomographic (CT) scan of the abdomen and pelvis has become the gold standard. Ultrasonography remains the primary modality to evaluate for biliary or adnexal disease. Intravenous (IV) contrast should always be used and is helpful in characterizing necrosis, inflammation, and delineating abscesses. In most cases, especially those with well-established abscesses, the wall will be hyperemic and "light up" on contrast CT scanning (Fig. 2). With modern contrast agents, there is no concern of renal failure. Oral contrast should be

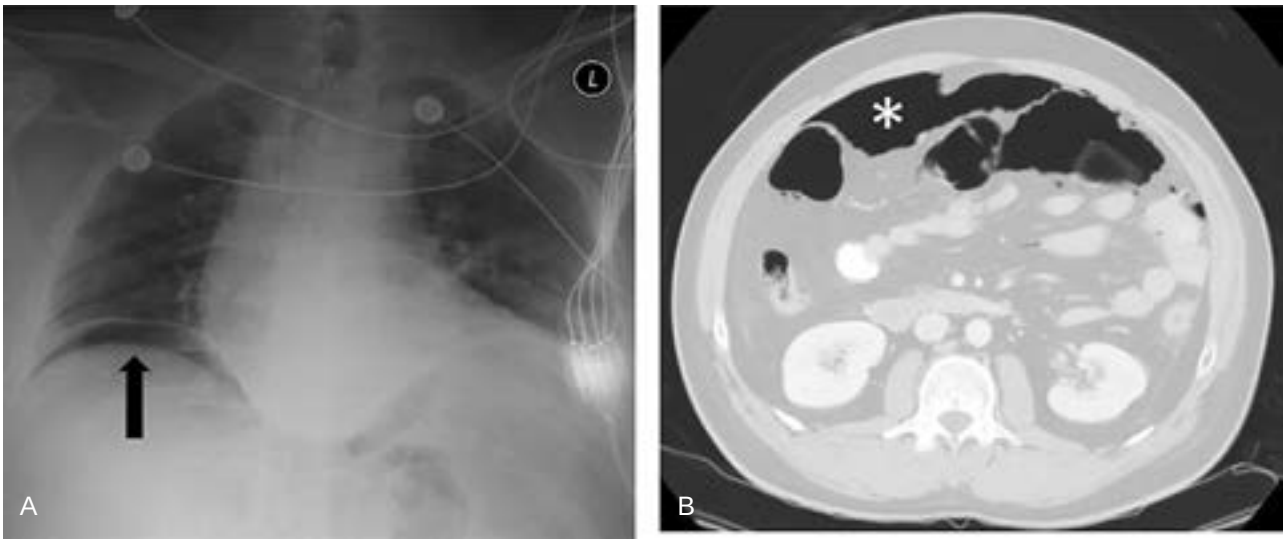


FIG. 1 (**A**) Plain chest radiograph clearly identifying free air under the left hemidiaphragm and over the liver *(arrow)* in a patient with a perforated gastric ulcer. (**B**) Unnecessary CT scan of the patient identifying the free air *(asterisk)*. Of note, the CT scan did not delineate the gastric perforation despite administration of oral contrast.

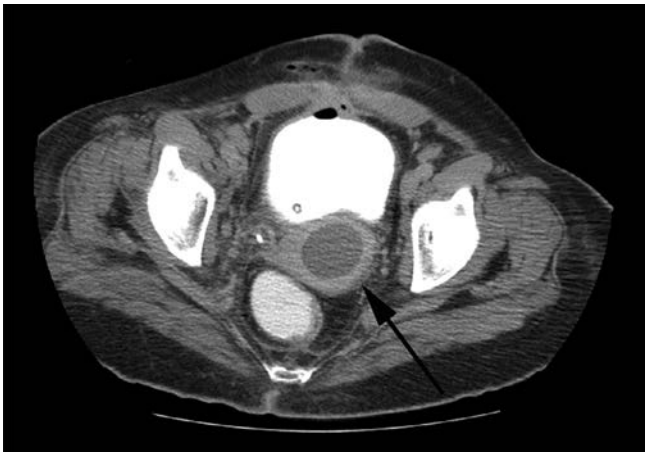


FIG. 2 Pelvic abscess following gunshot wound to the abdomen. Note the thick hyperemic wall of the abscess that is highlighted by the use of intravenous contrast. The use of both intravenous and oral contrast help identifies the abscess and separate it from the bladder (anteriorly) and rectum (posteriorly).

employed when possible. There is no longer any reason to obtain a noncontrast CT scan, and these studies are rarely useful. The administration of oral contrast can help differentiate between bowel loops and intraabdominal fluid collections and can aid in both identifying pathology and planning radiographic intervention. Unfortunately, in patients with a severe ileus, the contrast may not make it out of the stomach or proximal bowel. CT can also identify retroperitoneal collections and may also identify small-volume pneumoperitoneum or pneumatosis intestinalis that may not be seen on plain film.

In the postoperative population, CT scanning before day 5 is often unhelpful in differentiating IAI from postsurgical changes. It is in these patients that clinical judgment is required to ascertain which patients are not progressing in the expected manner. The operative wound should be examined by experienced individuals at least once daily if not more frequently. Although many superficial wound infections are in fact just that, it is not uncommon for a "superficial" wound infection to be the tip of the iceberg of a subfascial or intraabdominal infection (Fig. 3). Although with proper attention



FIG. 3 Right-sided intraabdominal abscess *(star)* that was observed necessitating through the midline laparotomy incision *(arrow)*. This initially presented as a "superficial" wound infection before recognition of the intraabdominal component.

to appropriate administration of prophylactic antibiotics, there has been some success in decreasing overall wound infection rates, one needs to remember that these interventions have no impact on IAI.

Bariatric surgical patients are a unique cohort, and the presentation of an intraabdominal catastrophe in this group can be quite subtle. These patients often present with an unexplained mild tachycardia without abdominal pain. The usual postoperative care of these patients involves defined care plans of early mobilization and oral intake. Deviation from the normal progression, especially in the presence of tachycardia, should prompt rapid investigation for leaks or compromised bowel. Rapid reexploration in the absence of diagnostics before physiologic deterioration will be lifesaving in this group.

MANAGEMENT

Although a myriad of primary pathologies can result in IAI, the principles of management are the same: volume resuscitation, targeted antimicrobial therapy, and source control. Early recognition and aggressive treatment of IAI is paramount as delay in treatment can result in progression to septic shock and death. Workup and treatment should occur simultaneously, and broad-spectrum antimicrobial treatment should be started as soon as an infection is suspected without waiting for cultures to be obtained.

Resuscitation

Patients presenting with IAI have several risk factors for intravascular volume depletion. These include nausea, vomiting, and diarrhea; increased insensible losses from fever and increased respiratory rate; and local and systemic fluid sequestration because of peritonitis. Thus, volume resuscitation is a critical step in the management of IAI. Patients with sepsis with or without shock should be managed in the ICU. A Foley catheter should be placed to monitor urine output and ensure adequate perfusion. Central venous access and vasopressor support may be necessary.

The 2016 Surviving Sepsis Campaign Guidelines recommend several goals for the first 1 to 3 hours of resuscitation: (1) Measuring serum lactate levels and trending if >2, (2) obtaining blood cultures and administering antibiotics within the first hour after presentation, and (3) resuscitating with 30 mL/kg crystalloid for patients with hypotension or serum lactate ≥ 4 mmol/L. Within the first 6 hours, volume status and tissue perfusion in patients should be frequently reassessed, lactate normalized, and vasopressors added for persistent hypotension, defined as mean arterial pressure ≤ 65 mm Hg. Although many patients require at least some resuscitation, this should not delay intervention for source control for more than a short period. Patients with severely altered physiology will never be resuscitated to "normal" values without source control and will lead to delay in potential lifesaving interventions. In these patients, operative source control may be the only way to halt an ongoing process, and resuscitation should be concomitant with the procedure. Thus, the true goal of resuscitation is to restore enough physiology such that these interventions can be undertaken.

Antimicrobial Therapy

According to the Surviving Sepsis Campaign Guidelines, presumptive broad-spectrum antimicrobial therapy should be initiated within 1 hour of diagnosing sepsis. Although optimal antimicrobial therapy for the management of IAI is in continuous evolution, several published guidelines synthesize high-quality evidence to assist in the selection of appropriate agents, including revised guidelines published by the SIS in 2017. These guidelines recognize challenges such as an aging population with more comorbid conditions as well as the increasing prevalence of resistant bacteria and fungi. Categorizing patients into low-risk CA-IAI, high-risk CA-IAI, and HA-IAI can guide antibiotic selection, as shown in Figure 4. For low-risk

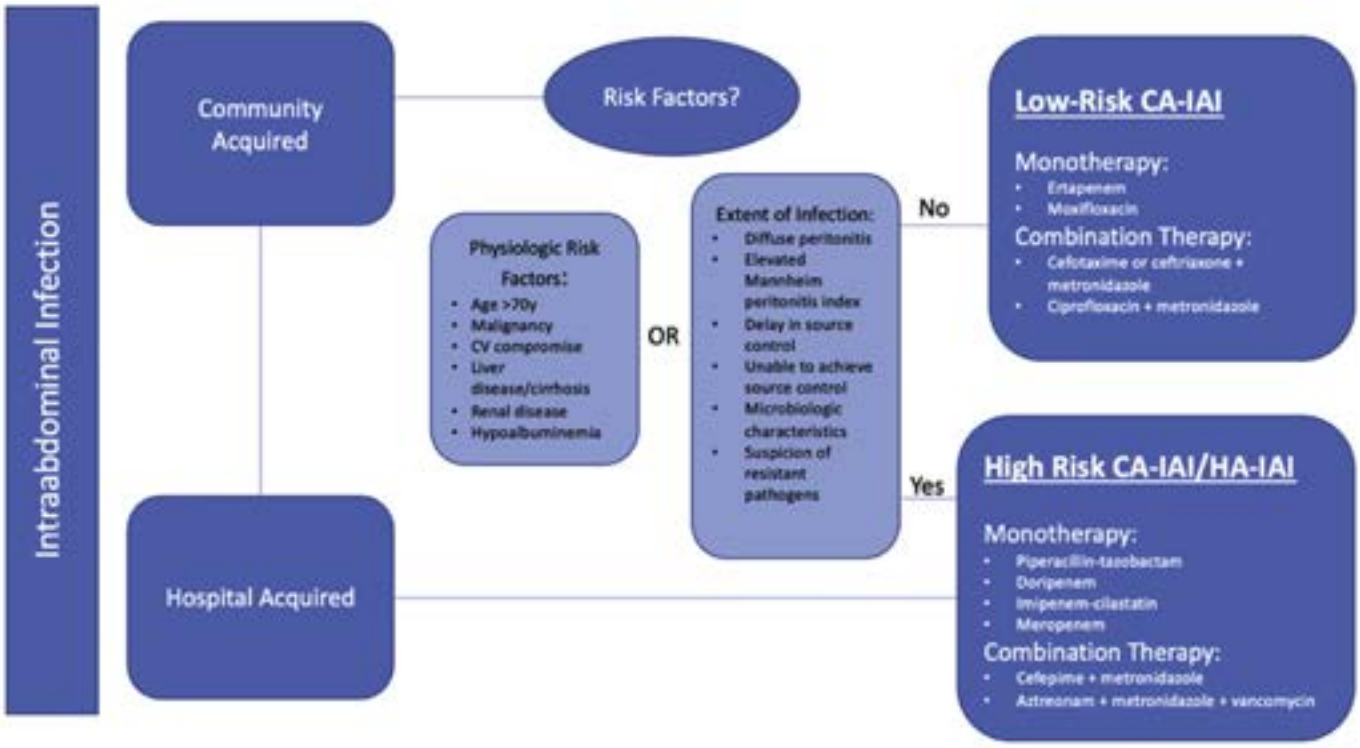


FIG. 4 Algorithm for initial presumptive antibiotic choice for intraabdominal infection based on location and risk factors.

CA-IAIs, presumptive treatment with a single agent that covers gram-negative Enterobacteriaceae, aerobic streptococci, and obligate anaerobes is appropriate. Routine coverage for pseudomonas, enterococcus, or fungus is not recommended in this low-risk population. Some patients with high-risk CA-IAIs will be infected with organisms resistant to the narrower-spectrum antimicrobials used in lower-risk patients; therefore, antimicrobials with broader activity are recommended. The routine use of antifungal agents is not recommended outside of critically ill patients with an upper gastrointestinal source. Those patients with HA-IAI are at increased risk for infection from resistant or opportunistic organisms. Each patient with HA-IAI should be assessed for their risk of infection with *Enterococcus* spp., methicillin-resistant *Staphylococcus aureus*, resistant gram-negative bacilli, and *Candida* spp. Both patient history of resistant infection and local antibiotic susceptibility mapping should be considered in choosing an appropriate antimicrobial regimen. In all cases, antimicrobial therapy should be deescalated to the agent most appropriate for the organism being treated as soon as culture data are available. A subset of patients will display a prolonged systemic inflammatory response despite adequate treatment of the causative organism. This response is more a reflection of host immune activity than an indication of the persistence of viable microorganisms and is best treated with supportive care rather than antibiotic escalation in the face of negative cultures.

The duration of therapy is another important consideration. Historically treatment has continued until all evidence of systemic inflammatory response has resolved—often a period of 7 to 14 days. More recently, a shorter course of therapy has been favored. Evidence suggests that with adequate source control, a 3- to 5-day course of antimicrobial therapy is sufficient for cure and may decrease the risk of antimicrobial resistance. Joint guidelines by the SIS and the Infectious Diseases Society of America recommend a 4- to 7-day duration of therapy provided appropriate clinical response.

Sawyer et al. conducted the Study to Optimize Peritoneal Infection Therapy (STOP-IT), which randomly assigned patients to compare a fixed short course of antibiotic therapy (4 +/– 1 day) to a traditional strategy of therapy lasting 2 days past the resolution of systemic inflammatory response, for a maximum of 10 days. They reported similar rates of surgical site infection, recurrent intraabdominal infection, and death, with a median duration of therapy of 4.0 days in the experimental group and 8.0 days in the control group. Infectious complications were the most prevalent, occurring in over 20% of patients in either group. Recurrent intraabdominal infections were most common despite the duration of initial antimicrobial therapy. Thus, we strongly endorse shorter courses of antibiotic treatment.

In addition to utility in identifying bacterial sepsis and predicting mortality, procalcitonin has also shown to have value in individualizing duration of antibiotic use. A recent Cochrane Review reported that using procalcitonin levels to guide initiation and duration of antimicrobial therapy lowered not only antibiotic consumption and risk for side effects, but also mortality. This not only has implications for antimicrobial stewardship in limiting unnecessary antibiotic exposure, but it may also have an economic impact in reducing the overall cost of sepsis care.

Source Control

Source control is defined as any procedures that remove the foci of infection, eliminate factors promoting ongoing infection, and restore normal physiologic function. The majority of IAIs require either a surgical or interventional radiology intervention in addition to antimicrobial therapy. The choice of operative versus nonoperative intervention will depend on the underlying pathology and the clinical status of the patient. The decision to pursue primary nonoperative management for a patient with an IAI *must* be made in concert with a surgeon, and surgeons should remain actively involved in the decision making. The least invasive approach that provides adequate control is preferred. However, as detailed later, the degree of intervention depends on the extent of the underlying process, the degree of physiologic derangement, and available resources. Although it is

seductive to attempt to limit the scope of intervention in patients who are frail or have higher illness severity (APACHE ≥15), extensive comorbidities, or poor nutritional status, it is this group of patients that will not tolerate delays or inadequate source control.

Once a need for intervention has been established, the time to intervention becomes critical. Source control should proceed immediately. Many IAIs can be treated using percutaneous drainage under either CT or ultrasound guidance. Despite improvements in imaging technology and the expertise of interventional radiologists, the general principles for successful drainage have not changed. Absolute necessities include a window in which to drain the collection and material that can be drained though a catheter. Well-localized collections, especially in patients without diffuse peritonitis, are ideal candidates for percutaneous drainage and appropriate antibiotics (Fig. 5). This can even include those with small amounts of localized free air. Examples of infections that are usually amenable and well handled by percutaneous drainage include subphrenic abscesses after splenectomy, pelvic abscess following perforated appendicitis, and diverticulitis with localized abscess (Hinchey class 1b or 2). Loculated or multiple abscesses are not necessarily contraindications to percutaneous drainage. However, these authors have observed patients being treated with three or four or more percutaneous drainages over several weeks to "spare the patient an operation." In many of these cases, one open operation would have taken care of the problem easier, more expeditiously, and at a lower cost. Patients with poorly localized or diffuse collections, necrotic tissue, or inaccessible collections require open operative intervention. Patients with diffuse peritonitis or massive amounts of free air require immediate surgery. Inadequate initial source control significantly increases mortality, and there should be a low threshold for operative exploration if clinical status fails to improve if percutaneous intervention was attempted initially.

The operation performed should be based on the extent of the infection, the organs involved, and the patient's physiologic status. There is no doubt that a significant amount of surgical pathology that was formerly treated by open laparotomy can now be accomplished by laparoscopic techniques, and this modality is now the standard for many disease processes. Minimally invasive techniques to drain diverticulitis and other abscesses are commonly performed. In the case of pancreatic necrosis, for example, minimally invasive retroperitoneal necrosectomy is the approach and procedure of choice. Initially, there was some concern of spreading localized infection throughout the peritoneal cavity, but with experience, this fear has lessened somewhat. It should be recognized that patients with deranged physiology from abdominal sepsis will not tolerate the pneumoperitoneum and alteration in hemodynamics that accompany laparoscopic surgery. Significant abdominal distention may also make laparoscopic approaches impossible. Thus, open surgery remains the preference for this group.

As with most surgical cases performed either open or laparoscopically, complete dissection and identification of the pathology is an absolute necessity to affect proper therapy. Drainage of an intraabdominal abscess while failing to identify a necrotic intestinal segment or anastomotic disruption is of no benefit to the patient. The groups of patients that require operative intervention for IAI are often sicker and more complicated. These cases can be exceedingly challenging, and even senior surgeons can often benefit from another experienced pair of hands in the operating room. For less experienced surgeons, liberal consultation and collaboration with senior partners can also help in the overall intraoperative decision making. Once the anatomic problem is identified, the goal is to achieve source control. If source control can be obtained at the index operation, there is no need for planned reoperation; however, damage control techniques may be necessary in unstable, critically ill patients or those with evolving ischemia and tissue loss. In patients undergoing large-volume resuscitation, abdominal compartment syndrome must be considered and promptly treated when encountered.

In patients with intraabdominal infection without an obvious gastrointestinal perforation, unroofing of all abscess cavities and collections is all that is required. Intraoperative cultures should be performed and transported immediately to the laboratory. It is always unfortunate to perform these procedures in the middle of the night only to find out that the "negative cultures" of obvious purulence did not make it to the microbiology laboratory until sometime the next day. In patients without any definable residual abscess cavities, there is no need for drains. In fact, drains in this situation are more often associated with subsequent infection than no drainage.

In our estimation, drains are often placed poorly and exit the abdominal wall wherever it is convenient. In other words, almost all drains are of the closed-suction variety; therefore, little thought is often given to drain placement, assuming that the suction will allow for drainage in all circumstances. Although it may be true in concept, it is not always accurate in practice. Suction bulbs become filled, resulting in a loss of suction; tubing may be kinked by patient positioning, its egress from the abdominal wall, or even the dressing itself. Additionally, consideration should be given to how the drain is brought out through the abdomen once the laparotomy incision is closed. One must always remember that the drain exit site will ultimately end up several inches more medial when the abdomen

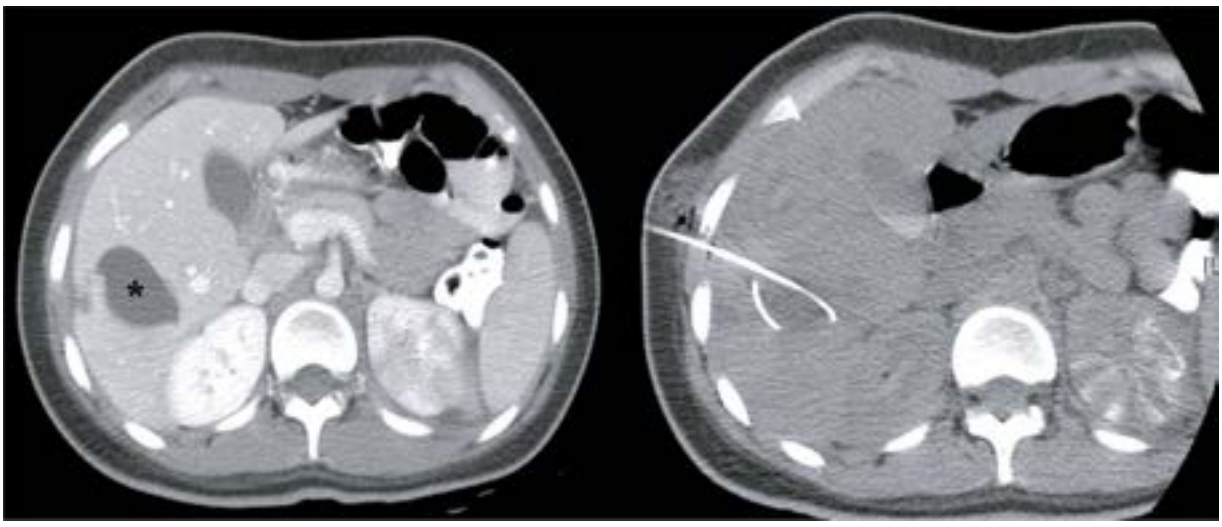


FIG. 5 Clear path for draining a unilocular intrahepatic abscess after liver trauma.

is eventually closed. This can result in a loss of the "direct" path of the drain and can further decrease efficacy. We believe and teach that placement of drains in a more "gravity-friendly" fashion with more lateral exit tracts will result in shorter and more direct drain paths and can even aid closed-suction drainage. In addition, we do not advocate large, sump-type drains. These drains often come with filters that are quickly clogged with serum and particulate matter, rendering the sump feature of the drains nonfunctional. If the material is too thick to be drained through a closed-suction drain, it is also likely to clog a sump drain. In these circumstances if sump drainage is employed, we have utilized a short course of continuous irrigation either through one of the sump ports or through a second drain. Lastly, all current drains on the market are made from silicone or a similar nonreactive material. As such, they induce little or no inflammation; they will not form a tract. Although in most cases this is beneficial, there are times when one is relying on the inflammation induced by a latex or rubber drain to "seal the area" and control the infection (Fig. 6).

When the genesis of the infection is related to a break in the gastrointestinal tract, source control involves eliminating or controlling the ongoing contamination. The two overriding concepts in these circumstances are: Do not make the existing hole in the intestine larger, and do not create any new (unnecessary) holes. Although on the surface these concepts appear obvious, the compulsion to put "just one stitch" in a leaking inflamed anastomosis in the face of gross peritonitis can sometimes be irresistible. This approach is doomed to failure and will most assuredly lead to further breakdown, a larger hole, and a bigger problem. The complexity of entry into the abdomen itself along with the actual dissection toward the primary pathology should not be underestimated. Creation of inadvertent enterotomies can occur but must be recognized and treated, and one must critically decide how they should be handled similar to the primary pathology.

In most cases, intestinal perforation in the face of peritonitis is best treated by resection of that segment of bowel. One exception to this is perforated duodenal ulcers, which are treated by graham patch. Perforation in the body of the stomach can be closed primarily followed by imbrication using Lembert sutures as there is abundant gastric tissue to cover a suture line. In the proximal small bowel, resection is usually followed by anastomosis, whereas in the distal small bowel and colon, one must consider the risk-to-benefit ratio of performing an anastomosis against creation of a stoma. If one chooses to restore intestinal continuity, it is necessary to use bowel that is not involved in the inflammatory process. Although there have been many studies demonstrating equivalence between stapled or hand-sewn anastomosis in elective procedures, there is some suggestion in emergent surgery and multiple trauma, especially, to suggest that hand-sewn anastomosis may be superior. In any event, when faced with peritonitis and bowel edema, it is our preference to perform only hand-sewn anastomosis. The decision to perform an anastomosis must also account for the patient's physiologic status and the risk of failing to achieve source control. There is a surgical truism that the anastomosis never created will never leak. Although a stoma commits the patient to a subsequent operation, surviving intraabdominal infection and sepsis should be considered a success and an acceptable trade-off. In patients with gross peritonitis, pressor requirements, and hemodynamic instability, a truncated procedure (i.e., damage control) should be employed. This allows the surgeon to eliminate the source of infection and provide ongoing resuscitation in a more controlled environment such as the ICU. During the subsequent operations, hopefully in a much less hostile abdomen, one can plan a more definitive approach to control infection and restore intestinal continuity.

There are also circumstances in which a bowel resection or revision of an anastomosis is not possible. Some examples include duodenal stump blowouts, associated phlegmons compromising surrounding vascular structures, "frozen" abdomens, or pancreaticoduodenal anastomotic leaks. In these types of cases, the goal is controlling the effluent to create a controlled fistula while allowing the inflammatory and fibrotic process to "scar" over the problem. An important part of the management is the use of latex or red rubber drains placed in the lumen of the intestine. This allows both drainage and enhances the inflammatory process. T-tubes can be particularly useful as they are not prone to inadvertent removal. Liberal use of suction drains in proximity to these processes and placed as outlined earlier will further capture the effluent not coming through the latex drains. This drain strategy combined with appropriate nutritional support will lead to a controlled fistula that will often allow the clinician to remove the latex drains at a much later time when the infection and inflammation have subsided (see Fig. 6).

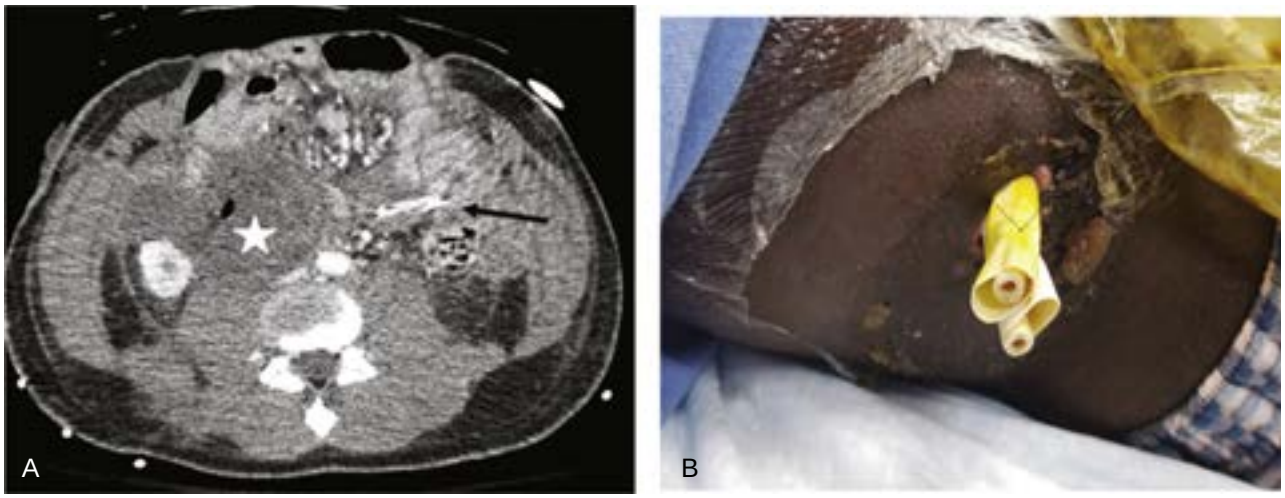


FIG. 6 Patient with an extensive retroperitoneal and pelvic abscess from an anastomotic leak in a "frozen" abdomen. (**A**) CT scan shows extent of the abscess/collection with air *(star)*. A portion of a percutaneous drain that failed to drain the thick material can be seen on the left *(arrow)*. The abscess was accessed through a left-sided retroperitoneal approach to provide straight drainage. Latex Foley catheters surrounded by Penrose drains allowed both irrigation, suction, and passive drainage. Over a period of 2 weeks, the fistula closed. (**B**) After 6 weeks, the drains were cut close to skin level and slowly backed out, and the entire cavity closed down aided by extensive inflammation from the latex drains.

CONCLUSION

IAI is a commonly encountered pathology in general surgery with a common treatment algorithm despite multiple potential sources of infection. All patients with IAI should undergo adequate fluid resuscitation with the goals of lactate clearance and maintenance of mean arterial pressure >65. Vasopressor support should be promptly initiated for patients with persistent hypotension despite volume resuscitation. Appropriate broad-spectrum antibiotics should be initiated without delay, and antimicrobial therapy should be tailored according to cultures. Source control is paramount. Although percutaneous drainage may be sufficient, patients with ongoing contamination or who fail to improve should undergo operative exploration. Once adequate source control has been obtained, antibiotic duration should be critically assessed, and shorter courses are preferred.

SUGGESTED READINGS

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Epidemiology, Prevention, and Management of Occupational Exposure to Bloodborne Infections

Ethel D. Weld, MD, PhD, and Shmuel Shoham, MD

INTRODUCTION

Each year, there are 600,000 to 800,000 reported cases of occupationally related percutaneous injuries among US healthcare workers (HCWs). The pooled global annual prevalence of percutaneous injuries in HCWs is 36.4% (95% CI, 32.9–40.0), and the highest 1-year prevalence by job category is found in surgeons (72.6%; 95% CI, 58.0–87.2). Human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) are by far the most important bloodborne pathogens to which HCWs might be exposed. At one academic medical center, on the general surgery service, 20% to 38% of operative cases were found to involve patients infected with HIV, HBV, or HCV. This chapter will focus on these three viruses. With careful attention to the epidemiologic risks at hand, knowledge of current guidelines, and timely evaluation by clinicians with expertise on the topic, the harm from such exposures can be minimized or averted entirely. Major gains have been made over the past several decades in prevention of occupational bloodborne infection transmission. Safety engineering of medical equipment has reduced sharps injuries, robust universal HBV vaccination programs have reduced the number of occupationally acquired cases of HBV from 17,000 annually in 1983 to 263 cases in 2010, and occupationally transmitted HIV has been all but eliminated in the United States. Nonetheless, occupational exposures remain a common problem, and complacency must be avoided.

Although exposure can happen at virtually any site where healthcare is delivered, there are certain scenarios in which risk is particularly high. Per procedure, the rate of blood contact has ranged from 3% of all procedures performed by interventional radiologists to as high as 50% of procedures performed by surgeons at one center in Milwaukee, Wisconsin. Percutaneous injuries are most commonly (in 73% of cases) related to suturing and are especially associated with gynecologic surgeries. Sharps injuries are twice as common at teaching hospitals compared with nonteaching facilities; the operating room and postanesthesia care units are the highest-risk settings. Junior clinicians with less experience and/or who are fatigued are most likely to be exposed. Nurses are at highest risk, accounting for nearly one-half of cases, followed by residents, fellows, and attending surgeons. In one national academy meeting for orthopedics, 87.4% of the surveyed surgeons reported that they had sustained blood-to skin contact and 39.2% reported that they had sustained percutaneous contact within the past month. The annual rate of percutaneous exposure for trainees is ~20%, and nearly all (99%) surgical residents sustain at least one needlestick injury by the end of their training, with a mean of 7.7 total injuries sustained by the fifth postgraduate year.

Victims of such exposures often experience a range of emotions such as anxiety, fear, embarrassment, anger, and a sense of betrayal by the profession to which they have devoted themselves. Some develop posttraumatic stress disorder. Only about one-half of exposures are actually reported. Reasons include fear of reprimand, concerns regarding confidentiality, and time constraints. Institutions must ensure that staff and trainees are knowledgeable about what to do to following an exposure and that practical mechanisms are in place to expeditiously access care. Occupational health practices that interface with surgeons directly in or immediately outside of operating rooms are a practical stopgap measure while working to change a surgical culture that strongly discourages scrubbing out of cases at the time of needlestick. Champions for improving surgical trainee safety can and should include attending surgeons at the highest levels, particularly those present in the operating room at the time of injury.

Per-exposure transmission of bloodborne pathogens are very low across populations of HCW as a result of decades of concerted effort and policies to safeguard the occupationally exposed. Complacency about risks of bloodborne disease must be vigilantly guarded against, both from an employee and patient safety perspective. Furthermore, HCWs facing an accidental needlestick or other percutaneous injury should rightly be far less concerned with population health statistics than with the *individual* particularities of the *exact* source patient, the virus(es) involved, and their particular circumstances. For example, HBV cannot be transmitted to HBV-immune individuals, which is reassuring in the era of universal HCW HBV vaccination.

However, 10% to 20% or more of vaccinated individuals are immune nonresponders and are often not aware of this; thus, they are at risk of acquiring HBV at work. The decision about reporting and managing exposures should be taken out of the hands of the exposed individual, who is likely to be distracted by external stressors.

EPIDEMIOLOGY

Assessment of an occupational exposure to bloodborne infection should start with an assessment of the level of risk of the individual exposure. Knowledge of the relative risk of infectious transmission after an exposure can often be reassuring to the exposed individual (Boxes 1 and 2).

The following factors are critical determinants of whether transmission will occur after exposure to a bloodborne pathogen:

1. *The pathogen:* HBV is the most transmissible bloodborne pathogen. Following percutaneous exposure in an unvaccinated individual, the rate of developing clinical hepatitis can reach 30%, with serologic evidence of HBV infection twice that. By contrast, rates for HCV and HIV are approximately 0.2% and 0.3%, respectively.
2. *The inoculum* (determined by the following factors):
   - Amount of circulating virus in the source patient's body:
     - Patients with HBV- and eAg-positive status (HBeAg+ is a sign of significant viral replication) are more likely to transmit virus than are those with eAg-negative status.
     - Patients with advanced HIV infection and high viral loads are more likely to transmit virus than are those with undetectable viral loads. However, transmission is still possible, even when the source patient is on antiretroviral drugs.
   - The source fluid: Blood, having the highest concentrations of transmissible bloodborne viruses, is the most important fluid. Semen, vaginal fluid, CSF, breast milk, pericardial fluid, synovial fluid, and pleural fluid can also transmit HIV but are less common in the healthcare setting. Unless visibly bloody, saliva, urine, vomitus, feces, nasal or respiratory secretions, sweat, and tears will not transmit HIV and rarely transmit HBV or HCV. Ebola, which is also considered a bloodborne infection, can also be transmitted through feces and vomitus and possibly saliva and tears.
   - Needlestick injuries with hollow-bore needles that were placed within the vein or artery of a source patient carry the highest risk for transmission.
3. *The site of exposure:* The most important site is percutaneous, particularly with deep tissue injury. Bloodborne infections can also be transmitted through mucous membrane and across nonintact skin barriers. In human bites, it is imperative to consider that *both* the biter and the victim may have been exposed to bloodborne pathogens.
4. HCW's level of protective immunity:
   - Immunocompromised HCWs are at higher risk for acquisition of bloodborne pathogens.
   - Immunocompetent HCWs who have received ≥3 doses of the HBV vaccine series and have achieved anti-HBS levels of ≥10 mIU/mL (vaccine responders) are protected against infection. This vaccine is mandatory for all HCWs, and approximately 90% attain seroprotective levels with vaccination. Immune titers do wane over time.

BOX 1 Factors That Increase the Risk of Transmission of All Infectious Bloodborne Pathogens

1. *High-risk exposure:* Percutaneous, mucous membranes exposed, nonintact skin exposed, bites with blood exposure, visible blood on device, deep injury, large volume, hollow needles, blood from vessel
2. *High-risk body substance*: Blood, *bloody* fluid, potentially infectious tissue
3. *High-risk source patient:* Hepatitis B virus surface antigen (HBsAg)+, HCV Ab+ with HCV RNA PCR at high levels, HIV Ab+, HIV RNA PCR at high levels, injection drug use, clinical or epidemiologic risks, advanced disease (likely a proxy for high viral load in HIV)

BOX 2 Relative Average Risk of Infectious Transmission After Percutaneous Exposure to Blood (Based on Aggregate Data)

By source patient serostatus:

HBV sAg+: risk varies according to e-antigen positivity (directly confers infectiousness)
- HBeAg+: 37%–62% transmission risk per exposure*
- HBeAg-: 23%–27% transmission risk per exposure*

HCV: Historically risk of transmission after percutaneous exposure has been reported as **1.8%, newer data suggest risk is much lower (0.2%)**
- HIV co-infection in source point may increase risk of HCV transmission
- One study only found transmission (1.2%) with hollow-bore needles

HIV: **0.33% transmission risk** for a percutaneous exposure (1 in 300)
- 0 cases reported after intact skin exposure
- 0.23%–0.36% transmission risk from needlestick injury
- 0.03%–0.09% transmission risk for a mucocutaneous exposure (~1 in 1000)

*Healthcare worker not HBV immune at time of exposure.

At the time of exposure, it is not always known whether the source patient is infected with a bloodborne pathogen. Exposure to blood or infectious fluids of a patient with known HIV or hepatitis is one situation, the management of which is discussed later. Exposure to blood or infectious fluids of a patient whose infectious status is unknown is a separate scenario in which the risk of transmission of infectious illness reflects the risk of undiagnosed infection in the general population and the particular population that a given hospital or healthcare setting serves.

The following statistics are relevant in this regard:

1. In the general US population, an estimated 1.1 million people are living with HIV, of whom 15% are unaware of their infection; in the youth population, among 13- to 24-year-olds, 51% are unaware that they have HIV.
2. HIV transmission risk is increased when the virus is detectable in the source patient's blood; therefore, it is highly relevant that only 49% of the US population living with HIV have achieved and sustained viral suppression.
3. In the United States, 847,000 people are chronically infected with HBV. It is estimated that about one-fifth of those infected with HBV in the United States are unaware of it. HCV infects 3.5 million persons in the United States, of whom approximately 50% are unaware of their infection.
4. Efforts to increase diagnosis of all three infections in the general population are underway. Routine screening of all individuals between 15 and 65 years of age for HIV and all individuals born between 1945 and 1965 (or in other age groups but with HCV risk factors) for HCV is now recommended by the CDC and the US Preventive Services Task Force.

PREVENTION

In general, robust efforts at prevention of occupational exposures to bloodborne infections should include universal HBV vaccination for all HCWs, education of personnel, and protection with universal precautions including using eye shields and gloves (double-gloves when necessary), rigorous procedure training, eliminating needle recapping, and minimizing exposure to sharps. Interventions that enable this include vigilant use and regular emptying of sharps containers and engineering fixes such as needleless devices, autoretracting needles, and safety lancets, among others.

Management of Any Exposure to Bloodborne Infection

Postexposure Immediate Care

Cleansing the Affected Area

Once an occupational exposure has occurred, fastidious local wound care should be performed as follows:

- Cleanse the wounds (scrub with soap and water in a prolonged, thorough fashion).
- Use alcohol-based agents on the exposed area.
- Flush any exposed mucous membranes with water.
- Flush the eyes with water, if exposed.
- Avoid the use of bleach or caustic products, which can further irritate and abrade skin.
- There is no evidence that squeezing or milking the site helps.
- At minimum, after a percutaneous injury that occurs through a surgical glove, surgeons should deglove and reglove, and follow standard protocols for when sterility is breached.

Management of an HIV Exposure

Testing the Source Patient

- Rapid HIV-1 and HIV-2 testing should be performed on the source patient's serum (rapid tests on oral secretions or blood are often available that have a less than 20-minute turnaround time).
- The window period of detection of HIV is 2 weeks after acute infection (fourth-generation HIV Ag/Ab testing may be followed with HIV RNA PCR if the source patient is high risk or had a recent high-risk exposure).
- The recent history and clinical picture of the source patient should be investigated, with particular attention to whether there is any recent syndrome that could be consistent with acute HIV (e.g., fever, sore throat, rash, headache, fatigue, enlarged cervical lymph nodes). *If yes, HIV RNA PCR should be ordered.*
- Negative predictive value >99% for negative rapid HIV test.
- In cases in which there is incomplete or missing data on the source patient, the exposed person should be actively involved in the decision-making process. Sometimes postexposure prophylaxis (PEP) is withheld in situations of epidemiologic low risk. However, often in these scenarios of incomplete information, the exposed person chooses to proceed with taking PEP, as the potential benefits likely outweigh the risk, even in situations of low risk.

Postexposure Prophylaxis

Evidence for PEP efficacy in HIV is derived from animal models, retrospective human data, and analogies from mother-to-child transmission studies (prevention of mother-to-child transmission). The antiretroviral regimens available today are far better tolerated and more potent than the earlier zidovudine (AZT)-based regimens. If taken properly, they should reduce the risk of transmission to virtually zero (Table 1).

For effective prevention of transmission, both the timing of initiation and the duration of therapy matter (Table 2). Treatment should ideally be started within 1 to 2 hours of exposure; efficacy drops off after 24 hours and is negligible after 72 hours, so initiation of PEP is not recommended if 72 hours have elapsed (see Tables 1 and 2). The exposed HCW should be counseled to abstain from or practice safe sex until the source patient's HIV serology returns negative. The CDC-recommended regimens for PEP are displayed in tabular form in Box 3. If the source patient is infected with an HIV strain that is known to be resistant to certain antiretrovirals, it is advisable to choose regimens that are active against the source patient's virus. For guidance with the time-sensitive initiation of PEP, the PEP line is a telephone hotline that can be a valuable resource: 888-448-4911 or http://www.nccc.ucsf.edu/.

Failures of Multidrug PEP Reported to the CDC through 2005

- All used ADT or ddI/d4T-based older regimens as PEP.
- All were with hollow-bore needles.

What about exposed pregnant/breastfeeding women?

- Pregnancy does not alter the calculus for PEP. There is risk of transmission to the fetus during acute infection, hence the benefits outweigh the risk.
- There are safe regimens (AZT/3TC + lopinavir has the most safety data in pregnancy).
- Discontinue breastfeeding during the time on therapy (pump/dump).
- Consult with experts in obstetric infection.

Monitoring and Follow-up Care

Follow-up testing for HIV is recommended at 6 weeks, 12 weeks, and 4 to 6 months postexposure. The newer fourth-generation HIV combined p24 antigen/Ab tests detect new HIV infection within 14 days of exposure and will always be positive by 4 months after

TABLE 1 Effect of Zidovudine (AZT) on Prevention of Occupationally Acquired HIV in Humans*

Human Study*	Cases (*n* = 33)	Controls (*n* = 679)
No AZT	24 (73%)	435 (64%)
AZT	9 (27%)	244 (36%)

*Adjusted odds ratio for acquisition of HIV after AZT PEP = 0.2 (0.1–0.5).

TABLE 2 Timing to Tenofovir (PMPA) PEP Initiation and Duration of Treatment Both Affect Efficacy of Prevention of HIV Transmission of SIV in Macaques

TDF Treatment		
Initiation Delay (Hours)	Treatment Duration (Days)	HIV Infected (No.)
–	–	14/14
48	28	0/15
4	28	0/5
24	28	0/9
48	28	2/4
72	28	2/4
24	10	1/4
24	3	3/4

BOX 3 CDC-Recommended Regimens for Postexposure Prophylaxis of HIV[**3]**

Preferred

Tenofovir disoproxil fumarate (TDF)-emtricitabine (FTC)[2] 300 mg/200 mg qd + dolutegravir (DTG) 50 mg PO qd

or

Tenofovir disoproxil fumarate (TDF)-emtricitabine (FTC)[2] 300 mg/200 mg qd + raltegravir (RAL) 400 mg PO BID

Alternative

Elvitegravir (EVG)-cobicistat-TDF-FTC[2] 150 mg/150 mg/300 mg/200 mg qd

or

TDF-FTC 300 mg/200 mg[2] + pharmacologically boosted[1] protease inhibitor (darunavir (DRV) or atazanavir (ATZ) qd[4]

or

Rilpivirine (RPV)-TDF-FTC[2] 25 mg/300 mg/200 mg qd with food

[1]With cobicistat 150 mg or ritonavir 100 mg, to increase levels of protease inhibitor: DRV dose 800 mg daily; ATZ dose 300 mg daily. DRV should not be prescribed to individuals with sulfa allergy, but ATZ may be.

[2]Available as single-tablet coformulations.

[3]For patients with glomerular filtration rate (GFR) <50 mL/min, dose adjustment of TDF and FTC will be necessary, and single-tablet coformulations cannot be used.

[4]Regimens containing both cobicistat and TDF should not be prescribed to anyone with GFR <70 mL/min.

[**]*PEP should be started within 1 to 2 hours from exposure, and transmission-blocking efficacy drops off significantly after 24 hours. PEP should be administered for a total duration of 28 days.* In the United States, the PEP hotline is a useful resource when making decisions surrounding PEP: Telephone: (888) 448-4911.

infection. This is in contrast with the older Ab-based tests in which people sometimes did not seroconvert (test positive) until >6 months after exposure, but all were positive by 12 months. Therefore, fourth-generation HIV Ag/Ab testing is recommended for postexposure monitoring whenever possible.

Management of HBV Exposure

The three-vaccine series for HBV immunization confers 90% protection. Those who have had past natural HBV are also considered to be immune. Persons at risk are those who have not been vaccinated or who have had an inadequate response to vaccine. The highest concentration of virus is found in blood. Virus can also be found in CSF, saliva, semen, and breast milk, but most other body fluids do not contain infectious levels. The incubation period for HBV is 120 days on average from the time of exposure (range: 45 to 160 days).

*Prevention: HBV Vaccination (**Figs. 1 and 2**)*

- Two-dose HEPLISAV-B (Dyna-Vax) HBV vaccine is more effective (95%) than older vaccines. It increases the completion rate as there are only two doses separated by 1 month, and should be considered for unvaccinated or non-seroresponder HCWs exposed to a patient with HBV.
- Older HBV vaccines, such as Recombivax HB (Merck, Kenilworth, NJ), Engerix-B (GSK), Elovac B (Human Biologicals Institute, a division of Indian Immunologicals Limited), Genevac B (Serum Institute), and Shanvac B, are administered in a three-dose series at 0, 1, and 6 months.
- Anti-HBs titers decline to <10 mIU/mL in 30% to 50% of adults 8 to 10 years after immunization.
- Despite this, immune memory in seroresponders remains intact for at least 20 years after immunization.
- It is very rare for prior responders (+ anti-HBsAb after vaccination) to acquire chronic HBV infection.
- It is important to check anti-HBs response after completing the three-vaccine series (5%–19% do not seroconvert afterward).
- Booster doses of HBV vaccine are recommended for nonresponders who do not become HBVsAb positive
- Booster doses of HBV vaccine among known prior responders are *not* recommended

Immediate Management of Occupational Exposure to HBV

1. Verify HBsAb status of the exposed HCW.
   - Ask the HCW if they have been vaccinated against HBV.
   - If HCW gives permission, look up their anti-HBsAb status in the medical record.
   - If HCW is positive for HBsAb (i.e., has confirmatory titers anti-HBs ≥10 mIU/mL), then STOP; there is no need for further intervention regardless of HBsAg status of the source patient.
2. If HCW is unvaccinated, ascertain HBVsAb status of the source patient.
   - Ascertain previous HBsAg and anti-HBsAb for source patient and proceed as follows:
     - **HBsAg unknown** → send HBsAg from source patient
     - **HbsAg positive**
     - Immediately administer **both HBIG 0.06 mL/kg IM × 1** and **HBV vaccine** to HCW
     - [Optional]: Draw HBeAg from source patient to get a sense of the magnitude of transmission risk
     - **HbsAg negative → Optional:** Initiate HBV vaccination series in source patient.
3. If HCW vaccinated, but seroresponse is unknown (i.e., no anti-HBs available).
   - Test HCW for anti-HBsAb
   - **Determine HBsAg status of source patient**
   - **HbsAg positive** → Administer HBIG × 1 PLUS vaccine booster to HCW
   - **HbsAg unknown** → Test source patient for anti-HBs
   - If source patient is anti-HBs positive, no treatment needed
   - If source patient is anti-HBs negative, administer vaccine booster to HCW and check titer in 1 to 2 months
   - **HbsAg negative** → No treatment necessary
4. If HCW vaccinated against HBV but is a known non-seroresponder after vaccination (HBsAb negative; anti-HBs <10 mIU/mL)
   - Determine HBsAg status of source patient
   - HBsAg positive → Administer HBIG × 2 (separated by 1 month) and HBV vaccine
   - HBsAg unknown
   - Test source patient for anti-HBsAb
   - If source patient anti-HBsAb positive, no treatment needed
   - If high risk, treat as though HBsAg positive
   - HBsAg negative → No treatment needed

Management of HCV Exposure

Because 20% to 50% of cases of acute HCV spontaneously clear, it is important that HCV Ab positivity be followed by HCV RNA PCR to confirm that the source patient indeed has chronic HCV rather than spontaneously cleared HCV with residual antibody positivity.

Appropriate management of HCV exposure depends on the status of the source patient, as follows:

Healthcare personnel status	Postexposure testing		Postexposure prophylaxis		Postvaccination serologic testing
	Source patient (HBsAg)	HCP testing (anti-HBs)	HBIG	Vaccination	
Documented responder after complete series (≥3 doses)	**No action needed**				
Documented nonresponder after 6 doses	Positive/unknown	–	HBIG ×2 separated by 1 month	–	No
	Negative	**No action needed**			
Response unknown after 3 doses	Positive/unknown	<10 mIU/mL	HBIG×1	Initiate revaccination	Yes
	Negative	<10 mIU/mL	None		
	Any result	≥10 mIU/mL	**No action needed**		
Unvaccinated/incompletely vaccinated or vaccine refusers	Positive/unknown	–	HBIG×1	Complete vaccination	Yes
	Negative	–	None	Complete vaccination	Yes

FIG. 1 Postexposure management of healthcare personnel after occupational percutaneous and mucosal exposure to blood and body fluids, by healthcare personnel HepB vaccination and response status. *(From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices*. MMWR Recomm Rep. *2018;67[No. RR-1]:1–31.)*

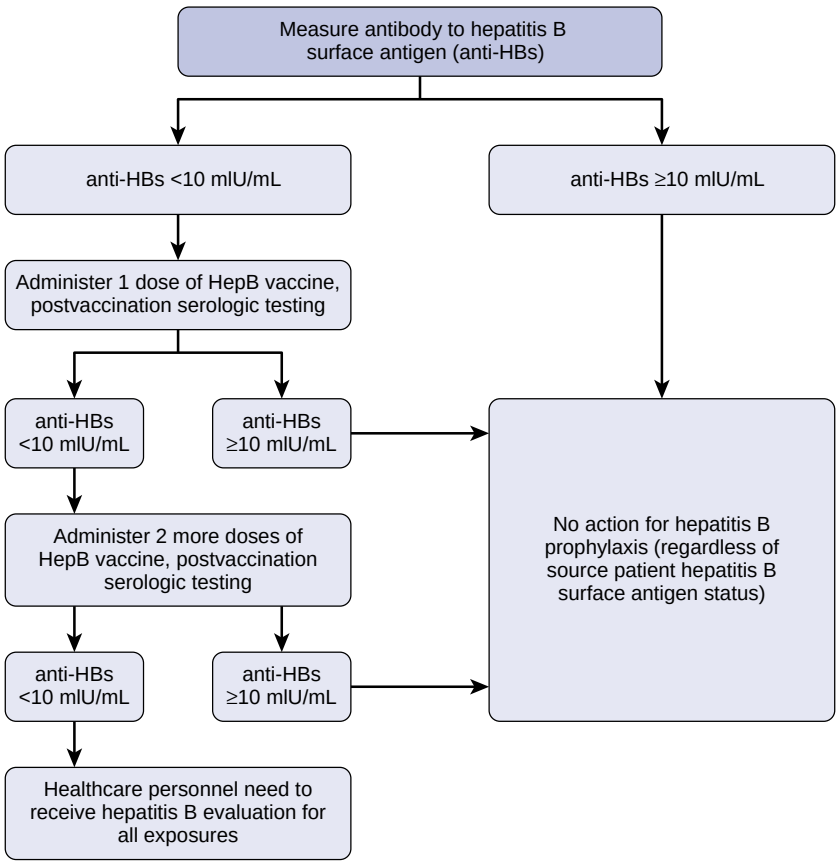


FIG. 2 Algorithm for conducting preexposure evaluation for healthcare personnel who previously received at least three doses of HBV vaccine series but have not yet had postvaccination serologic testing. Should be performed 1 to 2 months after last vaccine dose using a quantitative method (e.g., ELISA) to detect protective concentrations of anti-HBVs Ab titers ≥10 mIU/mL *(Modified from Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices*. MMWR Recomm Rep. *2018;67[No. RR-1]:1–31.)*

If HCV RNA undetectable:

- Source patient previously treated and cleared, *or*
- Source patient independently cleared HCV
- HCW *not* at risk for acquiring HCV

If HCV RNA detectable:

- Source patient is at risk for transmitting HCV to HCW

If HCV Ab positive:

- Check to see if HCV RNA has previously been ordered, to determine chronicity
- If no HCV RNA available, order HCV RNA PCR

If source patient is of unknown HCV status:

- Draw HCV Ab
- HCV Ab should be followed by HCV RNA PCR if positive
- If high-risk patient, can draw HCV RNA PCR with initial draw

If source patient has chronic HCV (HCV Ab AND HCV RNA +), exposed HCW should have:

- HCV Ab test and liver function tests at baseline (time of exposure) and at 6 months postexposure
- HCV RNA at 4 to 6 weeks postexposure

HCV will spontaneously clear in 20% to 50% of patients by 6 months. The American Association for the Study of Liver Diseases and Infectious Diseases Society of America joint guidelines on acute HCV recommend that the patient and their clinician jointly decide whether a delay in treatment initiation while monitoring for spontaneous clearance is favored, and even if the decision is instead to initiate treatment during acute infection, monitoring HCV RNA first for a minimum of 12 to 16 weeks before starting treatment is recommended. In such cases, the same HCV regimens used for chronic HCV are used for acute HCV, are safe and well-tolerated, and are >99% likely to result in cure. However, we advocate treatment of acute HCV for HCWs who are found to have HCV RNA positive at 4 weeks postexposure. (The risk-benefit ratio favors this, especially with regard to minimizing the impact on the HCW, their potentially exposed family, and their patients over the period of high HCV viral load.)

No preexposure or PEP for HCV is currently recommended.

- Immune globulin not recommended by CDC
  - Little evidence that humoral response critical in clearance
  - No efficacy in chimpanzees to prevent infection
- Interferon (IFN) +/– ribavirin not recommended
  - Toxic
  - IFN may only be effective in established infection
  - No effect in (underpowered) Japanese study
- ***Early identification and treatment of infection offers best course of action currently for occupationally acquired HCV.***

Suggested Readings

American Association for the Study of Liver Diseases and Infectious Diseases Society of America joint guidelines on management of acute hepatitis C infection. Available at: https://www.hcvguidelines.org/unique-populations/acute-infection.

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Antifungal Therapy in the Surgical Patient

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Fungal infections in the surgical patient may present from the community or nosocomially through extended hospitalization. Patient populations grow increasingly complex, and an understanding of fungal pathogens, patient characteristics, and pharmacology becomes critical to provide optimal care. *Candida* species remain the most common nosocomial fungal pathogen; however, advances in fields such as oncology or organ transplantation have led to increasing populations of immunocompromised patients with increased risk for less commonly encountered organisms such as *Cryptococcus,* mucormycosis, or *Fusarium.* Fungal identification may be delayed, and surgeons frequently encounter patients with significant risk factors such as central venous catheters, burns, trauma, or critical illness. Noninvasive fungal infections typically carry a low risk for complications and may be cured with empiric regimens. Invasive fungal infections, on the other

hand, often require surgical intervention and microbiologic identification with susceptibility testing. These patients often require multidisciplinary care including specialists in infectious diseases, infection control, skilled nursing, or pharmacology, particularly for uncommon fungi, relapsed/refractory disease, or resistant organisms. This chapter focuses on fungal pathogens that may be encountered and provides an overview of available systemic antifungal agents. Additional readings and guidelines are provided for the interested reader. Table 1 reviews the most common fungal infections with primary and alternative treatment regimens, but each patient requires individualized care based on their presentation and response to therapy.

SPECIFIC FUNGI

Candida, Yeastlike Organisms, and Dimorphic Fungi

Candida

Candida species are undergoing rapid taxonomic change but are the most common fungal pathogens. For the purposes of this chapter and in most clinical microbiology laboratories, *Candida* will still be utilized, but laboratories and testing systems may report new taxonomic names in the future. These species, particularly *C. albicans,* are commensal flora of the human gastrointestinal (GI) tract, genitourinary (GU) tract, and skin. They may colonize other sites, such as the respiratory tract, in hospitalized patients or those with risk factors. When isolated from nonsterile sites in an asymptomatic patient, they may represent colonization. *Candida* in blood cultures should never be considered a contaminant and warrants further evaluation for metastatic disease and treatment. Limited *Candida* cystitis, vulvovaginitis, or cellulitis is usually caused by local overgrowth or alterations to local microbiota resulting from patient factors, such as diabetes mellitus, antecedent antibiotic use, or corticosteroids. Oropharyngeal or esophageal infection may also occur with immunosuppression. In an otherwise immunocompetent host, investigation for immune deficiency such as human immunodeficiency virus (HIV) should be performed.

Complications of invasive *Candida* infection include endophthalmitis, endocarditis, osteoarticular disease, meningitis, or visceral

TABLE 1 Patient Types and Treatment Options for Fungal Infections

Infection	At-Risk Patients	Primary Treatments	Alternative Treatments	Duration of Therapy	Comments
Oropharyngeal candidiasis	Immunocompromised, radiotherapy, diabetes mellitus, corticosteroid use, ill-fitting dentures	Clotrimazole 10 mg 5 times/day PO Nystatin suspension (100,000 U/ mL) 4–6 mL QID PO Fluconazole 100–200 mg/day PO	Itraconazole solution 200 mg/day PO Posaconazole IR 400 mg BID × 3 days, then 400 mg/day daily IR Voriconazole 200 mg BID PO Caspofungin 70 mg × 1, then 50 mg/day IV Anidulafungin 200 mg × 1, then 100 mg/day IV Micafungin 100 mg/day IV	7–14 days	Consider systemic therapy for severe or refractory disease; relapses more common with echinocandins. Potassium hydroxide (KOH) preparation can be performed on scrapings if the diagnosis is in doubt. Evaluate for immune deficiency if found in healthy patient.
Esophageal candidiasis	Immunocompromised, rarely inhaled corticosteroids	Fluconazole 200–400 mg/day PO or 400 mg/day IV	Fluconazole up to 800mg maximum daily Caspofungin 70 mg × 1, then 50 mg/day IV Anidulafungin 200 mg/day IV Micafungin 150 mg/day IV Itraconazole solution 200 mg/day PO Posaconazole 300 mg/day DR Voriconazole 200 mg BID PO or IV Lipid formulation AmB 3 mg/kg/day IV	14–21 days	An increased fluconazole dose may be attempted if refractory. Topical agents should not be used. Relapses more common with lower doses of echinocandins. *C. glabrata* or *C. krusei* may be resistant to fluconazole. Endoscopy may be required to confirm diagnosis or obtain culture.

TABLE 1 Patient Types and Treatment Options for Fungal Infections—cont'd

Infection	At-Risk Patients	Primary Treatments	Alternative Treatments	Duration of Therapy	Comments
Vulvovaginal candidiasis	Antibiotic use, diabetes mellitus, intrauterine device, increased estrogen levels, immunocompromised	Topical therapy (e.g., clotrimazole, nystatin, miconazole) Fluconazole 150 mg × 1 PO	Fluconazole 150 mg PO × 1 then repeated 72 hours later (2 total doses) Fluconazole 150 mg PO every 72 hours for 10–14 days	Variable by regimen	All criteria for uncomplicated infection must be met for one- time fluconazole dosing. Consider further evaluation to confirm diagnosis, and evaluate for resistant organisms if refractory or recurrent.
Candida cystitis	Indwelling urinary catheter, antibiotic use, urinary tract abnormalities, diabetes mellitus, immunocompromised	Fluconazole 200–400 mg/day PO or IV for 14 days	Deoxycholate AmB 0.3–0.6 mg/kg/day IV 1–7 days	Variable by regimen	Asymptomatic candiduria does not usually require treatment unless neutropenic, undergoing urologic instrumentation, or very low birth weight (<1500 g). Evaluate for ascending infection if recurrent or with significant risk factors. Echinocandins and lipid formulation amphotericin B have poor urinary concentrations. Microbiologic workup and susceptibility testing required if refractory or recurrent.
Candidemia	Critically ill, multifocal *Candida* colonization, hemodialysis, TPN, central venous catheters, broad-spectrum antibiotic use, intraabdominal surgery, gastrointestinal perforation, immunocompromised	Caspofungin 70 mg × 1, then 50 mg/day IV Anidulafungin 200 mg/day IV, then 100 mg/day IV Micafungin 100 mg/day IV Fluconazole 800 mg IV × 1, then 400 mg/day IV or PO	Lipid formulation AmB 3–5 mg/kg/day IV Voriconazole 6 mg/kg BID IV × 2 doses, then 3–4 mg/kg BID IV or PO	14 days after last positive culture At least 4 weeks if disseminated infection	Echinocandins preferred, especially for critically ill patients. Remove vascular access devices if possible. Evaluate for metastatic sites of infection. Echinocandins poorly penetrate ocular tissue or CSF. *C. glabrata* requires higher doses of fluconazole if susceptible. May change to oral therapy once stable with negative repeat cultures.
Candidal intraabdominal infection	Intestinal perforation, anastomotic leak, necrotizing pancreatitis, gangrenous cholecystitis	Caspofungin 70 mg × 1, then 50 mg/day IV Anidulafungin 200 mg/day IV, then 100 mg/day IV Micafungin 100 mg/day IV Fluconazole 800 mg IV × 1, then 400 mg/day IV or PO	Lipid formulation AmB 3–5mg/kg/day IV Voriconazole 6 mg/kg BID × 2 doses, then 3 mg/kg BID	At least 14 days, until abscess and all signs and symptoms of peritonitis resolved	Typically requires surgical intervention and antifungal therapy. Fluconazole and oral step-down therapy after organism identification through percutaneous or surgical sampling.

(Continued)

TABLE 1 Patient Types and Treatment Options for Fungal Infections—cont'd

Infection	At-Risk Patients	Primary Treatments	Alternative Treatments	Duration of Therapy	Comments
Invasive aspergillosis	Neutropenia, structural lung disease, burns, immunocompromised	Voriconazole 6 mg/kg BID IV × 2 doses, then 3–4 mg/kg BID IV or PO	Lipid formulation AmB 3–5mg/kg/day IV Caspofungin 70 mg × 1, then 50 mg/day IV Posaconazole IV or DR 300 mg BID × 1 day, then 300 mg/day IV or PO Isavuconazonium 372 mg TID IV or PO × 2 days, then 372 mg/day IV or DR	At least 6 weeks, up to several months dependent on disease site and evidence of improvement	Monitoring of voriconazole and posaconazole levels recommended. Voriconazole superior to amphotericin B deoxycholate. Echinocandins sometimes used in combination without definitive clinical evidence.
Mucormycosis	Neutropenia, severe immunosuppression, burns, trauma, near-drowning, natural disasters, uncontrolled diabetes mellitus, deferoxamine	Lipid formulation AmB 5 mg/kg/day IV	Posaconazole IV or DR 300 mg BID × 1 day, then 300 mg/day IV or PO Isavuconazole 372 mg TID IV or PO × 2 days, then 372 mg/day IV or PO	Variable based on infection, source control, clinical response, and immune reconstitution	Surgical debridement and excision improve outcomes. Higher doses of amphotericin B have been used. Azoles should be used as step-down or salvage therapy only. Echinocandins occasionally used in combination with amphotericin B.

abscess. Though empyema or lung abscess occurs as a result of metastatic infection, *Candida* pneumonia remains extremely rare, even in the setting of growth from respiratory cultures. When encountered, it should prompt an exclusion of other pathogens. *Candida* colonization of nonsterile sites represents a risk factor for invasive candidiasis in the appropriate clinical scenario, such as critically ill patients, but treatment in most populations has not been shown to reduce this risk. *Candidemia* is the third or fourth most common bloodstream infection in the United States, carrying a 40% mortality. Risk factors include intensive care stay, known multifocal *Candida* colonization, high APACHE scores, renal replacement therapy, total parenteral nutrition, severe pancreatitis, use of extracorporeal circulation, central venous catheters, broad-spectrum antibiotics, burns, GI tract perforations, or intra-abdominal surgery. Patients with underlying malignancy or undergoing solid organ or hematopoietic stem cell transplant have additional risks. About one-half of patients with invasive candidiasis will not have detectable *Candida* in blood cultures, but when present *Candida* is readily recovered from standard blood cultures. Fungal blood cultures are generally not recommended. Clinical prediction rules, such as the Candida score or the Ostrosky-Zeichner rules, can help clinicians recognize patients at risk of candidemia warranting empiric antifungal therapy.

Although *C. albicans* causes the majority of infections, other notable species may have specific antifungal resistance patterns and geographic variations. Empiric therapy for candidemia or invasive disease usually includes an echinocandin with a potential step-down to fluconazole once a susceptible organism is isolated. *C. tropicalis, C. dubliniensis,* and *C. guilliermondii* carry resistance patterns similar to *C. albicans*. Typically these are susceptible to fluconazole and echinocandins. Notably *C. glabrata,* the second most common pathogenic *Candida* in the United States, may be resistant to fluconazole or require higher dosing to overcome resistance. Likewise, *C. krusei* maintains intrinsic resistance to fluconazole but susceptibility to echinocandins. *C. parapsilosis* may carry higher minimum inhibitory concentrations (MIC) to echinocandins but retains fluconazole susceptibility. Amphotericin B–resistant species include the rare *C. lusitaniae,* which is typically susceptible to fluconazole and echinocandins, and the emerging *C. auris,* which in some cases may be resistant to most available antifungal drug classes. Diagnostic platforms such as the T2Candida, Vitek-2, or MALDI-TOF (matrix-assisted laser desorption/ionization–time-of-flight) mass spectrometry may provide early identification before susceptibilities are available, and knowledge of species-specific or local resistance patterns should guide empiric therapy.

Other Yeastlike Organisms

The majority of pathogenic yeasts in surgical patients will be *Candida*. Other medically important organisms may be encountered, particularly in immunocompromised patients. They will not be discussed in depth, but when encountered expert consultation should be considered. *Cryptococcus* may cause meningitis, pneumonia, peritonitis, skin infection, or disseminated disease. Patients with CD4 levels <100/μL, solid organ transplants, cirrhosis or liver disease, and hematopoietic malignancy are at increased risk. Cryptococcal meningitis or pneumonia may affect otherwise immunocompetent patients. Detection necessitates evaluation for central nervous system (CNS) disease because of high morbidity and mortality usually as a result of increased intracerebral pressure. This may require repeated lumbar punctures or cerebrospinal fluid (CSF) shunting. A lateral-flow cryptococcal antigen assay may be run on serum or CSF with exceptional sensitivity to rapidly evaluate for infection. Initial therapy involves amphotericin B with flucytosine if CNS disease is

present. Fluconazole typically retains activity for isolated pulmonary infections or as step-down therapy. Echinocandins are not active and not recommended.

Pneumocystis jirovecii may cause opportunistic infection with pneumonia in immunocompromised hosts including patients with HIV (usually with CD4 <200/μL), solid organ transplants, or hematologic malignancy. Trimethoprim/sulfamethoxazole is preferred, and steroids may be required for severe disease.

Trichosporon and *Malassezia,* though rare, may be encountered in neutropenic patients, those with indwelling central venous catheters, patients with extensive burns, or those with prior cardiac valvular surgery.

Dimorphic Fungi

These fungal organisms grow as molds in the environment, and yeast forms at human body temperature. Encountered infrequently in surgical patients, they may present as chronic skin lesions or lymphadenopathy. Diagnosis may be delayed until histopathologic examination after biopsy or excision and debridement. *Histoplasma, Blastomyces,* and *Coccidioides* are endemic mycoses with geographic variation that may be encountered in patients with extensive travel histories or in local endemic areas. They may present with acute pulmonary or skin infections in immunocompetent patients, but severe or chronic disseminated infections are possible, particularly in immunocompromised patients. *Histoplasma* can cause oral ulcers, colitis, or masslike lesions in the GI system, or it can present with lymphadenopathy, skin lesions, hepatomegaly, or bone marrow infiltration. *Blastomyces* has a predilection for skin dissemination, and biopsies may be confused for malignancy. GU, CNS, and bone involvement are possible. Treatment of disseminated or severe disease for both involves upfront amphotericin B. Itraconazole is recommended as step-down therapy or for limited mild disease. *Coccidioides* rarely disseminates from a pulmonary infection in immunocompetent patients, but can cause infections of the CNS, skin, or bone. Similarly, amphotericin B is used for severe infection, but fluconazole may be used as step-down therapy or in mild disease. *Sporothrix* occurs worldwide, typically with skin lesions and lymphocutaneous spread after traumatic inoculation of wounds by soil or fungal organisms. Although pulmonary infection is possible and may present as a fibrocavitary pneumonia, it rarely occurs in immunocompetent hosts. Treatment is necessary for all patients. Lipid-based amphotericin B is recommended in severe disease, but organisms may be resistant. Itraconazole may be used for step-down therapy or in mild limited cutaneous disease. Surgical consultants are often involved in these cases when thoracic pathology requires resection of pulmonary cavities or pleural decortication.

Aspergillus, Mucormycosis, and Molds

Aspergillus

Aspergillus may contaminate nonsterile cultures in the setting of chronic lung disease or prolonged mechanical ventilation. It should be considered a possible pathogen in immunocompromised patients or those with pulmonary or sinonasal infection without another clear etiology. Osteomyelitis, endophthalmitis, empyema, visceral abscess, or pericarditis have been described. Patients with hematologic malignancy, solid organ or stem cell transplants, or HIV carry increased risk. Invasive aspergillosis occurs in immunocompetent patients with risk factors such as burns, critical illness, structural lung disease, or penetrating trauma contaminated by soil. The majority of invasive infections are caused by the *Aspergillus fumigatus* complex, but other species such as *A. flavus, A. niger,* and *A. terreus* may cause disease. Notably, *A. terreus* may have high MICs to amphotericin B. Pulmonary infections present with solitary or multiple nodules, cavitary pulmonary lesions with hemoptysis, or infiltrations in a consolidative or tree-in-bud pattern. Tracheobronchitis may occur. Laboratory studies such as the galactomannan or beta-D-glucan assays are potentially useful as adjunctive tests. They may suggest invasive infection, particularly if *Aspergillus* is isolated, but neither is sensitive or specific enough to diagnose. Biopsy showing tissue invasion is definitive. Voriconazole or isavuconazole are the primary treatments for invasive aspergillosis, but aggressive surgical management may be required. Lipid formulation amphotericin B or posaconazole are alternatives. Echinocandins may be used in combination therapy with voriconazole, but there are limited data to suggest a benefit to upfront use.

Mucormycosis

Mucormycosis is caused by one of several species of zygomycetes. These environmental fungi may be seen with burns or penetrating trauma, but they can cause pneumonia or rhinocerebral disease in immunocompromised patients. Underlying states such as poorly controlled diabetes mellitus, solid organ or hematopoietic cell transplant, iron overload, or HIV with severe immunosuppression are risk factors. Without prompt recognition and treatment, outcomes are exceedingly poor. Patients require aggressive and early surgical interventions when possible. Initial empiric therapy is lipid formulation amphotericin B at higher dosing. Posaconazole and isavuconazole have activity but require demonstrated source control and clinical improvement when utilized. Echinocandins lack in vitro activity, but caspofungin has a potential role in combination with amphotericin B, though this has not been definitively shown.

Other Molds

Other molds rarely may be encountered. This includes *Fusarium,* which may grow on standard blood cultures and can cause skin, lung, or disseminated infection, or dematiaceous (black or brown pigmented) molds such as *Alternaria, Bipolaris,* or *Curvularia.* Dematiaceous molds may contaminate nonsterile cultures, but they can cause infections in certain patients, including those with burns, penetrating trauma, or severe immunosuppression. Empiric lipid-based amphotericin B may be the best regimen for these suspected fungal infections; however, some pathogens may be resistant, and expert consultation is advised when encountered.

ANTIFUNGAL AGENTS

Polyenes

Available polyenes include amphotericin B and nystatin. They induce ionic leakage and osmotic instability by binding to ergosterol in fungal cell cytoplasmic membranes leading to cell death. Amphotericin B deoxycholate was the primary formulation and provides extensive antifungal activity against *Candida, Cryptococcus,* zygomycetes, *Aspergillus, Fusarium, Sporothrix,* and the dimorphic fungi including *Histoplasma, Coccidioides, and Blastomyces*. Although still available, use is limited because of side effects including nephrotoxicity and electrolyte abnormalities. Newer lipid formulations include liposomal amphotericin B, amphotericin B colloidal dispersion, or amphotericin B lipid complex. These carry reduced toxicities while maintaining broad activity. Close monitoring of renal function and electrolytes, particularly magnesium and potassium, is recommended. Extended infusion times or premedication with acetaminophen, diphenhydramine, or steroids may be useful should patients develop a reaction during initial administration that does not prohibit use. The drug is metabolized by complex methods, but dosing is not affected by renal or hepatic dysfunction. Typically IV administration is used, often with fluid volume loading to reduce nephrotoxicity. In some clinical scenarios, it may be administered topically for local GI or GU infections or intrathecally. Local inflammation can be substantial. Because of broad activity, it may be employed empirically when there is concern for severe fungal infection in critically ill patients or as salvage therapy when an organism is defined but the patient is not improving clinically. It is important to note organisms that may be resistant to amphotericin B including *Aspergillus terreus,*

Lomentospora prolificans (Scedosporium prolificans), Scedosporium apiospermum, Sporothrix schenckii, Pseudallescheria boydii, Candida lusitaniae, and some isolates of *Fusarium, Candia auris,* or *Trichosporon.* Nystatin, another polyene drug, is utilized for oropharyngeal candidiasis. Limited systemic absorption makes it unsuitable for systemic infections. The drug is given as an oral swish and swallow up to four times daily.

Flucytosine

Flucytosine, a pyrimidine analogue, inhibits DNA synthesis but carries antifungal activity. Susceptible organisms develop rapid resistance, so use is restricted to adjunct therapy in combination with another agent. It is given with amphotericin B during the induction phase of cryptococcal meningitis because of its CSF penetration; however, it may be used in the setting of other refractory or invasive fungal infections with expert consultation.

Echinocandins

Echinocandins inhibit beta 1,3-D glucan synthesis and include three commercially available agents: caspofungin, micafungin, and anidulafungin. They provide broad activity against *Candida* species, where they are fungicidal, and some activity against *Aspergillus* species, where they are fungistatic. The drugs undergo hepatic excretion; dosing adjustment for renal dysfunction is not required. Hepatic function should be monitored. Most invasive *Candida* infections, including candidemia, should be treated initially with an echinocandin. One may also be used for prophylaxis when azoles are contraindicated or for empiric therapy in neutropenic fever when fungal infections are suspected. Given its role in empiric *Candida* treatment, it should be noted that *C. parapsilosis* may have higher MICs to echinocandins but retain susceptibility to fluconazole. Clinical trials in susceptible isolates have not shown reduced activity, but clinicians should consider this for patients failing to improve on therapy. This class provides options for potential fluconazole-resistant species, such as *C. krusei* or some *C. glabrata*. Echinocandins are used as salvage therapy for *Aspergillus* infections. They may be used in combination therapy for zygomycetes or *Aspergillus* infections, but data showing definitive benefit is lacking. Although once-daily dosing and hepatic clearance provide convenient treatment options, this class has poor tissue penetration in the vitreous, important for endophthalmitis, or the CNS.

Azoles

This class includes the most commonly prescribed antifungal agents. Most come in oral and IV formulations and inhibit lanosterol demethylase, a crucial step in ergosterol and fungal cell membrane synthesis. Class side effects include reversible hepatic dysfunction, which may be life-threatening. Hepatic function should be monitored. With the exception of isavuconazole, QT prolongation may occur. Many pose significant drug interactions with the cytochrome P450 system, and drug interactions should be evaluated. Because of extensive use, resistance patterns have developed. Organisms should be evaluated for susceptibility if there is potential resistance. Each drug may have specific indications and not perform similarly for specific organisms. They will be discussed individually.

Fluconazole

Fortunately, a majority of *Candida* species retain susceptibility to fluconazole. Activity is maintained in most yeast infections, including *Cryptococcus,* but it should not be used for molds. For some dimorphic fungi, itraconazole may be preferred. At standard dosing, it is first-line therapy for *Candida* cystitis, vulvovaginitis, or esophagitis. It may be given in invasive candidiasis once susceptibility patterns are known, but often requires higher dosing (up to 400–800 mg/day). Adjustments are needed in the setting of renal dysfunction, and the most common side effects include nausea, vomiting, or GI upset. A rare but potentially severe skin rash can occur. Bioavailability is high, and fluconazole distributes to all body fluids. Although most *C. albicans* isolates are susceptible, resistance occurs, and testing is indicated with failed empiric therapy for noninvasive infections or for all cases of invasive candidiasis. Notably, *C. glabrata*, the second most common *Candida* isolate, may be resistant or require higher dosing, and *C. krusei* carries intrinsic resistance.

Itraconazole

Itraconazole builds on fluconazole and includes additional activity against *Aspergillus, Trichophyton,* and the dimorphic fungi including *Histoplasma, Blastomyces,* or *Sporothrix*. It is the preferred therapy for dimorphic fungi. An IV and multiple oral formulations are available. Hepatic metabolism occurs, and renal adjustment is unnecessary; however, the IV formulation is a cyclodextrin carrier and may be contraindicated in moderate to severe renal impairment. Side effects are similar to fluconazole, with nausea, vomiting, and GI upset, but a negative inotropic effect that may induce heart failure has been reported. Oral formulations require drug level monitoring to ensure therapeutic concentrations. An older oral capsule formulation is more unreliable than the oral solution, which may be a preferred agent. Tissue penetration is more restricted, making it unsuitable for ocular or CNS infections.

Voriconazole

Voriconazole expands on the activity of fluconazole and may be used in invasive candidiasis or aspergillosis, where it is first-line therapy. It is active against various molds, including *Fusarium* or *Scedosporium,* but it should not be used for zygomycetes or empirically when they are considered. Although some dimorphic fungi are susceptible, it may be inferior to itraconazole for treatment of *Histoplasmosis* and should be avoided for routine infections with these organisms. Formulations include IV and oral tablets and suspension. Although it is metabolized by the liver and may require adjustment in hepatic impairment, the IV formulation includes cyclodextrin, which may preclude use in patients with renal impairment. Drug interactions are significant, and a medication review or consultation with a pharmacist may be required. In addition to side effects of the azole class, voriconazole may cause visual changes ranging from photophobia and blurry vision to visual disturbances and hallucinations. A rare but severe photosensitive rash may occur. Long-term use is associated with squamous cell carcinoma of the skin. Drug levels should be monitored because of nonlinear pharmacokinetics and variable patient absorption and metabolism rates.

Posaconazole

Primarily used as prophylaxis against *Candida* or *Aspergillus* in high-risk patients, posaconazole maintains broad activity and may be used to treat fungal disease. This includes activity against *Candida* and molds including zygomycetes, *Aspergillus,* and *Fusarium.* It has oral (tablets and suspension) and IV formulations. The drug structure is closer to itraconazole than voriconazole. Although it may have activity, it has not been studied extensively in dimorphic fungi. Trials have demonstrated non-inferiority to fluconazole for oropharyngeal candidiasis, but additional studies are needed to demonstrate clinical activity for other infections. Drug absorption is variable, and administration with a meal is recommended. Drug levels should be monitored, and it can take longer than 1 week to achieve steady state. The drug is not significantly metabolized, but some hepatic metabolism occurs. Data are limited in patients with creatinine clearance <50 mL/min, but because of its cyclodextrin-based IV formula, the oral formulation or an alternative agent should be used. QT prolongation and hepatotoxicity may be less frequent than other azoles but may occur along with nausea, vomiting, and diarrhea. Adrenal insufficiency with hypotension or electrolyte abnormalities may occur on prolonged therapy.

Isavuconazole

The newest triazole, isavuconazole, is administered as the prodrug isavuconazonium sulfate in IV and oral (capsule) formulations. It carries broad activity against yeasts and molds, including *Aspergillus* and zygomycetes. Phase III trials have shown non-inferiority to voriconazole in invasive aspergillosis, for which guidelines note it is an alternative option. It performed well in case-control analyses compared with amphotericin B in zygomycetes infections. Notably, MICs are variable based on species, but it may be used for step-down therapy after amphotericin B or for salvage therapy if serious side effects develop. Cross-resistance between isavuconazole and voriconazole has been shown in some *Aspergillus* isolates. Bioavailability is high, and routine drug monitoring is not recommended or required. Dose adjustment is not required in hepatic or renal impairment. Side effects appear similar to other azoles including hepatic impairment, nausea, vomiting, and GI upset along with medication interactions among drugs metabolized by cytochrome P450 systems, but uniquely the drug appears to have a dose-related QTc shortening rather than prolongation.

INVESTIGATIONAL AGENTS

Several drugs are undergoing development or phase II or III trials and may be available in the near future. They should be used after expert consultation or as part of a clinical trial but are worth noting. Ibrexafungerp acts through a novel mechanism similar to echinocandins to inhibit beta 1,3-D glucan synthesis and may be useful for resistant *Candida, Aspergillus,* or dimorphic fungal infections. It has activity against *Cryptococcus,* which is resistant to all echinocandins, and has activity against echinocandin-resistant *Candida* including *C. auris*. Trials included patients with invasive candidiasis, pulmonary aspergillosis, or vulvovaginal candidiasis. Rezafungin, an echinocandin, has activity against *Candida* resistant to azoles and may have activity against fungi with low-level resistance to other echinocandins. In vitro activity against *Aspergillus* has been demonstrated, but trials are ongoing. Oteseconazole, a first in class tetrazole, has activity against *Rhizopus, Trichophyton,* and fluconazole-resistant *Candida* species. Fosmanogepix, a first in class Gwt1 inhibitor, has broad activity against most *Candida* species (including potentially *C. auris*), *Trichosporon, Cryptococcus, Coccidioides,* and *Aspergillus.* It retains activity against highly resistant mold species including some *Fusarium* and *Scedosporium*. Although not active against many yeasts, olorofim, a first in class dihydroorotate dehydrogenase inhibitor, demonstrates activity against highly resistant *Aspergillus, Scedosporium,* and *Lomentospora* species, which currently may have limited treatment options. These and additional agents in phase I or II trials may expand future options for resistant organisms.

COMMON FUNGAL INFECTIONS

The majority of fungal infections in surgical patients are attributable to *Candida*. This ranges from noninvasive cystitis to life-threatening candidemia with variable treatment options. This chapter briefly discusses some common clinical infections surgeons may encounter caused by *Candida, Aspergillus,* or zygomycetes; however, particularly as patient immunosuppression increases or previously discussed risk factors are present, other fungal organisms may be considered or encountered.

Mucocutaneous Candidal Infections

Risk factors for mucocutaneous *Candida* include diabetes mellitus, antecedent antibiotic usage, obesity, steroid therapy, or critical illness. Infections may be treated with azoles or oral agents in susceptible organisms if patients tolerate oral intake. Isolation from nonsterile sites is common and may represent colonization, but it is a strong risk factor for development of invasive candidiasis in immunocompromised or critically ill patients. Treatment of asymptomatic colonization is not recommended, however, and has not been shown to improve outcomes with few exceptions. These are discussed in the following sections.

Cutaneous Candidiasis

Candida may cause cutaneous infections including intertrigo, cellulitis, onychomycosis, balanitis, folliculitis, or paronychia. Intertrigo, a local infection of warm, moist, macerated sites in the intertriginous areas, presents with moist, red, confluent patches that may burn, itch, or have a malodorous discharge. Bacterial infection can present similarly, but if risk factors are present and a patient is not improving on antibiotics, *Candida* should be suspected. Similar infections occur with skin breakdown, including open incisions, decubitus ulcers, or wounds, particularly if excessive moisture is present. Most superficial lesions can be treated with a topical azole cream or nystatin. Care should be taken to improve aeration, ensure cleanliness, and remove sources of moisture. Barrier creams or zinc oxide may be as important as any therapy. In rare cases of recurrent, severe, or refractory disease, surgical resection of skin folds may be required. Extensive infection requires systemic therapy with oral or IV azoles. Refractory disease should prompt consideration of resistant species.

Oropharyngeal and Esophageal Candidiasis

Although occurring in immunocompetent or critically ill patients, oropharyngeal and to a greater extent esophageal candidiasis most often presents in immunocompromised patients. When encountered in an otherwise immunocompetent patient, an evaluation for HIV or other immune-compromising conditions should occur. Oropharyngeal candidiasis, or thrush, may present with oral pain, dysgeusia, or dysphagia and classic white patchy lesions or plaques, which can be scraped off. In other patients, symptoms may be absent. Oropharyngeal candidiasis may be associated with esophagitis. If oropharyngeal lesions are present, it should not be considered colonization. *C. albicans* causes up to 90% of infections, but a gram stain or potassium hydroxide (KOH) preparation can be performed on scrapings if the diagnosis is in doubt. For some patients, oral nystatin suspensions or clotrimazole troches (10 mg 5 times daily) may be appropriate, but systemic therapy is warranted in immunocompromised patients or in the setting of esophageal candidiasis.

Esophageal candidiasis almost exclusively occurs in immunocompromised patients, traditionally presenting with odynophagia, but it may be asymptomatic. Oropharyngeal candidiasis is often absent; when suspected, endoscopy may be required to diagnose. All cases require systemic therapy, typically oral fluconazole 200 to 400 mg/day for 14 to 21 days, but other azoles may be used. If the patient cannot tolerate oral agents, IV azoles or echinocandins are recommended. In refractory or recurrent disease, resistant isolates should be considered and endoscopic sampling for culture and susceptibility testing performed. Differential diagnoses include esophagitis caused by cytomegalovirus or herpes simplex virus but appear very different endoscopically. Though patients may require prophylaxis for other reasons, suppressive therapy is not indicated and has not been shown to reduce the frequency of oropharyngeal or esophageal candidiasis in patients with HIV and a history of oropharyngeal candidiasis.

Candidal Vulvovaginitis

Up to 75% of women have one lifetime episode of vulvovaginitis. Risk factors include antecedent antibiotic use, corticosteroids, diabetes mellitus, or immunosuppression along with intrauterine devices, diaphragm use, and increased estrogen levels. *Candida* is a commensal organism of the GU tract, but local overgrowth can lead to pruritis, dysuria, dyspareunia, or vaginal discharge, described as white or curdlike. When the diagnosis is uncertain, a KOH preparation or

wet mount may show budding yeast or pseudohyphae. Other differential diagnoses include bacterial vaginosis or trichomonas. Topical azole creams or vaginal suppositories exist, but uncomplicated infections may be treated with a one-time dose of oral fluconazole 150 mg provided all criteria for uncomplicated infection are present. This includes fewer than three episodes per year, mild to moderate symptoms, likely *C. albicans* infection, immunocompetent patients, nonpregnant, and without significant comorbidities. Ibrexafungerp (two 150 mg tablets in the morning and two tablets in the evening for one total day of therapy) has recently received approval by the US Food and Drug Administration for uncomplicated vulvovaginal candidiasis and may be considered for severe or refractory disease. Complicated infections or infections in immunocompromised hosts require two doses of fluconazole 150 mg taken 72 hours apart. This regimen can be extended to 7 to 14 days of therapy. Refractory disease should prompt investigations for resistant organisms such as *C. glabrata* or *C. krusei*. Some guidelines support the use of suppressive fluconazole 150 mg once per week for 6 months after induction therapy in the setting of multiple recurrent episodes.

Candiduria and Cystitis

Candida colonizes <1% of urine samples in healthy adults, but it may be present in up to 10% of urine cultures from inpatient samples and is strongly associated with indwelling urinary catheters. Although studies show *C. albicans* as the most common species, increasing rates of potentially fluconazole resistant *C. glabrata* occur. The majority of patients do not have cystitis or an infection, and in most candiduria clears over time without treatment. Treatment of asymptomatic candiduria has not been shown to reduce risk or alter outcomes for most patients, but it is indicated in patients undergoing urologic procedures, in the setting of neutropenia, or in very-low-birthweight infants (<1500 g). Catheter exchange may clear candiduria in a large portion of cases and can be performed with repeat testing if the diagnosis is uncertain. Treatment in patients undergoing solid organ transplantation is controversial. In renal allograft recipients, asymptomatic candiduria has been associated with reduced survival rates, but treatment has not been shown to improve outcomes and is no longer recommended. Data from early in the transplant period are unclear, and treatment is often given, particularly if a graft, device, or stent is in place.

Symptomatic patients present similarly to those with bacterial cystitis with dysuria, frequency, or suprapubic discomfort. When present, treatment is indicated. Pyuria may be helpful in the absence of an indwelling urinary catheter but loses sensitivity if present. Fungal casts suggest renal involvement. Evaluations to rule out complications from ascending infection, such as perinephric abscess, prostatic abscess, or fungal balls, may be indicated with recurrent infections or significant risk factors such as obstructive uropathy, indwelling nephrostomy tubes, or a chronic indwelling catheter. *Candida* cystitis may be treated with oral fluconazole (200 mg or 3 mg/kg daily) for 7 to 14 days in susceptible organisms, but microbiologic cultures should be obtained. Alternative therapy includes amphotericin B. Bladder irrigation with amphotericin B has been shown to resolve candiduria and may be necessary if use of other agents is precluded but is not generally recommended and may be temporary. Complicated infections may require surgical intervention. Although fluconazole and voriconazole concentrations in urine are sufficient to treat infection, levels of itraconazole or the echinocandins are low and not sufficient for treatment.

INVASIVE FUNGAL INFECTIONS

Candidemia

As previously discussed, surgical patients have risk factors for candidemia that carry significant mortality. Prompt recognition and treatment are required. Bloodstream access may occur from central venous catheters, GI translocation through an impaired mucosal barrier, or as a complication of a localized infection. Although diagnostic platforms may give early species identification to guide empiric antifungal therapy, all isolates should have susceptibility testing performed. Although fluconazole (800 mg or 12 mg/kg loading dose followed by 400 mg or 6 mg/kg daily dose) has been used successfully and remains an alternative therapy in non–critically ill patients with low likelihood of resistant species, echinocandins (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) perform better and are recommended as primary therapy. Local *C. glabrata,* the second most common species in candidemia, patterns should be reviewed as this species may be resistant to fluconazole or require higher doses. *C. parapsilosis* may carry higher MICs to echinocandins but has not been shown to have reduced outcomes in susceptible isolates. Voriconazole (400 mg or 6 mg/kg twice daily for 2 doses, then 200 mg or 3–4 mg/kg twice daily) and lipid formulation amphotericin B (3–5 mg/kg daily) remain therapy alternatives. Guidelines recommend that clinically stable patients with fluconazole-susceptible isolates and negative repeat blood cultures after initiation of therapy may be transitioned from an echinocandin to fluconazole after 5 to 7 days. Evaluation for metastatic infection sites is paramount. Any organ system may be involved and may require intervention for source control or involved foreign body removal. This could include additional imaging or procedures based on patient presentations and symptoms. Dilated fundoscopic examination by an ophthalmologist within the first week of diagnosis (or within the first week of neutrophil recovery in neutropenic patients) has been traditionally recommended but is controversial. Some guidelines recommend an examination to evaluate for chorioretinitis or endophthalmitis, while others do not in asymptomatic patients. Although all symptomatic patients require evaluation, caution should be applied when deferring evaluation in the setting of complicated candidemia or if an agent with poor ocular tissue penetration (such as echinocandins) is used. Any long-term central venous catheters presumed to be the source of candidemia should be removed as soon as feasible and all short-term catheters removed. Certain patient populations, such as those with implanted access devices in the setting of cytotoxic chemotherapy and neutropenia, are most likely to develop candidemia in the setting of GI translocation and may not require line removal in uncomplicated candidemia with documented rapid clearance from blood cultures. Persistent, complicated, or recurrent candidemia should prompt removal of any retained catheters.

Candidal Intraabdominal Fungal Infection

Intraabdominal fungal infections complicate GI tract perforation, leakage from anastomotic sites, gangrenous cholecystitis, or acute necrotizing pancreatitis ranging from peritonitis to discrete abscesses. *Candida* remains the most common organism and may present in monomicrobial or polymicrobial infections. Risk factors are similar to those for candidemia. Blood cultures are infrequently positive but still recommended as they may confirm a microbiologic diagnosis, prompt further evaluation, or extend treatment duration. Percutaneous or intraoperative sampling of lesions may yield a microbiologic diagnosis, and susceptibility testing should be performed to identify resistant organisms and optimize antifungal therapy. Routine empiric antifungal therapy is not needed in patients with low-risk for fungal infection, but it may be considered in high-risk scenarios. In most situations, including low-risk community acquired intraabdominal infection, the Surgical Infection Society does not recommend empiric antifungal therapy. In instances of hospital-acquired intraabdominal infection, an echinocandin (or fluconazole if less severely ill) is recommended in the setting of upper GI perforations, recurrent bowel perforations, surgically managed pancreatitis, patients receiving prolonged

broad-spectrum antibiotic courses, and those with known *Candida* colonization. These factors have been associated with an increased frequency of *Candida* infections. Most cases of *Candida* intraabdominal infection require antifungal therapy and surgical intervention. Source control through abscess drainage or relief of obstruction is indicated when present. Treatment duration varies depending on the organism isolated, if source control is obtained, and the mechanism of infection. Patients with intraabdominal *Candida* infection were included in the Surgical Infection Society's Study to Optimize Peritoneal Infection Therapy receiving as few as 4 days of treatment after source control; however, the study was not designed for this population. Because of variability of infections in this population, Infectious Diseases Society of America guidelines recommend duration of therapy based on adequacy of source control and clinical response. Patients should generally receive at least 10 to 14 days of therapy, which is extended until all signs and symptoms of infection, including abscesses, are resolved.

Surgical Site Infections

Fungal organisms may cause 2% to 4% of surgical site infections with *C. albicans* comprising the majority. *C. glabrata* is not infrequently isolated along with *Aspergillus* species and may need consideration. A microbiologic diagnosis with susceptibility testing may be crucial. Infections range from superficial to deep space and organ site, and cases of necrotizing infections attributable to *Candida* have been reported. Both *Candida* and *Aspergillus* have been isolated in poststernotomy wound infections, which can be complicated by osteomyelitis or mediastinitis. Treatment regimens vary based on depth of infection. Surgical debridement is required for deep infections, and several months of therapy may be required in the setting of osteomyelitis. Although antifungal prophylaxis is generally not indicated in routine surgical procedures, in patients undergoing liver transplantation fluconazole prophylaxis is recommended if two or more risk factors are present, including retransplantation, prolonged surgery, renal failure, transfusion of >40 units of blood products, choledochojejunostomy, or preoperative *Candida* colonization. Treatment of isolated preoperative asymptomatic candiduria is not recommended and has not been shown to improve outcomes or infection rates.

FUNGAL INFECTIONS COMPLICATING BURN PATIENTS

Burn sites are at risk for fungal infections, and incidence has increased in the past several decades. Fungal organisms may colonize burns, so a tissue biopsy showing invasion is required for early diagnosis and to guide empiric therapy. Infections mostly occur after 2 weeks from injury but may occur sooner. Incidence varies; some studies attribute 2% to 10% of burn infections to fungal organisms. It may be as high as 20% to 25% in those with polymicrobial infection. This may represent variability in infection control practices at individual institutions, and a change in rates of fungal infection or of certain organisms should prompt further investigation. *Candida* species are the most common, but molds including *Aspergillus, Fusarium,* or *Alternaria* may be implicated. Zygomycetes rarely occur but are notable for the ability to rapidly spread across fascial planes carrying very high mortality rates. Guidelines do not specify optimal therapy in burn infections. Patients with serious illness and suspected fungal infection are typically given amphotericin B until an organism is isolated and susceptibility testing performed. Systemic therapy is required. Aggressive surgical intervention, including wide excision before deeper invasion can occur, is essential and improves mortality.

FUNGAL RHINOCEREBRAL AND PULMONARY INFECTIONS

Yeasts and Yeastlike Organisms

Although rarely encountered in the surgical patient, dimorphic fungi such as *Histoplasma, Blastomyces,* or *Coccidioides* may present with isolated skin infection or acute or subacute pneumonia in an immunocompetent host. Incidence and organisms vary geographically. In immunocompromised patients, such as those with HIV, solid organ transplant, or hematopoietic stem cell transplant, these organisms along with *Cryptococcus* and *Pneumocystis* may cause pneumonia or disseminated infections. Yeast isolated in respiratory cultures may need workup for identification if risk exists. *Candida* rarely causes pneumonia; isolation from respiratory culture almost always represents colonization, even in immunosuppressed patients. Colonization increases the risk of invasive candidiasis in critically ill populations. Tissue biopsy may be required to diagnose if suspicion is high for true *Candida* pneumonia and other etiologies are excluded. *Candida* may cause lung abscess or empyema after hematogenous spread. Treatment for pneumonia caused by yeast typically involves empiric lipid formulation amphotericin B until an organism is identified, and patients may be transitioned to an azole once susceptibility is known. Expert consultation is generally advised.

Molds

Aspergillosis

Pulmonary aspergillosis is the most common form of invasive *Aspergillus* infection. It occurs in immunocompetent patients but is exceedingly rare. More often, neutropenia, corticosteroid use, or severe immunosuppression are present. In particular, recipients of lung, heart-lung, or liver transplants with neutropenia are at increased risk. Nonspecific symptoms including fever, pleurisy, or dyspnea may be present. Hemoptysis classically has been considered a more specific finding, but it is neither sensitive nor specific for disease. Diagnosis requires a high index of suspicion. Imaging and pulmonary pathology vary. Small subcentimeter nodules are most common but are seen in less than 50% followed by consolidations, large nodules, or peribronchial infiltrates that may have tree-in-bud patterns. "Air crescent" or "halo" signs may be present on CT imaging, suggesting infection but are not diagnostic. Patients with chronic infection present with necrotizing or cavitary lesions that may erode into local vasculature, leading to hemoptysis. Tracheobronchitis occurs more frequently in lung transplant recipients. They may have ulcers or pseudomembranes at anastomotic sites, a finding that is almost pathognomonic for *Aspergillus.* Laboratory evaluation can include a galactomannan assay, which detects components of the *Aspergillus* cell wall, but is neither sensitive nor specific enough to diagnose infection. False positives occur after receiving blood transfusions, receiving IV immunoglobulin, or as a result of other organisms including *Pseudomonas*. This assay can be used on bronchoalveolar lavage (BAL) specimens, which may increase sensitivity, particularly in hematologic malignancy. Fungal cultures from lavage should be obtained if suspected. Primary therapy involves voriconazole or amphotericin B if unavailable. Echinocandins may be used as salvage therapy but have not been shown to improve outcomes when used in combination with voriconazole. Angioinvasive or refractory lesions may require resection.

Rhinosinusitis due to *Aspergillus* presents variably dependent on the patient's immune status. In immunocompetent patients, colonization of the airway is not uncommon and rarely causes severe infection. Mild presentations include polyps or fungal balls that may require surgical removal or an allergic rhinosinusitis. Invasive infections in the setting of severe immunosuppression can present acutely with local vasculature invasion, appearing similar to mucormycosis,

or as a slow chronic infection over several months. CT or MRI imaging can demonstrate anatomic extent of disease, but endoscopic examination with biopsies are required for definitive diagnosis. Amphotericin B is used initially until *Aspergillus* is confirmed, at which time therapy may be changed to voriconazole in susceptible isolates. Wide surgical debridement may be required and improves outcomes.

Mucormycosis

Mucormycosis may rarely be encountered in surgical patients, but it is notable for the potential need for aggressive surgical intervention and devastating presentations. Patients typically carry substantial immunosuppression, such as stem cell or solid organ transplants, but overall infection occurs in less than 1% of these populations. Additional risk factors include poorly controlled diabetes mellitus, iron overload states, deferoxamine, or corticosteroid use. As environmental organisms, patient factors most often predispose to infection; however, traumatic injuries, burn injury, near-drowning, or natural disasters have been associated with sporadic infection, even in immunocompetent hosts. Hospital outbreak clusters have been linked with tongue depressors, linens, adhesives, and construction projects. Further analyses may be warranted if clusters of infection develop at a site.

Presentations include a devastating rhinocerebral disease with an acute febrile pan-sinusitis, purulent nasal discharge, sinus tenderness, and headaches. Zygomycetes may invade the orbits, CNS, and local vasculature. A stereotypical tissue necrosis of the overlying skin, black eschar in the nasopharyngeal or oropharyngeal mucosa, or evidence of cranial bone destruction may suggest infection. Diabetes mellitus is present in approximately 70% of patients with rhinocerebral disease, but it may appear without risk factors. Complications include cranial nerve palsies, venous sinus thrombosis, meningitis, or encephalitis, but hematogenous spread rarely occurs. Nasal endoscopy can demonstrate typical examination findings and provide an opportunity for biopsy. Histopathology may show nonseptated, broad hyphae of zygomycetes with evidence of tissue invasion providing a rapid presumptive diagnosis to guide therapy. CT or MRI imaging should be obtained and may demonstrate extent of intracranial spread. MRI provides increased sensitivity to detect complications at a drawback for time. Prompt treatment includes early, aggressive surgical debridement, systemic antifungal therapy, and correction of risk factors such as hyperglycemia, metabolic acidosis, and neutropenia. Lipid formulation amphotericin B at higher doses, starting at 5 mg/kg per day, is recommended. Echinocandins have no in-vitro activity against these organisms, but caspofungin has shown in-vitro synergy with amphotericin B. It may be used clinically based on limited anecdotal studies suggesting a potential benefit. Posaconazole or isavuconazole provide options for deescalation once source control and clinical improvement have been achieved, often after 2 to 3 weeks or more of initial induction therapy. Therapy should continue until there is resolution of symptoms, radiographic evidence of disease improvement, and underlying immunosuppression correction. In some, this may require lifelong therapy. Mortality is high, particularly if source control cannot be obtained and immunosuppression persists.

Pulmonary disease presents more often in the setting of hematologic malignancy or transplantation. Symptoms are similar to other invasive fungal organisms, but immunosuppressed patients may have nonspecific or mild complaints. "Halo signs" may be seen on CT imaging, but a reversed halo sign (focal ground-glass attenuation surrounded by a ring of consolidation) may be more specific. Additional factors associated with pulmonary mucormycosis in oncology patients include over 10 nodules, pleural effusions, sinusitis, or breakthrough on voriconazole prophylaxis. BAL may be helpful to identify hyphae characteristic of zygomycetes. Treatment should be aggressive and similar to rhinocerebral disease. Some case reports demonstrate clinical cure with lobectomy, but many patients have underlying diseases complicated by thrombocytopenia or coagulopathies that may preclude surgery.

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Use of Opioids in the Postoperative Period

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THE OPIOID EPIDEMIC

The United States opioid epidemic has been described as one of the worst public health crises in recent history. Nearly 50,000 Americans died from opioid-related overdose in 2019, of which 14,000 were from prescription opioids. In addition to the large death toll, opioids incur a significant economic burden due to added healthcare expenses and lost productivity. It was estimated that these costs exceeded $1 trillion in 2017 alone, mostly due to reduced quality of life and death from overdose.

The origin of the opioid epidemic is multifactorial. Misleading marketing strategies by a few pharmaceutical companies in the late 1990s downplayed their side effects and promoted opioids as the safest and most effective way to treat pain. This was accompanied by an increased awareness among healthcare providers of the humanistic need to better treat pain and the subsequent suggestion of "pain as the fifth vital sign" reinforcing the societal trend of zero pain expectation. Physicians started managing pain more diligently but mainly through prescribing opioids. The number of opioid prescriptions started increasing in 1999 and has nearly quadrupled over the past two decades alone. This was accompanied by a concomitant national increase in overdose events from prescription opioids. Surgeons are the second highest prescribers of opioid analgesics after pain specialists and account for 10% of all opioid prescriptions in the US. It is estimated that 51 million Americans undergo inpatient surgery each year, and more than 90% of those who undergo even low-risk surgery are prescribed opioids at discharge. According to the International Patterns of Opioid Prescription (iPOP) study, 91% of US patients were prescribed opioids compared with only 5% of non-US patients, and the average dose of opioids prescribed to US patients after common general surgery procedures is 40 times higher than that prescribed to non-US patients (Fig. 1). In fact, the US consumes more than 80% of the world's opioid supply despite accounting for less than 5% of the world's population. This poses a direct threat to patients' immediate and long-term well-being as well as the community in general because most of the opioids prescribed go unused and are diverted into the community.

The majority of surgeons have recognized the seriousness of the epidemic and have advocated for a change in opioid prescribing culture; however, some continue to express concerns over the undertreatment of pain and consider the pendulum to have swung too far in the other direction. This partially explains the high variability in opioid prescribing even for relatively homogenous patient populations undergoing similar procedures within the same institutions. Recent efforts have been directed to standardize the amount of opioids prescribed after surgery to mitigate the mounting toll of the epidemic.

OPIOID-RELATED ADVERSE EVENTS

Opioid analgesics may have unintended effects on different parts of the body due to activation of peripheral receptors. Their use is associated with significant increase in patient morbidity and mortality. As many as 80% of patients taking opioids experience an opioid-related adverse event. There is evidence that surgical patients are at an even higher risk of developing opioid-related complications due to the complexity of their care. These side effects include nausea, vomiting, respiratory depression, hyperalgesia, sedation, delayed gastric emptying, ileus, dysphoria, decreased concentration, confusion, sleep disturbances, lack of coordination, myoclonus, muscle rigidity, sexual dysfunction, urinary retention, immune system effects, anaphylaxis, and drug tolerance. In multiple recent studies, patients with opioid-related adverse events have been shown to have longer hospital length of stay, higher cost of care, increased risk of readmission, and increased inpatient mortality. Several factors are known to increase the risk of opioid-related adverse events, and we summarize them in Box 1. Alternative analgesics should be sought in high-risk patients, and considerable caution is advised if opioids need to be prescribed as a last resort.

NONOPIOID PAIN MANAGEMENT STRATEGIES

Current recommendations for postoperative pain management are based on multimodal techniques that include the administration of two or more analgesics that have different mechanisms of action. Nonopioid analgesics have a central role in multimodal pain management strategies as their use decreases opioid consumption and opioid-related side effects without affecting patient satisfaction. Several nonopioid analgesics and techniques are routinely implemented in enhanced recovery after surgery (ERAS) pathways, which we describe later.

Regional blocks are highly effective in controlling pain postoperatively. They are generally classified as neuraxial or peripheral and can either be administered continuously or as a single shot. Epidural analgesia is one of the most common types of regional blocks and should be considered as an adjunct treatment in patients undergoing surgery. Not only is it well established that epidural analgesia is superior to systemic opioids in controlling postoperative pain, but it is also associated with significantly better outcomes. A large meta-analysis of 125 trials demonstrated that among adults undergoing surgery under general anesthesia, concomitant epidural analgesia is associated with decreased mortality and complications including cardiovascular, respiratory, and gastrointestinal compared with systemic analgesia. Their use has been well described in many operations ranging from simple hernia repairs to major abdominal surgeries. Opioids may be added to local anesthetic agents during continuous epidural analgesia or may be given as a single neuraxial shot. However, caution is advised since opioids, especially lipophilic formulations, can still enter systemic circulation resulting in adverse events.

Transversus abdominis plane (TAP) block is a type of peripheral block that provides excellent pain control for laparoscopic or open lower abdominal surgeries. This technique improves early and late pain at rest (but not pain during movement) and decreases the need for opioids. Additionally, preoperative TAP blocks provide superior pain control compared with postoperative administration. Paravertebral blocks should also be considered as an anesthetic adjunct in thoracic or breast surgical procedures. Their use is associated with decreased intraoperative opioid administration in patients undergoing elective breast surgery, albeit their impact on postoperative opioid administration is not as evident. Local soft tissue analgesic infiltration at the end of surgery also provides substantial pain relief and can reduce postoperative opioid consumption.

Nonsteroidal antiinflammatory agents (NSAIDs) and selective COX inhibitors are highly effective in reducing acute postoperative pain, opioid consumption, and opioid-related adverse events. Unless contraindicated, they should be considered in all patients undergoing surgery on a scheduled basis rather than on an as-needed basis. In a large meta-analysis that examined the effects of 46 single-dose oral analgesic agents, Etoricoxib 120 mg and Ketoprofen 25 mg were the two most effective NSAIDs with the lowest number of patients needed to treat to achieve 50%

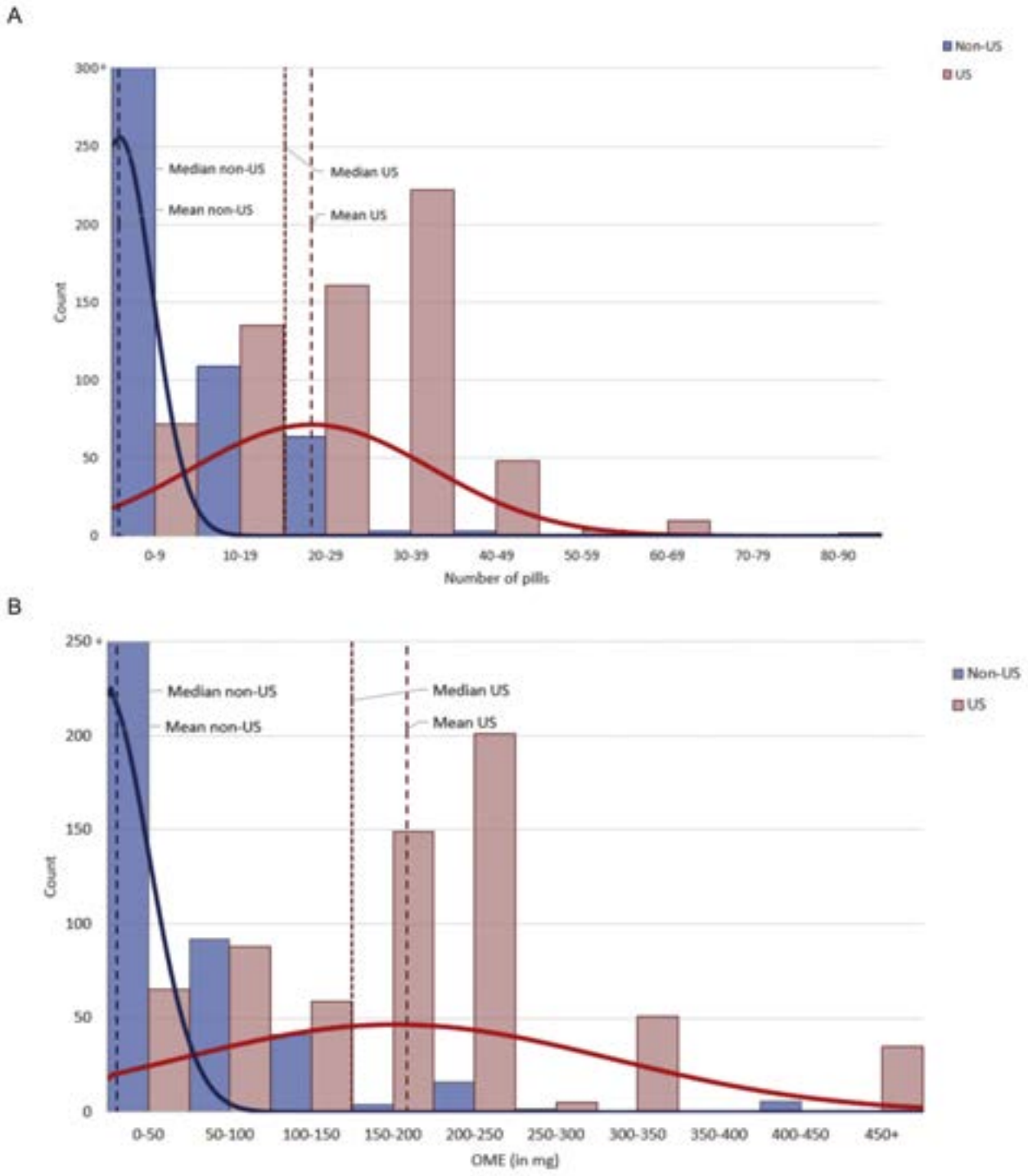


FIG. 1 Opioid dose in number of pills prescribed **(A)** and oral morphine equivalent (OME) **(B)** prescribed after herniorrhaphy, cholecystectomy, and appendectomy in US versus non-US patients. *(From Kaafarani HM, Han K, El Moheb M, et al. Opioids after surgery in the United States versus the rest of the world: the International Patterns of Opioid Prescribing [iPOP] multicenter study.* Annals of Surgery. *2020;272:879–886.)*

maximum pain relief over 4 to 6 hours. Similarly, paracetamol is also effective in managing postoperative pain and reducing the need for opioids; however, its effect is weaker than that of NSAIDs, and it should mainly be used as an adjunct to other analgesics. Systemic lidocaine in the perioperative period reduces postoperative pain severity, decreases the time to return of bowel function, reduces opioid consumption, and shortens hospital length of stay. Gabapentin and pregabalin have also been found to reduce postoperative pain and opioid consumption at 24 hours. Caution should be used when prescribing gabapentinoids, especially in the elderly, since they can cause sedation and dizziness.

PREOPERATIVE EDUCATION AND ASSESSMENT OF PATIENT NEEDS

Pain management should ideally begin as soon as the decision is made to proceed with surgery. At this stage, surgeons should inquire about patients' postoperative expectations and emphasize the goal of

BOX 1 Risk Factors for Adverse Effects and Death from Opioids

Medications/Substances

Benzodiazepines (F)
H_1 Antihistamines (F)
Illicit substances (including marijuana) (F)
Tobacco (F)
Alcohol (F)
Psychotropic medication use (F)
Substance abuse history (F)
Aberrant medication taking behaviors (F)

Neurologic

Dementia
Cognitive dysfunction
Gait problem
Tremor
Concentration problems
Coordination problems
Slow reaction time

Psychiatric Disorders

Depression (F)
Anxiety (F)
Personality disorder (F)
Thought disorders (F)
ADHD (F)
PTSD (F)
Impulse control problems (F)
Suicidal risk (F)

Pain-Related

Allodynia
Hyperalgesia

Cardiovascular

Coronary artery disease (F)
Dysrhythmia (F)
Cerebrovascular disease
Orthostatic hypotension

Sleep

Sleep disorders (F)
Insomnia

Respiratory disorders

COPD
Asthma
Recurrent pneumonia

Gastrointestinal

Abdominal pain
Gastroparesis
Constipation
Hepatitis (F)
Cirrhosis (F)
Nausea, emesis

Infectious Diseases

HIV

Metabolic/Renal

Severe obesity
Thermoregulatory problems
Water retention
Renal failure
Osteopenia
Osteoporosis

Reproductive

Testosterone deficiency
Erectile dysfunction
Pregnancy
Amenorrhea
Oligomenorrhea
Infertility
Ineffective birth control
Prostatic hypertrophy

Demographic/Social Support

Advanced age*
Family dysfunction (F)
Middle ages (teens to ~50s) (F)
Male
Unemployment (F)
Unmarried (F)
Less than high school education (F)
Lack of regular church attendance (F)
Legal problems (F)
White race (F)

Genotype(s)

Family history

F = Adverse effect includes reported fatality risk.

*Especially with mentation issues, fall risk, and debility.

ADHD, Attention-deficit/hyperactive disorder; *COPD*, chronic obstructive pulmonary disease; *HIV*, human immunodeficiency virus; *PTSD*, posttraumatic stress disorder. From Hegmann KT, Weiss MS, Bowden K, et al. ACOEM practice guidelines: opioids for treatment of acute, subacute, chronic, and postoperative pain. *Journal of Occupational and Environmental Medicine.* 2014;56(12):e143–159.

"tolerable pain" instead of "zero pain." Cognitive psychology plays a central role in how individuals perceive pain. Patients who understand that pain is a normal and expected response to injury and that their body needs time to heal recover faster than those without such mindful awareness. The goal of pain relief should be 30% to 50% improvement, and patients should expect to experience some level of tolerable pain. Surgeons should also be proactive about discussing with patients the adverse events and risks of dependence associated with opioid use. In a select few hospitals and clinics, opioid treatment agreements are sometimes created to document patient understanding, acknowledgment of potential side effects, and agreement with the expectations of opioid use.

In addition to standardizing pain management protocols, one of the other commonly used strategies in pain management is individually assessing a specific patient's needs to help determine whether opioids are warranted altogether, and if so, in what amount. The prescribing of analgesics is thus tailored to the level of discomfort and degree of pain severity. Patients whose postoperative pain is

comfortably managed with nonopioid alternatives do not have to be prescribed opioids. Physicians should also inquire about patients' desire to have or avoid opioids since studies have shown that patients are willing to experience some degree of pain to avoid the adverse effects of narcotics. This practice can decrease opioid prescribing because many surgeons tend to prescribe a set number of opioid pills depending on the surgical procedure performed, even in the absence of pain. A recent study showed that 83% of patients undergoing low-risk general surgery procedures are prescribed opioids despite reporting no postoperative pain. Only 25% to 40% of opioids that are prescribed are actually consumed by patients, and more than 75% of patients have leftover pills after surgery.

APPROPRIATE OPIOID PRESCRIBING

The goal of appropriate opioid prescribing is to bring postoperative pain to tolerable levels, while minimizing the adverse effects of opioids. This strategy helps mitigate the overprescription of unnecessary narcotics. Reducing the amount of opioids dispensed decreases postoperative opioid consumption without affecting the number of prescription refills and the level of satisfaction. Surgeons should communicate with other providers (e.g., emergency room physicians, primary care physicians) regarding pain management to ensure coordination of opioid therapy in terms of amount and duration.

If deemed necessary, opioids should be prescribed at the lowest effective dose possible and for a limited time period based on the expected duration to recovery without exceeding 7 days. Several recommendations have been published to help physicians manage postoperative pain. A 2017 systematic review identified a total of 41 articles with recommendations regarding postoperative opioid prescription, of which 15 were clinical practice guidelines. Additional recommendations have also been published since then. Procedure-specific guidelines provide surgeons with assistance on the level of opioids they should prescribe to patients at discharge after undergoing a particular type of surgery. These guidelines are mainly helpful in outpatient operations when surgeons have limited time to assess postoperative pain but may also be used for surgeries requiring inpatient admission. The publishing bodies of these recommendations include Massachusetts General Hospital (MGH), Mayo Clinic, University of Michigan, Johns Hopkins Health System, and Center for Opioid Research and Education. For example, the MGH consensus-built opioid guidelines provide surgeons with information on the maximum number of oxycodone pills they should prescribe for 42 different procedures across 11 specialties (Table 1). The MGH guidelines also emphasize the use of nonopioid alternatives including NSAIDs, gabapentin, acetaminophen, and regional anesthesia. A limitation of such procedure-specific guidelines is the assumption that all patients experience surgical pain in a similar way. The inpatient phase after surgery presents an opportunity for surgeons to assess the degree of pain and adopt a treatment strategy that is tailored to each patient's needs. Such a patient-centered approach accounts for individual variability in both the severity of pain experienced and the response to pain medications. There is evidence in the literature that the strongest predictor of opioid use after a procedure requiring inpatient stay is the number of opioid pills taken the day before discharge. The Dartmouth guidelines provide a simple way for determining the optimal number of opioid pills to prescribe at discharge based on this information (Table 2). This approach has been shown to satisfy the need of more than 90% of patients. Elderly patients, women, and those with low body weight should be prescribed lower doses of opioids. It is important to note that most recommendations apply to opioid-naïve patients who do not have a history of chronic pain. Special considerations should be given to patients already receiving opioid agonist therapy (e.g., methadone, buprenorphine). Their management is complex and consultation with a pain specialist may be necessary.

It is generally recommended that opioids be prescribed to be taken at night or when not at work to avoid the risk of impairment and lost time from work due to their side effects. Opioids should be discontinued when patients reach meaningful functional recovery with tolerable pain with nonopioid medications. Opioid-naïve patients who were treated for acute pain do not require opioid dose tapering. Patients who were continuously taking high doses of opioids (greater than 50 mg of morphine or equivalent dose) may benefit from gradually tapering the doses over 3 to 7 days.

CHRONIC OPIOID USE AFTER SURGERY

Opioids prescribed after surgery may trigger long-term use, even if prescribed for outpatient or short-stay surgeries associated with minimal postoperative pain. Opioid-naïve patients who are prescribed opioids after surgery could have up to a fivefold increase in the risk of chronic opioid use 1 year after discharge, and more than 60% of patients who receive continuous opioid therapy for 90 days remain on opioids years later. It is therefore important to identify patients who could be at increased risk of becoming long-term users and creating postoperative pain management strategies that decrease or mitigate such risk. The Stopping Opioids After Surgery (SOS) score was specifically developed for this purpose allowing surgeons to predict the risk of sustained postoperative opioid use at the bedside (Table 3). The score considers several factors including age, sex, discharge destination, socioeconomic status, complexity of the procedure, length of stay, psychiatric comorbidities, and history of opioid use. Other risk factors for persistent opioid use have been reported in other studies and include preoperative use of benzodiazepines, antidepressants, or antipsychotics, and history of alcohol or drug abuse. Patients who are deemed high-risk should be closely monitored for signs of opioid dependence such as failure to improve as expected and persistent requirement of high opioid doses, and proactively supported to prevent or mitigate opioid abuse. The Revised Opioid Assessment for Patients with Pain (SOAPP-R), the Pain Medication Questionnaire, and the Current Opioid Misuse Measure are well-studied tools that can help clinicians screen for aberrant drug-related behavior. Prescription drug-monitoring programs should also be routinely checked.

Opioid misuse should not be confused with persistent postoperative pain requiring long-term treatment. For patients with subacute or chronic surgical pain, alternative analgesics should be sought first. Nonopioid analgesics (e.g., NSAIDs, selective serotonin reuptake inhibitors, tricyclic antidepressants) have been shown to be at least equivalent if not superior to opioids in managing subacute and chronic pain. Opioids should only be prescribed as a last resort when pain cannot be adequately controlled with nonopioid analgesics. When opioids are prescribed for chronic pain, it may be beneficial to switch to a different opioid medication than the one used for acute pain to improve the response to analgesic therapy, achieve better functional outcomes, and reduce adverse effects. To avoid drug overdose when transferring one opioid to another, the new opioid must be started at a morphine equivalent dose that is half that of the previous opioid (Table 4). Several online resources are available to facilitate conversion of different opioid medications to morphine equivalents.

DISPOSAL OF EXCESS OPIOID PILLS

Unused opioid pills pose a serious threat to patients as well as the community at large. Excess opioid prescribing has been linked to increased emergency room visits. In addition, leftover pills often are diverted into the community, which further feed into the epidemic. The US Food and Drug Administration has established recommendations describing the proper disposal of unused pills to mitigate the mishandling of opioids. Patients may either return unused pills to designated and secure drop boxes or dissolve them in water and mix

TABLE 1 Massachusetts General Hospital Guidelines and Standardized Maximum Number of Pills to be Prescribed for 42 Different Procedures

Procedure	Number of Pills (Oxycodone 5 mg)
GENERAL SURGERY*	
Abscess incision & drainage	5
Appendectomy – laparoscopic	10
Cholecystectomy – laparoscopic	15
Colectomy – laparoscopic or open	20
Exploratory laparotomy	20
Gastrectomy	20
Hernia – hiatal laparoscopic	30
Hernia – inguinal laparoscopic or open repair	15
Hernia – umbilical repair	5
Muscle biopsy	5
Roux-en-Y gastric bypass	20
Sleeve gastrectomy	20
SURGICAL ONCOLOGY	
Lumpectomy and SLN biopsy	5
Mastectomy without reconstruction	10
Mastectomy with LND without reconstruction	20
Mastectomy with SNB without reconstruction	10
Pancreatectomy – distal – laparoscopic	25
Pancreatectomy – distal – open	40
Pancreatectomy – distal – Whipple procedure	40
VASCULAR	
Amputation – Toe	5
Aortic Aneurysm Repair – infrarenal open	20
Dialysis access placement or revision	10
Femoral popliteal bypass (with prosthetic)	15
Carotid endarterectomy	10
CARDIOTHORACIC	
Aortic valve replacement (hemisternotomy)	15
Coronary artery bypass graft (sternotomy)	20
Minimally invasive mitral valve repair	15
Tracheal resection	10
Thoracotomy	80
VATS lobectomy/wedge resection	60
HEAD & NECK	
Laryngeal medialization	15
Microlaryngoscopy	15
Parathyroidectomy	5
Thyroidectomy	10
Tonsillectomy	60
TRANSPLANT	
Transplant – kidney	15
Transplant – laparoscopic donor nephrectomy	20
Transplant – liver (discharged home >7 days)	20
Transplant – liver (HCC, or discharged home <7 days)	30
BURNS	
Burn – 5% partial thickness – discharged	35
Burn – 5% partial thickness treated with xenograft	26
Burn – focal – one or two operations	28

Surgeons should not exceed the maximum number of opioid pills for each procedure and are encouraged to prescribe even less than the recommendation. A multimodal approach to pain management is emphasized. Alternatives to opioids should be considered first such as non-steroidal anti-inflammatory drugs, acetaminophen, gabapentinoids, regional anesthesia, mindfulness exercises, virtual reality, and photobiomodulation therapy.

*Includes pediatric surgery, colorectal surgery, trauma & acute care surgery, bariatric surgery

HCC, Hepatocellular carcinoma; *LND*, lymph node dissection; *SLN*, sentinel lymph node; *VATS*, video-assisted thoracoscopic surgery.

From Kaafarani HM, Eid AI, Antonelli DM, et al. Description and impact of a comprehensive multispecialty multidisciplinary intervention to decrease opioid prescribing in surgery. *Annals of Surgery.* 2019;270(3):452V62.

TABLE 2 Dartmouth Guideline for Discharge Opioid Prescription After Inpatient Surgical Procedures

Opioid Pills Taken the Day Before Discharge	Number of Pills to Prescribe at Discharge (Oxycodone 5 mg)
0	0
1–3	15
≥4	30

them with dirt or cat litter. Despite these recommendations, very few patients dispose of their excess medications appropriately, largely due to lack of awareness and proper counseling. Surgeons should play an active role in discussing with their patients the appropriate methods of opioid disposal practices before they are discharged home. Other interventions such as calling patients a few days before their postoperative visit to remind them to dispose of any leftover pills have also proven to be effective. Finally, asking patients to record how much opioids they used and how they disposed of excess pills encourages them to handle opioids responsibly.

TABLE 3 The Stopping Opioids After Surgery (SOS) Score for Sustained Opioid Use After Surgery

Characteristic	Score
Age	
18–24	0
25–34	3
35–44	4
45–54	4
55–64	4
Sex	
Male	0
Female	3
Discharge Status	
Home	0
Nonhome	11
Socioeconomic Status	
High	0
Low	5
Procedure Category	
Minor	0
Major	4
Length of Stay, Days	
<3	0
>3	1
Depression	4
Anxiety	4
Prior Opioid Use	
No use	0
Prior opioid exposure	17
Prior sustained opioid use	36
Total score	**100**

Opioid Risk Score Range	Likelihood of Sustained Opioid Use, Mean (SD), %
<31	4.1 (2.5)
31–50	14.9 (6.3)
>50	35.8 (3.6)

A score of 31 or lower indicates low risk of sustained opioid use, a score of 31–50 indicates intermediate risk for sustained opioid use, and a score of 51 or higher indicates a high risk for sustained opioid use.
From Chaudhary MA, Bhulani N, de Jager EC, et al. Development and validation of a bedside risk assessment for sustained prescription opioid use after surgery. *JAMA Network Open.* 2019;2(7):e196673.

TABLE 4 Oral Morphine Milligram Equivalents (MME) Conversion Factor in Milligrams (mg)

Type of Opioid (Strength Units)	MME Conversion Factor
Buprenorphine film/tablet (mg)	30
Buprenorphine patch (mcg/h)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche (mcg)	0.13
Fentanyl film or oral spray (mcg)	0.18
Fentanyl nasal spray (mcg)	0.16
Fentanyl patch (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone (mg)	
>0, ≤20	4
>20, ≤40	8
>40, ≤60	10
>60	12
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine	0.37
Tapentadol (mg)	0.4
Tramadol (mg)	0.1

From cms.gov

METHODS TO DECREASE OPIOID PRESCRIBING

The drivers of postoperative opioid overprescription are multifaceted, and addressing this widespread practice requires intervening at multiple stages. Comprehensive institutional interventions that raise both provider and patient awareness of the opioid epidemic and create standardized guidelines for postoperative pain management have been shown to not only decrease the number of opioids prescribed without increasing refills but also eliminate sex and race opioid prescription disparities. Electronic medical records have default opioid prescription doses that are not procedure specific, and the amount of opioids that can be prescribed at discharge is not capped. Thus, changing the default opioid prescription to the maximum number of opioids that can be prescribed for a specific procedure is an important yet easy step that can help clinicians who are pressured with time from overprescribing. Clinical training programs should incorporate postoperative pain management as a core competency since interns and junior residents write the majority of prescriptions at discharge. At the state level, legislatures have been passed limiting the maximum number of opioids that can be prescribed to individuals.

CONCLUSION

The use of opioid medications in surgical patients presents a unique challenge that requires balancing two competing objectives: adequately controlling pain in the immediate postoperative period and

minimizing the short- and long-term adverse effects of opioids. Optimal management of postoperative pain should focus on a multimodal regimen primarily relying on nonopioid alternatives, with the addition of opioids only in patients with moderate to severe pain who are inadequately controlled with nonopioid analgesics. This approach maximizes the benefit of pain medications while minimizing the side effects of opioid use, thereby facilitating the return of patients to their baseline level.

SUGGESTED READINGS

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El Moheb M, Mokhtari A, Han K, et al. Pain or no pain, we will give you opioids: relationship between number of opioid pills prescribed and severity of pain after operation in US vs non-US patients. *Journal of the American College of Surgeons*. 2020;231(6):639–648.

Kaafarani HM, Eid AI, Antonelli DM, et al. Description and impact of a comprehensive multispecialty multidisciplinary intervention to decrease opioid prescribing in surgery. *Annals of Surgery*. 2019;270(3):452–462.

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Thiels CA, Anderson SS, Ubl DS, et al. Wide variation and overprescription of opioids after elective surgery. *Annals of Surgery*. 2017;266(4):564–573.

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Management of Postoperative Delirium

Amballur David John, MD, and Frederick Sieber, MD

INTRODUCTION

Delirium is common in the geriatric population, though incidence varies with the clinical context. This chapter will focus on management of postoperative delirium in older adults. A systematic review and meta-analysis reported an 18.7% pooled incidence of postoperative delirium after in-hospital elective surgery in patients greater than 65 years of age. The pooled incidence differed depending on surgical procedure, with general surgery having the highest at 26.6%, followed by cardiac (23.6%), vascular (15.8%), orthopedic (15.2%), and urologic surgery (12.7%). Postoperative delirium is expensive. Total direct 1-year healthcare costs attributable to delirium range from $143 billion to $152 billion nationally (in 2005 dollars). For hospitalized patients, development of delirium is an indicator of poor prognosis, with its associated increase in length of stay, decreased level of function, and increased requirements for nursing home placement. Severity of delirium is also associated with increased overall 1-year mortality.

DEFINITION

Delirium is a clinical diagnosis defined by the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) as a disturbance in attention and awareness that has an acute onset and fluctuates over time. Delirium represents a change in cognition that is not from a preexisting cognitive disorder or a state of severely reduced arousal such as coma. Delirium can result from multiple etiologies, underlying comorbidities, or drugs. Common symptoms of delirium that may be observed by the surgeon are outlined in Table 1 in approximate order of specificity.

It is important to distinguish delirium from other conditions that may appear similar—especially dementia, depression, and psychosis. Dementia occurs over months to years with a gradual progressive decline in function, and it is not reversible. Depression may occur after a specific life event or health issue and continues over weeks to months to years. Depressed patients often have normal attention, alertness, and perception. They display decreased interest in activities, may show concern for memory loss, and become progressively less physically active and withdrawn. If a patient experiences hallucinations and delusions, psychosis may be considered. However, it is unusual to develop psychotic psychiatric illness late in life; rather, these symptoms are more likely indicative of an acute medical issue.

Depending on the patient's level of activity, delirium may be further characterized as hypoactive, hyperactive, or mixed. Hypoactive is most common after surgery and is associated with decreased awareness, activity, and speech. Symptoms of hyperactive delirium include restlessness, increased motor activity, and loss of control. Mixed-type delirium has features of both hypo- and hyperactive delirium with fluctuation between hyperactivity and hypoactivity.

DIAGNOSIS

A clinical diagnosis of delirium requires bedside examination to detect disturbances in attention and cognition. In addition, the fluctuating course of disturbance in attention and awareness should be confirmed by using information obtained from the patient, family, members of the caregiving team, or the medical record. Numerous diagnostic instruments are available to help formalize and standardize the clinical diagnosis process. Choice of instrument depends on accuracy, feasibility, and training requirements. Table 2 shows

TABLE 1 Symptoms of Delirium in Approximate Order of Specificity

Specificity Rank	Symptom
1	Instability of mental status findings over time
2	Nonauditory hallucinations (visual hallucinations are symptoms of delirium until proven otherwise)
3	Misperceptions and illusions
4	Impaired attention
5	Disorientation
6	Impaired level of consciousness
7	Auditory hallucinations
8	Delusions
9	Affective symptoms

TABLE 2 Commonly Used Diagnostic and Screening Instruments for Delirium

Instrument	Time Required (Minutes)	Training Required
Diagnostic instruments		
Confusion Assessment Method (CAM)	10	Yes
CAM variants		
3D-CAM	3	Yes
bCAM	<2	Yes
CAM-ICU	3	Yes
CAM-S	5–15	Yes
FAM-CAM	5–10	Yes
4As Test (4AT)	<2	No
Delirium Rating Scale (DRS)	90–150	Yes
Memorial Delirium Assessment Scale (MDAS)	25–40	Yes
Nursing Delirium Screening Scale (Nu-DESC)	1–2	Yes
Screening instruments		
Ultra-brief 2-items (UB-2)	<1	Yes
Ultra-brief CAM (UB-CAM)	1–3	Yes

some commonly used delirium instruments. In the United States, the Confusion Assessment Method or one of its variants is often the instrument of choice.

The widespread prevalence of delirium in the hospital has led to the development of rapid screening tools that can be used in a variety of settings and require little training. However, evidence is insufficient to recommend routine delirium screening of all older surgical patients. The National Institute for Health and Care Excellence guidelines suggest that delirium screening be performed at presentation and daily for at-risk patients (see later in this chapter). Recognizing that delirium incidence is higher in the intensive care unit (ICU) than on the surgical wards, the Society of Critical Care Medicine recommends routine screening for delirium in all adult ICU patients.

Accurate diagnosis of delirium requires considerable expertise and training. Therefore, regardless of whether a screening or diagnostic instrument is used to detect delirium, it is important that its presence be verified by a specialty-trained individual to confirm the diagnosis.

RISK FACTORS

The important concept in assessing preoperative risk for delirium is that the onset of delirium often results from a deleterious interaction between predisposing factors for delirium vulnerability and precipitating factors or insults that provoke delirium. This relationship is a two-way interaction such that individuals with high baseline vulnerability require less severe insults to trigger delirium, whereas those with less baseline vulnerability require more severe insults to trigger delirium. The relationship between predisposing and precipitating factors for delirium is illustrated in Figure 1. Many baseline vulnerabilities and precipitating insults for delirium have been identified. Interventions to prevent or treat delirium are based on ameliorating

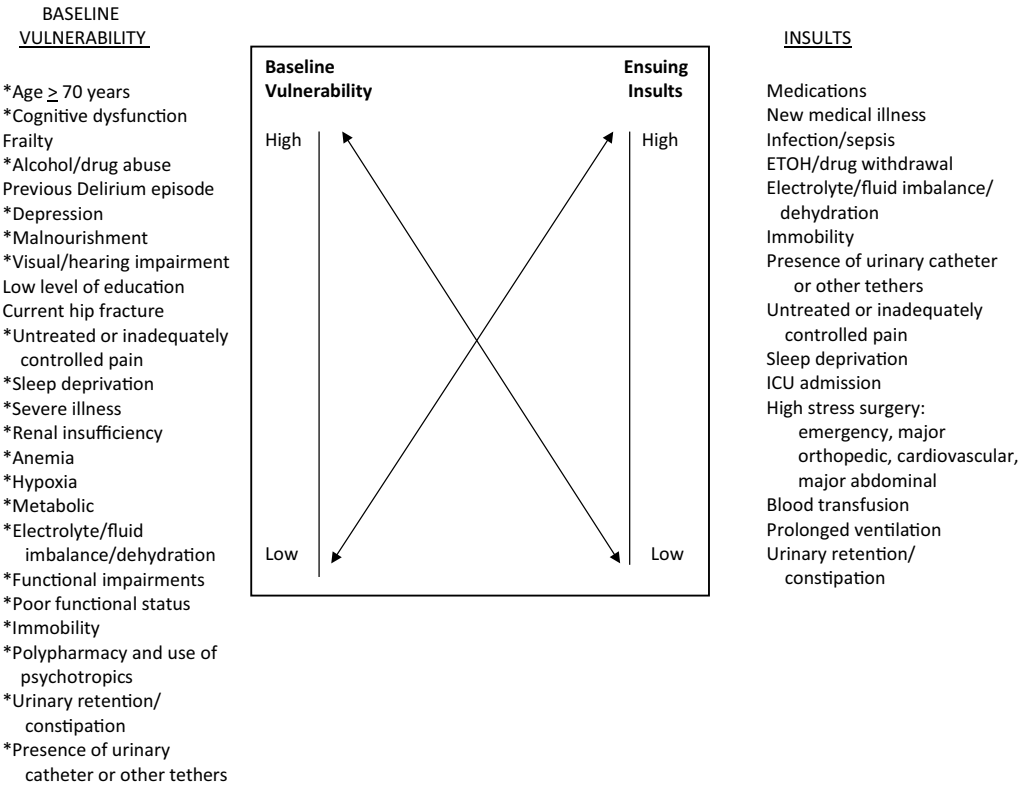


FIG. 1 Interaction between baseline vulnerability and ensuing insults. *Delirium risk factors to be assessed for preoperatively according to recommendations by the American College of Surgeons NSQIP/American Geriatrics Society Best Practice Guidelines: Optimal Preoperative Assessment of the Geriatric Surgical Patient.

the effects of recognized predisposing and precipitating factors that are amenable to intervention.

PRINCIPLES OF DELIRIUM PREVENTION

Although delirium management is important, the primary emphasis for the clinician should be prevention. The overall approach to delirium prevention involves recognizing and minimizing the effects of both underlying vulnerabilities and ensuing perioperative insults in surgical patients at risk of postoperative delirium. The most commonly employed evidence-based approaches and their strength of recommendation by the American Geriatrics Society are outlined in the following section.

The first principle in delirium prevention is preoperative screening and identification of patients at risk for postoperative delirium. The American College of Surgeons NSQIP/American Geriatrics Society best practice guidelines for optimal perioperative management of geriatric surgical patients recommend that preoperative evaluation for delirium risk include assessment for many of the baseline vulnerabilities outlined in Figure 1. The presence of one or more of these risk factors has been associated with an increased risk of postoperative delirium. Cognitive impairment is the most important risk factor for assessment. Simple tools, such as the Mini-Cog, which includes a clock draw and three-item recall, provide a validated, quick, and easy means to screen for cognitive dysfunction.

Certain medications with central nervous system effects are predisposing factors for delirium. Physicians and surgeons should avoid administering drugs associated with delirium (strong recommendation per American Geriatrics Society). Commonly used medications associated with delirium are listed in Table 3. Several drug classes have strong tendencies to provoke delirium. These include the anticholinergics, benzodiazepines, and meperidine.

Excessive medication dosing is a predisposing factor for delirium. All drugs should be dosed in an age-appropriate manner. Physiologic changes that occur with aging, such as decreases in kidney, hepatic, and brain reserve, as well as alterations in distribution volumes, act to alter both pharmacokinetics and pharmacodynamics. As a result, dosage of most drugs needs to be decreased. Careful consideration must be given to the dosing of anesthetic agents. Processed electroencephalography (BiSpectral index [BIS monitor]) may be considered for intraoperative use to help guide determination of optimal general anesthetic dosing in older surgical patients (insufficient evidence for any recommendation per American Geriatrics Society).

It is a common misconception that any anesthetic technique, particularly regional anesthesia, is associated with less postoperative delirium than general anesthesia. Comparisons of regional and general anesthesia have shown no difference in postoperative delirium incidence.

Pain is an important precipitating factor for triggering postoperative delirium, and optimizing pain control is an important principle of delirium prevention. Although regional anesthesia is not associated with a lower delirium incidence than general anesthesia, the efficacy of regional anesthesia lies in its role in postoperative pain management. Regional techniques for pain management may decrease postoperative delirium risk by providing better pain control while decreasing narcotic requirements (weak recommendation per American Geriatrics Society). Higher opioid doses are precipitating factors for delirium. In general, multimodal analgesic regimens focused on decreasing the need for narcotic administration are associated with improved cognitive outcomes (strong recommendation per American Geriatrics Society). Use of gabapentin, acetaminophen, and nonsteroidal antiinflammatory drugs should be incorporated, when appropriate, into the postoperative pain regimen. Recent data suggest that around the clock as opposed to PRN dosing of these drugs provides better pain outcomes. It is not always possible to avoid narcotic administration. In this circumstance, meperidine is the primary opioid that should be avoided. In comparisons of fentanyl, morphine, and hydromorphone, no differences in cognitive outcome are apparent.

TABLE 3 Commonly Used Medications Associated with Postoperative Delirium

Drug Class or Drug	Examples
Drugs with anticholinergic properties	
Tricyclic antidepressants	Amitriptyline, doxepin, imipramine
Antihistamines	Cyproheptadine, diphenhydramine, hydroxyzine
Antimuscarinics	Oxybutynin, tolterodine
Antispasmodics	Hyoscyamine, scopolamine
First-generation antipsychotics	Chlorpromazine, thioridazine
H_2-receptor antagonists	Cimetidine, ranitidine
Skeletal muscle relaxants	Cyclobenzaprine, tizanidine
Antiemetics	Promethazine
Olanzapine	
Paroxetine	
Corticosteroids	Methylprednisolone, prednisone
Meperidine	
Sedative hypnotics	
Benzodiazepines	Alprazolam, diazepam, lorazepam, midazolam
Sedative hypnotics	Zolpidem, zaleplon
Polypharmacy	Starting ≥5 new medications increases risk of delirium

Using multicomponent nonpharmacologic interventions simultaneously addresses several predisposing and precipitating risk factors for developing delirium and provides the best results for delirium prevention (strong recommendation per American Geriatrics Society). This approach entails a significant amount of effort, time, and resources but has been demonstrated to prevent up to 30% of all delirium episodes. Greatest success occurs with a multidisciplinary approach that incorporates input from surgery, nursing, and medicine. In addition, formal educational programs for healthcare professionals on delirium in at-risk older surgical adults should be implemented to improve understanding of its epidemiology, assessment, prevention, and treatment (strong recommendation per American Geriatrics Society). Best practice guidelines from the American College of Surgeons concerning nonpharmacologic approaches on the surgical ward are outlined in Box 1. Family involvement is important in management. Keep those concerned about the patient updated with information about the patient's condition, what delirium is, and how they can help, while letting the patient know that their loved ones are involved and inquiring after them. Maintaining constant communication with the patient while providing reassurance is a first step. A bed next to a window will help with day/night reorientation. Simple steps such as addressing sensory impairments by ensuring that hearing aids and glasses are available and ensuring that patients have their dentures should be routine. Assess pain by looking for nonverbal signs in patients with communication difficulties and starting appropriate pain management for those in whom pain is suspected. Early mobilization, whether walking or carrying out range of motion exercises to limit immobility, should be encouraged. Ensure that patients have adequate food, nutrition, and hydration and are not constipated. Limit location changes. Promote sleep by reducing noise, limit medication rounds

BOX 1 Multicomponent, Multidisciplinary, Nonpharmacologic Interventions for Delirium Prevention as Recommended by the American College of Surgeons

- Daily physical activity
- Cognitive reorientation
- Bedside presence of a family member whenever possible
- Sleep enhancement (for example, nonpharmacologic sleep protocol and sleep hygiene)
- Early mobility and/or physical rehabilitation
- Adaptations for visual and hearing impairment
- Nutrition and fluid repletion
- Pain management
- Appropriate medication usage
- Adequate oxygenation
- Prevention of constipation
- Minimization of patient tethers whenever possible (for example, Foley catheters, periodic removal of sequential compression devices, EKG cords)

to avoid disturbing sleep, and avoid nursing or medical procedures during sleep hours. For those patients who are high risk on discharge, physicians should ensure that adequate assistance is available and that follow-up care occurs. Although evidence is strong that nonpharmacologic approaches are efficacious on the surgical ward, at present it is unclear that these interventions are similarly efficacious in the ICU. Box 2 summarizes evidence-based interventions for delirium prevention.

Many studies have focused on prophylactic administration of various pharmacologic agents for delirium prevention. Among these, cholinesterase inhibitors, statins, ketamine, steroids, and melatonin have no proven efficacy for prevention of postoperative delirium. On the other hand, dexmedetomidine, when administered as a sedative to patients on mechanical ventilation in the ICU, has been associated with a lower incidence of delirium than have other sedative agents such as propofol or benzodiazepines. Prophylactic haloperidol does not prevent postoperative delirium. However, early studies suggest that low doses of second-generation antipsychotics such as risperidone or olanzapine may provide limited efficacy for delirium prevention (insufficient evidence for any recommendation per American Geriatrics Society). This finding merits further investigation before definitive recommendations can be made.

PRINCIPLES OF DELIRIUM MANAGEMENT

Despite practitioners' best efforts at prevention, delirium remains a common postoperative occurrence. When faced with managing postoperative delirium, a structured tiered approach is recommended. The first priority is to identify and treat any acute and life-threatening underlying condition, as acute delirium onset can indicate physiologic impairment. A broad assessment for possible life-threatening conditions such as sepsis, pulmonary pathology, urinary tract infection, myocardial infarction or dysfunction, fracture, and acute neurologic dysfunction should be undertaken. A detailed examination of recent medication administration or possible toxicology may be helpful. Aggressive management of any physiologic derangement such as bleeding, hypoxia, hypothermia, and hypotension is warranted.

Once acute life-threatening conditions have been treated or excluded, the next step is to identify and treat any precipitating factors of delirium. Medical evaluation, medication and/or environmental adjustments, and appropriate diagnostic tests and clinical consultations should focus on underlying contributors to delirium that are amenable to intervention (strong recommendation per American Geriatrics Society). Some of the common precipitating factors that patients should be evaluated for are outlined in Figure 1.

Finally, multidisciplinary interventions should be continued in all delirious patients (weak recommendation per American Geriatrics Society). Although this approach has proven efficacy in delirium prevention, these measures are less effective after delirium has ensued.

Antipsychotics are not first-line treatments for postoperative delirium (strong recommendation per American Geriatrics Society). Routine use of antipsychotics for delirium management is not associated with decreased duration or severity of the delirium episode. In addition, the use of antipsychotics for delirium treatment is *not* approved by the FDA! Antipsychotic medications should not be administered to older patients with postoperative delirium unless they are severely agitated and threatening harm to self and others. In addition, antipsychotics should be employed only if behavioral interventions have failed or are not possible. *If absolutely necessary*, antipsychotics can be used to calm patients with hyperactive delirium (weak recommendation per American Geriatrics Society). In this circumstance, antipsychotics may be used at the lowest effective dose for the shortest possible duration. Both typical and atypical antipsychotics have similar efficacy in management of hyperactive delirium. When dosing antipsychotics, go low and start slow, as these drugs have many associated side effects, including anticholinergic effects, orthostatic hypotension, extrapyramidal effects, acute dystonias, and prolonged QT interval. For example, with severe agitation in elderly/frail patients, initial recommended doses of oral/intramuscular haloperidol are in the range of 0.5 to 1.0 mg. Ongoing antipsychotic use should be evaluated daily with in-person patient examination.

Benzodiazepines are not a first-line treatment for the agitated postoperative delirious patient who is threatening substantial harm to self and/or others and should not be used to treat postoperative delirium except when they are specifically indicated (strong recommendation per American Geriatrics Society). Specific indications for benzodiazepines include, but are not necessarily limited to, treatment of alcohol or benzodiazepine withdrawal. Benzodiazepines should be administered at the lowest effective dose for the shortest possible duration and only if behavioral measures have failed or are not possible. Ongoing use should be evaluated daily with in-person examination of the patient. Box 3 summarizes evidence-based recommendations for delirium management.

BOX 2 Summary of Recommendations for Prevention of Delirium

- Identify at-risk patients
- Use multicomponent, nonpharmacologic interventions for prevention in non-ICU patients
- Avoid medications that may induce delirium
- Optimize postoperative pain management—preferably with a multimodal approach and regional anesthesia
- Consider intraoperative depth-of-anesthesia monitoring during general anesthesia

BOX 3 Summary of Recommendations for Treatment of Delirium

- Complete medical examination in patients diagnosed with postoperative delirium to identify possible precipitating factors amenable to intervention
- Antipsychotics should not be administered to patients with postoperative delirium unless they are severely agitated and threatening harm to self or others
- Benzodiazepines should not be administered to the agitated delirious patient unless specifically indicated (e.g., alcohol or benzodiazepine withdrawal)

CONCLUSION

Postoperative delirium is a common complication in the geriatric population. Efforts should be focused on prevention in at-risk patients. The best means of preventing delirium are through use of nonpharmacologic multicomponent interventions. Delirium management primarily entails recognition and treatment of underlying precipitating factors.

Suggested Readings

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The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *J Am Geriatr Soc*. 2015;63:142–150.

COVID-19 and Health Care Delivery in a Pandemic

Michael S. Burnim, MD, and Brian T. Garibaldi, MD

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, Hubei, China in December 2019. Within a matter of months, it caused the worst global pandemic since influenza in 1918. The following winter, the United States suffered at least 3400 deaths each day. Worldwide, by the summer of 2022, there were more than 600 million cases and 6 million deaths. Apart from its massive societal impact, SARS-CoV-2 has broadly affected the delivery of medical care.

The family of coronaviruses includes several endemic strains responsible for seasonal colds as well as 2% to 3% of cases of community-acquired pneumonia. Prior beta-coronaviruses have been responsible for more limited pandemics, most notably Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). SARS afflicted 8000 people in 12 countries between 2003 and 2004, ultimately killing almost 800.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Infection with SARS-CoV-2 may cause symptomatic disease, typically referred to as coronavirus disease 2019 (COVID-19). Disease is caused by several mechanisms including early direct viral cytopathic effects and later immune dysregulation, endothelial inflammation, and hypercoagulability. Among laboratory-confirmed cases in the United States in the first 4 months of the pandemic, 14% resulted in hospitalization, 2% in ICU admission, and 5% in death. The risk of a severe course (invasive mechanical ventilation/ECMO/discharge to hospice/death) increases exponentially with age. Other important risk factors for severe disease include male sex, liver disease, dementia, and obesity. African-American and Asian race, even after adjusting for traditional risk factors, are also associated with severe disease. Vaccination is highly protective against severe disease, even with newer variants. After widespread vaccination in the United States, most hospitalizations and deaths have occurred in nonvaccinated or incompletely vaccinated individuals, even with newer circulating variants of concern such as the alpha, delta, and omicron variants. Increasing vaccine coverage, through equitable global distribution and combating vaccine hesitancy, is the only realistic path to the end of the COVID-19 pandemic.

The typical incubation period of SARS-CoV-2 is 4 to 5 days but can be as long as 2 weeks. SARS-CoV-2 causes both pulmonary and nonpulmonary disease with radiographic abnormalities (e.g., ground glass opacities, patchy infiltrates) common even in asymptomatic individuals. In areas with high rates of transmission, clinical index of suspicion must be high as patients may initially present with nonspecific symptoms such as myalgia, fatigue, headache, diarrhea, and confusion. Fever is often absent. In those with severe courses, disease often worsens in the second week of illness. Among those with severe illness, acute kidney injury, encephalopathy, and venous thromboembolism are common. Rarer complications include cardiomyopathy, stroke and other arterial thrombi, secondary infections like invasive aspergillosis, and multisystem inflammatory syndrome in children and adults (often in patients who did not initially have symptomatic disease).

DIAGNOSIS

While a number of symptoms and laboratory abnormalities are associated with COVID-19, few are specific for it. Thus, COVID-19 is diagnosed by viral antigen or reverse transcription polymerase chain reaction (RT-PCR) testing. Antigen testing is less sensitive but more specific. RT-PCR testing is sensitive enough to detect minute amounts of either nonviable virus or viral debris. Thus, it will also identify patients who have recovered or had asymptomatic infections. RT-PCR testing is not recommended in individuals who have recovered from COVID-19 in the prior 3 months unless they are significantly immunocompromised and are presenting with symptoms consistent with recrudescent or recurrent infection. Diagnosis in these cases typically requires input from infectious disease specialists. Similarly, patients who present with classic signs and symptoms of COVID-19 in the absence of an alternate explanation may need to remain under isolation even if they have a negative RT-PCR result.

While no other laboratory tests are sensitive or specific for COVID-19, common findings include lymphopenia, elevated transaminases, and elevated inflammatory markers (e.g., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], ferritin, lactate dehydrogenase [LDH]). Plain chest radiograph is sufficient for initial evaluation unless an additional diagnosis such as pulmonary embolism (PE) is suspected. Typical radiographic findings include bilateral, peripheral, and lower lung predominant dense or hazy opacities (Fig. 1). Chest CT demonstrates ground glass opacities with or without consolidation in the same distribution and may also show pleural and/or interlobular septal thickening (Fig. 2).



FIG. 1 A 47-year-old woman with a history of thymectomy presented with 5 days of generalized body aches, fever, and dyspnea. AP chest x-ray shows multifocal hazy airspace opacities in middle and lower lung zones.

MANAGEMENT

The first consideration in caring for a patient with suspected or confirmed COVID-19 is proper infection control to protect healthcare workers as well as to prevent nosocomial spread. Organizational principles and environmental engineering are the first lines of defense. In areas of high levels of infection, SARS-CoV-2 patients are typically cohorted in dedicated units. Patients with suspected COVID-19 should be separated from noninfected patients, but they should not be exposed to (e.g., share rooms with) patients who have confirmed COVID-19. When possible, patients with suspected or confirmed COVID-19 should be managed in negative pressure rooms or a negative pressure ward. Staff caring for these patients must wear appropriate personal protective equipment (PPE) and be trained in its use. Gowns, gloves, and eye protection (ideally a full-face shield) should be worn. Eyeglasses do not provide sufficient protection. Where resources permit, all staff should wear a N95 respirator or power air-purifying respirator (PAPR). If these are in short supply, tight-fitting surgical masks can be used for routine care, and N95 and PAPRs may be reserved for aerosol-generating procedures including but not limited to bronchoscopy, noninvasive ventilation (NIV), high-flow nasal cannula (HFNC), open suctioning, tracheal intubation and extubation, cardiopulmonary resuscitation, and administration of nebulized medications (where meter-dosed inhalers are not feasible or appropriate). These precautions should apply regardless of staff vaccination status, and they should remain until COVID-19 has been ruled out or the patient is no longer infectious (typically 10 days in immunocompetent individuals or 20 days in immunocompromised or critically ill patients).

Mild cases of COVID-19 can be managed expectantly on an outpatient basis with appropriate instructions on self-isolation and/or referral to quarantine facilities where these exist. Patients at risk for severe disease (e.g., age >65 years or immunocompromised) should be offered therapy with nirmatrelvir-ritonavir, an oral antiviral medication. If nirmatrelvir-ritonavir is not available or cannot be used due to prohibitive drug interactions, the monoclonal antibody bebtelovimab and intravenous remdesivir are other potential treatment options (Table 1). When given promptly, these treatments reduce the risk of hospitalization or mortality by almost half. Regardless of whether or not one of these treatments is given, patients of advanced age or with medical comorbidities should be counseled that, while most infections improve without intervention, medical reevaluation is essential if symptoms progress.

For patients requiring hospitalization, multiple evidence-based pharmacologic and nonpharmacologic treatments exist. The intravenous antiviral remdesivir inhibits the RNA-dependent RNA polymerase of SARS-CoV-2 and is recommended by the National Institutes of Health (NIH) and the Infectious Disease Society of America (IDSA) for patients requiring low-flow supplemental oxygen. In the multinational randomized controlled Adaptive COVID-19 Treatment Trial (ACTT) trial, remdesivir reduced median time to recovery from 15 to 10 days and was associated with a significant reduction in mortality (4.0% vs. 12.7%) in the subgroup of patients who required oxygen supplementation but not high-flow nasal cannula (HFNC) or invasive mechanical ventilation (IMV). In the United States, remdesivir is routinely given early in the disease course (within 10 days of symptom onset) for patients who require hospitalization, particularly those who need low-flow oxygen therapy. In the larger WHO-sponsored Solidarity trial, there was a small effect of remdesivir in reducing mortality and progression to mechanical ventilation in patients who were not yet ventilated. Remdesivir is most effective when used early after disease onset and is probably not beneficial once someone

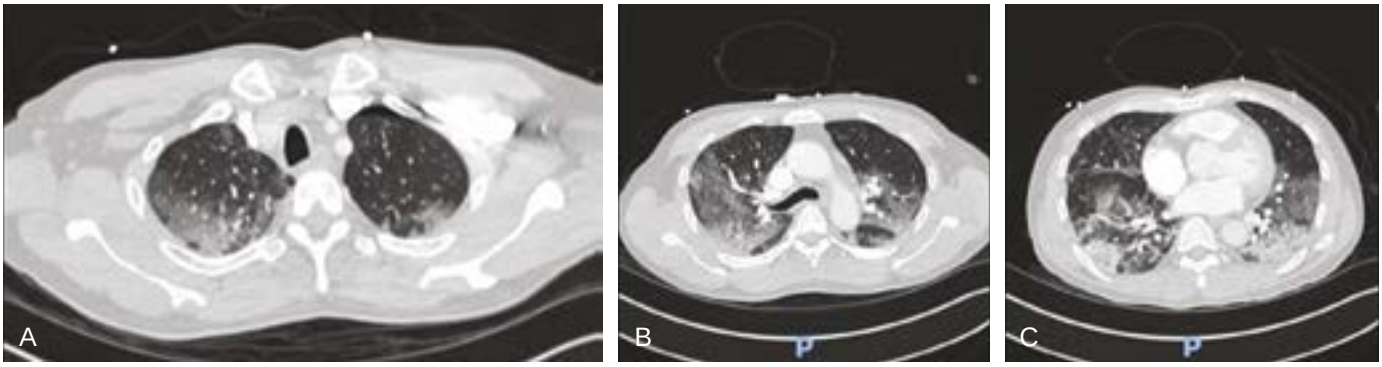


FIG. 2 A 53-year-old man with no significant past medical history presented with 1 week of malaise and 3 days of shortness of breath and chest tightness. Chest CT demonstrates patchy, predominately peripheral ground glass opacities, dense consolidations with air bronchograms in the middle and lower lung zones, and thickening and inflammation along the peribronchial trees toward the lung bases.

TABLE 1 Antiviral Treatments

Agent	Mechanism	Population	Effect
Nirmatrelvir-ritonavir	Orally bioavailable protease inhibitor that inhibits viral replication	Outpatients with high risk of progression to severe disease	Greater than 80% reduction of risk to progression to hospitalization or death. Must be given within 5 days of symptom onset
Remdesivir	Inhibits SARS-CoV-2 RNA-dependent RNA polymerase	Hospitalized patients on oxygen by low-flow nasal cannula or face mask High-risk outpatients when nirmatrelvir-ritonavir is unavailable or contraindicated	Shortens time to clinical improvement, greatly reduces risk of hospitalization in high-risk outpatients Likely mortality benefit
Monoclonal antibodies	Binds to receptor-binding domain (RBD) of SARS-CoV-2 spike protein	High-risk outpatients when nirmatrelvir-ritonavir and remdesivir are unavailable or contraindicated Prophylaxis in immunocompromised patients with inadequate response to vaccination	When given promptly (e.g., <72 hours from symptom onset), significantly reduces risk of hospitalization Reduces risks of infection in immunocompromised patients with inadequate response to vaccination

TABLE 2 Immunomodulatory Treatments

Agent	Mechanism	Population	Effect
Corticosteroids (e.g., dexamethasone)	Pleiotropic	Hospitalized patients with any degree of hypoxemia requiring supplemental oxygen	Reduces mortality in patients with severe and critical disease
Tocilizumab/sarilumab	IL-6 antagonism	Hospitalized patients with rapidly progressing disease ± elevated inflammatory markers, patients on HFNC/immediately following intubation	Reduces progression to invasive mechanical ventilation and mortality in patients with severe and critical disease
Baricitinib/tofacitinib	JAK inhibition	Hospitalized patients with elevated inflammatory markers	Reduces mortality in patients with severe and critical disease

is already critical ill. Other agents such as hydroxychloroquine, lopinavir, and ivermectin have been shown to reduce viral replication in vitro. However, these agents have failed to improve outcomes in large, randomized trials, and they should not be used for prophylaxis or treatment.

As severe COVID-19 illness progresses, direct viral replication and damage subside, and immune dysregulation, endothelial inflammation, and hypercoagulability became the principal drivers of illness. Consequently, immunomodulatory therapies have the greatest benefit at this stage (Table 2). Corticosteroids are a treatment mainstay for hypoxemic patients. They have been the standard of care since the UK Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial demonstrated that 6 mg of dexamethasone daily reduced overall mortality by almost a fifth and mortality in mechanically ventilated patients by one-third. However, no mortality benefit was seen in patients not requiring oxygen, and *systemic steroids are not recommended for this group*. If dexamethasone is not available, other corticosteroids may be substituted at equivalent strengths. However, most trials of other corticosteroids were stopped early when the RECOVERY trial results became available. At the dose studied in the RECOVERY trial, corticosteroids have relatively few contraindications, and they have not been shown to be associated with significantly increased rates of secondary infection when used for severe COVID-19. However, strict glycemic control, while challenging, is essential as hyperglycemia is associated with increased mortality in this population. There is some evidence that older patients may have increased side effects that could blunt the mortality benefits of dexamethasone; the decision to use corticosteroids should consider individual patient characteristics, particularly among the elderly. Children and young adults who develop severe multisystem inflammatory syndrome—a syndrome with multiorgan involvement, fever, and hemodynamic instability occurring 2 to 6 weeks after initial infection—require much higher doses of corticosteroids and may also benefit from intravenous immunoglobulin.

Other immunomodulatory treatments with growing evidence include IL-6 pathway inhibitors and Janus kinase (JAK) inhibitors. In addition to standard care including corticosteroids, the recombinant humanized anti-IL-6–receptor monoclonal antibody tocilizumab was shown to reduce 28-day mortality in the RECOVERY trial when given to patients with hypoxia and a CRP >75 mg/L. In the Randomized, Embedded, Multifactorial Adaptive Platform Trial of Community-Acquired Pneumonia (REMAP-CAP) trial, tocilizumab also reduced mortality in patients requiring organ support regardless of baseline CRP. A large meta-analysis from the WHO provided further evidence that tocilizumab reduced mortality and progression to mechanical ventilation and that these benefits were additive to the effects of corticosteroids. The IDSA recommends adding tocilizumab to routine care (including corticosteroids) in patients with progressive or severe COVID-19 with elevated inflammatory markers.

The ACTT-2 trial showed that the JAK inhibitor baricitinib, when used in addition to remdesivir, led to a further decrease in the time to clinical improvement, which was most pronounced in patients on high-flow nasal cannula. The ACTT-4 trial showed no clear difference between the combination of remdesivir and dexamethasone vs. the combination of remdesivir and baricitinib. In the phase 3 COV-BARRIER trial, baricitinib reduced 60-day mortality by one third when given in addition to standard care (including dexamethasone) to patients with at least one elevated inflammatory marker. This effect was most pronounced among patients requiring HFNC or noninvasive ventilation. Coadministration of baricitinib and tocilizumab has not been studied. Access to both agents is limited by cost, and selection may ultimately be guided by cost and supply. With either agent, benefit is maximized if administration occurs before patients are intubated or at least within the first 24 hours of mechanical ventilation.

In addition to administering appropriate COVID-19 specific therapies, management of COVID-19 patients requires provision of the appropriate level of care and monitoring, prevention and recognition of thromboembolic complications, and application of preexisting best practices in the management of acute hypoxemic respiratory failure and ARDS. Risk stratification starts in the outpatient arena with phone triage, ambulatory evaluations when necessary, and consideration of antivirals or monoclonal antibodies. Remote patient modalities such as pulse oximetry may be a useful adjunct for monitoring outpatients, although they may underestimate hypoxia in underrepresented minorities. In acute care settings, demographic, clinical, and laboratory data help to identify patients at risk of decompensation. Markers of inflammation (e.g., elevated CRP) in addition to more traditional prognostic markers (BUN, albumin) may help identify patients at risk of decompensation. Risk calculators such as the Severe COVID-19 Adaptive Risk Predictor (SCARP, https://rsconnect.biostat.jhsph.edu/covid_trajectory) can supplement clinical judgment in selecting patients for increased monitoring including continuous pulse oximetry or placement in intermediate level units.

Early case series of COVID-19 reported frequent venous thromboembolic events (VTE) including PE, particularly among critically ill patients. Prospective data collected after corticosteroids became standard of care have indicated more modest but still significant rates of VTE. For example, recent estimates of prevalence of acute PE among hospitalized COVID-19 patients vary between 1.3% and 8.2%, with critical illness associated with greater risk. Elevated D-dimer is typical in COVID-19 and has a poor positive predictive value for acute PE. Importantly, in situ microthrombi secondary to endothelial dysfunction and coagulopathy are hypothesized to contribute to pulmonary and extrapulmonary pathology, and these microthrombi cannot be detected on conventional computed tomography angiography (CTA). Thus, a rationale exists for therapeutic anticoagulation even in the absence of deep vein thrombosis (DVT) or PE. In a large, open-label, adaptive controlled trial performed by the investigators of Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTAC); the Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (Activ-4A); and REMAP CAP, full-dose anticoagulation for patients on low-flow nasal cannula or face mask oxygen increased the probability of survival to hospital discharge without receipt of organ support. Most patients received low-molecular-weight heparin, and the effect was independent of baseline D-dimer level. In critically ill patients, however, full-dose anticoagulation increased risk of bleeding without improving outcomes.

Patients with COVID-19 may present with hypoxemia out of proportion to the rest of their signs and symptoms ("happy" or "silent hypoxemia"), although respiratory distress will often follow. Some have speculated that this may be due to a blunted response to hypoxemia caused by a direct effect of SARS-CoV-2 on the carotid bodies. However, this phenomenon could also represent the known heterogeneous response to hypoxemia across individuals or a blunted response to hypoxemia due to other factors such as age or preexisting conditions like diabetes. Placing patients in the prone position often improves their oxygenation, is generally well tolerated, and reduces the risk of intubation among patients on HFNC. Before the COVID-19 pandemic, high-flow nasal cannula had been shown to reduce the need for invasive mechanical ventilation in patients with severe pneumonia. Observational data in COVID-19 supports the use of HFNC and suggests a possible mortality benefit in more hypoxemic patients, although subsequent randomized trials have produced conflicting results.

Patients requiring intubation often require high doses of sedation as well as paralysis to treat ventilator dyssynchrony. Particularly early in their course, these measures are essential to prevent ventilator-induced lung injury. However, paralytics and deep sedation should be weaned as soon as feasible since they contribute to prolonged weakness and delirium. Low tidal volume ventilation (for all mechanically ventilated patients) and prone positioning (for patients with PaO_2:FiO_2 ratio <150) interventions, known to reduce mortality in ARDS, should be universally applied. Barotrauma is not uncommon with higher rates of pneumomediastinum observed compared with ARDS from other etiologies. Patients not infrequently require chest tube thoracostomy for pneumothorax. Tension pneumomediastinum requiring surgical decompression is a very rare but possible complication of pneumomediastinum.

Extracorporeal membrane oxygenation (ECMO) should be considered when patients cannot be oxygenated or ventilated without injurious tidal volumes and airway pressures. Case fatality rates (CFR) for COVID-19 patients requiring mechanical ventilation vary widely based on geography and time point in the pandemic. With current standard of care, CFR is 25% to 50% in this population. ECMO outcomes in COVID-19 are comparable to those in other etiologies of severe ARDS. In properly selected patients, 90-day survival rates in ECMO can exceed 60%.

POSTDISCHARGE, PERIOPERATIVE, AND HEALTH SYSTEMS CONSIDERATIONS

Survivors of critical illness due to COVID-19 face similar challenges to other survivors of critical illness and ARDS, including significant rates of chronic physical, cognitive, and psychologic impairment. Less severely ill patients, including those who never required hospitalization, also have persistent symptoms and impairments at rates higher than those of other viral illnesses (e.g., influenza). Common physical symptoms include fatigue, dyspnea, chest discomfort, cough, and exertional intolerance. Common psychologic and neurocognitive symptoms include impaired memory and concentration, anxiety, and depression. These symptoms can last for months. Long-term radiographic abnormalities (e.g., ground glass opacities and fibrosis) and pulmonary function impairment is common. For example, one-third to one-half of patients hospitalized with COVID-19 will have impaired diffusion capacity at 6 months. High quality evidence for the management of post-ICU syndrome (PICS) and post-COVID syndrome ("long haul COVID") are lacking. Society guidelines recommend postdischarge evaluations for high-risk patients, aggressive physical rehabilitation, and multidisciplinary care that includes psychosocial support.

One manifestation of physiologic impairment secondary to even mild or asymptomatic COVID-19 is increased rates of postoperative respiratory failure and mortality up to 6 weeks following diagnosis. When considering elective surgery in patients who have recently recovered from COVID-19, the risks of these complications should be weighed against the risks of delaying surgery. In areas with high rates of transmission, preoperative SARS-CoV-2 screening should be universal to assist with perioperative risk stratification in addition to infection control.

Postponement of elective surgeries, as well as screening and diagnostic tests, have been employed at times in areas experiencing COVID-19 surges. Although these delays are often necessary to reduce healthcare strain and high caseloads that are in themselves risk factors for worse COVID-19 outcomes, they have also been associated with patients presenting with more advanced disease (e.g., more advanced stages of cancer). Delays in routine care have disproportionately impacted socially disadvantaged populations, further exacerbating healthcare inequalities. With the widespread availability of vaccines that reduce the risk of hospitalization, these delays in routine care due to COVID-19 stressors on the healthcare system will hopefully be unlikely in the future.

SUMMARY

Infection with SARS-CoV-2 causes coronavirus disease 2019 (COVID-19). Risk factors for severe disease include advanced age, male sex, liver disease, dementia, and obesity. Race, ethnicity, and socioeconomic status are also important factors in the risk of acquiring COVID-19 and having more severe outcomes. Progressive disease is caused by immune dysregulation, endothelial inflammation, and hypercoagulability. Consequently, antiviral treatment—nirmatrelvir-ritonavir, remdesivir, and monoclonal antibodies—is most important in early illness while immunomodulatory treatments—dexamethasone, IL-6, or JAK inhibition—are most efficacious in progressive disease. In hospitalized patients on low-flow oxygen and oxygen by face mask, therapeutic anticoagulation may also reduce the risk of progression to critical illness. Treatment of patients with ARDS should follow standard evidence-based practices such as low tidal volume ventilation and prone positioning. Robust randomized clinical trials have identified a wealth of treatments, highlighting the critical importance of clinical research even in the most challenging circumstances. Finally, the rapid development of vaccines against SARS-CoV-2, based on preceding work on SARS and MERS as well as recent developments in vaccine technology, allowed for more effective control of the pandemic in areas where vaccine uptake was near universal. Widespread vaccination can prevent future surges, reduce the likelihood of the emergence of dangerous new SARS-CoV-2 variants, and save countless lives.

Suggested Readings

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Surgical Palliative Care

Avani Amin, MD, Brenda S. Nettles, DNP, ACNP-BC, and Thomas J. Smith, MD

INTRODUCTION: WHAT AND WHY SURGEONS SHOULD KNOW ABOUT PALLIATIVE CARE

The goals of surgical oncology and palliative care are the same: to help the patient live longer with a better quality of life and adapt to a serious illness. Despite a reputation of palliative care being the "death squad" or only interested in helping people die peacefully, there are now multiple randomized controlled trials showing that patients who receive specialist palliative care alongside their prescribed regimen of cancer care have better symptom control, less distress, enhanced support for caregivers, and even longer survival. The mechanism of longer life has not been fully explained, but two recent randomized trials showed the survival benefit. In these trials, half the cancer group reported symptoms electronically every week to a nurse who could address them, which produced an absolute overall survival benefit of 6 to 12 people of every 100. This fits with earlier work that when pain control was optimized with an intrathecal pump leading to relief of severe cancer pain, it gave an absolute overall survival benefit of 15 people of every 100 people at 6 months when compared with the best medical management that did not relieve pain adequately. The evidence is so compelling for palliative care alongside standard oncology care that the American Society of Clinical Oncology recommends concurrent palliative care by an interdisciplinary team for *every* advanced cancer patient within 8 weeks of diagnosis. In this chapter, we provide a brief overview of the benefits of incorporating palliative care into routine oncologic practice and offer clinical pearls on how best to deliver palliative care in the inpatient and outpatient settings.

DEFINITION OF PALLIATIVE CARE

The following definitions are accepted for the medical specialty of Hospice and Palliative Medicine (Box 1).

There is a distinction between primary palliative care, which all surgeons should know, and specialty palliative care practiced by palliative specialists. Primary palliative care skills include at least the following: (1) honest and compassionate communication about prognosis, achievable treatment outcomes including goals of care,

BOX 1

"Palliative care is **specialized medical care** for people with serious illnesses. This type of care is focused on providing patients with **relief from the symptoms, pain, and stress of a serious illness, whatever the diagnosis**. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work with a patient's other doctors **to provide an extra layer of support**. Palliative care is appropriate at any age and at any stage in a serious illness, and **can be provided together with curative treatment.**" – Diane Meier, MD, Director, Center to Advance Palliative Care www.capc.org

Or, more simply: "Palliative care is expert symptom assessment and management, open and honest communication, and medically appropriate goal setting." – Tom Smith

and code status; (2) management of common symptoms such as pain, nausea, intestinal and other obstructions, diarrhea and constipation, and delirium; (3) recognition of the patient who is predictably going to do poorly and possibly die; and (4) knowing when to refer to specialty palliative care.

It is useful to think of primary palliative care as comprising two skill sets or "bundles": symptom assessment and management, and communication. Symptom assessment begins with the use of a standardized scale, such as the Edmonton Symptom Assessment Scale, that emphasizes the assessment of anxiety, depression, physical symptoms, and coping strategies. In one study, patients volunteered just one symptom when asked, but noted 10 symptoms with 5 being significant when given a standardized assessment.

Communication requires the evaluation of how much information the patient and/or family want to know about the diagnosis and prognosis, involves shared decision making, and establishes goals of care. It also encompasses advance care planning, starting with the identification of a medical power of attorney and proceeding to a discussion about hospice and end-of-life treatment choices. The communication skill set also includes providing caregiver support, making referrals for spiritual care, offering culturally sensitive decisions, and providing a specific statement of nonabandonment near the end of life. ("We will be with you every step of the way, no matter what happens.") If specialty palliative care is involved, data has shown that the effect on quality of life and end-of-life choices is most meaningful if consultation is started at least 3 months before death. The main reason behind late referrals is physician/surgeon reluctance. If a physician is saying, "This patient is not ready for palliative care yet", they almost certainly are.

Communicating bad news and giving informed prognostic awareness are among the hardest tasks faced by any oncologist. However, we have found that a simple technique is to follow the first two questions on our Communication Temporary Tattoo (Fig. 1). It is critical to ask how much the patient wants to know first, as 10% to 15% of patients will not want to know. Then, simply and directly ask, "What is *your* understanding of *your* situation?" We often use best-case/worst-case scenarios to explain what the future might hold; this



FIG. 1 Communication temporary tattoo. *(Arm photo used with permission of Dr. Victoria Powell, University of Michigan.)*

is available as a 10-minute video and has been found by surgeons to be preferred to their usual method of communication (https://www.youtube.com/watch?v=FnS3K44sbu0; Best Case/Worst Case (BC/WC) SURGEON Communication Tool - Whiteboard Video) (Fig. 2).

WHEN TO CALL A PALLIATIVE CARE CONSULT—THE "SURPRISE QUESTION"

An interdisciplinary team providing specialty palliative care can help manage complex or refractory symptoms, as well as patient, family, or caregiver distress. Early access to palliative care is key to empowering patients and caregivers with enhanced symptom management and supportive care resources. We have modified the list available on the Center to Advance Palliative Care Website for practicality. These

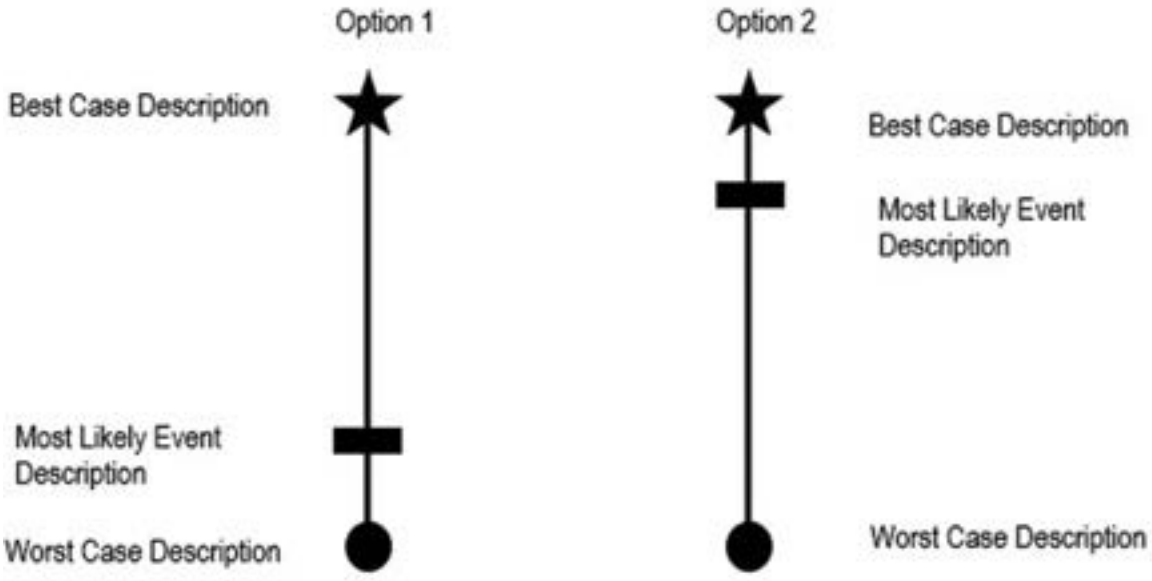


FIG. 2 Best Case/Worst Case illustration that can be given to patients and families.

have been used in several studies with automatic consult "triggers" for concurrent care that show high patient, family, and provider satisfaction; reduced length of stay; increased referral to hospice when appropriate; reduced 30-day readmissions; and lessened patient/caregiver distress. Some suggested reasons for referral are listed in Table 1.

A prognostication tool that can be helpful to determine if a palliative care consult needs to be considered is to consider the question, "Would I be surprised if this patient died within 12 months?" The positive predictive value of the question is 93%, so it is helpful in identifying patients who will live longer than a year. If the answer to the question is no, a palliative care consult may be beneficial.

DIFFERENCES BETWEEN PALLIATIVE CARE AND HOSPICE

The specialty of Hospice and Palliative Medicine grew from hospice, which started in England in the mid-1950s to get dying patients out of hospitals and into residential hospices that could concentrate on symptom management and finding peace in the dying process. Balfour Mount, a urologic oncology surgeon, is credited with coining the term "palliative care" (from the Latin word *pallidum*, to throw a cloak over symptoms). In the United States, hospice has expanded exponentially since 1984, such that nearly half of all cancer patients die with hospice. Hospice has been accepted by the relevant surgical, medical, and radiation oncology societies as the best way to manage death from cancer since a 1998 White Paper from the American Society of Clinical Oncology.

There are three usual types of hospice: (1) outpatient, at the person's home, with visiting healthcare professionals, social workers, and chaplains; (2) inpatient, for those patients whose symptoms cannot be controlled at home; and (3) residential, where the hospice becomes the patient's home until death. (Residential hospice is unusual, as insurers do not reimburse the room and board.) Some of the most relevant differences between hospice and palliative care are listed in Table 2. Hospice eligibility can easily be assessed with a free app, Hospice in a Minute (https://apps.apple.com/gb/app/hospice-in-a-minute/id511997344).

The United States is the only country that forces patients to choose either standard oncology care or hospice care, forgoing further anticancer therapy. This is because hospice is truly capitated care, with the hospice agency getting $190 a day to cover ALL expenses. Expensive surgical, radiation therapy, targeted treatments,

TABLE 1 Reasons to Refer to Specialist Palliative Care Providers

Inpatient	Consider referring for *inpatient* specialist palliative care if any of the following criteria are met:
	Length of stay 7 or more days with no pending plan for discharge (some centers use 3 or 5 days)
	Admission from long-term care facility (nursing home or assisted living)
	Patient or family requests for futile (medically ineffective) care
	Do Not Resuscitate order conflicts
	Conflicts or uncertainty regarding the use of non-oral feeding/hydration in cognitively impaired, seriously ill, or dying patients
	Two or more hospitalizations for illness within three months, or prior hospitalization within 30 days
	Patient, family, or physician request for information regarding hospice appropriateness
	Difficult-to-control physical or emotional symptoms
	Patient, family, or physician uncertainty regarding prognosis
	Stage IV (any cancer) or Stage III lung or pancreatic cancer
	Uncontrolled symptoms: pain, nausea/vomiting, dyspnea, constipation/diarrhea, delirium, and psychological distress
General or outpatient	Consider referring for *outpatient* specialist palliative care if any of the following criteria are met:
	New diagnosis of life-limiting illness for symptom control, patient/family support
	Progressive metastatic cancer
	Declining ability to complete activities of daily living
	Karnofsky <50 or Eastern Cooperative Oncology Group (ECOG) >3
	Malignant hypercalcemia
	Progressive pleural/peritoneal or pericardial effusions
	Brain metastases, spinal cord compression, or leptomeningeal spread
	Patient or family psychological or spiritual/existential distress
	Limited social support in the setting of a serious illness (e.g., homeless, no family or friends, chronic mental illness, or overwhelmed family caregivers)
	Patient, family, or physician uncertainty regarding appropriateness of treatment options
	Weight loss >10% of original body weight
	Metastatic or locally advanced cancer progressing despite systemic treatments
	Any advanced or symptomatic cancer

TABLE 2 Differences Between Hospice and Palliative Care

	Hospice	Palliative Care
Lifespan	Reserved for those who have a good chance of dying in the next 6 months if the disease runs its natural course	Access care anytime during course of illness Early referral is key to address unmet supportive care needs and enhance quality of life
Intent of therapy	Must give up curative or life-extending therapy, if such exists	Concurrent surgery, radiation, chemotherapy, and immunotherapy allowed
Reimbursement	Capitated: $190 a day for outpatient care (must cover all expenses); $600 a day for inpatient	Treated and reimbursed the same as other medical specialties (e.g., cardiology or geriatrics)
Place of care	Usually the patient's home	Can be home-, clinic-, or hospital-based

TABLE 3 Specialist Palliative Care Measures

Symptom	Assessment	Intervention
Pain	Determine if it is neuropathic pain (burning, shooting, stabbing), and/or nociceptive pain (dull, aching, throbbing) as the treatment is different.	Nociceptive pain responds best to COX-2 inhibitors like acetaminophen, non-steroidal antiinflammatory drugs, and opioids. Neuropathic pain does respond to opioids, but neuroleptic drugs such as duloxetine or pregabalin may be more effective long-term. They are also synergistic with opioids. Visceral pain is difficult to control and often requires steroids and opioids. Intestinal colic may be helped by antispasmodic agents such as hyoscine. Liver capsule pain from metastases often responds to steroids such as dexamethasone. Motion or incident pain due to bone metastases is extremely difficult to control. There is one report showing success by adding gabapentin at usual doses; pregabalin should work as well and has less ceiling effect.
Nausea	Determine the cause if possible (obstruction, opioids, other drugs, brain metastases, anxiety)	The most effective drug for generalized nausea (not chemotherapy related) is likely olanzapine 2.5 to 5 mg hs. In one randomized trial the effect was dramatic and happened within 24 hours, with beneficial effects on sleep and appetite.
Delirium and agitation	Assess for confounding drugs (steroids, opioids, benzodiazepines, etc.) and electrolyte abnormalities	Reorient frequently Small doses of haloperidol, 0.5 to 2.0 mg intravenously, are the accepted treatment. One randomized trial showed that the combination of haloperidol and lorazepam was more effective. Psychiatric symptoms (agitation, jitteriness) due to steroids can often be reversed with low dose olanzapine, 2.5 to 5 mg hs.
Refractory cough or hiccups	If chronic, has likely become a centralized mechanism like centralized pain	Gabapentin at usual doses is often effective at relieving chronic cough, very quickly. About 1 in 6 people will not metabolize codeine to morphine, the active ingredient, so it should rarely be used for cough.
Dyspnea	Evaluate for usual causes such as anemia, deconditioning, pulmonary emboli, pneumonia, effusions, etc.	Treat the underlying cause, if possible. If not possible, low dose opioids (e.g., 5 mg morphine or oxycodone) can often relieve dyspnea by mimicking the natural effect of beta-endorphins on the brain. Doses less than 20 mg/day are safe and effective.
Intestinal obstruction	Gastrointestinal rest, nasogastric tube placement, and intravenous fluids are the most conservative approach	If not relieved, treatment with octreotide (to reduce small bowel secretions) and haloperidol for nausea is recommended. The clinical trial evidence is either lacking or contradictory to absolutely recommend one approach. Many surgeons will add steroids if there is no resolution. Do not use prokinetic agents.

TABLE 3 Specialist Palliative Care Measures—Cont'd

Symptom	Assessment	Intervention
Constipation	Assess for hypercalcemia, obstruction, dehydration and other common causes	Stimulant laxatives such as senna and bisacodyl are indicated if there is no obstruction. Stool softeners such as docusate do not add any effect, at least in hospice patients, and should not be used. Osmotic agents such as polyethylene glycol are well tolerated and helpful. If opioid-induced, several agents reverse the opioid effect on the bowel without reversing pain relief, such as methylnaltrexone, naloxegol, an opioid-naloxone fixed combination, or lubiprostone. Do not use in the presence of obstruction. These are underused, in our experience.
Anorexia/cachexia syndrome	Assess for reversible cause (medications, constipation, oral ulcers/thrush, depression, anxiety); in advanced illness, patients don't sense hunger	To increase appetite, can use megestrol acetate (contraindicated if high risk for thrombosis), steroids, and dronabinol No treatment for chemotherapy associated taste changes. Regular oral hygiene and dental care are recommended to address concerns of dry mouth, pain, tongue irritation, and possible infections

TABLE 4 Palliative Procedures Performed Near the End of Life

Nature of Procedure	Examples
Symptom relief for incurable benign disease	Excision of large condylomata
	Procedures (e.g., banding of esophageal varices or shunt procedures) for end-stage liver disease
Symptom relief for incurable malignant disease: *nonresectional*	Biliary and/or gastric bypass for unresectable (obstructing periampullary, gastric, and proximal small bowel cancers)
	Chemical splanchnicectomy for intractable pain (e.g., locoregionally advanced pancreatic cancer)
	Intestinal bypass or ostomy for malignant bowel obstruction
	Decompressing gastrostomy tube placement for malignant bowel obstruction
	Peritoneal catheter placement for the drainage of recurrent malignant ascites
Symptom relief for incurable malignant disease: *resectional/debulking (cytoreductive) procedure*	Resection of primary tumor or metastatic lesion(s) for pain, obstruction, and/or bleeding in setting of unresectable distant disease (e.g., palliative mastectomy, bowel resection, resection of primary tumor in stage IV colorectal cancer)
	Resection/debulking of symptomatic carcinoid tumor
Intended prolongation of survival: *resectional/debulking procedure*	Debulking of advanced gastrointestinal or ovarian cancer
	Metastasectomy or ablation of advanced cancer with incomplete response to therapy or suboptimal treatment (e.g., R2 – gross disease remaining)

From Mosca PJ, Blazer DG 3rd, Wheeler JL, Abernethy AP. When a chance to cut is not a chance to cure: a future for palliative surgery? *Ann Surg Oncol.* 2011;18:3235–3239.

and chemo- or immunotherapy simply cannot be supported on such a restrictive budget.

Some healthcare providers will be surprised to learn—despite the limitations placed on care by the current capitated payment model—that those who use hospice for the dying process actually live a month longer on average compared with those who do not. In addition, the likelihood of the surviving spouse surviving the next 2 years is increased. Multiple studies have shown that those who use hospice have better symptom control, less distress, less caregiver distress, and less posttraumatic stress disorder. This is likely due to better symptom management that is possible when a trained hospice team has the time, energy, and expertise to relieve symptoms. Hospice also provides trained bereavement services for up to 2 years after the patient's death. The Center for Medicare and Medicaid Services is currently testing an "open access" hospice that allows patients to receive both anticancer therapy and a modified hospice benefit based on successful models piloted by private insurers. The Veterans Administration Medical Centers already allows concurrent hospice and antineoplastic treatment for up to 2 years.

SPECIFIC SPECIALIST PALLIATIVE CARE MEASURES THAT CAN HELP THE SURGICAL ONCOLOGIST

Palliative care is an essential component of cancer care that should be introduced at time of diagnosis to minimize suffering and assist

the patient in achieving a better quality of life. The surgical oncology team has the expertise to manage the common symptoms that patients may experience as the result of cancer surgery; however, most models of clinical practice allows for a limited amount of time to identify and treat unmet supportive care needs. However, there are some effective measures known to board-certified palliative care specialists that may be useful to enhance their current everyday practice (Table 3).

PALLIATIVE PROCEDURES PERFORMED NEAR THE END OF LIFE

There may be times when the surgical oncologist is called upon to perform palliative procedures on acutely and chronically ill patients who have no other options. We have listed some of the most common surgical procedures in Table 4. One cogent fact is that survival is often very short after any of these procedures, especially venting gastrostomies. Palliative care should routinely be consulted to help address prognostic awareness, advance care planning, legacy work, family distress, hospice referral, and the myriad of symptoms these patients may be experiencing due to their advanced stage of disease.

This chapter provides an overview of palliative care as applied to surgical practice. The primary palliative care competencies previously listed—symptom management and communication skills—are required of all surgeons. Palliative care is an essential component of cancer care that should be introduced at time of diagnosis to minimize suffering and assist patients, families, and caregivers in achieving a better quality of life. Early referral to specialty palliative care is key to addressing the complex needs of patients who require advanced symptom management, advanced care planning, and end-of-life care.

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CARDIOVASCULAR PHARMACOLOGY

John Nikolhaus Smith, MD, Thomas S. Metkus Jr., MD, PhD, and Glenn J.R. Whitman, MD

INTRODUCTION

Given the recent changes in drug therapy, this chapter reviews drug therapy for each phase of care for a patient undergoing surgery to aid the caregiver in appropriately managing this patient population. This chapter focuses on the pharmacology of the crucial, most impactful drugs used in these patients, with particular emphasis on indications and mechanism of action.

ANTIPLATELET AGENTS

Antiplatelet agents are foundational drugs in the secondary prevention of atherosclerotic cardiovascular disease and are perhaps most commonly associated with their mortality benefit in the management of acute coronary syndromes (Table 1). Their use in primary prevention is more controversial. Commonly prescribed antiplatelet agents include aspirin, clopidogrel, prasugrel, ticagrelor, and cangrelor.

Aspirin (ASA)

The benefits of aspirin in cardiovascular disease relate to both antithrombotic and antiinflammatory properties. Aspirin inhibits platelet function through the irreversible binding of cyclooxygenase (COX) (Fig. 1). Many patients will already be taking aspirin at the time of surgery and this can be continued safely; indeed, it is prescribed preoperatively in close to 90% of coronary surgery patients. Aspirin (81–325 mg) administered within 6 hours of coronary artery bypass grafting (CABG) is associated with higher rates of short- and long-term saphenous vein graft patency, and long-term aspirin use after CABG reduces recurrent coronary events. If aspirin is to be combined with a second antiplatelet agent or an anticoagulant (see later in this chapter), aspirin dose should be 81 mg. For patients undergoing valve replacement, regardless of whether an anticoagulant is prescribed or whether the valve is mechanical or a bioprosthetic, aspirin at a dose of 81 mg of aspirin is recommended.

The major adverse effect of aspirin is gastrointestinal bleeding due to its toxic effect on gastric mucosa. When considering whether to administer aspirin before CABG, randomized controlled trials (RCT) have shown no difference in major postoperative bleeding in aspirin vs. placebo.

Clopidogrel

Clopidogrel belongs to a class of drugs called thienopyridines and is an irreversible adenosine diphosphate (ADP) receptor antagonist that inhibits platelet aggregation. The most common indication for clopidogrel is in the management of acute coronary syndromes, and large RCTs have shown reduced death, stroke, and recurrent MI when used in combination with aspirin. It is used for at least 30 days after percutaneous coronary intervention (PCI) with bare metal stents and for 6 to 12 months (and sometimes longer) after PCI with drug-eluting stents (DES) to prevent stent thrombosis during the vulnerable period before full stent endothelialization. Patients who undergo coronary artery bypass have a 2% increase in major bleeding (tamponade, reoperation, transfusion) when clopidogrel is discontinued <24 hours before surgery. As such, guidelines recommend clopidogrel be withheld for approximately 5 days before elective surgery, though when clinically necessary, patients should proceed to surgery immediately.

TABLE 1 Antiplatelet Therapy

Drug	Mechanism	Clinical Indication	Half-Life (Active Metabolites)	Duration of Effect	Discontinuation before CABG
Aspirin	COX Inhibitor	Lifelong after: PCI, ACS, CABG	Plasma half-life 20 minutes*	~10 days	None
Clopidogrel (Plavix)	ADP receptor blocker	PCI, ACS	30–60 min	3–10 days	At least 5 days
Ticagrelor (Brilinta)	ADP receptor blocker	PCI, ACS	7–9 hours	3–5 days	At least 5 days
Prasugrel (Effient)	ADP receptor blocker	PCI, ACS	Distribution half-life (60), Elimination half-life 2–15 hr	7–10 days	At least 7 days
Cangrelor (Kengreal)	ADP receptor blocker	Awaiting CABG after PCI, ACS	3–6 min	1–2 hours	1 hour

*However, because platelets cannot generate new COX, the effects of aspirin last for the duration of the life of the platelet (≈10 days).

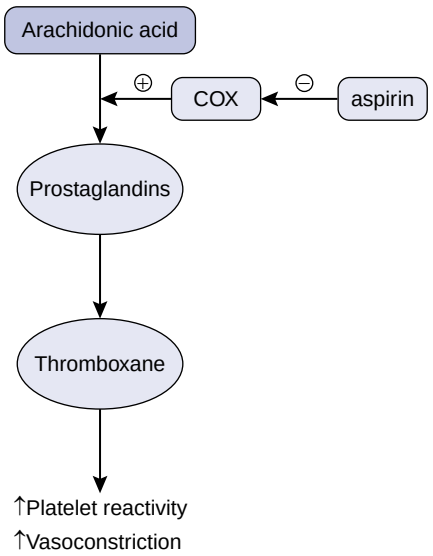


FIG. 1 The arachidonic acid pathway is catalyzed by COX, leading to increased platelet reactivity and vasoconstriction. Aspirin irreversibly inhibits COX, leading to reduced platelet reactivity.

Prasugrel

Prasugrel is a thienopyridine similar to clopidogrel but with greater potency of platelet inhibition. Large RCTs of patients with acute coronary syndromes have reduced cardiovascular death and MI in comparison to clopidogrel. However, those who underwent subsequent CABG—approximately 10%—experienced an increase in major bleeding (13.4% vs. 3.2%). As with clopidogrel, due to its potency and irreversibility, guidelines recommend stopping prasugrel at least 7 days before surgery to limit bleeding and reoperations.

Ticagrelor

In contrast to prasugrel and clopidogrel, ticagrelor is immediately bioavailable, undergoes no metabolism in the liver, and binds the ADP receptor reversibly. Similar to prasugrel, large RCTs have demonstrated that ticagrelor reduces death, MI, or stroke in comparison to clopidogrel, at the expense of greater bleeding rates when surgery is undertaken. It is recommended to stop ticagrelor 5 days before surgery, if possible.

Cangrelor

Dual antiplatelet therapy with aspirin and either clopidogrel, prasugrel, or ticagrelor is standard of care in patients undergoing PCI. The greatest risk of stent thrombosis is in the acute period, between 1 and 30 days from stent deployment. A common situation is the patient who receives an emergent DES and requires dual-antiplatelet therapy but who also requires urgent coronary bypass for residual disease. Cangrelor is an intravenous, short-acting, reversible platelet ADP receptor antagonist similar to ticagrelor but with a very short half-life of 5 to 6 minutes. Given its very short half-life, it is particularly well-suited as a therapy to provide short-acting, reversible platelet inhibition to protect against ischemic events while awaiting clopidogrel, prasugrel, or ticagrelor washout. Postoperative dual antiplatelet therapy should be resumed when deemed safe to do so from a bleeding perspective.

LIPID-LOWERING THERAPY

Statins via inhibition of hepatocyte HMG-CoA reductase decrease cholesterol synthesis in the liver, increase LDL clearance, and have an antiinflammatory effect. In large RCTs, statin therapy has been shown to reduce the long-term incidence of stroke, MI, and death, and when given after CABG, this class of drugs may also improve vein graft patency and, furthermore, reduce perioperative adverse events among patients undergoing vascular surgery. The ACC/AHA 2015 guidelines give a class I recommendation for statins when coronary artery disease (CAD) is first documented preoperatively, that they be restarted early after CABG surgery and continued indefinitely. Adverse effects of statin drugs include myalgia, myopathy and myositis, new onset diabetes, and liver function test abnormalities.

ANTICOAGULANTS

Management of the coagulation cascade is essential in caring for surgical patients. The coagulation cascade is shown schematically in Figure 2.

Heparin

Heparin is the standard anticoagulant used in cardiac surgery for the routine conduct of cardiopulmonary bypass, for bridging anticoagulation to warfarin, for management of deep venous thrombosis, for stroke prophylaxis in AF, during extracorporeal support, and for ventricular-assist devices, as well as a myriad of other uses. When bound by heparin, Antithrombin III (ATIII) is 1000 times more avid for factors Xa and thrombin (factor II) (see Fig. 2). Unfractionated heparin

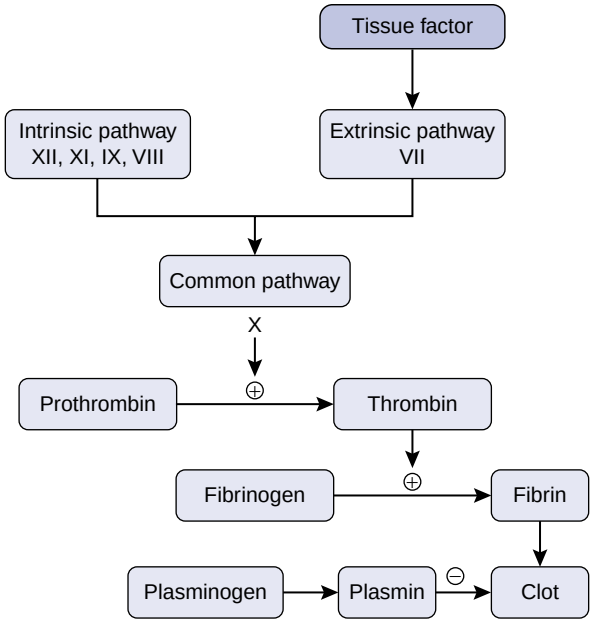


FIG. 2 Coagulation cascade.

in association with ATIII, an enzyme that inhibits multiple factors in the coagulation cascade, but most importantly inhibits factors Xa and thrombin (factor II), prevents the formation of fibrin, and thus clot formation. Low-molecular-weight heparin, on the other hand, consists of a more uniform set of smaller molecules than unfractionated heparin and only inhibits factor Xa, not thrombin, higher up in the cascade. One of the greatest advantages of heparin is that it is short-acting and easily neutralized by its reversal agent, protamine.

The most-feared adverse event associated with heparin use is heparin-induced thrombocytopenia with thrombosis (HITT). This is the result of an immune reaction leading to formation of antibodies that bind to the heparin-PF4 complex, leading to thrombocytopenia (heparin-induced thrombocytopenia [HIT]), which less commonly results in hypercoagulability (HITT). Management of HITT includes avoiding all heparin products and providing anticoagulation with a direct thrombin inhibitor (e.g., argatroban or bivalirudin) until platelet counts recover and then long-term Coumadin therapy. For patients with a history of HIT(T) who require surgery, management options include (1) performing the procedure with heparin if the platelet count is normal and PF4 antibodies are not present, (2) performing surgery with heparin but after plasmapheresis to remove PF4 antibodies, or (3) performing surgery using bivalirudin as the anticoagulant rather than heparin.

Warfarin

Warfarin is a vitamin K antagonist that depletes the vitamin K-dependent clotting factors II, VII, IX, and X, as well as proteins C and S. It can be used for common clotting conditions such as deep vein thrombosis (DVT), pulmonary embolism (PE), or in stroke prophylaxis for atrial fibrillation but has been largely replaced by direct oral anticoagulants in these instances. However, it is still the anticoagulant of choice in patients with mechanical heart valves, left ventricular assist devices, antiphospholipid disorder, left ventricular thrombi, and in patients with any indication for an anticoagulant who have a body mass index >40 or who weigh more than 300 lbs. Due to the half-life of these factors, there is a lag of several days between the dosing of warfarin and its resultant therapeutic effect. More dangerous is the shorter half-life of proteins C and S upon introduction of Coumadin, with a resultant transient, hypercoagulable state. Consequently, clinicians should decide whether bridging Coumadin anticoagulation with heparin, which is immediately active, should be prescribed during this interval.

Warfarin effect is titrated by following the prothrombin time in the form of the international normalized ratio (INR), with specific therapeutic targets dependent on the anticoagulation indication. Warfarin's anticoagulant effect is also easily reversed with vitamin K, although it can take many hours, or immediately with fresh frozen plasma.

Bivalirudin

Bivalirudin belongs to a class of drugs that directly inhibits thrombin by binding to its active site. As with heparin, the effect of bivalirudin is titrated to reach a target activated clotting time (ACT) or partial thromboplastic time (PTT). Unlike heparin, there is no reversal agent for this drug. Nevertheless, in patients who have heparin-induced thrombocytopenia with circulating antiheparin antibodies and who require cardiac surgery, bivalirudin has been used for periprocedural anticoagulation to support cardiac surgery with over 90% efficacy and acceptable bleeding outcomes in both off-pump and on-pump procedures. Bivalirudin is used to treat heparin-induced thrombocytopenia, as discussed earlier; however, this is an off-label use of the medication in the United States. Argatroban, another direct thrombin inhibitor, is FDA approved for the treatment of HIT(T). Both drugs have been used successfully for HITT treatment. Bivalirudin and argatroban are generally well tolerated, with bleeding as their major adverse reaction. Given their irreversible anticoagulant effects, though, hemorrhagic complications associated with their use may be difficult to manage.

Direct, Nonvitamin K, Oral Antagonists

The direct oral antagonists (DOACs), formerly known as novel oral anticoagulants (NOACs), include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. (Note the "xaban" indicates an anti-Xa effect.) These drugs have been introduced for the oral treatment of AF and DVT. Unlike warfarin, which is used for similar reasons, the drugs are immediately effective, are not associated with a procoagulant effect at initiation of therapy, and do not require any anticoagulant testing to follow the degree of anticoagulation. Current guidelines recommend their use over warfarin for thromboprophylaxis in chronic AF except in the presence of moderate-severe mitral stenosis or a mechanical heart valve. Of significance is the outcome of the RE-ALIGN trial, which tested warfarin vs. dabigatran anticoagulation for patients with mechanical aortic or mitral prostheses; the trial was stopped early due to the increased incidence of thromboembolism and bleeding in the dabigatran group. Thus, the DOACs should be avoided for patients requiring anticoagulation for heart valve prostheses. Effective reversal agents for both dabigatran (the dabigatran-binding antibody idarucizumab) and the factor Xa inhibitors (andexanet) are clinically available, but cost largely prohibits their routine use.

MEDICATIONS THAT IMPACT CARDIAC RHYTHM

This section describes drugs affecting cardiac rhythm that are commonly used in surgical practice, not only for rhythm complications in the perioperative period, but as continuing therapy for patients with preexisting rhythm disturbances.

β-Adrenergic Receptor Antagonists

β-Adrenergic receptor antagonists block endogenous or exogenous catecholamines from interacting with either β_1 receptors (present in cardiac tissue and responsible for increased chronotropy and

inotropy) or β_2 receptors (present on smooth, skeletal, and cardiac muscle; responsible for smooth muscle relaxation). Metoprolol, atenolol, bisoprolol, and esmolol have higher selectivity for β_1 receptors, thus reducing inotropy and chronotropy without unwanted side effects of β_2 blockade, most notably bronchospasm. Propranolol, nadolol, labetalol, and carvedilol are considered nonspecific β-blockers, as they antagonize β_1 and β_2 receptors. Labetalol and carvedilol also block α_1 receptors, leading to peripheral vasodilatation, lowering blood pressure, and reducing cardiac afterload.

Clinically, β-blockers are mainstays of therapy (1) for patients with acute coronary syndromes and stable angina, as they reduce myocardial oxygen demand; (2) for the treatment of AF and supraventricular arrhythmias when rate or rhythm control is needed; and (3) for the management of ST-elevation myocardial infarction in patients with chronic heart failure. For patients undergoing surgery, guidelines recommend β-blockers as prophylaxis against postoperative AF. Use of β-blockers is currently a National Quality Forum (NQF) indicator in the perioperative management in CABG patients, although observational studies have shown conflicting associations of perioperative β-blockade and outcomes. Outside of the immediate postoperative period, the use of β-blockers can be guided by the underlying clinical condition. In heart failure patients, when prescribed acutely, β-blockers can worsen heart failure due to negative inotropic effects on an already failing ventricle. Thus, in patients with left ventricular systolic dysfunction, slow, gradual titration of β-blockers is mandatory, but their use in acute heart failure (e.g., the immediate postoperative period) should be with caution, if prescribed at all. However, with long-term use, they paradoxically evince a mortality benefit due to blockade of pathologically elevated catecholamine levels that increase left ventricular afterload, detrimental cardiac remodeling, and fibrosis. Recommended β-blockers in heart failure include metoprolol succinate (extended release), carvedilol, and bisoprolol.

Amiodarone

Amiodarone is an antiarrhythmic agent that inhibits multiple ion channels in the heart, including sodium, potassium, and calcium channels. Its overall electrophysiologic effect includes prolongation of the action potential, increasing refractoriness of cardiac tissue, prolongation of the QT interval, increased AV nodal refractoriness, decreased conduction velocity, bradycardia, and decreased myocardial oxygen utilization. The drug is very lipid-soluble, a property that is responsible for the drug's very long half-life of several weeks or longer. Amiodarone is routinely prescribed perioperatively as its use reduces postoperative AF, stroke, and length of stay. The postoperative duration of therapy, whether as prophylaxis or for the treatment of new, postoperative atrial fibrillation, is limited to a few weeks.

Amiodarone has multiple adverse effects as well as many clinically relevant drug-drug interactions. Pulmonary toxicity can be seen in up to 17% of patients and manifests as acute pneumonitis, acute respiratory distress syndrome, as well as other injury patterns. Abnormalities of thyroid function tests are commonly observed, and clinically relevant hyper- and hypothyroidism occur in 2% to 10% of patients on long-term therapy. Hepatoxicity with amiodarone can be seen in up to 30% of patients, manifesting as an increase in transaminases or alkaline phosphatase, but only rarely does it cause fulminant hepatic failure. The intravenous form of amiodarone can cause a profound hypotensive vasoplegic response related to the carrier. During the postoperative period, amiodarone potentiates warfarin and is synergistic with other drugs that prolong the QT interval, placing patients at risk for torsade de pointes. Despite the prolongation of the QT interval, amiodarone does not generally induce torsades or other arrhythmias on its own, but QTc monitoring is warranted. Overall, adverse effects with amiodarone are proportional to total cumulative dose, and so the short duration of therapy in the postoperative cardiac surgery setting diminishes the potential for inadvertent harm.

Diltiazem

Diltiazem is a nondihydropyridine calcium channel blocker that increases AV nodal refractoriness, as well as smooth muscle relaxation leading to some degree of vasodilatation, much less than that seen with amlodipine, another dihydropyridine calcium channel blocker. Diltiazem is both a negative inotrope and a negative chronotrope. It is metabolized via the CYP enzyme system and, as such, drug-drug interactions should be considered when prescribed in tandem with other medications. It is used for rate control in patients with AF and to reduce symptoms in patients with left ventricular outflow obstruction as seen in hypertrophic cardiomyopathy. Due to its negative inotropic effect, caution is recommended in patients with low cardiac output.

Digoxin

Digoxin is a cardiac glycoside that inhibits the Na-K-ATPase on myocytes, leading to increased intracellular Na, increased intracellular calcium, and ultimately increased cardiac inotropy. The electrophysiologic effects of digoxin include increased myocyte automaticity (particularly at higher doses) as well as potentiation of vagal tone and reduction in sympathetic tone, giving rise to lower heart rates, which can be beneficial. Digoxin is cleared by the kidneys; levels should be monitored to avoid toxicity. The use of digoxin in chronic heart failure and chronic AF is decreasing overall due to equivocal trial data. Digoxin can be considered for acute heart rate control in patients with AF, particularly with heart failure if hemodynamics preclude the use of β-blockers or calcium channel blockers.

INHALED DRUGS THAT CAUSE PULMONARY VASODILATION

Nitric Oxide and Inhaled Prostacyclins

Inhaled nitric oxide gas (iNO) as well as prostacyclins, such as epoprostenol and iloprost, delivered to airways via the ventilator circuit or via high-flow nasal cannula diffuse to airway smooth muscle, causing pulmonary vasodilation. Neither iNO or the prostacyclins have significant direct, systemic hemodynamic effects when administered through the lungs. Both classes of drugs improve pulmonary ventilation/perfusion matching and hypoxemia, as well as pulmonary vascular dilation. After surgery, these agents can reduce right ventricular afterload by decreasing pulmonary vascular resistance. They are particularly useful when faced with right ventricular failure, after left ventricular assist device placement with right heart dysfunction, heart transplantation, and lung transplantation. In patients after heart or lung transplant, iNO and inhaled prostacyclins were shown to have similar effects on the cardiac index and right heart pressures. Of note, lowering pulmonary vascular resistance can precipitate an increase in left heart filling pressure by virtue of increased flow to the left side due to improved right ventricular ejection. In patients with left heart failure, this can precipitate pulmonary edema due to left ventricular volume overload.

VASOACTIVE DRUGS

Vasoactive drugs broadly refer to drugs that can be used to manipulate preload, afterload, and contractility in surgical disease; these include catecholamines, inotropic agents, vasoconstrictors, and vasodilators (Table 2).

Epinephrine

Epinephrine is a catecholamine, which stimulates β_1 and β_2 receptors, leading to increased cardiac contractility and increased chronotropy. Epinephrine also has α-agonist effects at higher doses, with a resultant vasopressor effect. Epinephrine increases cardiac output, mean arterial pressure, and heart rate, and it is a mainstay in the treatment

TABLE 2 Dosing of Vasoactive Medications

MEDICATIONS	CONCENTRATION	DOSAGE
Diltiazem IV (for a-fib rate control)	125 mg in 125 mL (1 mg/mL)	5 mg q 5 mins X3 as an IV bolus 5–15 mg/h
Nicardipine (Cardene)	50 mg/100 mL (0.185 mg/mL)	5–15 mg/h
Dopamine (Intropin)	400 mg in 250 mL (1600 μg/mL) 800 mg in 250 mL (3200 μg/mL)	1–25 μg/kg/min
Dobutamine (Dobutrex)	500 mg in 250 mL (2000 μg/mL)	1–20 μg/kg/min
Epinephrine (Adrenalin)	2 mg in 100 mL (20 μg/mL) 10 mg in 250 mL (40 μg/mL)	0.01–0.4 μg/kg/min
Norepinephrine (Levophed)	8 mg in 250 mL (32 μg/mL)	0.01–0.4 μg/kg/min
Isoproterenol (Isuprel)	2 mg in 100 mL (20 μg/mL)	0.02–0.2 μg/kg/min
Milrinone (Primacor)	20 mg in 100 mL (200 μg/mL)	0.125–0.75 μg/kg/min
Esmolol (Brevibloc)	2500 mg in 250 mL (10 mg/mL)	Loading dose 500 μg/kg over 1 min Maintenance dose 12.5–300 μg/kg/min
Nitroprusside (Nipride)	50 mg in 100 mL (500 μg/mL)	0.1–10 μg/kg/min
Nitroglycerin	100 mg in 250 mL (400 μg/mL)	5–400 μg/kg/min
Phenylephrine (Neo-Synephrine)	20 mg in 100 mL (200 μg/mL)	0.1–4 μg/kg/min
Vasopressin (Pitressin)	50 units in 100 mL (0.5 units/mL)	0.01–0.04 units/min

of low cardiac output. Adverse effects include tachycardia and arrhythmias, as well as an associated increase in myocardial oxygen consumption. Epinephrine stimulates aerobic glycolysis and potentially could contribute to an increased serum lactate level.

Dopamine

Dopamine is a catecholamine that has dose-dependent effects, typically prescribed at a dose of 1 to 25 μg/kg/min. Lower doses agonize dopamine receptors, including those on the renal vasculature that are thought to cause increased renal blood flow, though there have been no RCTs demonstrating improved postoperative kidney function. At moderate doses, dopamine has β-agonist effects that increase heart rate and inotropy, whereas at high doses, α-agonist effects predominate with resultant arterial vasoconstriction. As with epinephrine, dopamine increases myocardial oxygen consumption.

Isoproterenol

Isoproterenol is a pure β-agonist that predominantly increases heart rate with an associated increase in contractility. The main clinical uses include pharmacologic overdrive pacing, such as in symptomatic bradycardia, and preventing bradycardic-dependent arrhythmias such as torsades de pointes.

Dobutamine

Dobutamine is a β-agonist that stimulates β_1 receptors to increase heart rate and myocardial contractility, as well as β_2 receptors, which provide vasodilation. Hence, dobutamine is considered an inodilator, possessing both inotropic and vasodilatory properties. Dobutamine increases myocardial oxygen consumption.

Milrinone

Milrinone is a phosphodiesterase inhibitor and inodilator with peripheral and pulmonary vascular vasodilatory properties. The dose range of milrinone is 0.125 to 0.75 μg/kg/min. It increases cardiac output by increasing cardiac contractility while simultaneously reducing right and left ventricular afterload. In patients with cardiogenic shock, milrinone results in increased cardiac output, lower heart rates, and decreased filling pressures. It prevents the breakdown of high-energy phosphates (HEP) as opposed to inducing their production, as seen with the other inotropes that stimulate β_1 receptors. With a resultant increase in HEP concentration as a result of inhibiting their breakdown, milrinone is a logical addition to the β_1-agonistic drugs that effect myocardial contractility by increasing HEP production. Of clinical importance is its longer half-life (30–60 minutes) compared with catecholamines (2–3 minutes) and its clearance by the kidney, which can lead to significant increases in its concentration in the postoperative patient with renal insufficiency. Its side effects include hypotension and thrombocytopenia. The latter can be confusing as thrombocytopenia is so common postoperatively, with multiple causes.

Norepinephrine

Norepinephrine is a catecholamine with mixed α- and β-agonist effects that provide vasopressor and inotropic support. Norepinephrine is useful in treating vasoplegic shock where there is a need for concomitant inotropy. The typical dose range is 0.01 to 0.4 μg/kg/min. Its main disadvantage is splanchnic vasoconstriction. Compared with dopamine, norepinephrine was associated with improved outcomes in patients in cardiogenic shock with a trend toward benefit in shock of all subtypes.

Vasopressin

Vasopressin is a hormone analogue that provides pure vasoconstriction and is useful for treating vasoplegic states. The dose range is 0.01 to 0.06 units/minute. Among postoperative patients with vasoplegic shock whose mean arterial pressure was less than 65 with a cardiac index over 2.2 L/min/m^2, looking at a composite primary endpoint, vasopressin proved superior to high-dose norepinephrine, but this result was solely due to a lower incidence of renal failure, not mortality. Furthermore, the difference was only seen in patients on preop ACE inhibitors/ARBs. There were fewer cases of postoperative AF in the vasopressin group as well, but there were no differences in intestinal or peripheral ischemic events. In patients with sepsis, however, RCTs have found no differences in mortality among patients treated with vasopressin or norepinephrine. Overall, vasopressin can be considered as a catecholamine-sparing vasopressor for patients with postoperative vasoplegic shock, but it is significantly more expensive, $550/day vs. $20/day for norepinephrine.

Neo-Synephrine

Neo-Synephrine looks very much like a catecholamine but, like vasopressin, is a pure α-agonist. It can be used at a dosage of 0.1 to 4 μg/kg/min for patients with severe vasoplegia. As with vasopressin or any alpha agent for that matter, it increases cardiac afterload. As with vasopressin, Neo-Synephrine may be a particularly useful vasopressor for patients with hemodynamically significant, dynamic left ventricular outflow tract obstruction (LVOT), including hypertrophic obstructive cardiomyopathy and systolic anterior motion of the mitral valve after mitral valve repair. In these conditions, providing peripheral vasoconstriction while avoiding inotropy lowers the LVOT gradient and can improve hemodynamics.

Midodrine

Midodrine is an oral α-agonist—and the only one—that provides purely α-agonistic vasopressor support. The typical dosing is 10 to 40 mg every 8 hours. Midodrine can be considered for vasodilated patients, many of whom are chronically ill, and is particularly useful when unable to wean intravenous blood pressure support (e.g., vasopressin, norepinephrine, or dopamine). As is the case with any of the pure vasoconstrictors, a note of caution should be raised, as one needs to be certain that causes of hypotension other than pure vasodilation (e.g., sepsis, low cardiac output, or cortisol deficiency) are not contributing to the problem.

Vasodilators

Nitroprusside is an extremely effective, short-acting arterial vasodilator, which is dosed intravenously at 0.1 to 10 μg/kg/min. In the patient with ischemic heart disease, nitroprusside can cause a coronary steal phenomenon, particularly for those with incomplete revascularization. Furthermore, nitroprusside can cause intrapulmonary shunting by increasing flow to unventilated alveoli with resultant hypoxia. An additional important adverse effect is the accumulation of thiocyanate as a drug metabolite, which can lead to cyanide toxicity, particularly among patients with renal failure. This diagnosis must be kept in mind in patients with a lactic acidosis in the face of good perfusion. Thus, thiocyanate levels should be followed in patients on nitroprusside, particularly with high dose or a prolonged period of infusion.

Nitroglycerine is another intravenous vasodilator that affects both the arterial as well as the venous system. Nitroglycerine has predominant venodilating properties at low doses and progressive arterial vasodilating properties at higher doses. Nitroglycerine is commonly used postoperatively in the coronary bypass surgery patient with arterial grafts to prevent early arterial conduit spasm. Like nitroprusside, nitroglycerine can sometimes cause increased intrapulmonary shunting with resultant hypoxemia. Its dose range is 0.01 to 0.5 μg/kg/min.

Nicardipine is a calcium channel blocker that has direct arterial vasodilating effects with a longer half-life than either nitroglycerine or nitroprusside. Its intravenous dosage is 2.5 to 15 mg/hour.

Hydralazine is an oral and intravenous direct arteriolar vasodilator and is useful for patients who require afterload reduction. As an oral agent, it is common for chronic heart failure in those patients unsuitable for other afterload reducing agents. However, as it is dosed every 8 hours, it is cumbersome. It should be used with significant caution, if at all, in the early postoperative period because of its long half-life (several hours). Adverse effects include hypotension, reflex tachycardia, and, rarely, a lupus-like syndrome that typically results from high doses over a prolonged time period.

CONCLUSION

This chapter describes the common drugs used in the surgery patient. The vasoactive and inotropic drugs are a mainstay of acute cardiac critical care, and the practitioner working in this field must be fluent in their use. Similarly, antiplatelet drugs, statins, and anticoagulants are used so commonly in the chronic, postoperative patient that physicians should have an in-depth knowledge of the drugs' mechanisms of action as well as their indications and effectiveness.

It is the authors' hope that this chapter has covered a significant portion of those areas of knowledge so crucial to the pharmacology of cardiac care, with references that can supplement that knowledge.

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Glucose Control in the Postoperative Period

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Diabetes mellitus and dysfunction of glucose metabolism continue to be a growing problem worldwide. The 2020 National Diabetes Statistics Report, published by the Centers for Disease Control and Prevention (CDC) estimates that 34.2 million people are living with diabetes, accounting for 10.5% of the population in the United States. Of these, approximately 26.9 million people, the vast majority of them adults, have been formally diagnosed with diabetes, with the 7.3 million people who are undiagnosed representing over 20% of all adults with diabetes. One-third of the population is estimated to have prediabetes. In the United States, the total direct and indirect estimated cost of diagnosed diabetes in 2017 was $327 billion, a 25% increase over a 5-year period.

Perioperative hyperglycemia is described in 20% to 40% of patients having noncardiac surgery; up to one-third of these patients have not been previously diagnosed with diabetes. In the perioperative period, glucose dysregulation has been associated with increased perioperative complications and mortality. Given the increasing prevalence of diabetes and aging of the population, and as the surgical acuity and premorbid conditions in patients escalate, postoperative glycemic control becomes increasingly important. Evidence from large, prospective, randomized studies demonstrate that optimal glucose management results in improved outcomes, reduced complications, and a decreased hospital length of stay. Thus, prompt recognition and appropriate management of abnormal glucose is both a patient safety and quality of care issue.

INDICATIONS

Adverse consequences of hyperglycemia in the perioperative period are well described. Elevated postoperative glucose has been strongly associated with respiratory complications, venous thromboembolism, myocardial infarction, cardiac arrest, and need for reoperation. Additionally, hyperglycemia appears to be an independent predictor of surgical site infection (SSI), pneumonia, urinary tract infection, and sepsis within 30 days of surgery. Elective surgery patients who develop hyperglycemia have a twofold higher risk of infection, and patients who receive noncardiac general surgery procedures have a 30% increase in postoperative infectious complications for every 40 mg/dL increase in hyperglycemia. The association of hyperglycemia after cardiac surgery, hepatectomy, colectomy, and general and vascular surgeries correlating with worse outcomes in the postoperative period has been repeatedly demonstrated. Hyperglycemia causes a state of chronic inflammation leading to an exaggerated inflammatory response. Neutrophil phagocytic activity is impaired, contributing to poor postoperative wound healing. Additionally, endothelial dysfunction caused by hyperglycemia and vascular damage leading to relative tissue ischemia also impairs postoperative wound healing.

Postoperative hyperglycemia occurs in three categories of patients: those with a known diagnosis of diabetes, those with unrecognized diabetes, and those experiencing stress-induced hyperglycemia. Examination of glucose dysregulation in the perioperative period requires that stress-induced hyperglycemia be distinguished from an established diagnosis of diabetes and that the three domains of glycemic control (hypoglycemia, hyperglycemia, and glycemic variability) be considered. Among hospitalized patients, the occurrence of each of these domains is associated with adverse outcomes, including death.

Stress-Induced Hyperglycemia

Physiologic stressors, including surgery, infection, and injury may lead to elevations in blood glucose, even in the absence of diabetes. Surgical procedures cause metabolic stresses characterized by increases in sympathetic pathways leading to increases in catecholamines, cortisol, glucagon, and growth hormones. Stress-induced hyperglycemia refers to transient hyperglycemia during physiologic stress, such as illness or surgery, in patients with no previous evidence of diabetes. Stress-induced hyperglycemia has been defined as a blood glucose level greater than 140 mg/dL in nondiabetic patients and a blood glucose level greater than 180 to 220 mg/dL in diabetic patients, with levels returning to normal values of less than 126 mg/dL after removal of the stressor and discontinuation of any glucose-lowering treatment.

Dungan and colleagues characterized stress-induced hyperglycemia as insulin resistance during illness caused by the inability to suppress central hepatic glucose production and insulin resistance in the periphery through two pathways. The first pathway is a reduced insulin-mediated glucose uptake resulting from defects in post-receptor insulin signaling and downregulation of glucose transporter (GLUT)-4 caused by cytokines. The second pathway is impaired nonoxidative glucose disposal from decreased muscle glycogen synthesis mediated by excess cortisol and epinephrine. Hyperglycemia itself causes increased cytokine, inflammatory, and oxidative stress responses that exacerbate this cycle, ultimately causing further hyperglycemia. Insulin levels normally increase with blood glucose to suppress hepatic glucose production and promote peripheral glucose uptake. With injury and sepsis, hepatic glucose production, which is often refractory to exogenous insulin, may increase markedly. Hepatic insulin resistance with elevated levels of insulin-like growth factor binding protein also contributes to hyperglycemia. However, these responses are normalized with control of hyperglycemia and the use of exogenous insulin.

In a review by Vogt and Bally, patients undergoing abdominal surgery were shown to have decreased insulin sensitivity, by 50% on average, for up to 5 days postoperatively. The time to normalization ranged from 9 to 21 days postoperatively and was partially dependent on the complexity and invasiveness of the procedures. This highlights the need for continued postoperative glucose control in nondiabetic patients.

The risk of postoperative complications is correlated with the level of hyperglycemia. Park and colleagues found that patients who had elevated glucose levels preoperatively were more likely to have myocardial infarction after noncardiac surgery, but this association was not seen in patients with elevated hemoglobin A1c (HbA1c) levels. This suggests that glucose dysregulation has a more significant role in the development of complications than preexisting diabetes. Other studies have also confirmed that elevated postoperative glucose levels are associated with postoperative complications, whereas HbA1c levels are not. But these studies have also demonstrated that glucose monitoring and treatment with insulin occurs more frequently in patients with increased HbA1c levels compared with patients without known diabetes.

THE THREE DOMAINS OF GLYCEMIC CONTROL: HYPOGLYCEMIA, HYPERGLYCEMIA, AND GLYCEMIC VARIABILITY

The three domains of glycemic control, described by Krinsley et al. as hypoglycemia, hyperglycemia, and glycemic variation, are important factors with regard to mortality that differ in patients with and without diabetes. Derangements in more than one domain are associated with a cumulative increase in mortality in patients without diabetes, but not in patients with diabetes.

Hyperglycemia

Hyperglycemia in the perioperative period has also been shown to be associated with adverse outcomes including wound infection, pneumonia, sepsis, thromboembolic events, renal insufficiency, cardiovascular events, and increased length of stay. Measuring HbA1c during hospitalization also allows differentiation between stress-induced hyperglycemia and undiagnosed diabetes.

Hyperglycemia leads to limited vascular reactivity by the angiotensin II and nitric oxide synthase pathways, inhibition of neutrophil chemotaxis and phagocytosis, and increased vascular permeability and leukocyte and platelet activation. Through these mechanisms, hyperglycemia plays a significant role in the development of stroke, myocardial infarction, SSIs, and impaired wound healing, increasing morbidity and mortality in surgical patients. In colorectal nondiabetic patients, one single postoperative elevated glucose value has been associated with infectious and noninfectious complications, with the rates of complications increasing parallel to the degree of hyperglycemia.

Hypoglycemia

Hypoglycemia is defined as a blood glucose level less than 70 mg/dL, with severe hypoglycemia occurring at levels below 50 mg/dL. Numerous studies have shown that hypoglycemia is associated with increased risk of mortality. Krinsley and colleagues demonstrated that this increased mortality rate was more profound in patients without diabetes and in any patients who experience severe hypoglycemia. The occurrence of hypoglycemia, defined as blood glucose lower than 80 mg/dL, was independently associated with mortality regardless of diabetes status.

Hypoglycemia has been associated with increases in cardiovascular mortality thought to be related to QT prolongation and derangements in cardiac cell repolarization. Hypoglycemic episodes have been independently associated with increased risk of mortality among diabetic and nondiabetic patients. Diabetic patients hospitalized with acute myocardial infarction had a 93% increased mortality rate when hypoglycemia was present during their hospitalization.

A group of 2601 patients hospitalized in the intensive care unit (ICU) were evaluated for ICU mortality when moderate or severe hypoglycemia was present and compared with a group with no episodes of hypoglycemia. Patients with severe and moderate hypoglycemia had 34% and 18% increases in 90-day mortality, respectively, compared with their normoglycemic counterparts. Patients with multiple hypoglycemic events had a 44% increase in mortality compared with normoglycemic patients. Optimal therapy regimens must treat hyperglycemia without inducing episodes of hypoglycemia.

Glycemic Variability

Beyond concerns of hypoglycemia and hyperglycemia, glycemic variability also must be managed. Krinsley and colleagues performed a multicenter cohort analysis of 44,964 critically ill patients evaluating hypoglycemia, hyperglycemia, and glucose variability. However, diabetic patients tolerated higher levels of glucose better. Diabetics with blood glucose of 110 to 180 mg/dL had a decreased risk of mortality, and increasing glycemic variability was not associated with an increased risk of mortality in these patients. Conversely, in patients without diabetes, the lowest mortality occurred in those with mean blood glucose of 80 to 140 mg/dL, and in this group increasing glycemic variability was associated with increased risk of mortality. Glycemic variability, or greater than 20% changes in glucose levels, were associated with increased mortality in patients without diabetes, but not in patients with diabetes. A glycemic variability greater than 40% was associated with a three fold increase in mortality compared with those with only a 20% variability.

This effect is additive when it occurs with hypoglycemia and is more pronounced in patients without diabetes. It is suggested that glycemic variability impairs endothelial function, causes oxidative stress at the cellular level, and enhances cell apoptosis. Additionally, wide fluctuations in blood glucose may mask occult hypoglycemia, which has been recognized as a risk factor for mortality in the critically ill patient. Iatrogenic swings in blood glucose levels can occur with overly aggressive correction of dysglycemia. The optimal management strategy to minimize variability remains unclear.

MANAGEMENT

Glucose dysregulation can lead to serious complications and mortality, and it must be managed in the perioperative period. Insulin, administered either subcutaneously (SQ) or intravenously (IV), is the indicated agent for inpatient glucose control. The use of oral agents in the acutely ill and hospitalized patient is challenging and associated with hazards. Several studies have investigated the optimal target blood glucose range; however, this has not been entirely defined. Although it is clear that perioperative hyperglycemia (glucose >180 mg/dL) is associated with increased risk of infection, need for reoperative surgery, and death in surgical patients, efforts at more rigorous glucose management have not been shown to improve outcomes. Preoperative hyperglycemia is associated with increased 1-year mortality, with patients without diabetes showing higher mortality at similar preoperative glucose levels. A Cochrane review by Kao and colleagues evaluated perioperative glycemic control and its effects on outcomes including SSIs, hypoglycemia, and mortality. The rate of SSIs did not differ between strict and conventional glucose control groups. More episodes of hypoglycemia occurred in strict glucose control groups; however, no study reported adverse outcomes caused by hypoglycemia, and short-term, all-cause mortality was not different between the treatment groups. More stringent glucose control also has been examined in the management of critically ill patients. In a randomized controlled trial by Van den Bergh in 2001, patients in the ICU were randomized to either conventional insulin therapy (blood glucose levels 180 to 200 mg/dL) or intensive insulin therapy (blood glucose levels 80 to 110 mg/dL). Irrespective of diabetes status, patients in the intensive therapy group had decreased morbidity and mortality.

However, the NICE-SUGAR trial, a large, multinational, randomized controlled study, demonstrated increased mortality in critically ill adults with an intensive glucose control goal compared with those with a conventional glucose control of less than or equal to 180 mg/dL, and patients had a significant occurrence of hypoglycemia. As a result of this trial, the American Diabetes Association recommends initiation of treatment for persistent hyperglycemia above 180 mg/dL in hospitalized patients. Once insulin therapy is initiated, a blood glucose level of 140 to 180 mg/dL is recommended in both critically ill and other hospitalized patients. The CDC similarly recommends implementation of treatment to maintain a blood glucose level less than 200 mg/dL as a preventive measure for SSI in patients undergoing surgery. More intensive glycemic control in the perioperative period has been further explored. A meta-analysis by De Vries and colleagues showed that utilizing a more intense hyperglycemic protocol to maintain blood glucose levels less than 150 mg/dL in the perioperative period reduced the rates of SSI. An increased risk of hypoglycemia was observed, but not an increase in adverse events.

Perioperative glycemic control must be considered throughout the perioperative period, as preoperative and intraoperative management also influence postoperative glucose regulation.

Preoperatively

Blood glucose levels should be assessed during preoperative preparation, particularly in patients with risk factors such as previously elevated glucose levels, age greater than 45 years, or obesity. Patients with diabetes should have an HbA1c level measured within the previous 3 months. Greater HbA1c levels (specifically greater than 8%) and severe hyperglycemia (greater than 250 mg/dL) in the

preoperative period are associated with poorer surgical outcomes. Delaying elective surgery to improve glycemic control is recommended. Palermo and Garg demonstrated that early preoperative identification of patients with poorly controlled diabetes and proactive treatment before surgery improved glycemic control, lowered the risk of surgical complications, and decreased the length of hospital stay.

In patients with known diabetes receiving treatment, management should be continued in the perioperative period with relatively few adjustments. The night before or morning of surgery, long-acting basal insulin dosing should be reduced in anticipation of NPO status before surgery. The dose should be decreased by 50% to 75% of the normal dose. Patients with renal or hepatic insufficiency are at increased risk for hypoglycemia, so long-acting basal dose insulin should be decreased closer to 50%. However, for patients with type 1 diabetes mellitus, to prevent diabetic ketoacidosis, the basal insulin dose should not be interrupted. Patients taking intermediate-acting insulin should reduce the dose by 50% on the morning of surgery. Those taking premixed insulin preparations should take half of the basal component of their dose as an intermediate-acting insulin and hold the rapid-acting component.

Blood glucose should be checked once the patient arrives in the preoperative care area. If blood glucose is less than 70 g/dL, glucose should be administered. Preoperative patients with a blood glucose of more than 180 g/dL should be given a supplemental dose of rapid-acting insulin.

Intraoperatively

Intraoperatively, blood glucose levels should continue to be monitored in patients with glucose dysregulation. The goal for all patients is to maintain a blood glucose level of less than 180 mg/dL intraoperatively while simultaneously avoiding any episodes of hypoglycemia. This goal is most often achieved with blood glucose monitoring every 1 to 2 hours and utilizing supplemental subcutaneous rapid-acting insulin for correction. However, if blood glucose levels are persistently greater than 200 mg/dL, intravenous insulin infusion may be necessary.

Postoperatively

Postoperatively, blood glucose should be checked on all patients. If an intravenous infusion was initiated intraoperatively, it should be continued. Patients admitted to the ICU postoperatively, particularly those with significant physiologic stress, may require an intravenous insulin infusion for improved glucose control. In patients receiving insulin infusions, frequent bedside point-of-care testing is recommended to evaluate glycemic status and direct management.

However, in patients on the general surgical floor, a basal insulin regimen has been shown to be more effective than a supplemental correctional sliding scale alone. Glycemic control for postoperative patients and non–critically ill surgical patients who are receiving nutrition should include a basal insulin dose in combination with a "nutritional" subcutaneous insulin dose (linked to meals or nutritional supplementation) and a correction insulin regimen only if needed. Patients receiving continuous feedings should receive subcutaneous insulin every 4 to 6 hours. In patients with poor nutritional intake and those that are NPO, basal insulin or basal plus correctional insulin is recommended. In addition, a hypoglycemia management protocol should be in place to prevent and treat hypoglycemia (Table 1). Use of a correctional insulin sliding scale alone in patients with admission blood glucose > 180 mg/dL is discouraged as glucose control has been shown to be inadequate and unpredictable; overall, the use of sliding-scale insulin as sole therapy is discouraged.

Protocols and order sets for insulin and hypoglycemia management should be established, and recommendations are available from various sources. When transitioning from an insulin infusion to SQ administration, the most recent insulin infusion rate is used to estimate daily insulin needs. Approximately 50% of the calculated dose can be administered as basal insulin and the remaining 50% as prandial insulin administered in divided doses with meals. Initial basal doses of insulin are generally started at 10 units daily or 0.1–0.2 units/kg/day, administered every 12 hours. This scheduled dose should be adjusted daily based on blood glucose response, the total amount of insulin administered on the previous day, and the overall condition of the patient.

TABLE 1 Insulin Dosing for Enteral/Parenteral Feedings

Situation	Basal/Nutritional	Correctional
Continuous enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine/degludec daily Nutritional: regular insulin every 6 h or rapid-acting insulin every 4 h, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin 6 h or rapid-acting insulin every 4 h for hyperglycemia
Bolus enteral feedings	Continue prior basal or, if none, calculate from TDD or consider 5 units NPH/detemir every 12 h or 10 units glargine/degludec daily Nutritional: give regular insulin or rapid-acting insulin SQ before each feeding, starting with 1 unit per 10–15 g of carbohydrate; adjust daily	SQ regular insulin 6 h or rapid-acting insulin every 4 h for hyperglycemia
Parenteral feedings	Add regular insulin to TPN IV solution, starting with 1 unit per 10 g of carbohydrate; adjust daily	SQ regular insulin 6 h or rapid-acting insulin every 4 h for hyperglycemia

IV, Intravenous; *SQ,* subcutaneous; *TDD,* total daily dose; *TPN,* total parenteral nutrition.
From American Diabetes Association. Diabetes care in the hospital: *Standards of Medical Care in Diabetes-2018*. Diabetes Care. 2018;41:S144–S151.

In selecting goals for blood glucose ranges, recommendations from professional societies include similar ranges. For patients who have undergone routine cardiac surgery, glucose levels should be maintained below 180 mg/dL. However, for post–cardiac surgery patients who are anticipated to spend greater than 3 days in the ICU and require mechanical ventilation, myocardial support, renal support, or inotropic or antidysrhythmic medications, a level below 150 mg/dL is recommended (Society of Thoracic Surgeons). A blood glucose level below 150 mg/dL (absolutely < 180 mg/dL) and avoiding levels less than 100 mg/dL to prevent hypoglycemia for critically ill patients is endorsed by the Society of Critical Care Medicine. In neurocritical care patients, goal ranges of 110 to 140 mg/dL or 140 to 180 mg/dL are recommended if hypoglycemia cannot be prevented, and prevention of hypoglycemia should be emphasized, especially in patients with a traumatic brain injury. In patients with overwhelming sepsis, the Surviving Sepsis Campaign guidelines set a goal blood glucose of less than 180 mg/dL. The American Diabetes Association sets its target between 140 and 180 mg/dL in critically ill patients, and the Endocrine Society recommends 110 to 140 mg/dL for post–cardiac surgery populations.

Although the use of continuous glucose monitoring has greatly increased in the outpatient setting, data are sparse regarding the use of this technology in hospitalized patients. Recent recommendations include avoiding initiation of continuous glucose monitoring in patients with marked hypoglycemia or hyperglycemia (e.g., blood glucose < 40 mg/dL or > 500 mg/dL) or when significant variability in blood glucose is occurring. Similarly, the use of automatic insulin dosing devices in inpatient settings has not yet been adequately studied. Concerns have been expressed about the potential for unreliability in critically ill patients; the use of an automatic insulin dosing device can be considered in the non-ICU patient who has been utilizing it before admission. The need for hospital protocols, policies, and education for the use of these devices is evident.

CONCLUSION

Derangements in glucose metabolism occur frequently in the perioperative period and develop in response to physiologic stress, both in patients with known diabetes and in other patients. Although measurement of HbA1c is important, data indicate that proximate glucose management may be more crucial than long-term glucose control in patients undergoing noncardiac surgery. Hyperglycemia occurs frequently and has demonstrable and significant detrimental effects, but hypoglycemia and glucose variability are also associated with morbidity and mortality.

Specific targets: Aggressive regimens for tight glucose control increase the risk of hypoglycemia and mortality and are not indicated because of the risk of severe hypoglycemia. At the present time, most advocate for a glycemic target slightly above a normal physiologic scale, with a target range for glucose control in critically ill patients of 140 to 180 mg/dL, which should be managed via insulin infusion. In non–critically ill patients, a target premeal blood glucose level lower than 140 mg/dL, with any random blood glucose level lower than 180 mg/dL, is appropriate. These patients should be managed with a basal, bolus, and correction SQ insulin administration strategy. The use of sliding-scale insulin only is inadequate and should be abandoned.

Suggested Readings

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Postoperative Respiratory Failure

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INTRODUCTION

Pulmonary complications are among the most frequent and costly events after surgery. The development of respiratory failure is associated with increased morbidity, mortality, length of stay and healthcare costs, particularly if not recognized and treated promptly. This chapter focuses on identifying patients at risk for postoperative respiratory failure, as well as management from early interventions through current evidence-based practices of acute respiratory distress syndrome (ARDS).

TYPES OF POSTOPERATIVE RESPIRATORY FAILURE

Acute respiratory failure (ARF) has been classified as hypoxemic (type I) and hypercapnic (type II); these may occur concurrently. Postoperative respiratory failure (PRF) is not consistently defined but generally extends these criteria to include need for supplemental O_2, need for mechanical support for 48 hours postprocedure, and need for reintubation within 30 days of the index procedure (Box 1).

Postoperative hypoxemia is primarily attributed to increased dead space ventilation (ventilating underperfused regions) and shunt (perfusing unventilated regions). These occur most commonly secondary to atelectasis and decreased functional residual capacity. Additional causes are listed in Box 2. Hypercarbic respiratory failure is related to inadequate minute ventilation, whether from increased CO_2 production with insufficient clearance, increased work of breathing, or airway obstruction. Additional causes are listed in Box 3.

PREOPERATIVE RISK ASSESSMENT

The goal of risk assessment is to identify opportunities for prevention of perioperative complications (Box 4). The American Society of Anesthesiologist Physical Status Classification, with a score greater than 2 (more than mild systemic disease) remains a surprisingly strong predictor of postoperative pulmonary outcomes. Predictive models derived from large datasets have identified several other risk factors associated with postoperative pulmonary complications. Many are nonmodifiable (age, functional dependence, preexisting comorbidities, emergency surgery, major open abdominal, and

BOX 1 Acute Respiratory Failure

Hypoxemic respiratory failure (type I): Arterial partial pressure of oxygen (PaO_2) less than 60 mm Hg on room air
Hypercapnic respiratory failure (type II): Arterial partial pressure of carbon dioxide ($PaCO_2$) greater than 50 mm Hg on room air
Additional considerations for postoperative period
- *New onset hypoxemia* requiring oxygen supplementation for >48 h
- *Failure to wean* from mechanical ventilation within 48 h of a procedure
- *Need for reintubation* in the first 30 days after procedure

BOX 2 Common Causes of Postoperative Hypoxemia

Atelectasis
Aspiration
Cardiogenic pulmonary edema
Pulmonary embolism
Pneumothorax
Bronchospasm
Mucus plugging
Pulmonary contusion

BOX 3 Common Causes of Postoperative Hypercapnia

Residual inhaled aesthetic
Residual neuromuscular blockade
Opioid use
Sedatives
Neuromuscular disorders
Chronic obstructive pulmonary disease
Sepsis
Obesity

BOX 4 Risk Assessment for Postoperative Respiratory Failure

Patient Specific: American Society of Anesthesiologist (ASA) status, pulmonary comorbidities (OSA, COPD, respiratory infections, trauma/contusions), obesity, smoking status, heart failure, sepsis, frailty
Operation Specific: Type of operation, length of operation, administered fluid volume, thoracic operation, emergent operation
Pharmacologic: Residual anesthetic or neuromuscular blockade, opiate or benzodiazepine administration

thoracic, neurologic, and vascular surgical procedures). Nevertheless, if the patient's condition allows, potentially modifiable factors include preoperative rehabilitation, nutrition support, control of sepsis, and smoking cessation. For all patients, consideration of anesthetic and surgical approach, intraoperative ventilator and volume strategy, minimization of transfusion and volume overload, and postoperative multimodality care processes (adequate pain control, incentive spirometry, early mobility) may be opportunities for improving care. The etiology of PRF is often multifactorial, and many components of the planned operation can affect the patient's homeostasis and increase risk for PRF.

PREVENTION OF PULMONARY COMPLICATION

For elective operations, prevention of complications begins in the office. Prehabilitation programs have been studied in many surgical disciplines and decrease postoperative morbidity and mortality, although the optimal type of exercise and components of the program remain undefined. They have variable components but tend to focus on modifiable factors such as smoking status, nutrition, exercise and fitness, and comorbidity optimization. Preoperative infections, such as bronchitis or viral infection, increase the incidence of PRF, and it is recommended to delay general anesthesia 6 weeks after viral infection for elective cases.

As an example, management of a patient undergoing laparoscopic assisted esophageal resection for carcinoma includes preoperative assessment for common underlying conditions, such as chronic obstructive pulmonary disease (COPD) and smoking history, with further evaluation/intervention if symptomatic. A prehabilitation plan should be considered, with preoperative instruction in incentive spirometry. With planned laparoscopy, carbon dioxide insufflation can lead to higher $PaCO_2$ levels, which may be difficult to clear in the presence of underlying pulmonary conditions. Atelectasis is common after all types of operations but may be most pronounced during thoracic surgery requiring single lung ventilation. In this case, the intentional collapse and expansion may increase the inflammatory response and edema in that lung, increasing the risk of PRF. Enhanced recovery components such as multimodal pain therapy, minimizing opiate analgesia, early mobilization, and breathing exercises can be preplanned in an attempt to reduce PRF.

INITIAL EVALUATION AND TREATMENT

PRF can occur at any point after an operation, even in the recovery room. Protocols for postanesthetic monitoring and pulse oximetry as well as prespecified criteria for when patients can move out of recovery areas are recommended. Patients with new oxygen requirement, depressed levels of consciousness, or multiple risk factors should be watched carefully and assessed often by the surgical team. Monitoring of ventilation by capnography or blood gas determination is recommended. Other important considerations include chest radiograph, electrocardiogram, and potentially, anesthetic or opiate reversal agents.

Along with diagnosing PRF, it is important to identify those who may need a higher level of care. The initial evaluation of patients with suspected PRF begins with triaging patients by those who can undergo further workup and evaluation and those who require emergency airway intervention. Patients with increasing levels of oxygen support, oxygen requirements greater than 6 LPM nasal cannula, those who have received reversal agents such as naloxone, or those who have multiple comorbidities and risk factors for PRF may benefit from early upgrade to a monitored bed or intensive care unit.

Patients with persistent hypoxia (pulse oximetry <88%) despite increasing oxygen support, depressed mental status (GCS <8), or evidence of other airway compromise such as stridor need to be evaluated for reintubation immediately. There is a trend toward temporizing with noninvasive therapies such as high flow nasal cannula (HFNC) and continuous/bilevel positive airway pressure (CPAP/BiPAP) to prevent reintubation. These can be used for short periods while reversible etiologies such as opiate overdose are treated or as a bridge until intubating providers arrive.

Endotracheal intubation remains the most secure and safest airway in PRF/ARF. Emergent intubation carries different challenges than in an elective setting but can be done safely in an organized approach. These patients are at particular risk for postintubation hypotension. A preintubation fluid bolus and/or vasoactive medications, either phenylephrine or norepinephrine can be considered. Modified rapid sequence induction should be performed, considering that each induction agent has its own side effect profile. Propofol, midazolam, and fentanyl remain the mainstay; ketamine use is increasing outside

of the OR due to its preservation of respiratory drive and lower risk of hypotension and bronchodilation. Either direct or video laryngoscopy may be used; providers should use the method with which they are most comfortable. The position of the endotracheal tube should be confirmed with capnography and chest x-ray.

Mechanical Ventilation

The goal of mechanical ventilation is to ensure adequate oxygenation and ventilation while reducing the patient's work of breathing.

Oxygen uptake via the lungs is dependent on both the partial pressure of oxygen and ventilation-perfusion matching. To improve oxygenation, three main strategies are used:

1. Increasing the fraction of inspired oxygen (FiO_2). Systemic oxygen delivery varies with cardiac output and oxygen carrying capacity. Increasing the FiO_2 increases the amount of oxygen available for transport by hemoglobin. High FiO_2 levels (>50%) are generally well tolerated but may be associated with oxygen toxicity and absorptive atelectasis.
2. Increasing pressure gradient at the alveolar level. This is accomplished most efficiently by increasing the mean airway pressure. Mean airway pressure can be increased by increasing positive end expiratory pressure (PEEP), driving pressure, or by adjusting the inspiratory time to increase the inspiratory-to-expiratory (I:E) ratio. Care must be taken to limit increases in inspiratory plateau pressure to minimize the risk of barotrauma and ventilator-induced lung injury.
3. Recruitment maneuvers (RM). The goal of these maneuvers is to increase the fraction of lung recruited for gas exchange by applying transient increases in airway pressure. After recruitment, increased PEEP is necessary to prevent recurrent alveolar collapse. RM may cause barotrauma and transient decreased cardiac output.

Ventilation is determined by carbon dioxide elimination via the lungs and is largely dependent on alveolar ventilation. Alveolar ventilation is equal to the minute ventilation (respiratory rate × tidal volume) minus the dead space (the portion of gas that does not participate in ventilation). To increase ventilation, the tidal volume or the respiratory rate should be increased.

Delivery of Mechanical Ventilation

Mechanical ventilation can lead to additional lung injury, known as ventilator-induced lung injury (VILI). VILI mechanisms include barotrauma, volutrauma (diffuse alveolar injury resulting from overdistension), or atelectrauma (injury caused by repeated cycles of recruitment and derecruitment) (Figs. 1 and 2). Injury also can be related to the release of local mediators in the lung, referred to as biotrauma. In current ventilators, advanced options that limit tidal volume are used to potentially mitigate these harms.

Initial ventilator settings include the FiO_2, respiratory rate, PEEP, ventilator mode, and breath type. Positive pressure ventilation can be delivered using controlled, assisted, or spontaneous modes to achieve a set volume or pressure target.

Modes of Mechanical Ventilation

Continuous Mandatory Ventilation and Assist Control

Continuous mandatory ventilation (CMV) provides preset, mandatory, machine-delivered breaths at a set rate, using either a volume or pressure target, to achieve a prescribed minute ventilation. In pure CMV modes, the ventilator provides set mandatory machine-triggered breaths without consideration of patient triggering. CMV is commonly used in heavily sedated patients or those who are receiving neuromuscular blockade. CMV may result in diaphragmatic inactivity, promoting atrophy and contractility dysfunction.

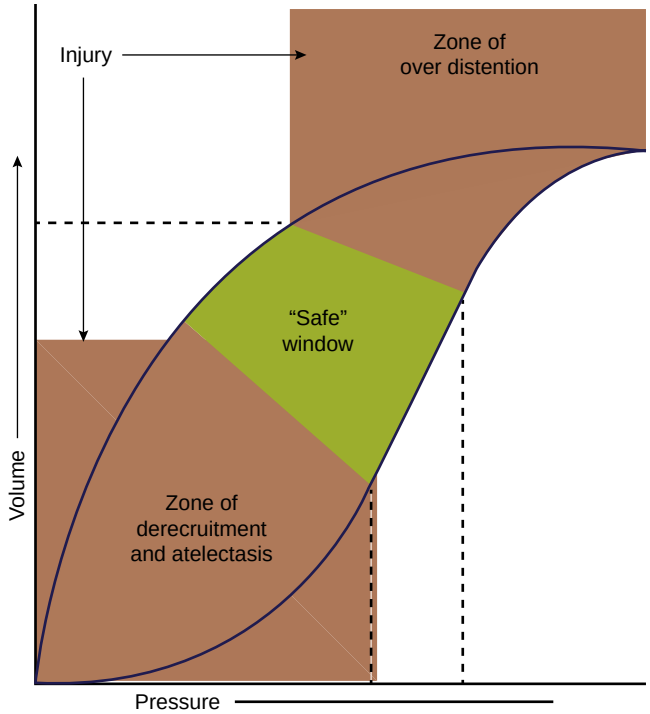


FIG. 1 Pressure-volume curve of a moderately diseased lung, such as in acute respiratory distress syndrome. Two hazard zones exist: overdistension and derecruitment/atelectasis. Higher end-expiratory pressures and small tidal volumes are needed to stay in the "safe" window. Open lung ventilation may have a larger margin of safety in keeping the lung open within the desired target range and avoiding alveolar overdistension. *(From Imai Y, Slutsky AS: High frequency oscillatory ventilation and ventilator-induced lung injury.* Crit Care Med. *2005;33[3Supp]:S129–S134.)*

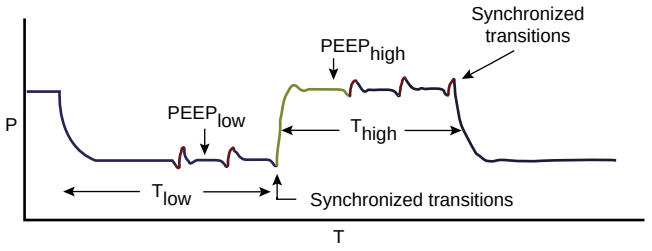


FIG. 2 Bilevel ventilation. Bilevel ventilation uses two pressure levels (PEEP low and PEEP high) for two time periods (time-low [T_{low}] and time-high [T_{high}]), with spontaneous breathing at both PEEP-low and PEEP-high. *PEEP*, Positive end-expiratory pressure; *T*, time.

Assist control (AC), the most commonly used type of CMV, allows patient participation in addition to preset machine support. When the ventilator is triggered by the patient or the ventilator, a full preset breath is delivered. If a patient-initiated triggering event does not occur in a set time interval, the ventilator will deliver a controlled breath. When a patient triggers, the ventilator delivers full preset breaths in coordination with the respiratory effort of the patient, facilitating patient participation. AC is associated with low work of breathing, as every breath is supported, and tidal volume is guaranteed.

Synchronized Intermittent Mandatory Ventilation

In this mode, the ventilator delivers mandatory breaths of set rate and permits the patient to initiate additional spontaneous, variable

patient-triggered breaths above the mandatory rate. If the patient does not trigger spontaneous breaths, the synchronized intermittent mandatory ventilation (SIMV) mode will deliver mandatory breaths in the time interval mandated by the preset respiratory rate. Synchronization of the tidal volume delivery with the patient's inspiratory effort attempts to minimize the barotrauma that may occur with mandatory nonsynchronized ventilation—by avoiding delivery of a preset breath to a patient who is already inhaling maximally (breath stacking) or exhaling forcefully.

Spontaneous Ventilation

Spontaneous modes of ventilation do not provide mandatory breaths; the respiratory rate is determined by the patient. Because this is a patient-triggered mode, hypoventilation is a risk and apnea alarms or back-up mandatory minimum ventilation are required to ensure patient safety in the event that spontaneous triggering ceases. Spontaneous modes can be used for patient comfort and to assist in ventilator liberation.

Volume and Pressure Breaths

Neither volume- nor pressure-based breath types are superior to the other, so the provider and respiratory care team must be aware of the benefits and potential harms for each breath type. In either mode, plateau pressure (measured during an inspiratory hold) should be monitored; plateau pressures greater than 30 cm H_2O are associated with VILI. In addition, when insufficient time is allowed for exhalation, intrinsic PEEP, also known as auto-PEEP, can develop. Intrinsic PEEP (measured during an expiratory hold) is equivalent to total PEEP minus the set PEEP.

Volume Control Breaths

In volume control (VC) breaths, tidal volume is set, and the airway pressure is variable. The airway pressure is then a result of the tidal volume, rate of delivery, and thoracic compliance. Tidal volume is typically set at 6 to 8 mL/kg predicted body weight (PBW). Barotrauma may occur if high plateau pressures are required to reach the preset volume; close monitoring of airway pressures is required when using this mode.

Pressure Control Breaths

In pressure control (PC) breaths, the airway pressure is set and tidal volume is variable. The tidal volume will be affected by any factor that changes the airway pressure, including thoracic compliance, pulmonary resistance, and inspiratory time. A sudden decrease in pulmonary compliance can cause a rapid reduction in tidal volume and minute ventilation, resulting in acute respiratory acidosis; thus, close monitoring of minute ventilation is necessary. Conversely, decreases in compliance or resistance can lead to overdistention and volutrauma.

Pressure-Regulated Volume Control Breaths

Pressure-regulated volume control (PRVC) combines pressure breaths with a volume target. Ventilator-based software monitors lung compliance during the prior ventilator cycles and then regulates the inspiratory pressure for the next breath to achieve a target tidal volume. When compliance or patient effort increases, the ventilator automatically decreases delivered pressure to a lower level. Decreases in compliance signal the need for increased pressure. Once the pressure limit is reached, no further volume is administered, so the pressure limit should be evaluated. Care must be taken to avoid hypoventilation in patients with severely diminished compliance.

Pressure Support Ventilation Breaths

Pressure support ventilation (PSV) is a spontaneous breath type, requiring patient triggering to a preset level of pressure to augment the patient's own efforts. Breaths are assisted by a set inspiratory pressure, which is delivered until inspiratory flow drops below a predetermined threshold (e.g., 25% of peak flow). PSV can be a standalone mode or incorporated with other modes, where PSV facilitates for spontaneous breaths. PSV as a primary mode has been advocated to limit barotrauma and decrease the work of breathing.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) refers to CPAP using preset high and low PEEP levels, allowing both controlled and spontaneous breaths. APRV is often specifically used to refer to pronounced inverse-ratio CPAP mode of mechanical ventilation with a longer inspiratory time (time at high PEEP, time-high), with an I:E ratio of commonly 7:1 to 10:1, and a very short expiratory time or "release" (time at low PEEP, time low). High PEEP is generally set between 25 and 30 cm H_2O, and low PEEP, usually 0 cm H_2O.

Tidal volumes are determined by the difference between high PEEP and low PEEP. Spontaneous breathing at the higher pressure is encouraged, and this mode is well tolerated hemodynamically and in terms of patient comfort with minimal sedation. APRV has been advocated for use in the treatment for severe hypoxemia, as it achieves high mean airway pressures and improved alveolar recruitment; however, randomized data supporting translation to improved patient outcomes is not extensive.

ARDS

ARDS is a common ICU entity in critically ill postoperative surgical patients. Despite modern ICU care, mortality remains between 20% to 50%, depending on severity of ARDS. Prompt identification, correction of the underlying cause, and appropriate supportive treatment are key tenets of management.

The hallmark of ARDS is patchy infiltration of the lung with normal and abnormal regions of the lung adjacent to one another. Posterior, dependent regions develop alveolar collapse. Inflammatory alveolar injury disrupts the alveolar-capillary interface leading to alveolar damage. This, in turn, activates the immune system and cytokine release, which potentiate further injury, leading to increased capillary permeability with alveolar and interstitial edema. Impaired gas exchange, decreased compliance, and pulmonary hypertension all contribute to clinical hypoxia and respiratory failure. The Berlin Criteria are used for the diagnosis and classification of ARDS (Table 1). ARDS outcomes vary with severity of disease classified primarily by the PaO_2:FiO_2 ratio.

Many components of ARDS management have been subject to large clinical trials, and among critical care disease states, ARDS remains one of the most extensively studied. Substantial variation in practice and mortality has been demonstrated across the United States, suggesting that opportunity exists to improve outcomes. A summary table of available interventions and timing with degree of severity is seen in Figure 3.

TABLE 1 Berlin Criteria for ARDS Diagnosis

	Mild	Moderate	Severe
Hypoxemia	P:F ratio 201–300 with PEEP ≥5	P:F ratio 101–200 with PEEP ≥5	P:F ratio ≤100 with PEEP ≥5
Timing	Within 1 week of known clinical insult or worsening respiratory symptoms.		
Chest imaging	Bilateral opacities on chest x-ray or CT scan of chest not explained by effusions, lobar collapse or nodules.		
Origin of edema	Respiratory failure not explained by cardiac failure or volume overload. Need objective assessment (i.e., echocardiography) to exclude hydrostatic edema if no risk factor present.		

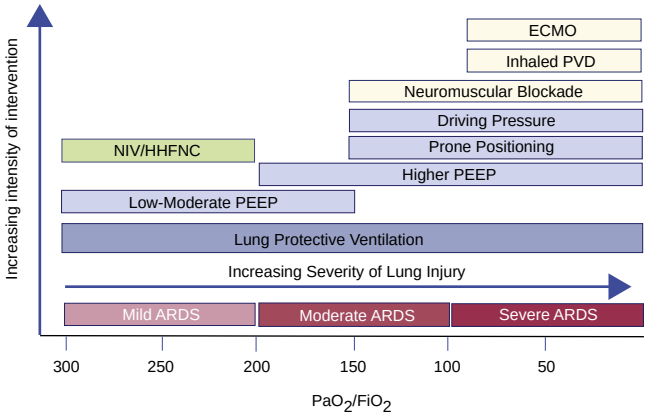


FIG. 3 Increasing intensity of treatment intervention for increasing severity of acute respiratory distress syndrome (ARDS). Treatment strategies, including extracorporeal membrane oxygenation (ECMO), available at an ARDS Referral Center. Blue shading indicates current evidence-based strategies associated with decreased mortality; yellow shading indicates salvage strategies; and green shading indicates strategies for non-intubated patients. *ARDS*, Acute respiratory distress syndrome; *ECMO*, extracorporeal membrane oxygenation; *FiO_2*, fraction of inspired oxygen; *HHFNC*, heated high flow nasal cannula; *NIV*, noninvasive ventilation; *PaO_2*, partial pressure of oxygen; *PEEP*, positive-end-expiratory pressure; *PVD*, pulmonary vasodilators. *(Modified from Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material.* Intensive Care Med. *2012;38:1573–1582.)*

Lung Protective Ventilation

Lung protective ventilation remains the standard of care in ARDS. It involves administering plateau pressure limited (<30 cm H_2O), low tidal volume (6 mL/kg PBW) ventilation to prevent excessive alveolar distension that may result in VILI and an exaggerated alveolar and systemic inflammatory response. The ARDS Network's landmark multicenter, randomized, controlled trial, ARMA, documented that lower tidal volume (6 mL/kg PBW) versus higher tidal volume (12 mL/kg PBW) ventilation in patients with ARDS was associated with a significantly decreased mortality rate. Initiation of low tidal volume ventilation should start at 6 to 8 mL/kg of PBW based on height (in men: 50 kg + 2.3 kg/inch for each inch over 5 feet; in women: 45.5 kg + 2.3 kg/inch for each inch over 5 feet). Tidal volumes should be reduced by 1 mL/kg at intervals of 2 hours until the tidal volume is set at 6 mL/kg PBW. Plateau pressure should be maintained at less than 30 cm H_2O; tidal volumes may be decreased to 4 mg/kg PBW to achieve this. Oxygenation goals include PaO_2 of 55 to 80 mm Hg or SpO_2 of 88% to 95% while using the lowest FiO_2 possible.

Permissive Hypercapnia

Permissive hypercapnia accepts the consequences of deliberate hypoventilation to prioritize reduction of alveolar overdistension and airway pressures in patients with poor lung compliance. Avoiding volutrauma and barotrauma in this fashion can lead to decreased minute ventilation to well below normal levels. The resultant hypercarbia and respiratory acidosis are managed medically with sodium bicarbonate or tromethamine. Hypercapnia may worsen intracranial pressure, and this strategy should be used with care in patients with traumatic brain injury.

PEEP Titration

Increased levels of PEEP may be used to support oxygenation in combination with the low tidal volume strategy. Higher levels of PEEP lead to recruitment of collapsed alveoli, reduced ventilation-perfusion mismatch, improved arterial oxygenation, and increased functional residual lung capacity. By maintaining an elevated PEEP, alveoli that are unstable and prone to collapse will remain open. Table 2 is an example of an open lung FiO_2/PEEP table that may guide PEEP setting.

The optimal PEEP level is difficult to determine, as both under distension and overdistension of the alveoli can lead to VILI. Variations in chest wall compliance may influence the "best" level of PEEP. Measurements of transpulmonary pressure and driving pressure (ΔP) may permit more individualized PEEP titration. Transpulmonary pressure can be calculated by subtracting the transpleural pressure (estimated by esophageal balloon manometry) from the measured airway pressure. Ventilator pressures are set to avoid negative transpulmonary pressure. Use of these ventilator titration approaches is being evaluated in clinical trials.

Driving Pressure

Driving pressure is defined as the change in tidal volume divided by respiratory system compliance, which effectively normalizes tidal volume to functional lung size. In patients receiving controlled ventilation (without spontaneous breathing), this can be calculated as plateau pressure minus the PEEP level. Initial studies suggest that even when patients are receiving "protective" plateau pressures and tidal volumes, increased ΔP may be associated with increased mortality. Clinical trials evaluating driving pressure-based strategies are in progress.

Prone Positioning

Prone positioning increases oxygenation through improving ventilation-perfusion matching and recruiting dependent portions of the lung. The PROSEVA trial, a randomized, multicenter trial, explored early prone positioning in moderate to severe ARDS presenting within 36 hours of onset. Patients were proned for at least 16 hours a day. Mortality at 90 days was 23.6% in the prone group and 41% in the control group. Meta-analyses support benefit in patients with early, moderate to severe ARDS (PaO_2:FiO_2 ratio <150 on FiO_2 60%, PEEP cm H_2O). Careful planning and execution are necessary to avoid unplanned extubation, soft tissue injury, and inadvertent removal of indwelling lines and tubes.

Neuromuscular Blockade

A neuromuscular blocking agent may be considered for early, moderate to severe ARDS (PaO_2:FiO_2 ratio ≤150, <36 hours after intubation). The ACURASYS trial, a multicenter double-blind trial of 340 patients with severe ARDS, confirmed that early administration of a neuromuscular-blocking agent improved 90-day survival and increased time off mechanical ventilation without increasing muscle weakness compared with placebo. A follow-up multicenter, unblinded, and randomized trial (the ROSE trial) showed no difference in mortality at 90 days between the light sedation and neuromuscular blockade with deep sedation groups. Although there is no clear mortality benefit, neuromuscular blockade remains a salvage approach for severe ARDS as it may assist in reducing ventilator dyssynchrony, consumptive hypoxemia, and excessive tidal volumes.

Conservative Fluid Management

A conservative fluid management strategy is recommended in patients with ARDS. Avoiding excess volume administration

TABLE 2 Example of High-PEEP Titration Table for Moderate to Severe ARDS

FiO_2	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1
PEEP (cm H_2O)	8	10	12	14	14	16	16	18	20	22	22	22–24

FiO_2, Fraction of inspired oxygen; *PEEP*, positive end-expiratory pressure.

decreases duration of mechanical ventilation and ICU stay. Diuretic therapy should be considered in patients with hypoxemia and a central venous pressure (CVP) greater than 4. A careful assessment of adequacy of perfusion and cardiac performance should be completed before initiation of diuresis, and reassessment should be continued while diuresis is ongoing.

Salvage Strategies in Refractory ARDS

Recruitment Maneuvers

RM refers to the dynamic process of reopening unstable, airless alveoli to improve pulmonary gas exchange and prevent VILI and atelectasis. Transient increase in transpulmonary pressure commonly occur during routine maneuvers such as hand bagging. Intentional recruitment using the ventilator has been described as a 2-minute period at high pressure of 40 cm H_2O, low PEEP of 20 cm H_2O, respiratory rate of 10 to 20, and I:E ratio of 1:1 or shorter holds for 2 minutes. Transient hypotension and desaturation during RMs are common but usually are self-limited. Following recruitment, the ventilator must be set at sufficient pressure to maintain recruitment.

The optimal approach, pressure, duration, and frequency of RMs have not been established in large clinical trials, as it is difficult to separate the effect of the recruitment maneuver from the underlying ventilator strategy. Of note, a randomized trial employing high pressure RM (to 45 cm H_2O) to set PEEP noted higher all-cause 28-day mortality in the recruitment group, and caution should be exercised.

Inhaled Pulmonary Vasodilators

Nitric oxide and prostacyclin are selective pulmonary vasodilators that decrease pulmonary vascular resistance, pulmonary arterial pressure, and right ventricular afterload. In clinical trials, the use of low dose inhaled pulmonary vasodilators has been shown to improve short-term oxygenation in patients with ARDS but not to reduce duration of mechanical ventilation or mortality rate. Inhaled nitric oxide and prostacyclin should be considered as salvage therapy in patients who continue to have life-threatening hypoxemia despite optimization of all other treatment strategies. Use of inhaled pulmonary vasodilators may also facilitate transport to a higher level of care.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) has seen increasing application in patients with severe ARDS who have failed standard of care and salvage therapies. The CESAR trial demonstrated improved outcomes with transfer to a specialized center that included ECMO capability. The subsequent EOLIA trial was stopped early for futility of the primary outcome of mortality at day 60; however, secondary outcomes suggested potential benefit. Experience with COVID to date has suggested that survival comparable to historical results (approximately 50%) may be attained; however, the run times may be prolonged.

ECMO involves percutaneous cannulation of the central venous system in either a dual or single site approach (Fig. 4). Traditional cannulation via the right femoral vein and right internal jugular vein

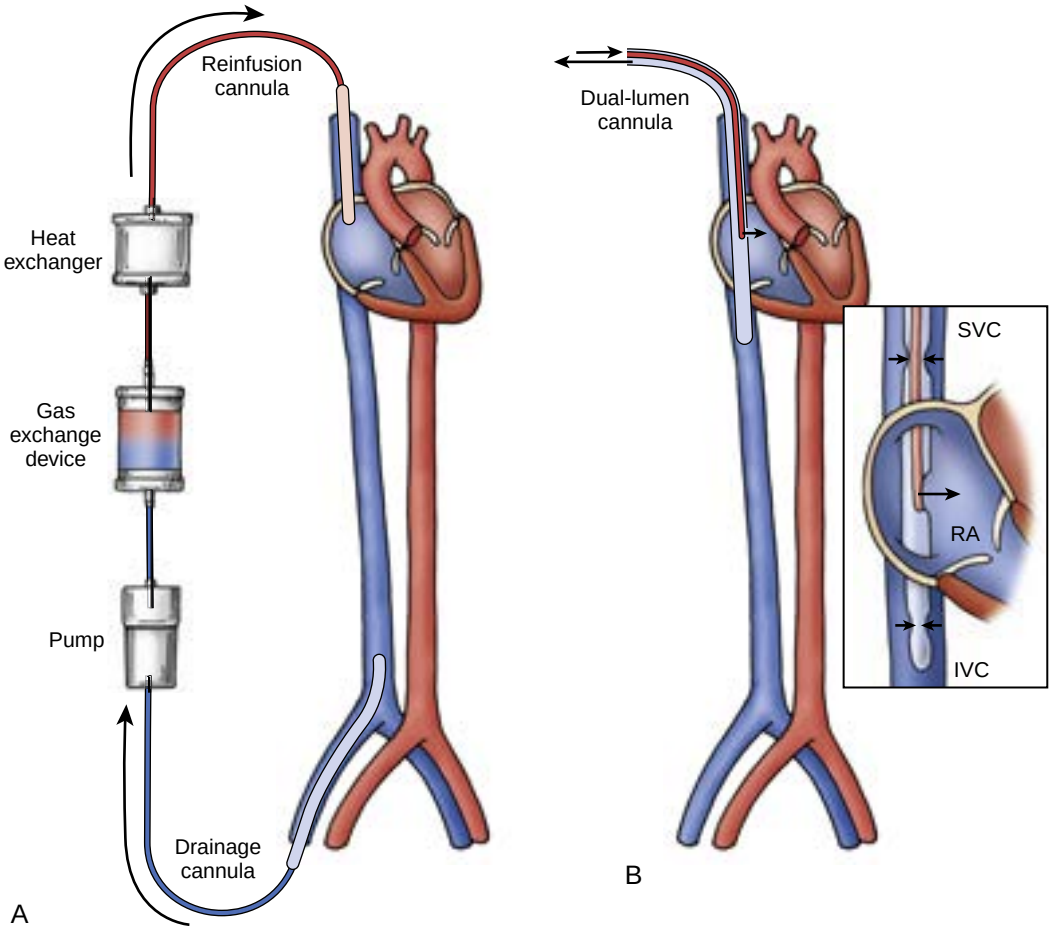


FIG. 4 Venovenous extracorporeal membrane oxygenation. **(A)** Dual-site configuration. Blood is drained from the femoral vein and then passes through a pump, gas exchange device, and heat exchanger before reinfusing into the internal jugular vein. **(B)** Single-cannula configuration using a dual-lumen cannula. Blood is drained from the SVC and IVC and reinfused to the RA. *IVC*, Inferior vena cava; *RA*, right atrium; *SVC*, superior vena cava.

is common. A single site approach with placement of a dual lumen cannula in the right internal jugular vein is increasingly popular, as it allows for earlier patient mobility and rehabilitation. ECMO allows for adequate ventilation and oxygenation with simultaneous lung rest and avoidance of complications related to mechanical ventilation such as barotrauma. Complications include those related to anticoagulation (i.e., GI bleed, intracranial hemorrhage, thrombosis, etc.) as well as mechanical circuit complications. Ongoing work is focused on determining optimal patient selection and ventilator management to identify patients who will benefit most from extracorporeal support.

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Ventilator-Associated Pneumonia

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the most frequently acquired intensive care unit (ICU) infections. It is defined as an infection of the lung parenchyma that develops at least 48 hours following endotracheal intubation. Existing literature reports the incidence of VAP between 4% and 28%, with higher rates noted in trauma and surgical patients. VAP usually manifests with fever, leukocytosis, worsening oxygenation, and increased secretions. Diagnosis is based on clinical suspicion, radiographic findings, and microbiology. Treatment consists of a course of antibiotics that are largely dependent on the severity of illness, comorbidities, risk factors for multidrug resistance pathogens, and local patterns of susceptibility. VAP can lead to prolonged mechanical ventilation, ICU, and hospital length of stay. Prevention is focused on head of bed elevation, ICU bundles and minimizing exposure, and early liberation from the ventilator. However, VAP continues to have a high attributable morbidity and mortality.

TERMINOLOGY/PATHOGENESIS

Pneumonia, an infection of the lung parenchyma, is caused by a variety of microorganisms including bacteria, viruses, and fungi, and is classified based on its etiology and timing.

Patients with an altered level of consciousness, swallowing dysfunction, gastric dysmotility, degenerative neurologic diseases, stroke, or seizure are at higher risk for aspiration. Aspiration of large-volume upper gastrointestinal or oropharyngeal contents puts patients at risk of chemical pneumonitis or aspiration pneumonia. Pneumonitis results from aspiration of irritative acidic gastric contents leading to injury of the lung due to the release of inflammatory mediators, including chemokines, proinflammatory cytokines, and neutrophil recruitment. Aspiration pneumonia is an infection caused by specific microorganisms and can be the etiology of community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP), depending on timing.

According to the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS), CAP is pneumonia that is acquired outside of the hospital versus HAP that develops following a minimum 48 hours of admission. VAP is a nosocomial infection of the lungs that occurs following 48 hours or more of mechanical ventilation. Endotracheal intubation breaches airway defenses, impairing cough and mucociliary clearance. Although endotracheal tubes (ETTs) have a cuff, this does not prevent microaspiration of bacteria-laden secretions that pool above the ETT, ultimately increasing the risk of pneumonia. Lastly, finding the optimal level of sedation to prevent ventilatory dyssynchrony, optimize oxygenation, and maximize patient safety can be challenging in the ICU. Sedative medications depress the central nervous system in a dose-dependent manner and, at high doses, may depress a patient's respiratory drive, increasing their risk for VAP.

RISK FACTORS

Elderly patients often have significant comorbidities in addition to declining physiologic and immune functions, making them more susceptible to VAP. Male gender, obesity, immunocompromised patients, smoking, and underlying lung pathology (in particular chronic obstructive pulmonary disease [COPD]) have all been reported as independent risk factors for VAP. Patients with a low Glasgow Coma Scale or disorders of consciousness such as delirium as well as burn patients have also been reported to have an increased risk of VAP. Risk factors for VAP specific to trauma patients include elevated injury severity score on presentation; emergent intubation; operative intervention; injury to the spine, face, or sternum; massive transfusion; and duration of ICU admission. Traumatic brain injury patients are at particularly high risk, with the incidence of VAP ranging from 23% to 60% in this patient population. Supine position, paralytics, and aspiration are also associated with VAP. Finally, although mechanical ventilation is a lifesaving intervention employed frequently in the ICU, the duration of ventilation increases the risk of infection, with the risk of VAP drastically increasing after 7 to 10 days of intubation.

PREVENTION

Preventing intubation is the primary strategy to avoid VAP; however, mechanical ventilation is often required as a lifesaving measure in the critically ill patient population. Therefore, the following preventive measures are the best ways to reduce the incidence of VAP in patients requiring mechanical ventilation.

VAP Bundle and Early Extubation

Bundles of care, which are common in the ICU, are evidence-based practices that are grouped together to encourage the consistent delivery of these practices. Although the literature is mixed with regards to VAP bundles and the prevention of VAP, they allow for standardized care as well as decreasing variation, thereby improving healthcare quality and safety. The first component of the VAP bundle is head of bed elevation. This consists of placing patients in a semirecumbent position at a minimum of 30 degrees, with the goal of avoiding aspiration of gastric contents.

Since mechanical ventilation predisposes patients to VAP, reducing the duration should ultimately reduce the risk of developing VAP. Spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs) are two strategies within the VAP bundle aimed at reducing the duration of mechanical ventilation. This focuses on setting a time each day to stop sedative medications, orient the patient to time and day, and conduct a SBT with a goal to liberate the patient from the ventilator. Studies have shown that using SAT and SBT synergistically help decrease mechanical ventilation days. It is also important to identify patients early in their hospital course who will not be successfully extubated secondary to their underlying pathology and to determine if a tracheostomy is warranted. Although tracheostomy is an invasive procedure and still associated with VAP, its risk of VAP is much lower compared with ETTs and has also been shown to shorten duration of mechanical ventilation and ICU length of stay.

Secretions that build up below the vocal cords but above the ETT cuff are a potential source of VAP. In three large meta-analysis trials, subglottic suctioning has been shown to reduce the rate of VAP. It is therefore a common component of a VAP bundle. There are also consistent trends toward subglottic suctioning reducing the length of mechanical ventilation and ICU stay.

Evidence suggests that frequent ventilator circuit changes are associated with an increased incidence of VAP. This is likely due to contaminated secretions that build up in the tubing entering the bronchial tree during manipulation of the tubing. It is recommended that the ventilator circuit be changed only when faulty or soiled. Finally, other common components of VAP bundles are gastrointestinal prophylaxis, venous thromboembolism prophylaxis, and oral hygiene with chlorhexidine mouth care.

Lung Protective Ventilation

Mechanical ventilation is one of the most effective ways to provide respiratory support in the ICU. Conversely, mechanical ventilation can result in barotrauma, lung inflammation, and oxidative stress leading to ventilator-associated lung injury. To combat this, lung-protective ventilation has become the standard of care. Lung-protective ventilation includes regulation of positive-end expiratory pressures and lower tidal volumes, usually 6 mL/kg × ideal body weight with the goal of maintaining plateau pressures less than 30 cm H_2O and driving pressures less than 15 cm H_2O.

Noninvasive Ventilation

Noninvasive ventilation (NIV) refers to the administration of respiratory support without the use of an ETT. NIV has been shown to improve gas exchange and decrease work of breathing with the goal of avoiding intubation, improving lung mechanics postextubation, and in some cases avoiding reintubation, therefore removing or diminishing the risk for VAP. The most common forms of NIV used in the ICU are high-flow nasal cannula (HFNC) and bilevel positive airway pressure (BiPAP). BiPAP is the ideal choice for patients with acute COPD/asthma exacerbation or pulmonary edema; however, it should be avoided in patients with significant secretions, at high risk for aspiration, or with facial trauma. Both HFNC and BiPAP have been shown to reduce rates of intubation and mortality in patients with acute exacerbations of COPD, acute cardiogenic pulmonary edema, acute respiratory failure, and most recently coronavirus disease (COVID).

DIAGNOSIS

VAP posts a diagnostic challenge due to the limited diagnostic tests and broad differential diagnoses associated with the clinical features of VAP. Clinical findings that should prompt suspicions of VAP include new systemic signs of infection including a sudden or gradual onset of fever, leukocytosis, an increase in volume or change in character of tracheobronchial secretions, and new or progressive infiltrates on chest imaging in a patient who has been intubated and on mechanical ventilation for more than 48 hours.

Due to the nonspecific nature of the systemic signs of VAP, these features, when presented as isolated findings, are neither sensitive nor specific for the diagnosis of VAP. Diagnosing VAP requires a combination of high clinical suspicion, radiographic findings, and microbiologic confirmation of lower respiratory tract secretions.

Chest Radiographs

A chest radiograph should be obtained in all patients with clinical suspicions of VAP. Radiographic findings in patients with VAP include infiltrates, consolidation, or cavitation. However, chest

radiograph findings alone are not sufficient for the diagnosis of VAP as pulmonary infiltrates can also be demonstrated in intercurrent noninfectious processes. Although a normal chest radiograph makes VAP unlikely, a chest CT can sometimes be useful in a patient who remains highly suspicious for VAP despite negative chest radiographs.

Sputum

It is important to identify the pathogen responsible in patients with VAP to guide antimicrobial management. Respiratory cultures should ideally be collected before initiating antimicrobial therapy for the most accurate microbiologic data results, but this should not delay empiric antibiotic therapy in patients with severe illness requiring prompt treatment. A simple Gram stain can be done for all cultures obtained to guide both initial empiric and changes in antibiotic therapy according to likely pathogens. There is a lack of agreement as to the preferred route for collecting respiratory samples due to variable sensitivity and specificity in invasive versus noninvasive methods and quantitative or qualitative analysis. For example, specimens can be collected from sputum, nasotracheal suctioning, and bronchoscopy. There is no gold standard for the diagnosis of VAP. Hence, the preferred method varies widely in different practices depending on the institution and the availability of the different sampling techniques. Our institution follows the IDSA/ATS 2016 HAP/VAP guidelines, which is noninvasive sampling with semiquantitative analysis to guide antibiotic therapy for our patients. If a patient has a severe illness or is showing signs of clinical deterioration and there is a high clinical suspicion for VAP, we will initiate empiric antibiotic therapy even if the semiquantitative results on the respiratory cultures are below the threshold needed for an official diagnosis of pneumonia.

Endotracheal/Tracheal Aspirates

Aspiration of respiratory secretions through an ETT or tracheostomy is a noninvasive way of collecting respiratory secretions that is cheap, safe, and efficient. Qualitative analysis of these aspirates is a standard method for diagnosis of VAP if the sample is positive. This method is considered highly sensitive, with low specificity, which is helpful for excluding the diagnosis of VAP on a negative culture. In terms of quantitative analysis, the threshold for diagnosis of VAP is 10^6 CFU per mL, which is more specific but less sensitive than qualitative analysis. The poor predictive value of this method is due to the risk of contamination of specimens with upper airway secretions.

Bronchioalveolar Lavage

Bronchioalveolar lavage (BAL) is an invasive testing method for collecting respiratory cultures and is performed by wedging the bronchoscope directly into an affected bronchial segment and performing infusion and aspiration of 60 mL of sterile water. In this method, the diagnosis of VAP is supported when the threshold of 10^4 CFU/mL is exceeded. Studies examining BAL data for guidance in VAP treatment have shown a lower rate of antibiotic overusage. Unfortunately, it does have the lowest sensitivity and specificity of all methods used in collecting respiratory secretions. However, when both qualitative and quantitative analysis of BAL aspirates are used in combination, BAL cultures have been shown to be the most accurate overall in diagnosing VAP. BAL was previously considered the gold standard for collecting respiratory samples for patients with VAP but has since fallen out of favor as studies have shown that endotracheal and tracheal aspirates are noninferior to BAL.

TREATMENT

While the most likely causative organisms in CAP include *Streptococcus pneumonia, Hemophilus influenza,* and methicillin-sensitive *Staphylococcus aureus* (MSSA), VAP is commonly caused by nosocomial multidrug-resistant (MDR) pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa,* and other gram-negative bacilli. Hence, when choosing an empiric antimicrobial regimen to treat, this should include antimicrobials with activity against these organisms (Table 1). In

TABLE 1 Empiric Antibiotics Therapy Based on the Risk of MDR Pathogens

Risk of MDR	Recommended Antibiotics Regimen
Low risk of MDR (low concern for MRSA and resistant gram-negative pathogens)	Choose one of the following: • Ceftriaxone • Levofloxacin • Moxifloxacin • Ampicillin/Sulbactam • Ertapenem
High risk of MDR	Antipseudomonal beta-lactams (choose one): • Cefepime • Ceftazidime • Imipenem • Meropenem • Piperacillin/tazobactam • Aztreonam **PLUS** one of the following non-beta-lactam agents if at risk for resistant gram-negative bacilli: • Fluoroquinolones: Levofloxacin, Ciprofloxacin • Aminoglycosides: Gentamicin, Tobramycin, Amikacin **PLUS** gram-positive coverage: • If at risk for MRSA: Vancomycin or Linezolid • If not at risk for MRSA in units where <10%–20% MRSA: Piperacillin/Tazobactam, Cefepime, Levofloxacin, Imipenem, or Meropenem

MDR, Multiple drug resistant; *MRSA*, methicillin-resistant *S. aureus*; *MSSA*, methicillin-sensitive *S. aureus*.
Modified from Kalil AC, Metersky ML, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical Infectious Diseases*. 2016;63(5):e61–e111.

TABLE 2 Risk Factors for Multiple Drug Resistance

Risks of MDR pathogens	Use of intravenous antibiotics in the past 90 days ≥5 days of hospitalization before the occurrence of VAP Septic shock at the time of VAP Acute respiratory distress syndrome (ARDS) before VAP Acute renal replacement therapy before VAP
Risks of MRSA	Any risk factor for MDR pathogens Patients being treated in units where >10%–20% of *S. aureus* isolates are methicillin-resistant Patients in units where the prevalence of MRSA is not known
Risks of resistant gram-negative pathogens	Any risk factor for MDR pathogens Patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy Patients in an ICU where the local antimicrobial susceptibility rates are not available

ICU, Intensive care unit; *MDR*, multiple drug resistant; *VAP*, ventilator-associated pneumonia.
Modified from Kalil AC, Metersky ML, et al. management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:e61–e111.

addition, the choice of antibiotics should also be based upon local distribution of pathogens and susceptibility patterns based on local antibiograms including antibiotic-resistance data.

Due to the variance in antibiograms in different institutions, including the prevalence of multidrug resistance, the IDSA/ATS 2016 HAP/VAP guidelines provide recommendations for empiric antibiotic regimens. Patients are considered to be at risk for MDR pathogens if they have any of the following (Table 2): prior intravenous antibiotic use within 90 days, 5 or more days of hospitalization before the occurrence of VAP, septic shock at the time of VAP, acute respiratory distress syndrome (ARDS) preceding VAP, or acute renal replacement therapy before VAP. For patients with any risk factors for antimicrobial resistance and in patients being treated in units where >10% to 20% of *S. aureus* isolates are methicillin-resistant or of unknown prevalence, an agent active against MRSA should be included in the regimen, with recommended agents including vancomycin or linezolid. Otherwise, agents active against MSSA that can be given include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, and meropenem. For patients with any risk factors for antimicrobial resistance, patients being treated in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and in units of unknown local microbiome, empiric treatment should consist of two antipseudomonal antibiotics from different classes. Otherwise, monotherapy with one agent against *Pseudomonas* is sufficient.

As respiratory cultures begin resulting, the antimicrobial regimen should be narrowed based on the culture data. Treatment duration of 7 days is typically sufficient, based on the 2016 IDSA/ATS HAP/VAP guidelines, unless there is evidence suggesting lack of improvement. Evidence has demonstrated no difference in mortality or recurrent infections in patients with VAP who receive 8 versus 15 days of antibiotics, with increased resistance observed with longer antibiotic courses. In our institution, we typically adhere to the current IDSA/ATS standard of care by treating our patients with a 7-day course. In some instances where patients show early clinical improvement with stable minimal ventilatory support (PEEP ≤5 cm H_2O and FiO_2 ≤40%) or extubation and have remained hemodynamically stable after initiating antibiotic therapy, we will consider discontinuing antibiotic therapy after 3 to 5 days. This is based on a study by Klompas et al. that showed similar outcomes in patients with suspected VAP on minimal and stable ventilator settings treated with ultra-short-course antibiotics (1–3 days) compared with longer courses (>3 days). In contrast, for patients who have persistent severe illness or who are showing evidence of clinical deterioration, we will continue antibiotic therapy beyond 7 days and collect repeat cultures to guide changes in antibiotic therapy, particularly in patients who have had a narrowing of their antibiotic regimen based on initial cultures. Repeat cultures are typically obtained via endotracheal aspirates unless a patient has had imaging showing a more localized infection where BAL can offer a more directed approach.

COVID-19

In December 2019, a novel coronavirus disease—COVID-19—emerged, rapidly spreading throughout the world and resulting in pandemic. The virus that causes COVID-19, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mainly affects the respiratory system, with immunosuppressive effects to the body's natural immune defense system causing an increased risk of respiratory failure. Hence, VAP in COVID-19–positive patients has become an increasingly important new topic to discuss due to the increased number of patients on mechanical ventilation.

Multiple recent studies have shown that the incidence of VAP is higher in mechanically ventilated patients with COVID-19 compared with non–COVID-19 patients on mechanical ventilation. This can be explained by the prolonged duration of mechanical ventilation, prolonged use of sedation and neuromuscular blocking agents, and more frequent prone positioning causing an increased risk of microaspiration. Chest imaging in COVID-19 patients typically demonstrates bilateral lung involvement with CT findings of ground-glass opacities and patchy consolidation bilaterally, which indicates diffuse alveolar involvement and severe lung injury. Recent studies have also found that patients with COVID-19 infection are more likely to present with ARDS compared with non–COVID-19 patients on mechanical ventilation.

The dominant bacterial composition based on respiratory samples has been found to be similar in both groups, including data on antimicrobial susceptibility. Hence, the general management of VAP in COVID-19 patients does not deviate much from the management in non–COVID-19 patients and should also be facilitated by microbiologic analysis. These patients are also treated with remdesivir for 5 days and dexamethasone for 10 days based on the RECOVERY trial to decrease the intensity of their COVID-19 illness. Interestingly, early retrospective studies have also shown evidence of a higher incidence of invasive pulmonary aspergillosis coinfections in patients on ventilators despite the absence of the typical risk factors for pulmonary aspergillosis including a severe immunocompromised state. It is unclear at this point if the higher incidence is due to the increased

testing for fungal cultures and galactomannan levels in COVID-19 patients on mechanical ventilation but is certainly an important topic to address given the associated high mortality and morbidity risk.

CONCLUSION

VAP is an important complication in patients on mechanical ventilation, as it increases the duration of mechanical ventilation and ICU stay, which in turn increases both the risk of mortality and overall cost. There should be a high index of suspicion for VAP in any sudden change in clinical status and oxygenation in a patient who has been on mechanical ventilation for more than 48 hours due to the lack of a gold standard for screening, and diagnosis should be based on the combination of clinical, radiographic, and microbiologic evidence.

SUGGESTED READINGS

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Extracorporeal Membrane Oxygenation for Respiratory Failure

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BACKGROUND

Acute respiratory distress syndrome (ARDS) is the most severe presentation of acute lung disease leading to respiratory failure affecting approximately 10% of patients admitted to the intensive care unit. Although first described over 50 years ago, it remains a major cause of morbidity and mortality. Mortality rates in the range of 35% to 60% have been reported. Commonly described etiologies include direct pulmonary sources (aspiration, toxic inhalation, infection, near drowning) or extrapulmonary sources (disseminated sepsis, thoracic trauma, circulatory shock) of lung injury.

ARDS results from a devastating injury producing intense pulmonary inflammation and parenchymal destruction at an alveolar and cellular level. This destruction results in profound hypoxemia and can be further exacerbated by necessitated ventilator support. Strategies for optimization of respiratory status on the ventilator include lung-protective strategies with a goal of minimizing barotrauma and tolerating degrees of hypercarbia. This is accomplished by selecting ventilator modes that limit pulmonary distension and promote recruitment of atelectatic alveoli, such as pressure-controlled ventilation, inverse-ratio ventilation, and low-frequency ventilation. With extracorporeal membrane oxygenation (ECMO) support, gas exchange occurs through an extracorporeal membrane perfused with venous blood, which may allow minimizing ventilator support and facilitating lung recovery through periods of "lung rest."

ECMO is an evolving technology that provides cardiopulmonary support and is increasingly used for varying indications, including ARDS. The use of ECMO initially increased dramatically with the H1N1 influenza pandemic in 2009, and another surge in utilization has been observed more recently during the COVID-19 pandemic.

The benefit of ECMO for severe respiratory failure has long been debated. There have been several trials looking at the use of ECMO support in this setting. Two randomized controlled trials, published in 1979 and 1994, were key in establishing the utility of ECMO. However, their application in modern ECMO is limited as the patients, protocols, and machinery have changed extensively since that time. The most relevant recent study to evaluate ECMO for severe respiratory failure was the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial. This 2009 UK-based multicenter randomized controlled trial used an independent central randomization service to randomly assign 180 adults with ARDS with <7 days of high pressure/oxygen support in a 1:1 ratio to receive either continued conventional management or referral to an ECMO center for treatment consideration. The goal of this study was to determine if ECMO would result in increased survival when compared with conventional ventilation in patients with severe but potentially reversible respiratory failure. Patients with severe ARDS placed on ECMO had a higher disability-free survival at 6 months compared with those who underwent conventional management, and the referral strategy was found to be cost-effective. However, this study was limited by the heterogeneous ventilation strategies in the control group (including higher tidal volumes than recommended) and the number of patients who never received ECMO because they were transferred to a higher level of care.

To address the limitations of the CESAR trial and the questions of the efficacy of ECMO in severe ARDS, an international randomized trial, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, was performed and analyzed 249 patients after randomization: 124 were assigned to the ECMO group and 125 to the control group. The EOLIA trial aimed to assess 60-day mortality in patients with severe ARDS who were managed with early initiation of ECMO versus conventional ventilator support. At 60 days, mortality with ECMO was 35% compared with 46% in the control group (relative risk, 0.76). In this study, 28% of the conventional group crossed over to the ECMO group, and unlike the CESAR trial, 98% of patients in the EOLIA trial who were supposed to receive ECMO received it. The trial ultimately showed no significant benefit to early ECMO when compared with conventional mechanical ventilator support. However, in a select group of patients, ECMO may be their only chance at survival.

ECMO: INDICATIONS AND CONTRAINDICATIONS

ECMO is indicated for any progressively severe but reversible disease process that can be treated with general lung healing or a specific therapy. Venovenous (VV) ECMO can either serve to allow for a temporary period of pulmonary rest until recovery or as a bridge to definitive therapy, such as transplant. ECMO cannot serve as

destination therapy, as no long-term ECMO options currently exist. Although neither the CESAR trial nor the EOLIA trial provided definitive support for ECMO over conventional ventilator strategies, both studies observed results in favor of ECMO with regard to survival and quality of life in patients with severe respiratory failure. Criteria utilized for determining eligibility includes the Murray Lung Injury Score (Table 1). The Murray Lung Injury Score assesses four factors: (1) extent of infiltration on chest film, (2) degree of hypoxemia, (3) level of positive end-expiratory pressure (PEEP) required to achieve oxygenation, and (4) respiratory system compliance. The score is calculated as the average of all four parameters. A score of 1 to 2.5 suggests mild to moderate lung injury. A score >2.5 indicates severe lung injury and is considered an indication for consideration of VV ECMO in patients with severe ARDS (Box 1). Additional indications and contraindications are listed in Box 2.

Contraindications to placing a patient on VV ECMO are mostly relative and include intracranial hemorrhage, prolonged high airway pressure and fraction of inspired oxygen (FiO_2), ventilator days >7, severe baseline advanced respiratory failure without a treatment option beyond ECMO, and primary or metastatic malignancy with a short life expectancy. Other important factors to consider include the patient's premorbid conditions such as functional status, baseline comorbidities, duration of illness, number of organ systems that are failing, and overall prognosis. Outcomes are improved among younger patients with fewer medical problems. Once on ECMO, patients require a collaborative multidisciplinary team effort with daily reassessment of disease progression, organ failure and other complications, and futility of care.

At the authors' institution, several additional exclusion criteria have been identified and include age >60 years, body mass index (BMI) >40, poor neurologic function, bleeding diathesis, immunocompromised state, multisystem organ failure, unwitnessed cardiac arrest, and chronic end organ disease such as chronic kidney disease

BOX 1 Berlin Definition of Acute Respiratory Distress Syndrome (All Criteria Must Be Present)

- *Timing of respiratory symptoms:* Onset of symptoms within 1 week of known clinical insult, or new or worsening symptoms arising during the past week
- *Radiographic findings:* Bilateral pulmonary infiltrates on chest radiograph or CT scan
- *Rule out other etiologies:* Respiratory symptoms that cannot be fully explained by cardiac failure or fluid overload
- *Hypoxemia:* The severity of ARDS is defined by the degree of hypoxemia, as indicated by the ratio of PaO_2/FiO_2
  - *Mild:* PaO_2/FiO_2 >200 mm Hg but ≤300 mm Hg on mechanical ventilator settings with PEEP or CPAP ≥5 cm H_2O
  - *Moderate:* PaO_2/FiO_2 >100 mm Hg but ≤200 mm Hg on mechanical ventilator settings with PEEP or CPAP ≥5 cm H_2O
  - *Severe:* PaO_2/FiO_2 ≤100 mm Hg on mechanical ventilator settings with PEEP or CPAP ≥5 cm H_2O

The Berlin Criteria, established in 2012, replaces previously accepted 1994 American-European Conference's definition of ARDS.
CPAP, continuous positive airway pressure; *FiO_2*, fraction of inspired oxygen; *PaO_2*, partial pressure of oxygen in arterial blood; *PEEP*, positive end-expiratory pressure.

TABLE 1 Murray Lung Injury Score

Category	Score
1. Extent of infiltration on chest radiograph	
No alveolar consolidation	0
Confined to 1 quadrant	1
Confined to 2 quadrants	2
Confined to 3 quadrants	3
Involving all 4 quadrants	4
2. Degree of hypoxemia (partial pressure of oxygen in arterial blood/fraction of inspired oxygen)	
>300	0
225–299	1
175–224	2
100–174	3
≤100	4
3. Level of positive end-expiratory pressure (cm H_2O)	
≤5	0
6–8	1
9–11	2
12–14	3
>15	4
4. Respiratory system compliance (mL/cm H_2O)	
>80	0
60–79	1
40–59	2
20–39	3
<19	4

BOX 2 Indications and Contraindications for Venovenous Extracorporeal Membrane Oxygenation

Indications

1. Hypoxic respiratory failure resulting from any cause when there is ≥80% risk of mortality. Consider venovenous ECMO when the risk of mortality is ≥50%.
   - PaO_2/FiO_2 ratio of <150 on FiO_2 ≥0.9 and a Murray score of 2–3 is associated with a 50% risk of mortality
   - PaO_2/FiO_2 ratio of <100 on FiO_2 ≥0.9, and a Murray score of 3–4 is associated with an 80% risk of mortality
2. Refractory CO_2 retention despite high-pressure mechanical ventilation settings (peak plateau >30 cm H_2O)
3. Intubation in end-stage lung disease patient awaiting lung transplant
4. Massive air leak (bronchopleural fistula)
5. Acute cardiopulmonary collapse secondary to PE, airway obstruction, trauma, and so on

Relative Contraindications

1. Mechanical ventilation with high settings (FiO_2 >0.9 peak plateau >30 cm H_2O) for ≥7 days
2. Recent or expanding CNS hemorrhage
3. Immunosuppressed (ANC <400/mm^3)
4. Nonrecoverable comorbidity (i.e., terminal malignancy, major CNS damage, end-stage lung disease without transplant option)

ANC, Absolute neutrophil count; *CNS*, central nervous system; *ECMO*, extracorporeal membrane oxygenation; *FiO_2*, fraction of inspired oxygen; *PaO_2*, partial pressure of oxygen in arterial blood; *PE*, pulmonary embolism; *PEEP*, positive end-expiratory pressure.

(CKD) ≥ stage 3, moderate to severe COPD, and ischemic or nonischemic cardiomyopathy (NICM) with a history of congestive heart failure (CHF). More liberal exclusions for patients younger than 45 years of age are allowed if they have a BMI <50 or mechanical ventilation <10 days.

ECMO SYSTEM COMPONENTS

A standard ECMO circuit is composed of a roller or centrifugal pump, membrane oxygenator and heat exchanger, circuit tubing, and cannulas (inflow and outflow). Efficient CO_2 removal at low flow rates and increased oxygenation at higher flow rates can be provided by a parallel circuit. Some circuits utilize heparin-bonded components to decrease requirements for anticoagulation while the circuit is being used. Circuits can be simple or more complex, including things like continuous blood flow and continuous oxyhemoglobin saturation monitors.

TECHNIQUE

Cannulation requires coordination with perfusion and anesthesiology. ELSO guidelines outline three modes of vascular access: venoarterial, VV, and arteriovenous. For patients requiring ECMO support for respiratory failure, VV access can be obtained using either a dual-lumen cannula or two separate cannulas (ELSO guidelines), like femoral/internal jugular vein (IJV), or femoral-femoral:

1. Right femoral vein (RFV) to the inferior vena cava (IVC) and right internal jugular vein (RIJV) to the right atrium with two separate cannulas (Fig. 1).
2. RIJV into the right atrium and IVC with a single dual-lumen cannula (Fig. 2).
3. Femoral-femoral vein cannulation

In each of these cannulation approaches, deoxygenated blood is removed from the IVC (see Fig. 1) or, in the case of dual-lumen cannulation, IVC and SVC, and pumped through an oxygenator before oxygenated and decarboxylated blood is then returned to the right atrium.

At our institution, it has been helpful to delineate a specific area (Fig. 3), typically within a critical care unit or operating room where supplies are stored. This includes ECMO carts, cannulas, ECMO "go packs" for travel within or external to the hospital, and a variation of a central line cart that contains additional backup items. The go packs are sterile packs that are readily available to minimize time required in an emergent situation for compiling all the necessary supplies such as suture, drapes, clamps, a central line kit for venous access, and so on.

Right internal jugular cannulation steps are as follows:

1. Continuous telemetry and pulse oximetry during the procedure is necessary to monitor for potential induction of arrhythmias during wire manipulation in the right atrium of a hypoxic patient or for development of other potential cannulation complications.
2. Central line placement in the IJV as well as arterial line placement are necessary.
3. Transesophageal (TEE) probe placement by anesthesia/critical care (TEE preferred, but transthoracic echocardiography [TTE] guidance can be utilized as well).
4. Patient positioning with the head turned to the opposite side of the neck being accessed.
5. The neck is prepped widely from the ear down to the sternal notch. If the plan is for dual-lumen cannula placement in the IJV, both groins are still prepped as a secondary option in case there are difficulties/complications with access at the IJV. It is important to utilize sterile drape coverings from the patient's head down to the feet. (We prefer to utilize the dual-lumen cannula technique over the RIJV and right femoral vein. This encourages rehabilitation and is associated with improved outcomes.)
6. RFV/RIJV approach:
   a. Utilizing ultrasound guidance, the RFV and RIJV are accessed using the Seldinger technique, and wires are placed.
   b. A bolus of heparin (50–100 U/kg) is administered if the patient is not already anticoagulated.
   c. The RIJV is serially dilated and a 16Fr to 23Fr cannula is inserted (usually 1–2 sizes smaller than the femoral cannula). The wire and dilator are removed, and the tube is clamped.
   d. The RFV is also serially dilated (either simultaneously with the RIJV or in sequence), and a 23Fr to 25Fr cannula is inserted. Before inserting the femoral cannula, the estimated distance is measured between the patient's groin and xiphoid.
   e. The ECMO circuit tubing is brought onto the field, and the cannulas are connected to the circuit, being sure to prevent air entrainment into the circuit. Communication with perfusion is critical at this point in the process.
   f. Cannulas are secured with 0-silk sutures at the insertion point and at several points along the length of the cannula on the thigh and at the neck/ear. All ECMO cannulas should be sutured into place, and the skin will be marked to monitor for cannula migration.
7. RIJV/dual-lumen cannula approach:
   a. Utilizing ultrasound guidance, the RIJV is accessed using the Seldinger technique, and wires are placed. The dual-lumen

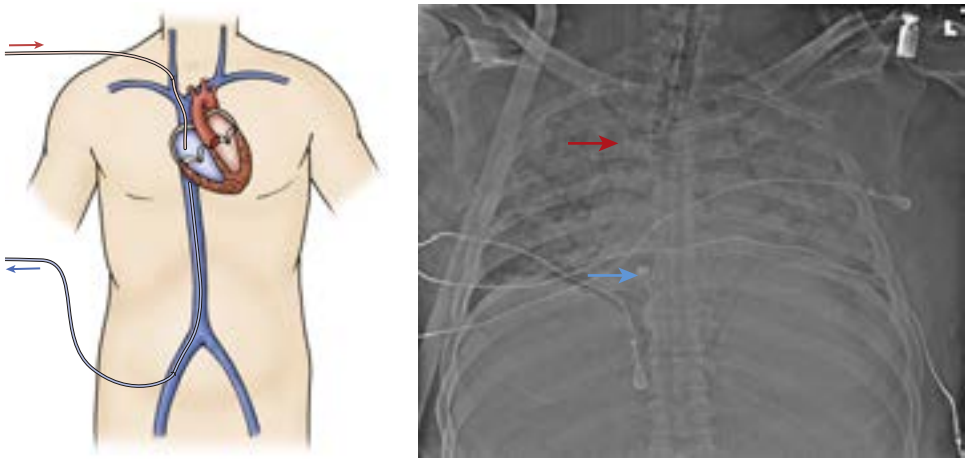


FIG. 1 Standard venovenous ECMO cannulation. Long venous cannula via the femoral vein to the inferior vena cava *(blue arrow)* and inflow cannula in the right internal jugular vein *(red arrow)* positioned at the superior vena cava/right atrial junction.

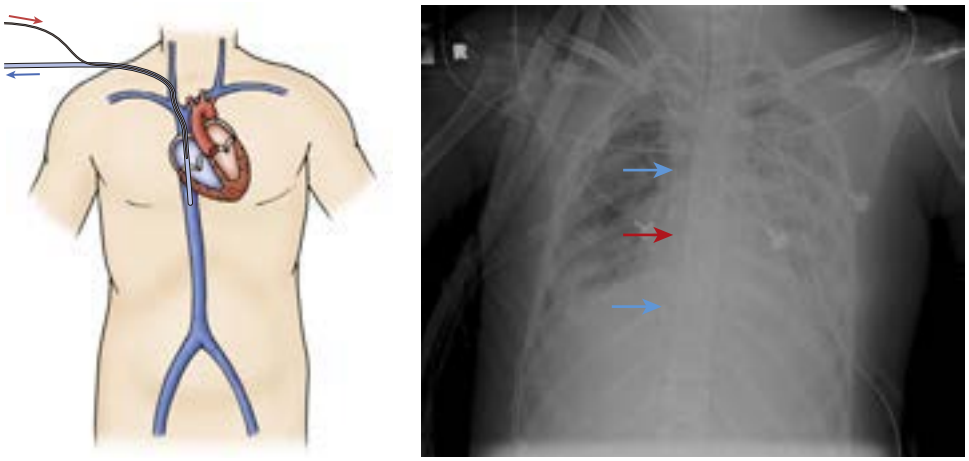


FIG. 2 Dual-lumen right internal jugular vein VV ECMO cannulation with drainage ports *(blue arrows)* in the superior vena cava and inferior vena cava and an inflow port in the right atrium *(red arrow)*.



FIG. 3 Example of ECMO emergency storage area at the authors' institution. This includes premade "go packs" that include all items needed for emergency bedside cannulation.

cannula must be inserted under ultrasound/echocardiographic guidance.

b. A bolus of heparin (50–100 U/kg) is administered if the patient is not already anticoagulated.
c. The RIJV is serially dilated and a dual-lumen cannula (range of 16–32 Fr) based on manufacturer is inserted under TEE (preferred) or TTE guidance. The wire and obturator are removed, and both the inflow and outflow ports are clamped. It is important to ensure correct orientation of the cannula, with the inflow portion oriented anteriorly toward the tricuspid valve (facing the patient's nose).
d. The ECMO circuit tubing is brought onto the field, and the cannulas are connected to the circuit, being sure to prevent air entrainment into the circuit. Communication with perfusion is critical at this point in the process.
e. After the circuit is connected and ECMO is initiated, TEE is utilized to visualize orientation of the inflow jet across the tricuspid valve (Fig. 4). Once this is visualized, the inflow cannula is briefly pinched to ensure that the jet is from the circuit and not resultant flow turbulence.
f. Cannulas are secured with 0-silk sutures at the insertion point and at several points along the length of the cannula (at the ear and around a single limb at the bifurcation of the cannula).

All ECMO cannulas should be sutured into place, and the skin should be marked to monitor for cannula migration.

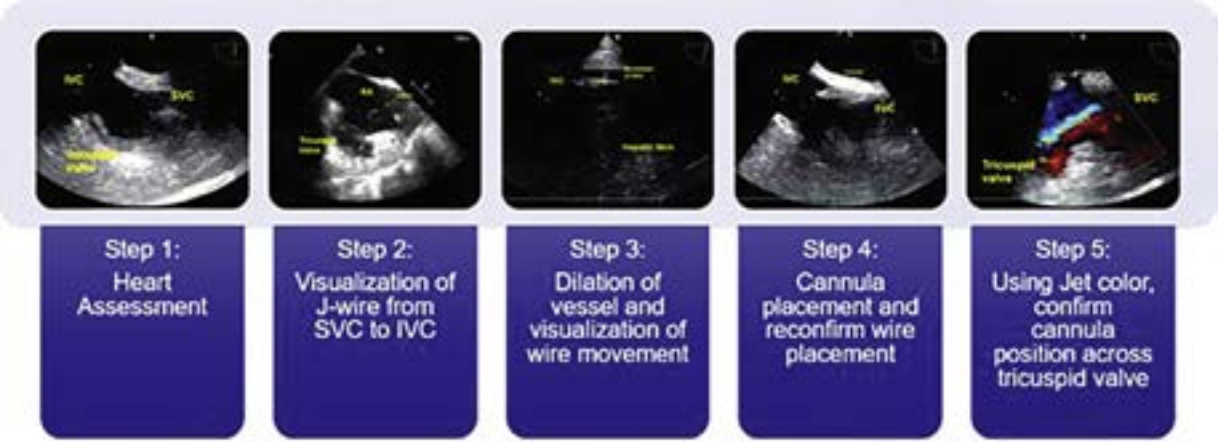


FIG. 4 Representative images of transesophageal-guided cannula placement. Visualization of the color jet across the tricuspid valve *(Step 5)* is utilized to confirm appropriate cannula position. *IVC,* Inferior vena cava; *SVC,* superior vena cava. *(From Cha S, Kim B, Bush E. A Safe Bedside Protocol for Dual-Lumen RIJ Cannulation for Venovenous ECMO in COVID 19 Patients with Severe ARDS. Oral Presentation at ASAIO, June 11, 2021; courtesy of the authors.)*

INITIATION OF VENOVENOUS ECMO

Initial VV ECMO settings are within the following ranges, with adjustments by our perfusionists based on the patient's needs:

Initial pump speed: 3000 to 4000 RPM
Flows (determined by pump speed): 4 to 7 LPM
Blender oxygen: 100% O_2
Sweep gas (controls CO_2 elimination): 3 to 10 LPM (maximum 20)
Temperature: 37°C
Initial PaO_2 goals: 60 to 90 mm Hg
pH goals: 7.30 to 7.40
No specific $PaCO_2$ goals

If a circuit is planned for CO_2 removal only, flows 10% to 25% of cardiac output should be sufficient. Maximum inflow suction pressures should not exceed ~200 mm Hg, and the maximum outflow pressures should not exceed 300 mm Hg. Chest and abdominal radiographs are obtained to confirm appropriate positioning of the ECMO cannulas. The tip of the femoral venous cannula should be just at the right atrial/IVC junction. Unless there is a known coagulopathy or bleeding risk, systemic heparin infusion is initiated. Given the risk of bleeding and lower risk of venous clot, goal-activated partial thromboplastin time (aPTT) is usually set in the range of 40 to 50 seconds. After cannulation and initiation of ECMO, a standard set of studies is obtained (Box 3).

BOX 3 Recommended Studies After Extracorporeal Membrane Oxygenation Circulation

- Serum chemistry
- Complete blood count
- Coagulation studies
- Patient arterial blood gas
- Preoxygenator circuit blood gas
- Postoxygenator circuit blood gas
- Activated clotting time
- Fibrinogen
- Chest radiograph
- Interval head ultrasound (neonates)

MANAGEMENT

Each institution is encouraged to develop clear protocols based on the Extracorporeal Life Support Organization (ELSO) guidelines and local expertise. These include creating an ECMO team that typically includes a surgeon, critical care physician, critical care nurse, perfusionist, physical and occupational therapists, dietitian, and respiratory therapist. Day-to-day management of the patient on VV ECMO will be discussed below by systems.

Neurologic

Patients are kept appropriately sedated to a degree that allows for adequate oxygenation without unnecessarily limiting patient alertness and even activity if desired. Neuromuscular blockade (NMB) is initially continued if previously utilized before ECMO. NMB is weaned off as the patient stabilizes. A combination of sedatives and anxiolytics are often used. Commonly used lipophilic sedatives including fentanyl, midazolam, and propofol are sequestered in the ECMO circuit; therefore, we often quickly transition our patients off these when ECMO is initiated (Dzierba). First-line sedation options include hydromorphone infusion, ketamine infusion, clonazepam, and vecuronium, if needed. Hydromorphone and lorazepam are utilized on an as-needed basis. Second-line sedation options include propofol infusion, dexmedetomidine infusion, and scheduled oxycodone. Seroquel is added as needed for agitation as sedation is weaned and to assist with tapering from benzodiazepines. NMB and sedation are weaned daily to perform waking trials. Neurologic monitoring is often initiated early and includes cerebral near-infrared spectroscopy (NIRS), transcranial Doppler imaging, emboli monitoring, somatosensory evoked potentials (SSEP), and continuous electroencephalography (EEG), adjusted for the patient.

Respiratory

No single ventilator mode has proven to be superior to another in managing patients on VV-ECMO. As a result, one of three modes is typically initiated on our patients. These include:

PC: Rate 10, pressure difference 10, PEEP 10 to 14, FiO_2 0.4.
VC: Rate 10, tidal volume 3 to 4 cc/kg of predicted body weight (PBW), PEEP 10 to 14, FiO_2 40%; goal plateau pressure ≤24, and driving pressure ≤14
APRV: P high 20 to 24, P low 10, T high 4 to 6 s, T low 0.5 to 0.8 s, FiO_2 0.4

Recruitment maneuvers are not recommended to avoid the risk of barotrauma if the lungs have not regained compliance. Patients remain on rest settings until there are signs of improvement in compliance. If the patient is weaned to the point of breathing spontaneously, we utilize pressure support (PS), volume support (VS) or wall continuous positive airway pressure (CPAP).

Standard PaO_2 goals are in the 60 to 90 mm Hg range. However, if that cannot be achieved, goals can be adjusted to >50 as long as saturation is >85%. It is important to match ECMO flows with cardiac output. When properly matched, oxygenation will be optimized. When flows are two-thirds or greater of cardiac output, then adequate PaO_2 is maintained. If oxygenation goals are not met, one should consider having higher hemoglobin goals to improve the oxygen-carrying capacity of blood. Monitoring is continued for signs of tissue ischemia, including NIRS.

A pH goal of 7.3 to 7.4 is utilized to guide the degree of hypercapnia that is accepted. To facilitate oxygen offloading at the tissue level, mild acidosis is preferred. Persistent hypercapnia for a prolonged duration can also promote bicarbonate retention by the kidneys. This compensatory metabolic alkalosis could impact weaning a patient from ECMO when the lungs start to recover. It may be necessary to add acetazolamide to the regimen to prevent high bicarbonate retention.

Daily bronchoscopies are not usually necessary and are encouraged only if there is a clinical indication. Prone positioning is rarely required on our ECMO patients. However, if needed, several other institutions have been successful in utilizing the technique, when the patient is hemodynamically stable. Chronic cough is an incidentally identified frequent symptom in our patients. Options that have proven useful include guaifenesin to thin secretions or inhaled lidocaine and dextromethorphan (only if the patient is COVID negative or resolved). Changing to a tracheostomy with a distal cannula extension has also proven helpful to minimize cough.

Tracheostomy at the time of ECMO cannulation is strongly considered in our patient population. As a result, the patient's family is often consented concurrently. There is no timing that has proven optimal, but tracheostomy should be done earlier rather than later with the knowledge that patients are often sedated on ECMO for an extended period, although there are increasing reports of awake ECMO utilization.

Cardiovascular

Norepinephrine is the first-line preferred agent to maintain mean arterial pressure (MAP) >60 to 65. Vasopressin is a second-line agent. If hypertensive, hydralazine is used as needed. Additional adjuncts include labetalol and nicardipine.

Control of tachycardia, relative and absolute, is important when oxygenation is inadequate because of high cardiac output. Scheduled enteral metoprolol is a first-line agent. Ivabradine can be added as needed. Atrial fibrillation prophylaxis is not routine, but amiodarone can be utilized as needed for arrhythmias that arise.

Echocardiogram (POCUS, point-of-care ultrasound) is indicated with any hemodynamic instability. Right ventricular dysfunction may arise as the ECMO course and systemic illness progress. One can add an inotropic agent to support the right ventricle and improve cardiac function. A dobutamine drip should be considered if the patient is normotensive versus an epinephrine drip if the patient is hypotensive. The placement of a pulmonary artery catheter may be helpful for management, but it is very challenging to position in a patient already cannulated for VV ECMO.

Gastrointestinal

Maintaining enteral nutrition is especially important as these patients are often ventilator dependent for prolonged periods. Although gastric feeds are not contraindicated, nasoduodenal tube placement is preferred initially with tube feeds starting by ECMO day 2. These patients should be followed by a nutritionist who can aid in calculation and monitoring of the patient's caloric needs through the Resting Energy Expenditure measurement. The patient can be transitioned over to gastrostomy tube placement either at the time of tracheostomy or later in the hospital course. A steady and consistent bowel regimen should be initiated and maintained.

Renal

Early in their ECMO course, patients are often intravascularly depleted, requiring the addition of volume to the circuit to maintain flows. There is some evidence (FACTT) that a restrictive fluid balance in ARDS patients is associated with a shorter ventilator time without a survival benefit demonstrated. During the earlier phase, optimizing ECMO flows will outweigh the need and ability for diuresis. However, it is important to transition to diuresis when the patient is stable, with the goal of minimizing interstitial pulmonary edema. Furosemide infusions are typically first line, with metolazone being added every 48 hours if necessary.

If renal function is compromised, the patient may require continuous VV hemofiltration to remove volume. Continuous VV hemofiltration can be integrated into the ECMO circuit, allowing one to avoid additional vascular access.

Hematology

All patients should be anticoagulated with heparin infusion at the start of ECMO support. Doses should be titrated by PTT goals of 1.5 times normal. This can be correlated with an Anti-Xa level of 0.3 to 0.5. It is not uncommon to see a decrease in platelet counts by as high as 50%. The transfusion threshold for the majority of our ECMO patients will be a hemoglobin <8.0 and platelets <30. However, institutional thresholds vary, and at times a higher goal is necessary. If there is a >50% decrease in platelet count, one should order a heparin-induced thrombocytopenia (HIT) panel to check PF4 and SRA levels.

Bleeding complications are a frequent occurrence in our patients on ECMO. The primary sites are oral, nasal, airway/tracheostomy site, and gastrointestinal sources. The assistance of the otolaryngology department has been instrumental in management of the majority of these bleeding episodes. The oropharynx can be packed with tranexamic acid (TXA)-soaked gauze and the nasopharynx with Afrin-soaked gauze. For surgical bleeding at the tracheostomy or PEG sites, topical hemostatic agents can be utilized locally for 72 to 96 hours. Persistent bleeding can be alleviated with DDAVP (0.3 μg/kg IV) and holding heparin but may require surgical intervention and, depending on the presentation, heightened suspicion for a tracheo-innominate fistula. If reintroduction of anticoagulation causes recurrence of bleeding episodes, heparin infusion can be held indefinitely. Coagulation laboratories should be checked and a thromboelastography (TEG) ordered. One should also check daily LDH levels. If they continue to trend up, this could be a sign of worsening hemolysis that can be secondary to microthrombi formation, disseminated intravascular coagulation, or sepsis.

If the patient is a bridge to transplant or is not a transfusion candidate by either self-identified, religious, or physiologic reasons, only necessary blood laboratory tests should be drawn using pediatric tubes, and anticoagulation should be held indefinitely, if possible, to minimize blood loss.

Infectious Disease

Patients are given prophylactic antibiotics before cannula insertion, and these should be discontinued within 24 hours. Daily laboratory tests including white blood cell count, C-reactive protein, and systemic vascular resistance measurements are often reliable indicators of an underlying infectious process. One cannot reliably

utilize temperature as a symptom of infection as a result of passive cooling secondary to the ECMO circuit. Biweekly cultures have been obtained by some, however, and are clinically indicated as the standard at our institution and many others.

Broad-spectrum coverage while pending speciation commonly includes vancomycin/Zosyn or vancomycin/Cefepime. If VV ECMO is performed for COVID positivity, remdesivir and dexamethasone are initiated after cannulation, if not given previously.

TROUBLESHOOTING

ECMO Flow Limitation (Chatter or Chugging)

Chatter or *chugging* refers to the transient but frequent decrease in ECMO flow. This occurs because the ECMO cannula is a cylindrical tube and follows *tube law.* As stated, when the pressure difference between the external pressure (atmospheric) and intraluminal pressure of a tube starts to increase, the intraluminal diameter does not decrease until a threshold is reached, at which time the intraluminal diameter collapses to zero. This collapse will cause intraluminal pressure to increase, allowing the tube to open and flow to resume, but as flow resumes, the pressure may drop again, causing the intraluminal diameter to collapse again. This cycle may be intermittent or continuous, causing the drainage tubing to pulsate, thus creating a limit to ECMO flows.

Differential:

- Decreased intravascular volume (e.g., overdiuresis, bleeding, insensible losses)
- Vascular wall obstruction or cannula malposition repositioning
- Low MAPs causing decreased venous return
- Agitation with increased intrathoracic/abdominal pressures (e.g., coughing, tachypnea)
- Thrombus formation limiting cannula flow
- Cannula compression or kinking
- Abdominal compartment syndrome
- Pneumothorax
- Cardiac tamponade

Management:

- Examine the venous drainage cannula to eliminate any kinks or external compression.
- Check hemodynamics, and maintain adequate MAPs to optimize venous return.
- If patient is agitated, can administer bolus dose of sedative; if persistent can use NMB.
- Turn down flows momentarily, and then increase slowly.
- Titrate to a lower pump speed that optimizes oxygenation.
- Administer IV fluid boluses to expand intravascular volume.
- Can check bladder pressure, chest x-ray, or echo if indicated.

Suck-Down Event with Flows Dropping <1.0 LPM (Extreme Form of Chatter)

Differential (similar to chatter):

- Cannula malposition with vessel wall causing obstruction
- Drop in intravascular volume: bleeding or dehydration
- Shock: any cause with very low venous return
- Rapid change in intrathoracic pressures: agitation, cough, vent dyssynchrony

Management:

- Call perfusion immediately; turn down pump speed, and then increase RPMs slowly, as tolerated.
- Consider fluid bolus to expand intravascular space.
- Pressors to keep MAPs >65
- For agitation, add more sedation or start NMB

Persistent Hypoxemia (PaO_2 <55, SaO_2 <85%)

Differential:

- Cannula malposition
- ECMO flows too low for patient's cardiac output
- Agitation increasing heart rate, cardiac output, and oxygen demand
- Oxygenator failure
- Chatter limiting ECMO flows as above
- Recirculation

Management:

- If there is persistent chatter, troubleshoot as above.
- For ECMO flow and CO mismatch, increase ECMO flows if not flow limited.
- Add heart rate controlling agents if unable to raise ECMO flows (ivabradine or beta blocker).
- For agitation, add more sedation or start NMB
- Check post-oxygenator gas; if PaO_2 <200 at 5 LPM flow, call cardiothoracic surgery and perfusion about oxygenator change.
- Increase hemoglobin transfusion goal.
- Check cannula position with chest x-ray plus an echocardiogram as needed, manipulate cannula position to assess improvement in oxygenation. If needed, can contact cardiothoracic surgery and anesthesia for repositioning cannula.

Recirculation

All forms of VV cannulation configurations have some degree of recirculation, with femoral-femoral being the highest, and dual-lumen cannula being the least and most efficient configuration. When returned oxygenated blood flow enters the venous outflow limb of the circuit before systemic circulation and ECMO venous saturation is > 75% or > $ScVO_2$ by 5% to 10% or greater without alternative explanation (severe sepsis with tissue dysoxia or hypothermia), then recirculation should be suspected and addressed.

Differential:

- ECMO flows are too high, leaving an inadequate amount of time for the heart to eject
- If a dual-lumen cannula is placed, then there may be malposition of the arterial inflow jet toward the tricuspid valve
- If IJV or femoral-femoral configuration, the outflow and inflow may be too close in proximity (<10 cm).

Management:

- Check positioning of cannula with chest x-ray and echocardiogram.
- Turn down the flows if oxygenation is in good range. Some degree of recirculation can be tolerated if flows and saturations are maintained.

VENOVENOUS ECMO WEANING

The decision to wean is based on the clinical progress of the patient. The patient's native lung function on the ventilator is one of the first clues that they are ready for weaning efforts. The first signs of this will be an increase in the tidal volumes on maintained airway pressure release ventilation (APRV) or Pressure Control modes of ventilation settings. One can also check daily plateau pressures if the patient is on volume control. In this case, one would expect to see improving compliance.

As gas exchange improves, the patient's sweep gas flows can be weaned on ECMO. This can be adjusted as needed to meet pH goals. When the sweep is 1 liter per minute (LPM) or less, patients should independently be using their native lungs for gas exchange. Pressure support or volume support can be used in the spontaneously breathing patient who is awake. Pressure control or volume control can be increased to tidal volumes ≤6 cc/kg of PBW to assist with lung-protective strategies. Finally, FiO_2 should be no more than 0.6 maximum during weaning.

When the patient has adequate gas exchange, with a sweep of 1 LPM with FiO_2 at 0.4, sweep can be turned to zero while flows are maintained at >3.0 LPM. The sweep of zero trial can continue for up to 24 hours. The patient can be decannulated when tolerating less-than-maximum lung-protective ventilation strategies and the PaO_2 >60, pH >7.30, and PCO_2 <60.

Decannulation should be coordinated with cardiothoracic surgery, perfusion, and the respiratory therapist. The blood from the circuit should be collected by the perfusionist and returned to the patient as autologous blood if there are no concerns for introducing bacteremia.

TERMINAL DECANNULATION

Despite full VV ECMO support, there are patients who have essentially zero chance of survival. In these settings, it is sometimes very difficult to determine futility of care. Constant communication with the patient's family is essential throughout this process. Once a decision for palliation or withdrawal of care is made and the goals of care are understood, the following is the manner in which terminal cannulation is completed at our institution:

- Communicate with the bedside nurse, respiratory therapist, perfusionist, and palliative care.
- Stop all laboratory draws and all medications except for sedatives and vasopressors.
- Stop continuous hemodialysis if ongoing.
- Increase hydromorphone infusion to 20 mg/hour, and add lorazepam infusion 5 mg/hour.
- If family is present, ask if they are ready to proceed.
- Ask the nurse to stop vasopressors, but keep sedation going.
- Ask the respiratory therapist to extubate and stop the ventilator.
- Ask the perfusionist to turn off the ECMO flows.
- Once the patient is pronounced dead, communicate this with the family.
- Complete necessary paperwork per institutional policy.

CONCLUSION

The use of VV ECMO remains a debated option in the care of patients with severe refractory respiratory failure. The increase in utilization with the COVID pandemic has brought with it some progress in the management of these patients. Despite this progress, in many institutions it remains mostly a salvage therapy, and not that of a preemptive or lung protective therapy, that is still often associated with poor outcomes. Ongoing efforts are necessary to clarify selection criteria for placement of patients on ECMO and improve understanding of the ECMO circuit and its associated complications.

Suggested Readings

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Tracheostomy

Jeffrey Thiboutot, MD, and David J. Feller-Kopman, MD

INTRODUCTION AND HISTORY

Tracheostomy is a common procedure performed by otolaryngologists, trauma surgeons, pulmonologists, and intensivists. Most recently with the rise in critical illness due to the COVID-19 pandemic, there has been an increased need for tracheostomy in the setting of prolonged mechanical ventilation. Tracheostomy is one of the oldest surgical procedures performed, with the first record of an open tracheostomy recorded more than 3500 years ago on stone slabs during the first Egyptian dynasty. Fabricius is credited with first describing a tracheal cannula in 1617, while another Italian surgeon, Sanctorio Sanctorius, documented the first percutaneous tracheostomy in 1626. He used a "ripping needle" to introduce a silver cannula into the tracheal lumen and then removed the needle. The first cuffed tracheostomy tube was developed in 1869 by Trendelenburg, but it was not until the early twentieth century that tracheostomy became a popular procedure due to the standardization of open surgical tracheostomy by the famous American surgeon Chevalier Jackson.

In the 1930s, tracheostomy use increased as it was advocated as an effective means to provide bronchopulmonary toilet in patients with poliomyelitis. However, not until the increasingly widespread use of positive pressure ventilation in the 1950s was considerable energy focused on the development of tracheostomy tubes as a means of providing long-term ventilatory support. In the late 1960s, Toye and Weinstein used a Seldinger guidewire to safely introduce a cannula into the tracheal lumen, and in 1985, Pasquale Ciaglia described what has now become one of the most popular techniques for percutaneous dilational tracheostomy (PDT).

TRACHEAL ANATOMY

Knowledge of the relevant anatomy is essential; this includes not only tracheal anatomy but an understanding of the surrounding structures such as the thyroid gland, musculature, and vasculature of the neck (Fig. 1).

The trachea is a centrally located unpaired organ extending in an oblique fashion from the superficial position of the neck and diving posteriorly into the mediastinum. The average length of the adult trachea is 11 ± 1 cm for males and 10 ± 1 cm for females. Importantly, for proper tracheostomy tube size selection, sex differences in tracheal diameter need be accounted for (2.5–2.7 mm for men,

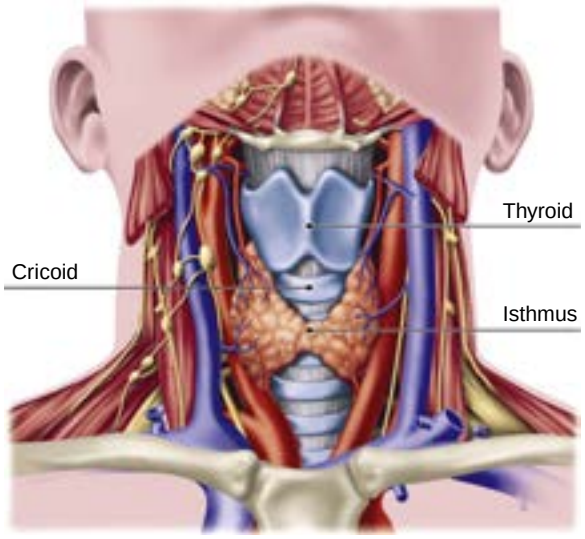


FIG. 1 Tracheal anatomy.

2.1–2.3 mm for women). Along the course of the trachea are 18 to 22 incomplete semicircular cartilaginous rings that maintain the structural integrity of the trachea. The cricoid cartilage in the larynx has the only complete cartilaginous ring and a membranous attachment to the first tracheal ring inferiorly as well as the thyroid cartilage superiorly forming the cricothyroid membrane. The posterior wall of the trachea or membranous trachea that courses cranially-caudally is comprised of fibroelastic tissue between the ends of the tracheal rings that abuts the anterior-lateral portion of the esophagus. The combination of the rigidity of the anterior two-thirds of the tracheal cartilaginous rings with the flexibility of the posterior one-third allow for a wide range of flexibility and stability.

There are several structures that lie anterior to the trachea that should be identified before tracheostomy to avoid damage. The thyroid isthmus is typically located between the second and third tracheal rings; the innominate artery most often crosses the anterior trachea in an oblique fashion distal to the third tracheal ring at about the level of the sternal notch. Though the blood supply to the cervical trachea enters posterolaterally from the inferior thyroid artery, the inferior thyroidal artery and vein as well as the anterior jugular vein may lie between the skin and trachea and the operator needs to be aware of these vessels.

INDICATIONS, CONTRAINDICATIONS, AND TIMING

The two major indications for tracheostomy are chronic ventilator dependence and upper airway obstruction (generally in a setting of head/neck malignancy). This includes chronic hypoxic or hypercapnic respiratory failure due to a multitude of respiratory, cardiac, or systemic conditions as well as airway protection after neurologic events such as cerebrovascular accidents, intracranial hemorrhage, or traumatic brain injury. Chronic debilitating neuromuscular diseases that require airway protection or chronic ventilator support are also common indications for tracheostomy. Tracheostomy can also be indicated in cases of central airway obstruction from neoplasm, inherited or acquired airway obstruction such as high-tracheal or subglottic stenosis, stricture from radiation therapy, angioedema, burn injury, trauma, or even obstructive sleep apnea. Finally, tracheostomy along with cricothyrotomy can be used as an adjunct in emergency situations where an airway cannot be established through endotracheal intubation and a patient cannot be ventilated.

There are a few absolute contraindications for tracheostomy including cellulitis/deep infection at the insertion site and operator inexperience. Relative contraindications to both surgical tracheostomy and PDT include coagulopathy or thrombocytopenia and worsening acute critical illness (i.e., septic shock/ARDS). In terms of ventilator setting, the most important variable to note is the positive end-expiratory pressure (PEEP). As for PDT, the stoma is created distal to the endotracheal tube (ETT) cuff with resultant derecruitment. The authors recommend that oxygenation be assessed with PEEP <12 cm H_20, increasing FiO_2 as needed to maintain oxygenation. Relative contraindications to PDT include inability to palpate relevant tracheal anatomy, overlying vessels, and emergent airways.

The timing of tracheostomy remains a controversial issue with set guidelines difficult to establish as the decision to perform a tracheostomy is still an individualized process. All factors of the clinical scenario, such as probable future need of a tracheostomy, daily weaning attempts, risk of continued endotracheal intubation, and the risk of the tracheostomy procedure itself need to be considered. Prolonged translaryngeal endotracheal intubation has been thought to contribute to several complications including laryngeal injury, subglottic and tracheal stenosis, tracheomalacia, ventilator-associated pneumonia, as well as the need for higher levels of sedation and associated morbidity. Several studies have been performed looking at these complications and the optimal timing of tracheostomy with mixed outcomes. Late tracheostomy was classically defined as tracheostomy performed after 3 weeks; however, more recently the cutoff has been moved up to as soon as 1 to 2 weeks, or even 48 to 96 hours of mechanical ventilation. There has been a general paradigm shift in critical care medicine toward early tracheostomy, but it is unclear whether this is actually supported by data as no clear benefit has been shown in recent trials. In a multicenter trial of 1,032 patients at 57 sites who were randomized to early (within 4 days) versus late (greater than 10 days) tracheostomy, no difference was seen in 30-day or 2-year mortality, length of mechanical ventilation, antibiotic use, or sedative use. Of note, over half of the subjects randomized to the late tracheostomy arm did not end up getting the procedure, indicating that possibly delaying surgery significantly reduces the need for tracheostomy. Multiple meta-analyses of early versus late tracheostomy fail to show any mortality benefits; however, a reduction in ventilator-associated pneumonia with early tracheostomy was observed. These data emphasize the timing of tracheostomy remains a clinically based decision that should be made on a case-by-case basis.

SURGICAL TRACHEOSTOMY

Surgical tracheostomy is generally performed under general anesthesia but can theoretically be done under conscious sedation in a spontaneously breathing patient if an airway cannot be established orally. It can be performed in the operating room or at the bedside. When performed at the bedside in the ICU setting, all the appropriate equipment including adequate lighting, electrocautery, and surgical tools need to be available. The patient is supine on the table or bed and the neck is moderately extended with a shoulder roll to improve anatomic landmarks. The head of the bed should be slightly elevated either through flexion at the hip or through reverse Trendelenburg to reduce pressure in the cervical veins. Before prepping the skin, proper identification of the appropriate anatomic landmarks including the thyroid cartilage, the cricothyroid membrane, the cricoid cartilage, and the tracheal rings should be completed (Fig. 2).

After prepping and draping in sterile fashion from the nipple line to above the thyroid cartilage, a transverse incision is preferred in a controlled setting with a stable airway as this follows Langer's lines and is more cosmetically appealing. A 3- to 4-cm incision should be made 1 cm below the cricoid cartilage and not based on the sternal notch as the trachea and larynx move independently of the sternum (Fig. 3). The subcutaneous tissue and platysma can be dissected with electrocautery at which point the sternohyoid and sternothyroid muscles are encountered and retracted laterally. Deep to the strap muscles lies the thyroid isthmus, which can then be ligated using sutures or electrocautery and then retracted laterally. The pretracheal fascia should then be sharply dissected, exposing the trachea anteriorly from

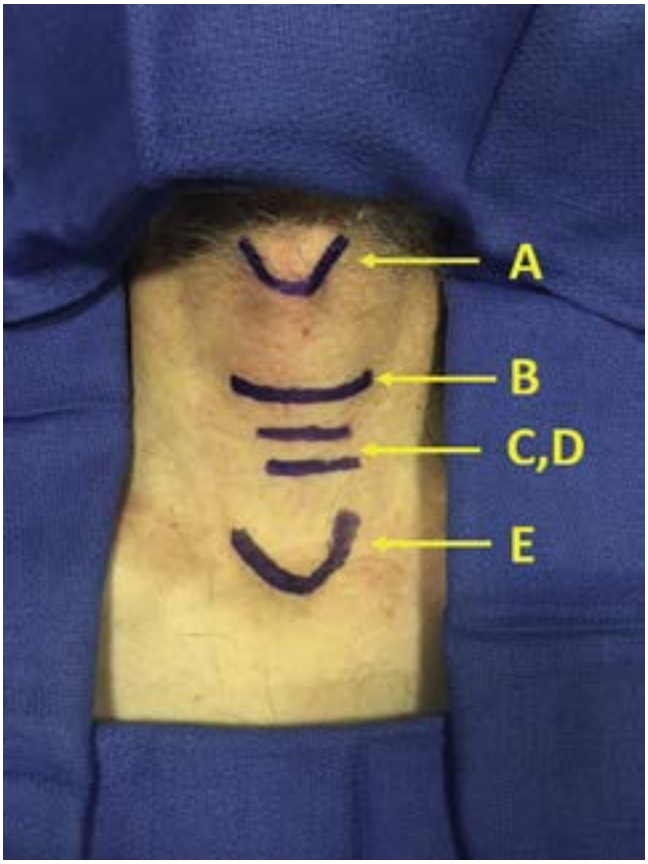


FIG. 2 Preoperative landmarks: *(A)* thyroid cartilage, *(B)* cricoid cartilage, *(C)* first tracheal ring, *(D)* second tracheal ring, *(E)* sternal notch.



FIG. 3 Horizontal incision.

just below the cricoid cartilage to the fourth tracheal ring. A cricoid hook can then be used to elevate the tracheal rings and facilitate the tracheal incision. This incision can be made using a #11 blade horizontally between the second and third tracheal rings or vertically dividing the second and third rings. Once the tracheal lumen has been exposed, the ETT should be retraced just proximal to the lumen at which point the surgeon can insert the tracheostomy tube under direct visualization. The tube should then be connected to a ventilator circuit with adequate placement and ventilation ensured using auscultation, CO_2 detectors, and adequate return of tidal volume without a significant leak. The ETT can then be removed and 3-0 Prolene sutures can be used to secure the tracheostomy neck plate.

PERCUTANEOUS DILATATIONAL TRACHEOSTOMY

PDT is generally performed at the bedside in the ICU. Preprocedure evaluation includes a careful review of the history and respiratory status of the patient, as well as a careful physical examination focused on the neck and tracheal structures. Especially when starting to do PDT, patients should have ideal anatomy with an easily palpable thyroid cartilage, cricoid cartilage, and first to third tracheal rings, with no underlying vessels. It is important to palpate and inspect for overlying vessels as ligation and electrocautery control of bleeding is generally not performed in PDT as it is during surgical tracheostomy. Though not necessary, often patients for whom bedside PDT is being considered have existing cross-sectional imaging (computed tomography) that should be reviewed, focusing on vascular neck anatomy (high riding innominate artery or aberrant/collateralized vasculature). Given reliance on palpable landmarks and lack of direct visualization during the procedure, the authors suggest ultrasound assessment of the neck to evaluate vasculature that may be in the pathway of cannulation. Pertinent lab studies include a platelet count, PT, PTT, as well as BUN to evaluate for uremia.

PDT can be safely performed in patients with uremia; however, pretreatment of these patients with DDAVP should be considered, and a PT/PTT <1.5 times control and a platelet count >50,000/mm is ideal. Generally high-risk patients or those with difficult anatomy or significantly noncorrectable coagulopathy should be referred for surgical tracheostomy.

Optimal staffing includes an anesthesiologist or a physician who is trained in airway management and basic bronchoscopy positioned at the head of the bed to control the ETT, perform the bronchoscopy, and administer anesthetic medication. Sedation, analgesia, and short-acting paralysis are preferred to minimize patient discomfort and coughing as well as optimize the first attempt success. A nurse familiar with the procedure should be available to assist with monitoring of vital signs, administration of medications, and to act as a nonsterile circulator if supplies or tools are needed during the case. As with surgical tracheostomy, a shoulder roll is placed, the skin is prepped and draped in sterile fashion, the patient's FiO_2 is increased to 1.0, and a mode of ventilation is selected to ensure adequate minute ventilation.

Just as with surgical tracheostomy, anatomic landmarks should be identified. The ideal entry site is between the first and second or second and third tracheal rings. Some data suggest a higher incidence of tracheal stenosis if the cricothyroid membrane is involved. The risk of tracheo-innominate artery fistula increases if the tracheostomy tube is placed too inferiorly or in the setting of a high-riding innominate artery. The skin and subcutaneous tissue is infiltrated with up to 10 cc of 1.5% lidocaine with epinephrine, mostly for the vasoconstrictive properties. After an initial 1- to 1.5-cm horizontal or vertical incision is made through the skin and subcutaneous fascia, the soft tissue is bluntly dissected until the tracheal rings are palpated. With the bronchoscope positioned at the distal end of the ETT, the scope is withdrawn and transillumination through the anterior neck incision is visualized, giving the bronchoscopist an estimation of how far to pull back the ETT after the cuff has been deflated. After the ETT has been pulled back, the operator can then insert the 14-gauge needle under direct bronchoscopic visualization optimally in the midline of the trachea, avoiding the posterior membrane (Fig. 4). Aspiration of air and direct visualization confirms the proper location of the needle in the lumen of the trachea. Holding the needle in place, the syringe is removed and a J-tipped guidewire is advanced in the direction of the carina. Using Seldinger technique, the tract is initially dilated with the short 14-French dilating catheter followed by a single tapered dilator over the wire (Fig. 5). The tracheostomy tube that is loaded over a separate obturator is passed over the wire, and the cuff is then inflated once in the tracheal lumen (Fig. 6). Adequate position is confirmed via bronchoscopy through the ETT, then through the tracheostomy tube, in addition to observing return of tidal volume from the ventilator once the circuit is connected to

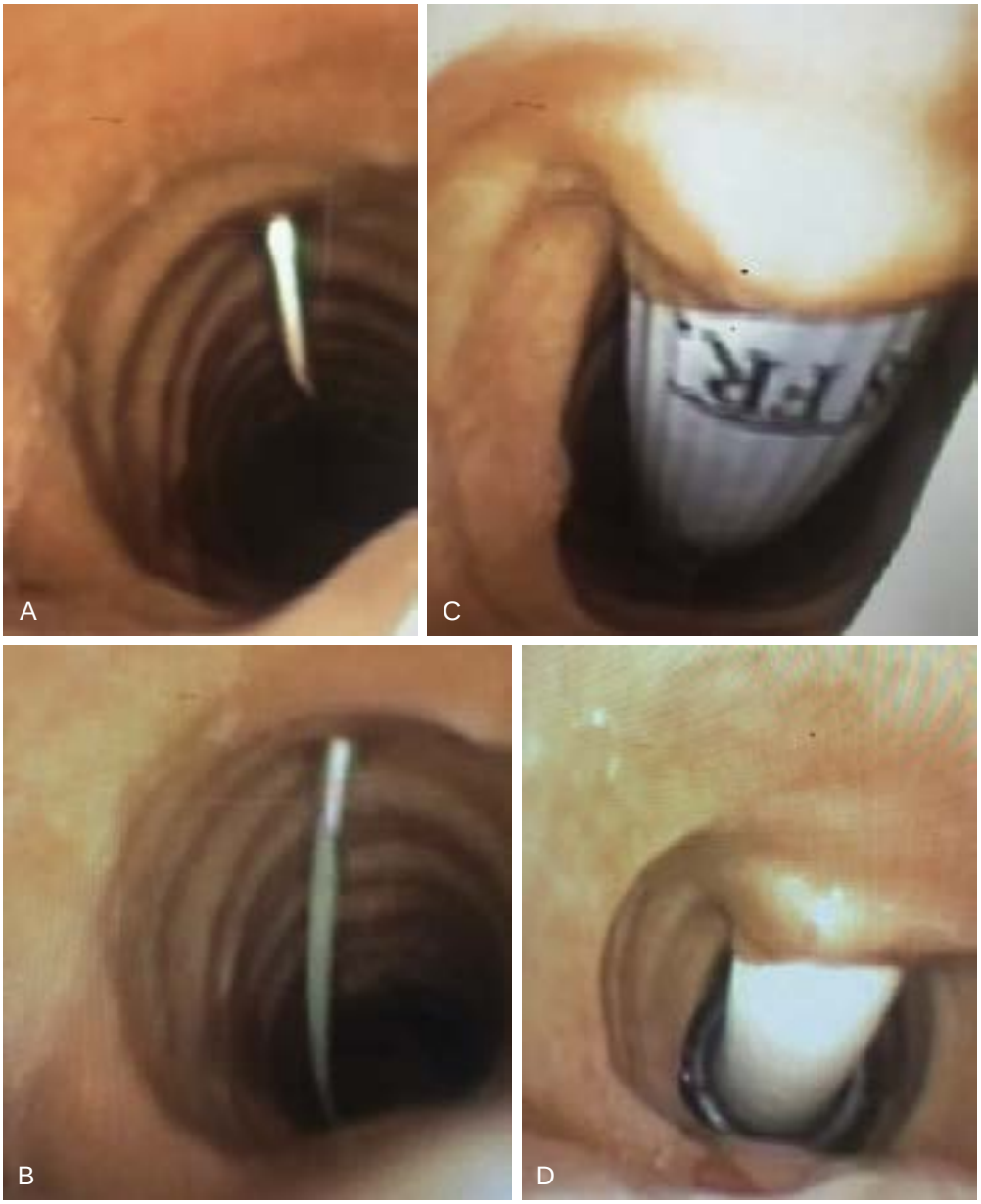


FIG. 4 Bronchoscopic view during percutaneous dilational tracheostomy. **(A)** Needle below first tracheal right. **(B)** Wire visualized descending toward carina. **(C)** Tapered dilator over wire. **(D)** Tracheostomy tube in place.

the tracheostomy tube. The tracheostomy tube is secured with a strap such that one finger can be placed between the strap and the skin, and the neck plate is either sutured or stapled to the neck. It is crucial that one operator always hold the tracheostomy tube as it is being secured. If accidental decannulation occurs, the patient should be reintubated with a translaryngeal ETT with the cuff of the tube distal to the stoma. Attempts at reinserting the tracheostomy tube should only be done when the airway is secure, and as the tract is immature, the introducer needle and guidewire should be used to avoid misplacement into the mediastinum.

COMPLICATIONS

In general, the complications of surgical and percutaneous dilatational tracheostomy are quite small and comparable between the two methods. Complications can be divided into early or late. Early complications for PDT include bleeding, infection, inadvertent decannulation, paratracheal insertion, injury to the posterior tracheal membrane, pneumothorax, pneumomediastinum, and tracheal ring fracture. Overall, the rate of these complications is quite low, with subcutaneous emphysema and pneumothorax being cited at 1.4% and 0.85%, respectively. Significant hemorrhage is also extremely low, with one retrospective study of 3162 bedside PDTs citing only one significant bleeding event requiring surgical intervention. Early complications for surgical tracheostomy are similar including hemorrhage, pneumothorax, pneumomediastinum accidental decannulation, and airway fire as electrocautery is used frequently in surgical tracheostomy while generally not in PDT. However, tracheal ring fractures and posterior tracheal wall injury or paratracheal insertions are very rare in surgical approaches as the tracheostomy tube is placed in the tracheal lumen under direct visualization.

Most complications following tracheostomy can be easily managed. Almost all bleeding around the tracheostomy stoma can be stopped with simple maneuvers including tightening the

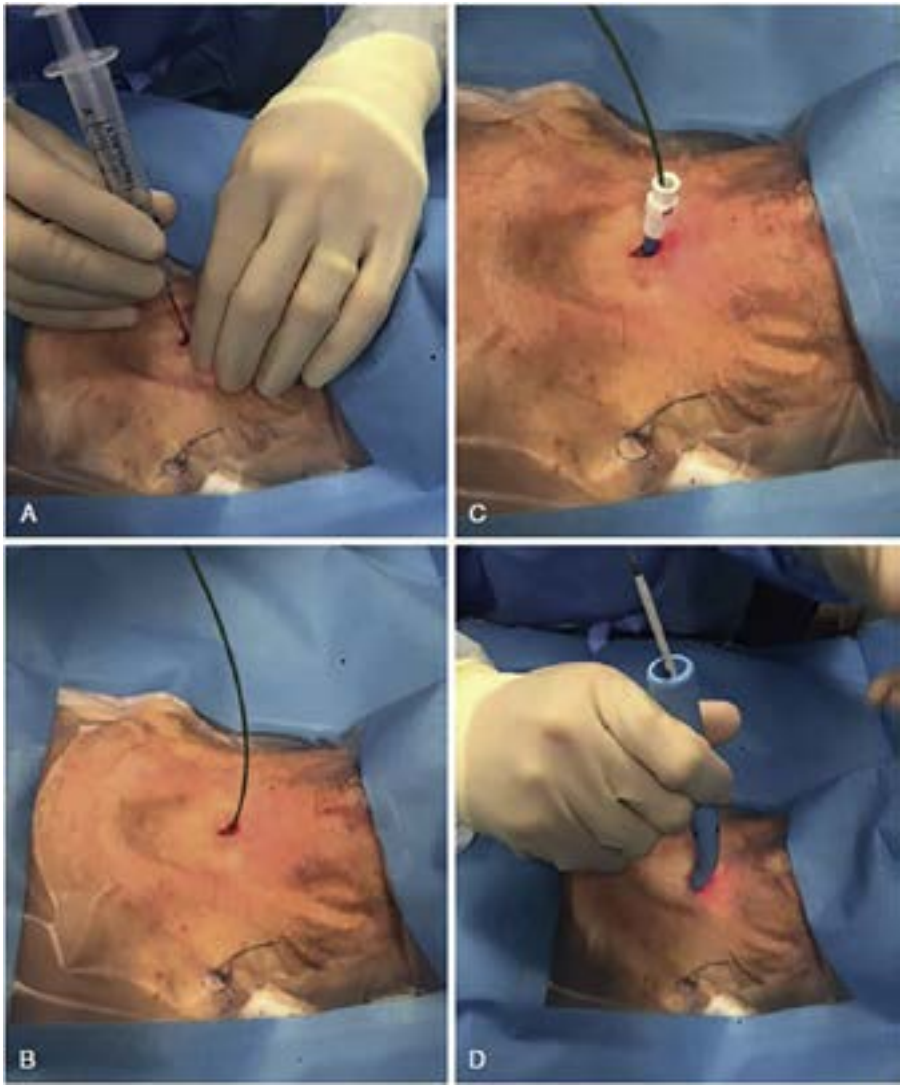


FIG. 5 **(A)** Insertion of introduce needle before wine insertion. **(B)** Wire in place. **(C)** 14Fr dilator over wire. **(D)** Tapered dilator over wire.



FIG. 6 **(A)** Tracheostomy tube loaded on obturator over wire. **(B)** Obturator and wire being removed. **(C)** Tracheostomy tube in place.

tracheostomy collar or placing a hemostatic agent such as Surgicel (Ethicon, Somerville, NJ) or Quick Clot (ZMedica, Wallinford, CT) circumferentially around the stoma. Additionally, for superficial skin bleeding, 10 mL of lidocaine with epinephrine can be injected subcutaneously to the area to promote vasoconstriction and hemostasis. Infections should be treated with antibiotics and rarely require surgical intervention unless a paratracheal abscess develops. If accidental decannulation occurs before a mature tract has developed (typically ~7–10 days), orotracheal intubation should be performed and the cuff of the tube placed distal to the tracheal stoma to prevent

development of subcutaneous emphysema. Reinsertion of the tracheostomy tube through an immature stoma can result in generation of a false tract into the subcutaneous tissue or mediastinum with disastrous consequences. After a secure airway has been established, the stoma can then be redilated and the tracheostomy replaced under more controlled circumstances. Pneumomediastinum and pneumothorax following tracheostomy can generally be managed conservatively unless the patient is unstable or the pneumothorax is expanding, at which point a tube thoracostomy would be indicated. Finally, airway fire is a serious complication that should be avoided by careful collaboration between anesthesiology and the surgeon during surgical tracheostomy, keeping the FiO_2 <0.4 during the use of electrocautery. If an airway fire does occur, the FiO_2 should be lowered, the inciting stimulant needs to be stopped, and if any foreign bodies are in the airway including a bronchoscope, ETT, or tracheostomy tube, they need to be removed as they can further propagate a fire. The patient can then be bag-masked and reintubated to reestablish a secure airway.

Late complications of both approaches are similar and include laryngotracheal stenosis, tracheomalacia, delayed stomal closure after prolonged cannulation, and most seriously tracheoinnominate artery fistula (TIF) formation. Tracheal stenosis can occur after both translaryngeal intubation and tracheostomy. The stenosis can occur in the subglottic space, at the level of the tracheal stoma, or at the level of the cuff of the endotracheal or tracheostomy tube. As almost all patients with tracheostomy tubes have had orotracheal tubes, it can be difficult to identify the causal factor. With this in mind, the overall incidence of clinically significant tracheal stenosis is low and cited to be as low as 0.16% in a large meta-analysis of over 3000 patients undergoing PDT. The overall rate of tracheal stenosis has markedly decreased since the 1960s and is due in part to the development of high-volume, low-pressure cuffs. It is also important to understand that tracheal stenosis is generally not clinically significant until there is a 75% reduction in luminal diameter and that stridor will not develop until the luminal diameter is <5 mm.

TIF formation is a feared complication that can be fatal if not recognized and intervened upon early. TIF is a rare complication generally occurring in <1% of all tracheostomies and can occur 48 hours after insertion but is most common 7 to 14 days postoperatively. The mortality associated with TIF is extremely high, with survival being cited around 14.3%. If a patient is suspected to have a TIF, the tracheostomy cuff should not be deflated until the proper personnel are present to manage the bleeding, preferably in the operating room. If the patient is stable, CT scanning of the neck can be obtained with contrast to visualize the relationship of the tracheostomy cuff to the innominate and if a fistulous tract is forming. If that is the case, the patient should be taken to the operating room for immediate repair before any further significant bleeding occurs. If a patient is actively hemorrhaging, the tracheostomy tube should be replaced with an ETT through the vocal cords with the cuff inflated distal to the bleeding source, and digital pressure with one's finger should be applied in the stoma, applying force anteriorly. The patient should then be taken to the OR for surgical repair. The best way to avoid a TIF is to place tracheostomy tubes above the third tracheal ring, ideally between the second and third rings and as with ETTs, tracheostomy tube cuff pressures should be monitored and kept below 25 mm Hg to avoid focal ischemic necrosis. Once ventilation is no longer required, thought should be given toward changing the tube to an uncuffed tube and/or proceeding with downsizing and decannulation.

COMPARISON BETWEEN SURGICAL AND PERCUTANEOUS DILATATIONAL TRACHEOSTOMY

PDT offers advantages over a surgical approach as it is generally a quicker procedure and is performed sooner as the surgical or critical care team does not have to wait for scheduled operating room time and staff. PDT is also generally more cost effective than surgical tracheostomy as the procedure does not take up operating room time and staff. In terms of complications, numerous studies have been completed comparing both approaches, some indicating a higher incidence of bleeding and infection with surgical tracheostomy as compared with PDT, with others reporting no significant difference. There have also been several meta-analyses published comparing complication rates between surgical tracheostomy and PDT, generally with equivocal results. A meta-analysis of 17 randomized controlled trials containing a total of 1212 patients found PDT was associated with fewer infections and bleeding as compared with surgical tracheostomy completed either in the operating room or at the bedside. Another meta-analysis of five prospective studies performed by Freeman and colleagues involving 115 patients receiving PDT (via the Ciaglia technique) and 121 STs found no significant difference in the overall operative complication rate.

However, not all meta-analyses have shown complication rates in favor of PDT. An earlier meta-analysis of 65 observational, retrospective, and prospective trials published by Dulguerov and colleagues examined serious perioperative complications, including death, cardiorespiratory arrest, pneumothorax, and pneumomediastinum, which were significantly less common in the surgical tracheostomy group as compared with the PDT group (86 vs. 149 per 10,000 cases respectively). Intermediate perioperative complications such as desaturation, hypotension, and injury to the posterior tracheal wall were also less common in the surgical approach. It is important to note, however, that the incidence of these complications is quite small, with injury to the posterior tracheal wall occurring in 6/10,000 patients in the surgical tracheostomy group as compared with 50/10,000 in the PDT group. The rates of serious postoperative complications (death, tracheoesophageal fistula, mediastinitis, sepsis, postoperative cannula obstruction or displacement, and tracheal stenosis) were similar in the surgical tracheostomy and PDT groups.

SUMMARY

Tracheostomy is an extremely common procedure that can be performed safely in the operating room or at the bedside in the ICU using a surgical or percutaneous dilational technique. As with any procedure, tracheostomy should be performed by experienced personnel with knowledge of airway anatomy and additional expertise in airway management. Benefits to PDT over surgical tracheostomy include cost savings, possibly fewer bleeding complications, and less delay once the decision to perform tracheostomy is made. There are still many circumstances when surgical tracheostomy is the preferred safer option making it important for intensivists and surgeons to understand the relative benefits and risks of both techniques.

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Acute Kidney Injury in the Injured and Critically Ill

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INTRODUCTION

A variety of events may perturb renal function. Although normal kidneys demonstrate excretory, regulatory, neuroendocrine, and detoxification capabilities, during critical illness clinicians acutely focus on the excretory and regulatory components (Fig. 1). Oliguria, acidosis, and a rise in serum creatinine (Scr) and blood urea nitrogen (BUN) commonly trigger renal function evaluation. A departure from baseline function that fulfills specific urine flow, Scr, and/or glomerular filtration rate (GFR) criteria is termed acute kidney injury (AKI; see later). AKI may also occur in the context of nondialysis-requiring chronic kidney disease (CKD). As the population ages, and elective but often complex surgery commonly occurs in those over the age of 65 years, AKI complicating CKD is likely to be increasingly encountered. Accordingly, several collaborative groups—such as the Acute Dialysis Qualitative Initiative (ADQI), the Acute Kidney Injury Network (AKIN), and the Kidney Disease: Improving Global Outcomes (KDIGO) group—have delineated the spectrum of departure from normal renal function as well as pathways of management into recovery. Regardless of acuity, surgical patients are at risk of AKI based upon the combined effects of anesthesia, tissue manipulation, therapeutic agents, comorbidities, hypovolemia, and, for many, radiocontrast. Addressing risk, and managing AKI when present, is essential as AKI adversely impacts major organ systems including the brain, heart, liver, intestine, and its microbiome, as well as bone marrow and the immune system. This chapter explores the current AKI knowledge base, prevention and management strategies, and the role of consultation to provide a framework for optimal care.

EPIDEMIOLOGY

Between 30% and 60% of critically ill patients will develop some stage of AKI (three stages of increasing severity exist) as well as associated acute morbidity and excess attributable mortality. AKI risk seems higher in those with multiple comorbidities and is associated with excess mortality ranging from 30% to 40% in resource-replete nations. Mortality reaches 50% in low- and middle-income countries (LMIC) related to contaminated water supply as well as the influence of endemic diseases including, most notably, malaria. An episode of AKI also engenders a future risk of CKD as many fail to recover their pre-AKI level of function. Although some patients completely recover, many survive with abnormal function and laboratory profiles, and a smaller portion survive but with CKD. AKI exerts an untoward influence of survival during the index hospitalization as well as during convalescence that is most pronounced in those who have not recovered to within 25% of their pre-AKI baseline Scr. In the AKI-Epidemiologic Prospective Investigation (AKI-EPI) study exploring AKI in critically ill patients, AKI occurred in 57.3% of patients. Relatedly, mortality increased with AKI severity ranging from an OR of 1.679 for stage 1 to 2.945 for stage 2 and 6.884 for stage 3. Unsurprisingly, they noted that those with AKI evidenced worse hospital discharge GFR than those without AKI, suggesting postdischarge resource utilization need, and a convalescent period follow-up requirement. Unexpectedly, this study found that, when risk-adjusted, AKI rates as well as attendant mortality were similar around the globe.

It is important to note that the previous data include heterogenous populations and were not limited to those with surgical disease where AKI incidence may substantially depend on patient comorbidities, reason for index admission, and the use of extracorporeal techniques such as cardiopulmonary bypass. Indeed, postcoronary artery bypass graft AKI has been extensively explored in terms of pathophysiology, altered renal blood flow, anemia, and the impact of hemolysis and free hemoglobin on a nearly 50% AKI. Vascular surgery patients similarly demonstrate an aggregate AKI risk of approximately 49% with reduced risk noted for uncomplicated endovascular aneurysm repair (EVAR) (3.5%–18%) compared with open ruptured abdominal aortic aneurysm (AAA) repair (74%–76%) (Fig. 2). Key risk influencers in general surgery patients who developed AKI (47.3% incidence) include elevated BMI, increased APACHE-II score, septic shock, invasive mechanical ventilation, acute nonsurgical complications, and preadmission CKD. Importantly, AKI severity was nearly equally distributed across the three stages (see AKI classification later), with the highest level associated with a nearly eightfold risk of 28-day mortality. Injured patients demonstrate an aggregate AKI rate of 24% in a recent meta-analysis, with accelerated mortality (RR = 3.4) noted in those with AKI versus non-AKI patients. Major AKI risk factors included African-American race, older age, chronic hypertension, diabetes, high Injury Severity Score, abdominal injury, shock, sepsis, high APACHE-II score, and low Glasgow Coma Score. While some form of renal support technique was used in 10%, recovery was noted in 96% of the AKI group. Therefore, it is essential to understand AKI pathophysiology to facilitate accurate categorization, align treatment, and identify those at risk to deploy preventive strategies.

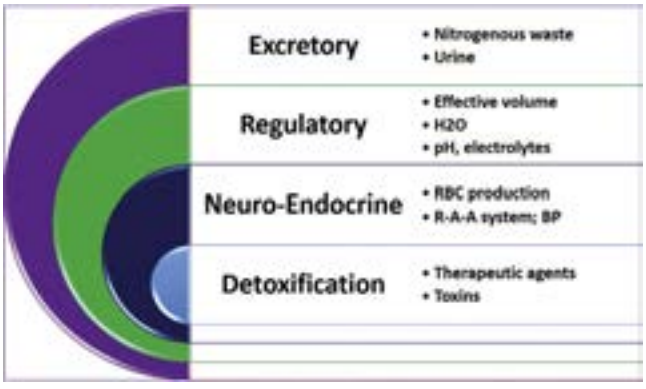


FIG. 1 Renal functions span four major domains. *BP*, Blood pressure; *R-A-A*, renin-angiotensin-aldosterone.

CLASSIFICATION AND STAGING OF AKI

GFR serves as the functional benchmark in assessing CKD, but its estimation performs less well than desired during AKI evolution when function is rapidly changing. Current GFR estimating equations (Cockcroft-Gault, Modification of Diet in Renal Disease Study, and Chronic Kidney Disease Epidemiology Collaboration) leverage steady-state Scr kinetics and are therefore less applicable to AKI. Moreover, GFR is impacted by nonrenal influences, especially evident during different phases of the resuscitation-optimization-stabilization-evacuation (ROSE) approach to fluid management. During the acute phase of resuscitation, plasma volume expansion may impact laboratory profiles as a function of dilution. In contrast, during the evacuation phase, hemoconcentration may increase Scr. Furthermore, critical illness and injury may also

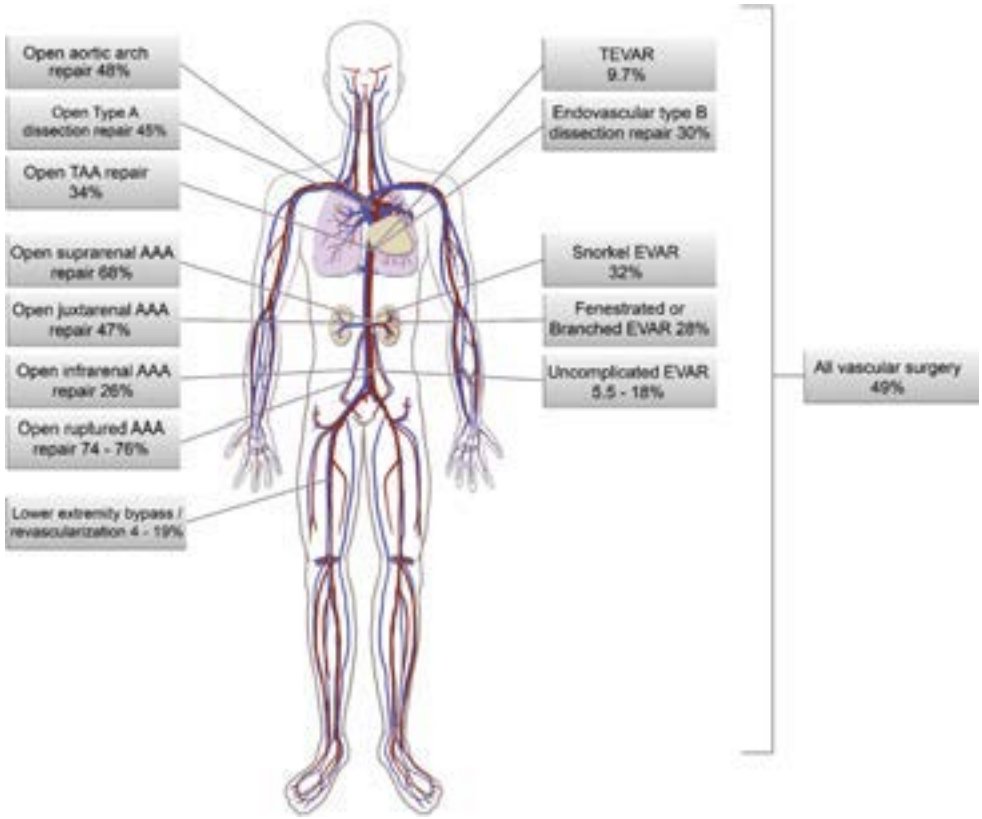


FIG. 2 Postvascular surgery AKI rates. Breadth of AKI rates after common vascular operations and procedures. *AAA*, abdominal aortic aneurysm; *EVAR*, endovascular aneurysm repair; *TAA*, thoracic aortic aneurysm; *TEVAR*, thoracic endovascular aortic repair. *(From Hobson C, Lysak N, Huber M, et al. Epidemiology, outcomes and management of acute kidney injury in the vascular surgery patient.* J Vasc Surg. *2018;68:916–928.)*

influence Scr through hypercatabolism-induced lean body mass reduction. Equations for kinetic GFR calculation when Scr is fluctuating have been proposed but not validated, and renal recovery may precede Scr decline or normalization. Other approaches such as 2-hour or 4-hour measured creatinine clearance to aid kinetic GFR calculation or measuring the rate of decrease of an injectable plasm marker that depends on renal clearance are not well deployed in clinical care. Therefore, metrics that link the repeatedly assessable laboratory profile with a functional measure such as urine output (Uop) appear more appropriate for the dynamic and heterogeneous condition of AKI. Such metrics have evolved from the work of three interwoven groups.

ADQI and RIFLE

The ADQI group parsed AKI into three severity classes (Risk, Injury, and Failure) and two outcome states (Loss and End-stage disease), known by the mnemonic RIFLE (Fig. 3). RIFLE defined both fold and absolute increases in Scr or GFR, as well as oliguria for specified periods of time to define severity class. The duration of derangement defined the outcome state. RIFLE grade on admission to ICU strongly correlates with mortality, with AKI yielding attributable mortalities of 8.8%, 11.4%, and 26.3% for classes R, I, and F, respectively, compared with a 5.5% mortality in matched patients without AKI. The notion that the Injury class represented heterogeneous patient populations and that the most injured as well as those in the F class received similar therapy spurred further metric refinement. Nonetheless, ADQI changed the language by which deranged renal function was described during acute critical illness or after injury, which standardized comparisons across patient groups.

AKIN and KDIGO

The AKIN group further modified RIFLE for both diagnostic criteria and injury state and eliminated GFR from their AKI rubric (see Fig. 3). The AKIN AKI diagnostic criteria evaluate changes in Scr or Uop over a 48-hour timeframe. An increase in Scr ≥0.3 mg/dL, increase in Scr ≥50% (baseline SCr × 1.5 or more), or a decrease in Uop (<0.5 mL/kg per hour for >6 hours) mark AKI stage 1. Greater perturbations for longer periods of time define stages 2 and 3. Patients must only fulfill one criterion to be assigned a stage; any patient on renal replacement therapy (aka renal support techniques) regardless of modality qualifies for stage 3. Importantly, other elements that could impair Uop must be excluded—including the frequently occurring high antidiuretic hormone (ADH) tone after major surgical intervention. Using absolute and percentage increases over baseline values for a patient reduces intersubject variation driven by gender, lean body mass, and age, and facilitates large data set analysis to assess outcomes and trends. Both ADQI and AKIN assessed changes in Scr from a known baseline value. Patients with septic shock, those pursuing medical tourism, and those who are in a nonnative healthcare system may not have such information available to the clinician. KDIGO further refined the AKIN criteria and developed a method to address unknown baseline Scr values and created parameters for staging AKI in patients less than 18 years of age.

The KDIGO collaborative created a definition of AKI and accompanying staging criteria that serve as the current standard. AKI presence is defined by any Scr increase ≥0.3 mg/dL within 48 hours, *or* Scr increase ≥1.5 times baseline (known or presumed to have occurred within the prior 7 days), *or* Uop <0.5 mL/kg/hour for 6 hours. AKI criteria also establish three stages with subtly changed elements for Scr but no change in those for Uop volume or duration

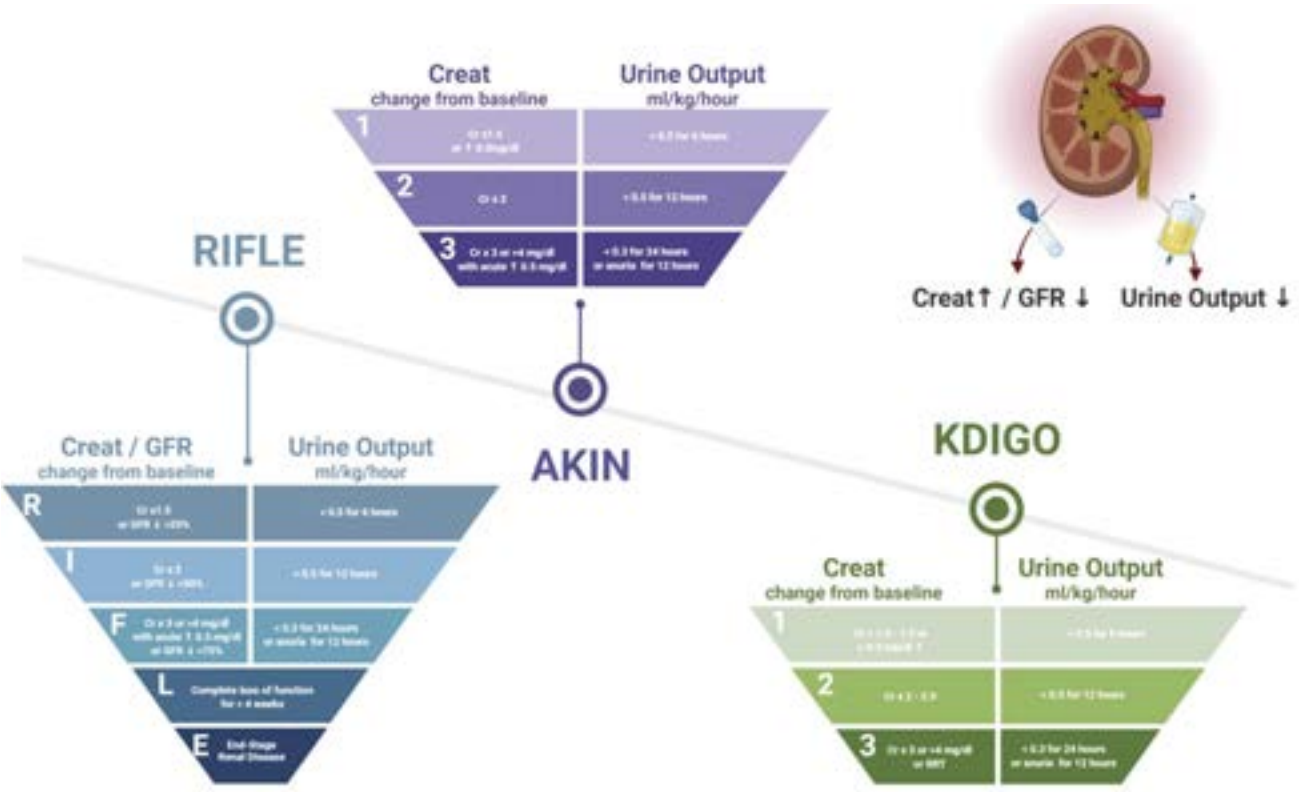


FIG. 3 Renal injury severity grading. Comparison of renal injury severity grading systems (RIFLE, AKIN, and KDIGO).

compared with those from AKIN (see Fig. 3). KDIGO also defines stage 3 AKI in patients younger than 18 years of age as a GFR <35 mL/min per 1.73 m^2 body surface area regardless of urine flow. AKI in children greater than 1 month of age is best achieved using the pediatric RIFLE (pRIFLE) criteria to account for lesser muscle mass compared with adults that will impact Scr concentration. Understanding key AKI triggers and their impact on renal cellular health enables diagnosis, management, and time course prognostication. It is important to note that the KDIGO AKI criteria solely represent organ-based function and do not provide insight into the underpinnings of identified injury or failure.

AKI TRIGGERS

AKI has been traditionally evaluated using the prerenal (i.e., shock, cardiorenal syndrome, abdominal compartment syndrome, nephrotoxic medications including immunosuppressive agents), intrarenal (i.e., sickle cell anemia, sepsis, acute cellular rejection, interstitial nephritis), and postrenal (i.e., bladder outlet obstruction, bilateral ureteric obstruction or injury) rubric, an approach that lends itself to identifying key clinical entities that may direct focused evaluation and therapy. However, there are commonalities such that cross-clinical conditions may be conveniently grouped into four heterogenous triggers that result in AKI. The four major AKI triggers span sepsis (including septic shock), flow (including hemorrhagic or hypovolemic shock), toxins (including therapeutic agents), and radiocontrast agents (Fig. 4). Within each domain, there are a host of specific etiologies, some of which vary by geography (i.e., malaria) and others by resource availability (high vs. LMIC therapeutic agent supply). Regardless, all AKI events appear to be preceded by a period of renal injury that is not captured by current laboratory profiling or urine flow tracking approaches. That specific event is known as subclinical AKI (see biomarkers later) and may represent an opportunity for early recognition and potential therapeutic intervention. To understand how and when to optimally intervene, it is essential to delineate the impact of any of the four previously detailed triggers on renal parenchymal including tubular cells. Indeed, while AKI appears to be a heterogenous syndrome, the underlying pathophysiology seems consistent across multiple etiologies.

COVID-19

Special note is made of the AKI that has been identified in those with SARS-CoV-2 infection. These individuals appear to demonstrate the common profile of tubular injury but also demonstrate a unique glomerular pathology termed *collapsing glomerulopathy*, which has been noted in other viral diseases. This pathology seems strongly associated with Apolipoprotein L1 (APOL1) polymorphisms, and APOL1 genotypes occur most commonly in those of Western African descent. Importantly, APOL1 expression is upregulated by viral infection as well as by interferons and Toll-like receptor 3 activation. Thus, the inflammatory milieu of severe SARS-CoV-2 infection may serve as a potent trigger.

PATHOPHYSIOLOGY

AKI-Relevant Cellular Events

Three principal events inform our knowledge of how AKI triggers interface with renal cells: inflammation, distorted microcirculation, and bioenergetic adaptive responses to acute injury. Septic AKI provides a paradigm within which AKI may be explored. Unlike AKI from hypovolemia, in sepsis, global renal hypoperfusion appears less relevant than disturbed microcirculatory dynamics that hinge on endothelial injury and inflammation. Autoregulatory processes such as the myogenic response and tubule-glomerular

feedback both constrict afferent arterioles to reduce excess flow and salt bioburden. These sequential adaptive processes have response times of approximately 5 to 10 seconds and are plausibly triggered by excess plasma volume expansion presented to an already stressed renal parenchyma. Afferent vasoconstriction exacerbates abnormal flow but may also exist as a consequence, rather than a driver, of tubular injury. Nonetheless, heterogenous flow may lead to areas of hypoxia or anoxia. Inflammation in septic AKI—like other sepsis syndromes—flows from damage (DAMPs) and pathogen-associated molecular patterns (PAMPs) that interface with embedded epithelial receptors including Toll-like receptors on tubular cells after glomerular filtration. Cellular injury drives neutrophil and other effector cell trafficking and augments local inflammation. Sluggish flow may prolong tubular exposure to inflammatory mediators including DAMPs and PAMPs as well as immune effector cells (Fig. 5). This paradigm is influenced by a variety of related processes that derail normal metabolism and energy production (see Figs. 4 and 5). Ferroptosis is an important

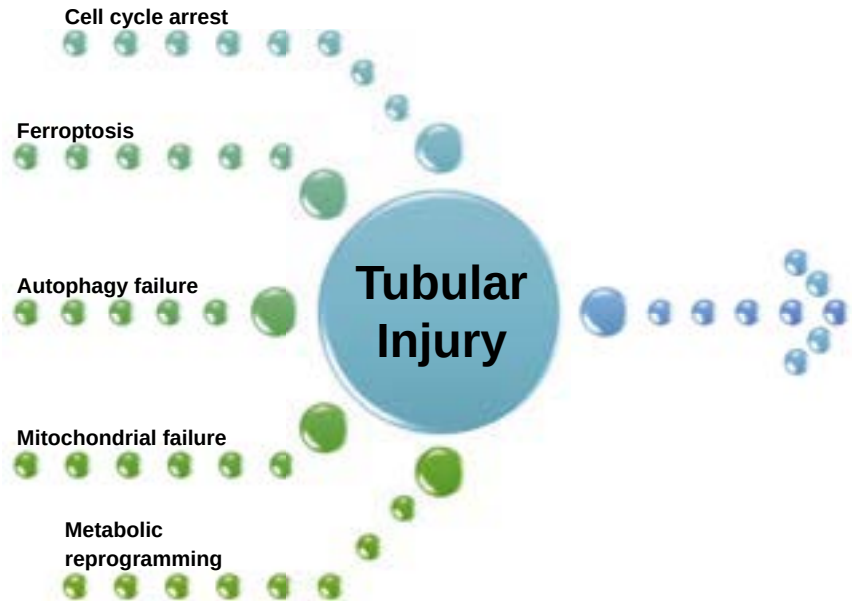


FIG. 4 Processes impacting tubular injury.

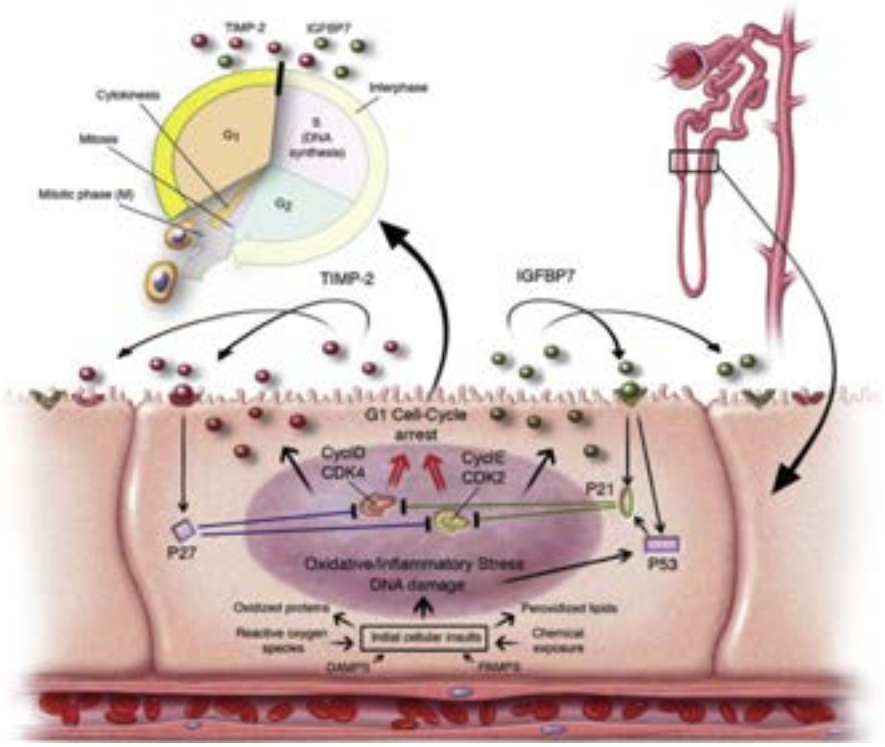


FIG. 5 **Bioadaptive cell cycle arrest biomarkers in AKI.** *(From Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury.* Crit Care. *2013;17:R25.)*

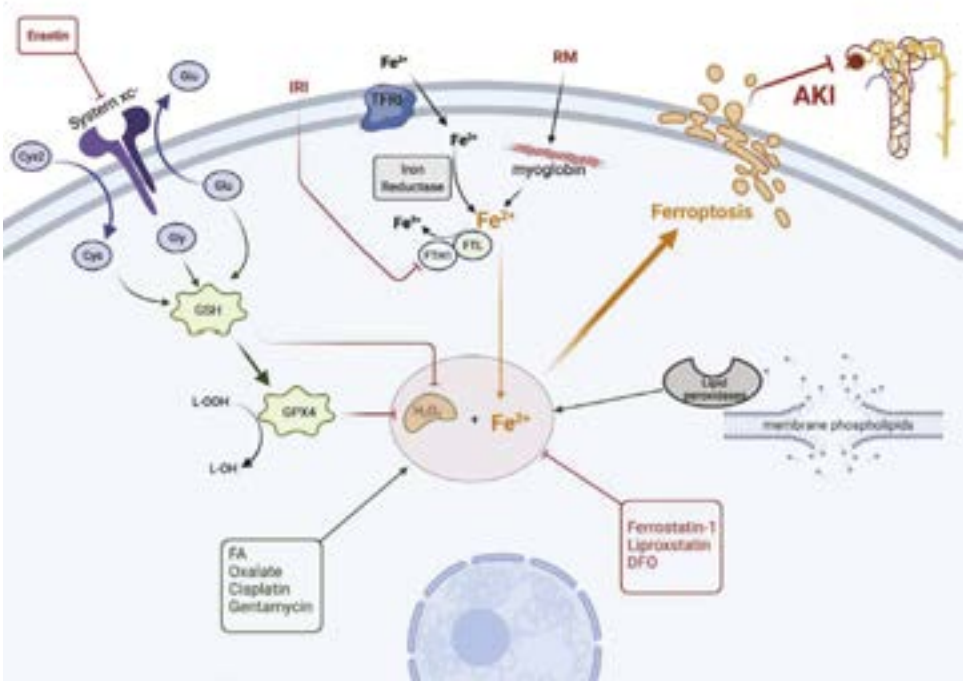


FIG. 6 In renal tubular cells, abnormal increases in Fe^{2+} or H_2O_2 caused by various pathogenic factors trigger the Fenton-like chemistry, which oxidizes membrane lipids to lipid peroxides, and mediate ferroptosis thus leading to AKI. RM initiates ferroptosis by raising the level of Fe^{2+}, while IRI induces ferroptosis by inhibiting the conversion of Fe^{2+} to Fe^{3+}. Other pathogenic factors such as FA, oxalate, cisplatin, and gentamicin can also promote the occurrence of Fenton-like chemistry, induce ferroptosis, and lead to AKI. The Fenton-like chemistry can be inhibited by intracellular GPX4, a key enzyme that maintains tissue homeostasis. Ferrostatin-1, liproxstatin, and DFO alleviate or delay the development of AKI by inhibiting the Fenton-like chemistry in a protective role in ferroptosis induced by various pathogenic factors. *AKI*, acute kidney injury; *RM*, rhabdomyolysis; *IRI*, ischemia reperfusion injury; *FA*, folic acid; *GPX4*, glutathione peroxidase 4; *DFO*, deferoxamine. *(Adapted from Hu Z, Zhang H, Yang S-K, et al. Emerging role of ferroptosis in acute kidney injury.* Oxid Med Cell Longev *2019;2019:8010614.)*

mechanism as it explains how iron-based electron donation can mediate oxygen-induced membrane injury that leads to nonapoptotic cell death. Indeed, protection from ferroptosis relied on glutathione-based systems for which there are known inhibitors (erastin; Fig. 6). Alternatively, agents like hepcidin induce iron sequestration in macrophages and may be protective. Other processes support cell survival, as septic AKI biopsy data do not demonstrate the typical pattern of acute tubular necrosis that is well described in ischemia-reperfusion-related AKI following hemorrhagic shock and resuscitation.

Cell cycle arrest in G1/S is an AKI hallmark and appears to be a bioenergetic adaptive response to cellular stress (see Fig. 5). Normal cell cycle progression is intimately dependent on the formation of a mitochondrial tubular network, which is an oxygen-dependent process. This process is derailed by oxidative stress, both local and global. Furthermore, two biomarkers, TIMP-2 and IGFBP-7, are sensitive indicators of the G1/S checkpoint (see Fig. 5; see Biomarkers later). This paradigm establishes mitochondria as central elements in AKI in that they may integrate adaptive responses to cellular stress and survival by limiting autophagy and driving cell cycle arrest—an essential step in preparing for mitosis. Arresting progression allows survival when normal cell machinery integrity is threatened.

However, when cell cycle arrest persists, it is a key step in the transition to CKD as is persistent mitochondrial dysfunction from the failure of normal autophagy mechanisms or mitophagy to support new mitochondrial biogenesis. Furthermore, a variety of pathways that initiate and sustain fibrosis are also implicated in the progression to CKD. Nephron loss may occur at any time during an episode of AKI, an event that may hasten progression to CKD that shortens renal functional lifespan. Along the continuum of stress, injury, and recovery, key events may be signaled by biomarkers that are detectable in urine, blood, or both.

Biomarkers

Investigations into biomarkers that reflect tubular injury and renal stress are ongoing (Fig. 7). Well-investigated tubular injury biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), cystatin-C (Cys-C), interleukin-18 (IL-18), urinary liver-type fatty acid-binding protein (L-FABP), kidney injury molecule 1 (KIM-1), and Klotho. Renal stress biomarkers include tissue injury metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7), currently marketed as the NephroCheck Test System (Astute Medical Inc.; San Diego, California), which identifies patients at high risk of developing KDIGO AKI stage 2 to 3 within the subsequent 12 hours. NGAL, cystatin-C, and KIM-1 can help identify patients who may develop AKI when the disease process is still in the subclinical phase (i.e., subclinical AKI) before detectable change in Uop or Scr. It is hoped that biomarkers will allow early and accurate assessment of AKI risk that pairs with specific therapeutics that can rescue stressed cells (see Fig. 7). A variety of permutations of biomarkers may more accurately identify AKI risk than a single or even paired biomarkers. It is in this domain that machine learning algorithms and artificial intelligence big data approaches may be exceedingly helpful. However, it would be ideal to train such models using a host of inputs throughout the time span of an episode of AKI that spans preadmission health data through convalescence (Fig. 8). Table 1 lists blood, urine, and functional assays that are commercially available. Recognizing that there is a period of stress that precedes injury offers the potential for AKI prevention.

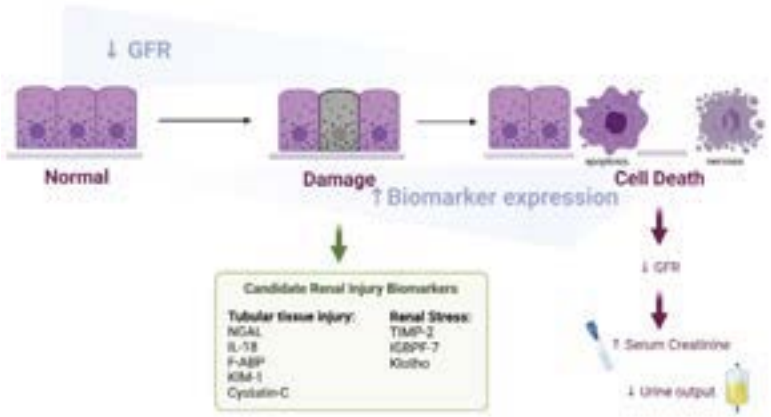


FIG. 7 Some biomarkers of renal injury. Candidate biomarkers of renal injury may fill the opportunity gap to detect subclinical renal injury that exists between normal renal function and cell death, where changes in GFR, serum creatinine, and urine output become clinically apparent. *F-ABP*, Fatty-acid binding protein; *NGAL*, neutrophil gelatinase-associated lipocalin; *IGBPF-7*, insulin-like growth factor binding protein-7; *KIM-1*, kidney injury molecule-1; *TIMP-2*, tissue injury metalloProteinase-2.

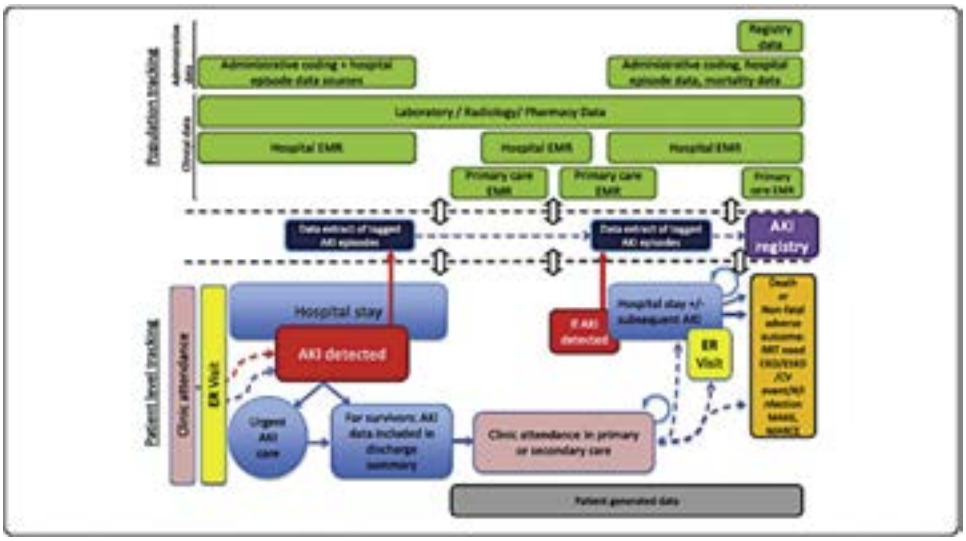


FIG. 8 Opportunities for AKI data flow. This schematic represents multiple opportunities to direct AKI relevant information into a single data stream to facilitate "big data" analysis and to track AKI relevant healthcare outcomes. *(From Mehta R, Bihorac A, Selby NM, et al., Acute Dialysis Quality Initiative (ADQI) Consensus Group. Establishing a continuum of acute kidney injury–tracing AKI using data source linkage and long-term follow-up: Workgroup Statements from the 15th ADQI Consensus Conference.* Can J Kidney Health Dis. *2016;3:102.)*

PREVENTION OF AKI

Radiocontrast

Understanding the at-risk patient population helps in designing preventive approaches when such patients require care. While prevention is far easier when care is planned and elective, certain interventions can help prevent AKI in those who need urgent or emergent care. Patients who present for elective care, including CT scanning or angiointervention employing radiocontrast, represent a group ideally suited for preventive intervention. A recent review of contrast-induced AKI outlined both direct and indirect effects of contrast that may explain the pathophysiology of contrast-induced AKI. Patients may be parsed into low- and high-risk categories based upon clinical features, comorbidities—notably including preexisting CKD—and planned procedural intervention where coronary angiography imparted the greatest risk. Diabetes is positioned as an amplifying comorbidity but not a direct risk factor as has been commonly believed. Avoiding high osmolarity contrast is ideal despite its lower cost because it offers no particular imaging advantage compared with low- or iso-osmolar agents and is associated with AKI. Even when using low- or iso-osmolar agents, high-risk patients should receive the lowest contrast volume possible, have concurrent nephrotoxic agents held or discontinued, and should most importantly have a planned follow-up renal function assessment. Finally, plasma volume expansion to ensure euvolemia is ideal in patients who can tolerate crystalloid infusion.

Unplanned Care

For those who present for urgent or emergent care, some degree of hypovolemia is common in the absence of concomitant heart failure. For this group, the mainstays of AKI prevention—a goal that may not be possible to achieve because many will already demonstrate subclinical AKI or at least cellular stress—include rapidly abrogating

TABLE 1 Available Assessments of AKI*

Biomarker/Functional Test	Mechanism	Clinical Application	Comment
BIOMARKERS AND TESTS AVAILABLE FOR CLINICAL USE			
Blood			
Cystatin-C	Glomerular filtration	Earlier detection of AKI, not dependent of muscle mass	Scr alternative Less non-GFR determinants
Proenkephalin (PenKid)	Glomerular filtration	Earlier detection of AKI	Scr alternative
NGAL	Tubular damage	Earlier detection of AKI	Also increased in other conditions such as infection Cutoff unclear
Urine			
TIMP-2 × IGFBP7 (NephroCheck)	Cellular stress tubules (cell cycle arrest)	Earlier detection AKI stage 2 or 3 within 12 h	High sensitivity cutoff >0.3 High specificity cutoff >2.0
NGAL	Tubular damage	Earlier detection AKI	Cutoff unclear
KIM-1	Proximal tubular damage	Earlier prediction of AKI	FDA recommends its use for assessment of drug toxicity
Cystatin-C	Tubular function	Earlier detection kidney injury	Limited evidence
Functional Tests			
Furosemide stress test	Tubular function	Prediction of AKI progression	Cutoff urine output >200 mL per 2 h
Renal Resistive Index (duplex ultrasound)	Kidney circulation	Prediction of AKI persistence	Controversial evidence
Loss of RFR	Loss of renal functional reserve	Prediction of AKI in cardiac surgery Marker of incomplete recovery	Cumbersome, predominantly used in research setting
TESTS NOT AVAILABLE FOR CLINICAL USE WORLDWIDE			
Blood			
SuPAR	Cellular bioenergetics and oxidative stress	Preexposure risk factor	Limited evidence
Urine			
IL-18		Inflammation, early detection AKI	Low predictive power for AKI
LFABP	Proximal tubular damage	Prediction of AKI	Available for clinical use in Japan
CHI3L1	Stress or damage tubules and macrophage activation	Prediction of AKI	Alternative name YKL-40 Limited evidence
DKK-3	Fibrosis	Preop DKK-3 predicts postop AKI and predicts long-term kidney function	Limited evidence
CCL14	Fibrosis	AKI persistence	Limited evidence

*This table displays readily available assessments of AKI including those from blood or urine as well as functional assessments of renal capacity or reserve.From Pickkers P, Darmon M, Hoste E, et al. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Med* 2021;2:1-6.

hypovolemia and hypoperfusion. Key in this process is repeated assessment of plasma volume and cardiac performance goals that may be accomplished using a wide variety of assessment tools spanning point-of-care ultrasound (POCUS) including transesophageal echocardiography (TEE) or hemodynamic monitoring TEE (hTEE), invasive hemodynamic monitors (PA catheter), as well as less-invasive approaches using transpulmonary dilution or noninvasive assessment devices including radial artery applanation tonometry, finger cuff plethysmography, thoracic electric bioimpedance, and bioreactance. Patients with heart failure will benefit from not exacerbating fluid overload, as fluid overload directly correlates with mortality in adult critically ill patients—a finding pronounced in those with AKI, CKD, or are postoperative—and major adverse kidney events (MAKE) in those with AKI who require management using a renal support technique. Diuresis should be undertaken in a guided fashion, using one of the aforementioned monitors, as injudicious diuresis may exacerbate AKI and impair renal recovery. Adjusting the dosing of potentially nephrotoxic agents when GFR, creatinine clearance, and Scr are in flux is important to avoid preventable injury; a PharmD functions as an essential and integral team member in adjusting therapeutic agents in this vulnerable population.

Although there remains debate regarding the optimal fluid for resuscitation, there is unambiguous evidence delineating untoward consequences of plasma volume expansion that impact multiple organ systems when unbalanced crystalloid solutions are infused. Hyperchloremic metabolic acidosis (HCMA) is a well-described consequence that triggers a host of undesirable effects including, but not limited to, renal artery vasoconstriction, pulmonary artery vasoconstriction, cardiomyocyte inflammation, decreased red cell deformability, Rouleaux formation, and microvascular hypoperfusion. There remains controversy whether HCMA is independently associated with AKI, but avoiding inducing HCMA or abrogating it when present are reasonable and safe goals and is a recommended intervention by the ADQI group. A variety of studies comparing balanced crystalloid solutions for resuscitation and ICU-based care demonstrate safety, decreased cost, improved Scr kinetics, and a decreased need for renal support techniques for AKI management. Nonetheless, there is conclusive evidence that starch-based resuscitation is to be avoided in those with sepsis or septic shock due to an increased—and entirely avoidable—risk of AKI and need for renal support techniques. Starch-based resuscitation was previously commonly practiced in the United States but has essentially vanished in the wake of its AKI association. Indeed, the FDA recommends avoiding starch-based solution treatment of hypovolemia in the presence of any other alternative treatment.

Prophylaxis

Despite earlier enthusiasm for specific medications to modify AKI risk—including low-dose dopamine, fenoldopam, n-acetylcysteine, and dopexamine as part of a "goal-directed" blood pressure management scheme—there is no compelling data that any therapeutic agent influences risk or outcome. Therefore, no specific agents are recommended for administration in a prophylactic or therapeutic fashion. Note is made of the continued use of n-acetylcysteine despite the absence of evidence to support its use in preventing AKI in surgical patients.

MANAGEMENT STRATEGIES

Stage-Based Therapeutics

Once AKI is diagnosed, two major pathways should be engaged: (1) delineating and treating the underlying cause, and (2) stage-based management of renal function. The panoply of diagnoses that may lead to AKI is beyond the scope of this chapter, but three surgically relevant etiologies deserve specific mention: intraabdominal hypertension and abdominal compartment syndrome, rhabdomyolysis, and sepsis/septic shock, each of which are explored in detail elsewhere within this text. Stage-based management of AKI is articulated by KDIGO in an implementable format (Fig. 9). Importantly, this approach identifies those at high risk in the management rubric. Specific note is made of early consideration of renal support techniques at the transition from stage 1 to stage 2, which should also prompt transfer to the ICU if the patient is not already located in a critical care unit. Since AKI is heterogeneous, early nephrology consultation seems warranted, with many recommending universal consultation for all patients with AKI to facilitate both inpatient management but also postdischarge care continuity through renal recovery or CKD evolution.

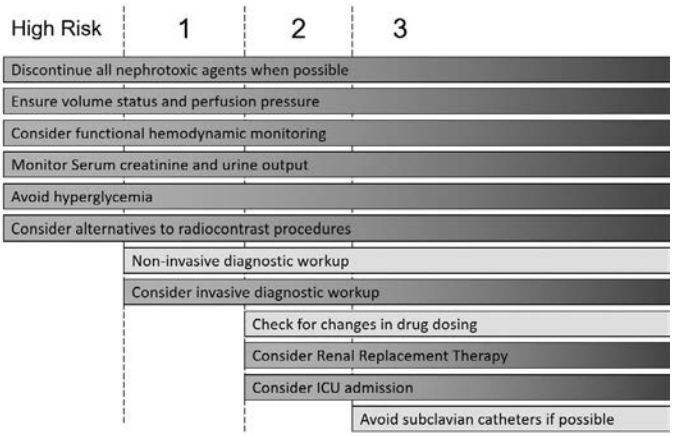


FIG. 9 Stage-based AKI management. This graphic depicts key aspects of managing patients with acute kidney injury based upon their AKI stage. *(Reproduced under a Creative Commons license from KDIGO; https://kdigo.org/guidelines/acute-kidney-injury.)*

Bedside Imaging

Renal ultrasonography is often pursued to evaluate for postrenal etiologies but may also assess renal blood flow when microbubble or color or spectral Doppler techniques are employed. More recently, dynamic contrast-enhanced ultrasound has been employed to assess renal perfusion but has not yet become standard; the employed contrast is non-nephrotoxic and provides an alternative to radiocontrast-based assessments. Renal blood flow is essential in evaluating postrenal transplantation graft dysfunction or failure. Intrarenal etiologies may be assessed using renal size, echogenicity, renal sinus adipose, and corticomedullary differentiation, as well as hydronephrosis (functional and obstructive). These are key elements in renal ultrasound evaluation, each of which provide clues into potential AKI etiologies. The value of ultrasound may be greatest in those with pelvic surgery, retroperitoneal exploration, renal trauma complicated by hematuria, known prostate enlargement, or known bladder dysfunction.

Renally Relevant Laboratory Profiling

Often, renal ultrasound is also accompanied by urine microscopy and determination of urinary and plasma electrolyte-coupled calculated indices such as the fractional excretion of sodium or urea. Such calculations are designed to provide information regarding circulating volume and how the kidney perceives that volume. Such determinations appear divorced from intrarenal processes, fail to correlate well with biomarker assessments of renal events and trajectories, and seem of limited value during acute management. Specific note is made of urinary sodium concentration that, when low, generally indicates sodium, and therefore, plasma volume avidity. An elevated

concentration suggests fluid sufficiency, but cannot exclude fluid excess, and is directly impacted by recent diuretic administration or conditions that drive salt wasting.

Routine laboratory profiling that includes electrolytes, BUN, creatinine, glucose, calcium, magnesium, and phosphorous should occur on a daily basis. Since there are multiple influencers of plasma bicarbonate concentration, it cannot be relied upon to reflect fixed or volatile acid burden that has a renal or hepatic source. Indeed, changes in sodium and chloride infusion, enteral administration, or ionic components of therapeutic agents may raise or depress the measured bicarbonate concentration. Therefore, while renal function is rapidly changing, arterial or venous blood gas assessments to determine pH-pCO_2 balance and assess lactic acid concentration are prudent, as progressive AKI may impose a substantial work of breathing to buffer the inability to excrete fixed acids.

Therapeutic Agent Adjustment

Nephrotoxic medications should be avoided or discontinued. Renally cleared therapeutic agents should undergo dose adjustment to avoid toxicity related to excess agent. As septic AKI is common, specific antibiotic selection should consider renal clearance, as well as the promotion of intrinsic renal injury (such as acute interstitial nephritis) as has been well detailed for the combination of vancomycin and piperacillin-tazobactam and, to a lesser extent, vancomycin and cefepime. Glycemic control, including intraoperatively, is ideal to help reduce AKI, especially in those with CKD and type 2 diabetes and those undergoing cardiac surgery or hepatic transplantation. Moreover, altered tubular glucose handling during AKI seems associated with untoward outcomes, including mortality, establishing glycemic control as a reasonable therapeutic goal for all patients regardless of the presence or absence of diabetes, stress hyperglycemia, or normoglycemia.

Phenotypes and Therapeutic Agent Selection

As is the case for sepsis, unique subphenotypes of AKI patients may be discovered using latent class analysis assessment that includes commonly available elements such as laboratory data, mechanical ventilation, and demographics coupled with specific assessments such as IL-6, IL-8, and sVCAM concentrations. Two AKI subphenotypes have been identified and assessed for 7-day nonrenal recovery as well as 28- and 90-day mortality. Interestingly, a subphenotype group described a differential response to commonly applied therapeutic agents where one group demonstrated improved outcomes with vasopressin compared with norepinephrine; no such benefit was identified in the other molecularly distinct group. In another assessment of patients with sepsis-related AKI, subphenotype-2 also demonstrated higher 90-day mortality and a more abnormal endothelial injury and inflammatory profiles. The value of subphenotype identification falls into three categories: improved therapeutic agent alignment, focused enrichment of clinical trials to support an adaptive trial approach to clinically relevant questions, and enhanced prognostication of outcome and invasive intervention need.

Furosemide Stress Test and Prognostication

Along the course of care of patients with AKI, some will progress to KGIGO stage 3 while others will present at that stage. Prognostication regarding the likelihood of renal recovery to at least manage salt, water, and metabolite clearance remains challenging. However, a reasonably reliable assessment may accrue from administering a furosemide stress test (FST). In critically ill patients with AKI regardless of etiology, an intravenous dose of furosemide is administered at 1 mg/kg bw (furosemide naïve) or 1.5 mg/kg bw (furosemide non-naïve) to differentiate responders (increased Uop) from nonresponders. Those who respond may be managed without employing renal support techniques and are less likely to progress to AKI stage 3, while nonresponders appear to have a higher likelihood of stage progression. Although renal support techniques may be initiated earlier, there was no mortality benefit despite the intuitively anticipated management benefits related to fluid overload, as well as ventilator management with extravascular lung water reduction and acidosis management. A key benefit of the FST is that the test is objective, leverages current patient level physiology and dynamics, and is unique from typical CKD indicators of the need for dialysis support. While many of the management modalities fall within the purview of the surgeon or intensivist, some management modalities such as dialysis generally require specialist consultation based upon facility privileging.

Renal Replacement Therapy (Renal Support Therapy)

Extracorporeal techniques that can temporarily replace some of the usual renal functions—generally salt, water, and solute clearance—are colloquially termed *renal replacement therapy* (RRT). They may be more properly termed *renal support therapy* (RST) because they do not replace any other renal dynamics (see Fig. 1). Regardless of terminology, there are several main approaches to RRT/RST in the patient with AKI: intermittent, hybrid, prolonged intermittent, and continuous, which may be collectively termed *kidney replacement therapy* (KRT) (Fig. 10). Note is made of peritoneal dialysis (PD) that performs best in the outpatient setting, as it is less well suited to achieve ideal clearance of metabolic solute related to the hypermetabolism of critical illness. Nonetheless, PD may play an important role in LMIC where access to other modalities is limited or nonexistent. It is germane to understand the different modes of dialysis that may be applied to surgical patients.

Solute clearance may be achieved through diffusion or convection, individually or in combination. Small molecule removal (size <1 kDa) is best achieved through diffusion, which leverages a concentration gradient across a semipermeable membrane. Convection, based on ultrafiltration, is ideal for water and molecule removal with sizes up to 50 kDa. The high-flow process of ultrafiltration is useful to correct fluid overload, as well as acute therapeutic agent overdose or life-threatening electrolyte disturbances.

Hemodialysis uses diffusive clearance on an intermittent schedule, typically for 4 to 6 hours per session, with three to four "sessions" per week. Blood and solution flow in opposite directions, creating a concentration gradient that facilitates diffusion across the semipermeable dialysis membrane. Hemofiltration is a related concept that uses hydrostatic pressure gradients to create solvent drag via friction, which in turn promotes convective clearance. During hemofiltration, no dialysis solution is used; instead, replacement fluid is used to replete cleared solutes. In hemofiltration, increasing the ultrafiltration (or effluent) flow rate will increase solute clearance. Hemodiafiltration, as the name implies, uses both diffusive and convective clearance. During hemodialysis, solute clearance is increased by increasing either the blood or dialysate flow rate.

A middle ground exists between intermittent and continuous RST techniques, deemed prolonged intermittent RRT (PIRRT), of which slow low-efficiency dialysis is a subtype. As the name would suggest, this type of dialysis uses a slower rate (and, in turn, longer treatment time) and typically occurs over 16 to 18 hours (every other day or daily). PIRRT creates more gradual changes in volume and solutes than IHD and is therefore better tolerated with regard to hemodynamics than shorter and more rapid dialysis approaches. PIRRT when prescribed on a daily basis more closely resembles continuous techniques in terms of solute, volume, and therapeutic agent clearance.

Continuous RRT (CRRT) modalities are performed 24 hours a day. The continuous modalities are also better tolerated by patients who require hemodynamic support including vasopressor or inotropic agent infusion. CRRT modalities include both venous and arterial cannulations approaches. Continuous arteriovenous hemodialysis,

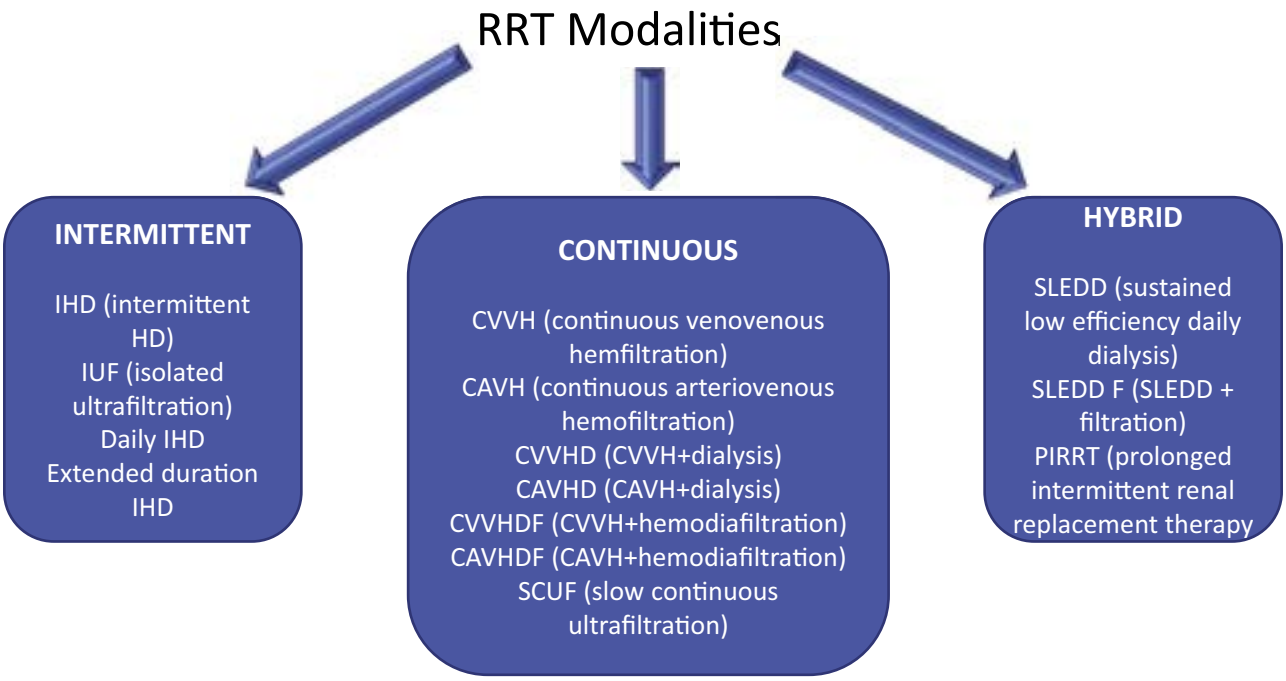


FIG. 10 Major modes of renal support therapies.

however, is not commonly utilized because of bleeding complications surrounding arterial cannulation. The venovenous approach accounts for the bulk of continuous RST modalities, including continuous venovenous hemofiltration dialysis, continuous venovenous hemofiltration, and continuous venovenous hemodiafiltration. These CRRT modalities apply the same concepts as described for their respective intermittent hemodialysis (IHD) counterparts in a treatment setting that can be run 24 hours per day at the bedside. The selection of modality is influenced by the target molecule identified for clearance, similar to IHD. Notably, continuous venovenous hemofiltration may be preferable for the clearance of immunomodulators in the setting of inflammation, an approach termed *blood purification*, which has been best explored for those with sepsis or septic shock. Additionally, a constant GFR is achieved with CRRT, enabling therapeutic agent dosing precision and predictable clearance of solutes that accompany nutritional support regimens.

At present, those who are able to maintain an appropriate hemodynamic profile can be managed using one of the intermittent techniques, while those with unstable hemodynamics—such as those who require continuous vasopressor infusion—are more appropriately managed using one of the continuous techniques. Regardless of mode, the support technique should address both solute and volume control. Anticoagulation is often required to prevent filter clotting when using continuous techniques and may be achieved using systemic or regional heparin as well as regional citrate anticoagulation. Operative concerns regarding systemic heparin may help guide the approach selected and should occur in concert with the team managing the dialysis technology and goals.

A host of studies have explored issues of timing of initiation, mode to management, and intensity of management for the critically ill or injured. No large, prospective, randomized, controlled trial demonstrates mode superiority. Some trials favor early initiation, and others



FIG. 11 Recovery after AKI. This graphic defines time frames for acute kidney injury *(AKI)*, acute kidney disease *(AKD)* as well as chronic kidney disease *(CKD)*. Moreover, time frames for early and late recovery are also indicated. *(From Forni LG, Darmon M, Ostermann M, et al. Renal recovery after acute kidney injury.* Intensive Care Med. *2017;43:855–66.)*

demonstrate no benefit. Moreover, some intensity-of-therapy trials demonstrate untoward effects from increased dialysis dose. Others reveal no impact on mortality regardless of dose. Accordingly, major decisions regarding mode often hinge on the hemodynamic appropriateness and tolerance of a given mode.

Indications

Common indications for acute dialysis in the critically ill or injured include severe acidemia, fluid overload not amenable to diuretic therapy, uremia, and impending acute respiratory failure. Other common uses include dialysis of toxins and medication overdose. Nonetheless, classic outpatient dialysis cues may not meet acute care needs. Moreover, the evolution of biomarkers to guide decision making—including dialysis initiation—continues to develop. However, tying initiation to a mortality benefit seems inappropriate, as the benefits of both volume and solute control to facilitate care have not been studied as robustly as the mortality endpoint. Furthermore, the emerging discipline of critical care nephrology will undoubtedly impact how future indications are articulated.

RECOVERY AND OUTCOMES AFTER AKI

Mortality is a commonly studied endpoint following AKI and averages about 23%. After discharge in the United States, Medicare beneficiary 90-day mortality reaches 35% in those with AKI, which is more than double that of their non-AKI counterparts. Because AKI affects cardiovascular health, it is not surprising that the most common cause of death is cardiovascular in these patients. However, AKI survivorship also engenders an increased risk of renal malignancy, putatively related to DNA injury and subsequent clonal expansion of abnormal cells during cell repair. Moreover, there is a global increase in cardiovascular disease, hypertension, and stroke that accompany AKI survivorship. Of course, there is also a risk of failing to recover baseline renal function as well as progression to CKD with or without requiring kidney replacement therapy. Furthermore, recovery may be assessed as early as within 7 days of AKI or as late as 7 to 90 days post-AKI; failure of recovery after 90 days may be categorized as CKD (Fig. 11). Accordingly, patients who develop AKI during an acute inpatient stay should also have rapid postdischarge follow-up and evaluation by a nephrologist.

The progression to CKD driven by permanent nephron loss as well as pericyte infiltration and fibrosis drives increased cost, decreased quality of life, dietary modification, and—for those who require dialysis—vascular access, vascular emergencies, infection, hospitalizations, and lifestyle alteration based on dialysis requirements. It is in this space that fluid overload, especially in the context of hypertension or hypotension, also exerts untoward effects on survival. Note is made of behavioral changes that may also accompany chronic dialysis, as well as potential rescue from chronic dialysis using renal allotransplantation—a modality that remains more limited than desired based on donor organ availability and donor risk variables.

CONCLUSION

AKI is a heterogenous syndrome that is common in surgical patients spanning subclinical AKI to three sequential stages. A variety of triggers that flow from a larger group of clinical entities helps frame AKI to direct clinical inquiry and care. Understanding the underpinning pathophysiology is essential in enabling earlier recognition and treatment to limit cell damage and preserve viable nephrons. Biomarkers of cell stress and injury have helped discover AKI subphenotypes that better enable clinicians to align care, especially in the ICU. Although prevention is ideal, it is not always feasible. When AKI occurs, careful assessment and treatment of the underlying cause is required and complements AKI stage-based management approaches. AKI stage 3 often benefits from a renal support technique to address volume and solute bioburdens while awaiting renal recovery. Recovery is variable during the acute hospitalization, and AKI exerts untoward impact after discharge as well. Therefore, careful and planned follow-up is essential to assess the degree of renal recovery or to identify progression to CKD. A collaborative approach between the surgeon, nephrology consultant, and the intensivist when critical care is required supports a team-based approach to this common and complex condition.

Suggested Readings

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Acid-Base Disorders

Zachary Obinna Enumah, MD, PhD, MA, and James E. Harris Jr., MD

Numerous theories have been proposed to understand the structure and function of acids and bases dating back to the nineteenth century with the work of Svante Arrhenius—hence the definition of Arrhenius acids and bases. It is important to understand the nature of acid and base terminologies that have been proposed over the years including the Arrhenius definition, the Bronsted-Lowry definition, and the Lewis definition (Table 1). In short, acids are often seen as hydrogen ion (H^+) donors and bases are H^+ acceptors. What must not be overlooked is that an understanding of acid-base physiology is vital to the practicing surgeon.

Acid-base physiology is tightly regulated in the human body. Two primary mechanisms of regulation occur at the level of the respiratory system and the level of the renal system with an interplay between the two. Each system works to achieve homeostasis of acid-base physiology to maintain pH in a narrow range. Departures from this range can have significant implications for enzyme and protein activities and other bodily functions.

TABLE 1 Acid and Base Definitions

Name	Definition
Arrhenius	Acid: Produces H^+ in solution Base: Produces OH^- in solution
Bronsted-Lowry	Acid: H^+ donor Base: H^+ acceptor
Lewis	Acid: Electron pair acceptor Base: Electron pair donor

HOMEOSTASIS AND BUFFERING SYSTEMS

The human body has multiple mechanisms and processes through which it maintains this delicate balance of pH in both intracellular and extracellular processes. Intracellular processes make up the majority of buffering capacity and is primarily driven by phosphate and protein processes, except in red blood cells where hemoglobin is the main buffer. Extracellular processes are primarily through bicarbonate buffering that can occur at the level of the respiratory system or the renal system. Plasma proteins (e.g., albumin) also contribute to buffering.

Respiratory System

The respiratory system regulates human body pH through changes in ventilation, and this can have an effect typically within minutes to hours. Hydrogen ions act directly at the level of the medulla oblongata and will subsequently cause an increase or decrease in respiration (and alveolar ventilation) in response to CO_2 changes. Alveolar ventilation is inversely proportional to changes in H^+. As the pH decreases, alveolar ventilation will increase, thus removing acid in the form of CO_2 as a result of the bicarbonate buffer system: $H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3$-. Le Chatelier's principle predicts that as CO_2 is removed, the concentration of H^+ will subsequently also decrease to reestablish equilibrium. Conversely, as the pH increases, alveolar ventilation will decrease.

Renal System

Kidneys may regulate acid-base homeostasis in a complex process by regulating rate of H^+ secretion and HCO_3^- filtration. This process takes longer than the respiratory buffering process and is usually on the order of hours to days. The respiratory and renal systems work in conjunction with one another to maintain acid-base homeostasis and respond to acid-base disorders.

ACID-BASE DISORDERS

Disorders of the acid-base system occur when the tight balance described earlier is altered or lost. Usually this is due to an underlying disease process. That is, acidemia (defined as pH <7.35) and alkalosis, also known as alkalemia, (defined as pH >7.45) are markers of underlying pathology as opposed to the pathology itself. Acidosis occurs when a primary process produces a net increase in hydrogen ions and thus a decrease in serum pH. Alkalosis occurs when a primary process produces a net decrease in hydrogen ions and thus an increase in serum pH. Alterations in acidbase balance can occur rapidly or over a period of time. For example, the management of acute traumatic brain injury classically involved intentionally hyperventilating the patient to lower the $PaCO_2$ (inducing a respiratory alkalosis) and thus cause cerebral vasoconstriction. This treatment could occur within minutes. Alternatively, other acid-base disturbances such as that seen with chronic obstructive pulmonary disease may occur over time. In this setting, elevated CO_2 levels in patients shift the normal acid-base equilibrium over time to being more acidotic.

There are both benefits and detriments to acidemia and alkalosis. Acute benefits to acidosis include improved dissociation of oxygen from the oxygen hemoglobin association curve and augmentation of cardiac output. Eventually, though, deleterious effects abound, such as having a negative effect on catecholamines and decreased cardiac contractility. Alkalosis may be associated with electrolyte derangements and can lead to arrhythmias.

APPROACH TO BLOOD GAS INTERPRETATION

The ability to quickly and accurately diagnose acid base disorders is essential in the intraoperative and postoperative periods. Arterial blood gas (ABG) is the most common tool, providing the clinician with results typically within minutes. Direct values obtained from an ABG include the pH, $PaCO_2$, and PaO_2. The HCO_3^- concentration is calculated using the Henderson-Hasselbalch equation, and the base excess (or deficit) is also a calculated value. Various approaches exist to calculate the base deficit. See "Base Deficit" later in this chapter.

Typically, interpretation of the blood gas follows a systematic approach beginning with direct interpretation of the values while simultaneously understanding that compensatory mechanisms are often at play (Table 2).

STEPS TO ARTERIAL BLOOD GAS INTERPRETATION

1. Evaluate the pH. The pH will provide a global understanding of the patient's acid-base balance. A pH less than 7.35 represents acidemia. A pH greater than 7.45 represents alkalosis.
2. Evaluate the $PaCO_2$. In respiratory processes, the $PaCO_2$ changes in the opposite direction of the pH. In metabolic processes, the $PaCO_2$ typically changes in the same direction. When compensation is occurring, the pH may be closer to normal or normal as a result of the compensatory mechanisms.
3. Evaluate HCO_3^-. Bicarbonate is reduced in metabolic acidosis, and it is increased in metabolic alkalosis.
4. Measure the base excess. Base excess is defined as the amount of base needed to titrate 1L of blood to a pH of 7.4 at 37°C. Values of greater than 4 or less than −4 are abnormal. A positive value for base excess indicates alkalosis, and a negative value, also known as a base deficit, indicates acidosis. Importantly, the base excess represents the metabolic component of acid base disorders and is a useful tool for blood gas interpretation (Fig. 1).
5. Remember to evaluate the PO_2. Hypoxemia and other pulmonary disorders may be a cause or stimulus of an acid-base disorder. Hypoxemia may exist concurrently with acidosis and/or alkalosis and should not be overlooked.

TABLE 2 Normal Arterial Blood Gas Values and Serum Bicarbonate

Variable	Normal Value	Range
pH	7.40	7.35 to 7.45
$PaCO_2$	40 mm Hg	38–42 mm Hg
PO_2	100	75–100
HCO_3^-	24 mEq/L	22–26 mEq/L

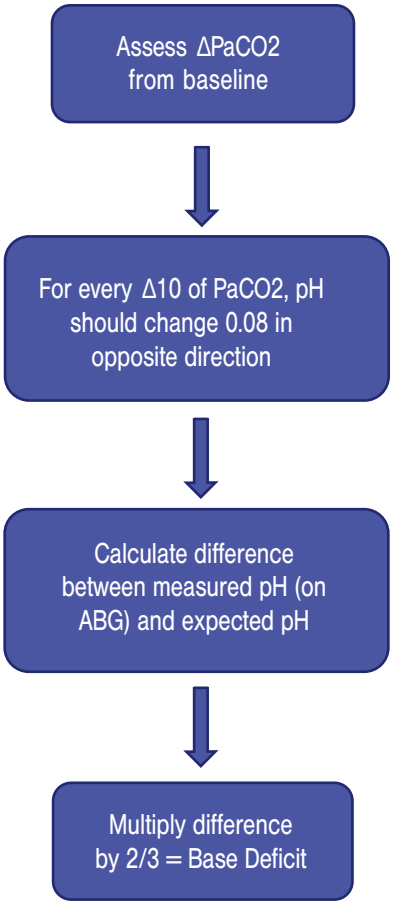


FIG. 1 Calculating base deficit.

TABLE 3 Compensation Calculations for Primary Acid-Base Disorders

Disorder	Calculation for Compensation
Metabolic acidosis	$PaCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$ (Winter's Formula)
Metabolic alkalosis	$PaCO_2 = 0.7 \times [HCO_3^-] + 20 \pm 5$
Acute respiratory acidosis	$\uparrow HCO_3^- = \Delta PaCO_2/10$
Chronic respiratory acidosis	$\uparrow HCO_3^- = 4 \times (\Delta PaCO_2/10)$
Acute respiratory alkalosis	$\downarrow HCO_3^- = 2 \times (\Delta PaCO_2/10)$
Chronic respiratory alkalosis	$\downarrow HCO_3^- = 4 \times (\Delta PaCO_2/10)$

6. Evaluate for presence of mixed acid-base disorders. The presence of a mixed acid-base picture can be determined based on expected versus observed changes in $PaCO_2$ and HCO_3^- ideally obtained from a concomitant chemistry panel. Recall that the HCO_3^- on the ABG is a calculated value and not observed. See "Mixed Acid-Base Disorders" later and Table 3.

Commonly, acid-base disorders are grouped into four general areas, and management is particular to the underlying disorder or disorders: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis.

METABOLIC ACIDOSIS

The most common acid-base disorder in the perioperative period is a metabolic acidosis occurring when the serum bicarbonate, HCO_3^-, is less than 22. The underlying cause can be determined by considering a broad differential diagnosis that breaks down potential causes into those that cause an anion gap and those that do not cause an anion gap. The anion gap is the difference between the primarily measured cations (Na^+ and K^+) and the primarily measured anions (Cl^- and HCO_3^-):

$$\text{Anion Gap (AG)} = (Na^+ \text{ and } K^+) - (Cl^- \text{ and } HCO_3^-)$$
$$\text{Units: Na, K, } Cl^-, HCO_3^- \text{ mEq/L}$$

A normal anion gap is less than 12. It is not zero because there may be other unmeasured cations (e.g., magnesium) and anions (e.g., proteins, phosphates, etc.). The differential diagnosis for a metabolic acidosis can be approached using the anion gap.

Anion Gap Metabolic Acidosis

The classic teaching for approaching anion gap metabolic acidosis is to use the MUDPILES approach (Box 1). Common causes in the perioperative period include lactic acidosis, ketoacidosis, and renal failure or insufficiency leading to uremia. In some cases, the MUDPILES mnemonic fails to provide an adequate reason for a patient's metabolic acidosis, which may indicate toxic ingestion. This is not to suggest that toxic ingestion is always the underlying reason, though, as a mixed picture could be present. Nevertheless, a calculation of the osmol gap should be performed using Equation 2. The osmol gap represents unmeasured solute in the blood and is the difference between measured and calculated osmolality. If the osmol gap is high, this suggests significant unmeasured solute in the blood, such as toxic agents.

$$\text{Osmol gap} = \text{Measured osmolality} - \text{Calculated osmolality}$$
$$\text{Calculated osmolality} = 2[Na^+] + \text{BUN}/2.8 + \text{glucose}/18 + \text{ethanol}/4.6$$
$$\text{Units: } Na^+\text{: mEq/L; BUN, glucose, ethanol: mg/dL}$$

Treatment should focus on correcting the underlying cause of the acidosis as opposed to the acidosis itself. For severe acidosis (e.g., pH <7.15), using adjuncts such as exogenous bicarbonate administration may be useful in the transient setting to potentially improve vasopressor activity, provide a high sodium (volume) load, or improve other protein function. Nevertheless, bicarbonate administration does not address the underlying cause of the acidosis, and treatment should be directed at the underlying reason (e.g., treatment of sepsis, removal of toxins, dialysis for renal failure).

Base Deficit

As described earlier, base deficit is a useful tool in understanding a patient's acid-base state. Over the years, it has proved useful as a marker of underlying disease and a means to trend improvement in a patient's acid-base status. It has also been useful in understanding the degree to which a patient is ill, as it has been shown to be associated with mortality in multiple studies. Numerous tools exist to calculate a base deficit, and it is a calculated value provided with an ABG. The practicing surgeon, though, should be aware of other quick modes of calculating the base deficit. In our institution, we use the approach described in Figure 1. The base deficit can then also be used to determine the bicarbonate deficit, which is described in Equation 3, to guide treatment.

$$\text{Bicarbonate deficit (mEq } HCO_3^-) = 1/3 \times \text{body weight (kg)} \times \text{base deficit}$$

BOX 1 Causes of Anion Gap Metabolic Acidosis

M	Methanol, muscle injury (rhabdomyolysis), metformin
U	Uremia (renal insufficiency/failure)
D	Diabetic ketoacidosis, other ketoacidosis (e.g., alcoholic, starvation)
P	Propylene glycol, paraldehyde
I	Isoniazid, iron
L	Lactic acidosis
E	Ethanol, ethylene glycol (antifreeze)
S	Salicylates, short gut

Nonanion Gap Metabolic Acidosis

When the anion gap is normal, this often suggests loss of bicarbonate or an increase in chloride concentration. Loss of bicarbonate can occur through gastrointestinal, renal, or exogenous mechanisms. Examples include excessive diarrhea, gastrointestinal fistulas, excessive nasogastric or nasoenteral suctioning, renal tubular acidosis, or exogenous administration of normal saline. Human blood has a normal concentration of Na^+ 140 mEq and Cl^- of 100 mEq. Normal saline is 1:1 of Na:Cl and has a concentration of 154 mEq of each. Thus, excessive administration of normal saline will lead to a hyperchloremic metabolic acidosis because as the chloride concentration increases in the serum, bicarbonate is displaced intracellularly. Similarly, as bicarbonate is lost, chloride can replace it to maintain a normal anion gap without necessarily correcting the underlying cause of the acidosis (e.g., excessive diarrhea).

Treatment focuses on correcting the underlying cause of the acidosis such as diarrhea, ceasing chronic laxative use, addressing underlying gastrointestinal fistulas, or other GI losses. For patients with renal impairment or failure, dialysis may be indicated.

METABOLIC ALKALOSIS

Metabolic alkalosis occurs when the serum bicarbonate is greater than 26 mEq/L. It is very common among hospitalized patients. The manifestation of a metabolic alkalosis can be broadly caused by any condition either causing a decrease or excretion of H^+ or an increase in or impaired excretion of serum bicarbonate. For surgical patients, this commonly occurs from GI losses such as vomiting or nasogastric suctioning (e.g., hypochloremic hypokalemic metabolic alkalosis with pyloric stenosis in the pediatric population) or with diuretic therapy. For hypovolemic patients, resorption of bicarbonate and sodium in exchange for hydrogen ions will cause a metabolic alkalosis.

Treatment should focus on treating the underlying cause of the alkalosis, which may involve judicious fluid resuscitation or cessation of diuretics. For those patients who have acute chloride loss-induced metabolic alkalosis, these patients can receive chloride in the form of normal saline, as an example, in addition to potassium supplementation.

RESPIRATORY ACIDOSIS

Inadequate CO_2 clearance or overproduction can lead to a respiratory acidosis, which is observed when the $PaCO_2$ is >40 mm Hg. It can be caused by pulmonary or nonpulmonary pathologies, such as stroke, trauma, medications (e.g., sedatives), neuromuscular paralysis (e.g., anesthesia or hypophosphatemia), or airway obstruction. Chronic respiratory acidosis can result from chronic pulmonary disease (e.g., chronic obstructive pulmonary disease) or neuromuscular disorders. The clinician should be mindful of overcorrecting a patient whose baseline $PaCO_2$ is higher than normal, as this may lead to cerebral ischemia or a false sense of "normal" that makes weaning from the ventilator difficult.

Ventilators can be adjusted to correct respiratory acidosis, usually by increasing the minute ventilation, which is calculated by multiplying the tidal volume by the respiratory rate. Other treatment should be directed at the underlying cause (e.g., reversal agents for drugs, therapeutic bronchoscopy for mucus plugging causing airway obstruction).

Noninvasive ventilation is an important adjunct in treating respiratory acidosis, commonly in patients with COPD exacerbations or underlying heart failure. Importantly, though, if improvement is not seen after 2 hours, one should have a low threshold to pursue invasive ventilatory support so as not delay appropriate supportive care. In the most extreme cases, venovenous extracorporeal membrane oxygenation (VV-ECMO) can be used as a salvage modality in patients who have persistent severe respiratory failure leading to acidosis and severe hypercarbia, as has been seen in the COVID-19 population.

RESPIRATORY ALKALOSIS

Respiratory alkalosis can be acute or chronic and is seen when the $PaCO_2$ is less than 40 mm Hg. It occurs when the rate of CO_2 elimination exceeds production and can be seen in the setting of pain, agitation, fever, sepsis, brain tumors, or underlying pulmonary pathology leading to an increased respiratory rate (e.g., pneumothorax, pulmonary embolism, pneumonia). Classically, while salicylate toxicity can lead to an anion gap metabolic acidosis, it first causes respiratory alkalosis. Chronic respiratory alkalosis is commonly seen in pregnancy, heart failure, liver failure, or high-altitude settings.

Treatment is directed at the underlying cause such as treating gram-negative sepsis, pain, agitation, or an underlying pulmonary pathology as described above. Importantly, inducing an acute respiratory alkalosis on a ventilated patient can be utilized in the treatment of an otherwise acidotic patient or traumatic brain injury patient as temporary adjuncts.

MIXED ACID-BASE DISORDERS

Acid-base disturbances are dynamic and compensatory. It is not uncommon to observe both expected compensation but also concomitant metabolic and respiratory acid-base disturbances. For example, a patient may present with inadequate ventilation and poor perfusion leading to both respiratory acidosis and metabolic acidosis secondary to lactemia. Table 3 describes expected compensation depending on the suspected primary acid-base disturbance. If the calculated value differs from the expected, a secondary acid-base disturbance is present.

SUGGESTED READINGS

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Catheter Sepsis in the Intensive Care Unit

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INTRODUCTION

The Centers for Disease Control and Prevention (CDC) estimates that in the United States, 3% of hospitalized patients will develop a healthcare-associated infection (HAI). HAIs have profound clinical and economic consequences for patients and hospitals. In 2016, the economic burden of surgical site infections, ventilator-associated events, catheter-associated urinary tract infections, *Clostridium difficile* infections, and central line-associated bloodstream infections (CLABSI) ranged from $7.2 billion to $14.9 billion. CLABSI accounted for 7% of infections and 14% of the attributable cost. In a recent meta-analysis, CLABSI is associated with a significantly increased risk of death with an odds ratio of 2.75.

Intravascular catheters are critical to providing today's health care and include an assortment of devices that range from peripheral venous catheters, peripherally inserted central catheters (PICCs), tunneled and nontunneled central venous catheters (CVCs), and indwelling devices such as ports. In the ICU, catheter-related bloodstream infections (CRBSI) are predominantly related to central venous catheters. In 2019, 18,009 central line-associated bloodstream infections were reported by 3602 general acute care hospitals in the United States.

Since 2008, CLABSI is recognized by the Centers for Medicare & Medicaid Services (CMS) as a preventable HAI; therefore, CMS no longer provides reimbursement to healthcare institutions for this complication. This spurred significant improvement in reducing the national incidence, improving patient care and outcomes. There was a 46% decrease in CLABSIs nationally from 2008 to 2013 and in the most recent CDC report, a 7% decrease from 2018 to 2019. This has been largely driven by implementation of standardized clinical practice guidelines, including evidence-based care bundles for proper placement and maintenance of CVCs.

Unfortunately, the coronavirus pandemic appears to have affected the incidence of CLABSI. From 2015 to 2019, there was a 31% decline in the national standardized infection ratio (SIR) for CLABSI, but in comparison of data from 2019 to 2020, there was a 28% increase in the SIR. This is suspected to be a result of the high-volume, high-acuity care for patients with COVID-19 that has posed increased challenges for preventing device-related infections when staffing and resources are limited.

This chapter will outline the surveillance, diagnosis, treatment, and prevention strategies involved in the management of ICU patients with bloodstream infections.

SURVEILLANCE DEFINITIONS

CRBSI and CLABSI

CRBSI and CLABSI are the two major terms used to define bloodstream infections due to the use of vascular catheters; they are often used interchangeably but have important differences. CRBSI is a clinical definition used when diagnosing and treating patients. A CRBSI requires specific laboratory testing to identify the catheter as the source of the bloodstream infection, such as a catheter tip culture, quantitative blood cultures, or a differential time to positivity of blood cultures, and other sources of infection must be ruled out. CRBSIs include those associated with both peripheral intravascular catheters and CVCs.

CLABSI is a standardized surveillance definition and is not synonymous with a CRBSI. Infection surveillance data are used to measure success of infection prevention and control programs, to identify areas for improvement, and to meet public reporting mandates and pay for performance goals. The CDC defines CLABSI as a laboratory-confirmed bloodstream infection that occurs in a patient with a CVC in place for at least 48 hours before the onset of the infection and is not related to an infection at another site. Because some bloodstream infections are secondary to sources other than the central line, the CLABSI surveillance definition may overestimate the true incidence of CRBSI.

Incidence and Monitoring

Whether it is for monitoring a single intensive care unit, between units, or between hospitals, there are several methodologies for comparison of CLABSIs. Historically, the CLABSI rate was expressed as an individual unit's rate per 1000 central line days; however, this rate cannot reflect differences in risk between populations. Therefore, the SIR was introduced as a summary measure to track CLABSIs at a national, state, or local level over time. The SIR is the ratio of the observed number of CLABSIs to the expected number of CLABSIs. The expected or predicted number of infections is calculated based on data from the National Health and Safety Network (NHSN) and are adjusted by type of patient care location, hospital affiliations with a medical school, and bed size of the location. An SIR of 1.0 indicates that the number of CLABSIs observed is consistent with what is predicted based upon the patient population. If the SIR is greater than 1.0, there are more CLABSIs than expected, and if the SIR is less than 1.0, fewer CLABSIs occurred than expected. A central line standardized utilization ratio (SUR) is a summary measure used to track central line use at a national, state, local, or facility level over time. The SUR compares the actual number of central line days reported compared with NHSN benchmark usage rates for like units. An SUR greater than 1.0 indicates that more central line days were observed than predicted, and conversely, an SUR less than 1.0 indicates that fewer central line days were observed than predicted.

INFECTION

Pathogenesis

There are a variety of mechanisms by which microbes can access and infect a vascular catheter: skin colonization, intraluminal or hub contamination, hematogenous seeding from a distant infection, or contaminated infusions (Fig. 1). The dermis is the most common source of contamination for most nontunneled short-term catheters. Longer-term temporary catheters and subcutaneously tunneled catheters often become inoculated at the hub and luminal catheter surfaces. Importantly, once microbes gain access to the catheter surface, biofilms develop that become difficult to eradicate without catheter removal.

Diagnosis

Possible CRBSI should be suspected in any patient with a CVC who exhibits signs or symptoms of infection without other apparent cause. Systemic signs of infection such as hypotension, tachycardia, tachypnea, evidence of decreased end organ perfusion, lactic acidemia, and altered mental status should suggest the possibility of sepsis or septic shock, and prompt treatment should follow standard guidelines.

If a patient is suspected to have a CRBSI, the catheter site must be inspected for erythema, purulent discharge or abscess, tenderness, and catheter integrity. The patient should also be evaluated for possible septic thrombophlebitis, endocarditis, and metastatic

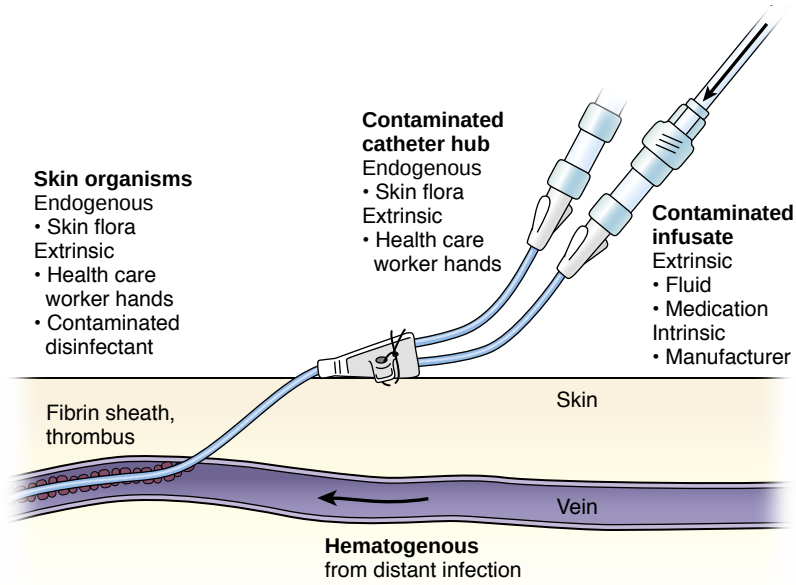


FIG. 1 Routes for central venous catheter contamination with microorganisms. *(Modified from Cmich CJ, Maki DG. The promise of novel technology for the prevention of intravascular device-related bloodstream infection. I. Pathogenesis and short-term devices.* Clin Infect Dis. *2002;34:1232–1242.)*

musculoskeletal infection. If there are implanted electronic devices, vascular grafts, or orthopedic hardware, these should also be considered a possible infectious source.

Two sets of peripheral venous blood cultures obtained from separate venipuncture sites should be drawn before starting antibiotic therapy. If two peripheral blood cultures cannot be obtained, one sample may be obtained from the catheter. However, there is a higher likelihood of contamination from skin flora when drawing blood from the catheter. Use of a dedicated phlebotomy team has been shown to lower blood culture contamination rates.

If there is high suspicion for CRBSI, the CVC should be removed as soon as safely possible. If a patient is clinically stable, antibiotic treatment may be delayed while awaiting culture results. Any patient with hemodynamic instability should have empiric antibiotic therapy instituted after blood cultures have been obtained.

The 2009 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines suggest the following methods to definitively diagnose CRBSI:

1. Growth of the same organism from at least one peripheral blood culture and from a culture of the catheter tip
2. A threefold difference in microbial colony count in blood drawn from the catheter compared to blood drawn from a peripheral vein
3. Growth of microbes in blood drawn from a catheter at least 2 hours before microbial growth is detected from a peripheral blood sample drawn at the same time (differential time to positivity)
4. If unable to obtain catheter segment culture or peripheral blood cultures, suspected CRBSI can be diagnosed by quantitative blood cultures from two distinct catheter lumens with a minimum of a threefold colony count difference

Currently, definitive diagnosis of catheter involvement in a bloodstream infection is rarely sought because surveillance requires only that the catheter be present within 48 hours of the positive blood culture. The bloodstream infection will be managed based upon the severity of illness, organism, and number of positive blood cultures. Definitive involvement becomes important if the risk or difficulty in placing new central access outweighs removal and catheter salvage is considered.

MANAGEMENT

The management of CRBSI depends on multiple patient factors, including the microorganism isolated, the severity of patient condition, removal or retention of the catheter, and the presence of complications of catheter-associated infections such as endocarditis, suppurative thrombophlebitis, and widespread septic dissemination.

Antibiotic Selection

The most common organisms causing CRBSIs are *Staphylococcus aureus*, coagulase-negative *staphylococcus*, gram-negative bacilli ,and *Enterococcus* and *Candida* species. Empiric antibiotics should cover gram-positive organisms, and due to higher prevalence of methicillin-resistant *Staphylococcus aureus* and coagulase-negative *staphylococci*, vancomycin or daptomycin are recommended. Empiric coverage for gram-negative bacilli is indicated in patients with critical illness, neutropenia, femoral catheter use, or possible gram-negative bacilli infection; the selection of antimicrobial for gram-negative coverage should be based on local susceptibility patterns. Empiric fungal therapy should be considered in critically ill patients with protracted exposure to antibiotics, immunosuppression, recent gastrointestinal surgery, and total parenteral nutrition use. Therapy should be tailored based on culture results and patient condition.

Catheter Salvage versus Removal

All short-term catheters in patients with CRBSI should be removed if possible. All catheters, including long-term ports and indwelling catheters, should be removed in patients who have severe sepsis, complicated CRBSI (endocarditis or septic thrombophlebitis), and/or persistent bacteremia >72 hours despite appropriate antimicrobial therapy. Catheter removal is also indicated for patients who are infected with challenging organisms such as *S. aureus*, multi–drug-resistant gram-negative bacilli, mycobacteria, or fungi. In some patients, catheter removal is not possible or practical, and salvage may be attempted through use of antimicrobial lock therapy. In this instance, antimicrobial lock therapy can be attempted in conjunction with IV antimicrobial therapy for catheter salvage; it involves a highly concentrated antibiotic mixed with an anticoagulant and

infused into the catheter lumen and allowed to dwell in place for hours. When attempted, serial surveillance blood samples should be drawn every 24 hours until negative, and if the bloodstream infection persists beyond 72 hours of therapy with appropriate antibiotic therapy, then catheter removal should be performed. Recent studies show reduced failure rates with antimicrobial lock therapy in patients with long-term indwelling catheters.

INFECTION PREVENTION

Catheter Care Bundles

Evidence-based guidelines in the form of catheter care bundles have been developed over the past 15 years to steer prevention efforts. With their use, the CLABSI rates have consistently been reduced. Based on recommendations by the IDSA, CDC, and Joint Commission, the methodologies to prevent infection have focused on two broad areas of catheter care: insertion of new catheters and maintenance of existing catheters (see Tables 1 and 2). Overall, the critical importance of healthcare provider education regarding insertion and maintenance of CVCs cannot be overstated, as appropriate education and training are the cornerstones of CLABSI prevention.

Selection of Catheter Site

A variety of factors must be considered and individualized when selecting a CVC insertion site, including patient anatomy, complication risk, provider experience, expected duration of and plan for catheter use, infection risk, and possible need for dialysis. The insertion site should be away from nonintact skin (burned or infected skin) or with a risk of contamination (tracheostomy) whenever feasible and practical. Subclavian vein catheterization is associated with the lowest risk of CRBSI compared with femoral and internal jugular catheterization; however, the risk of developing a pneumothorax is greatest with subclavian vein insertion site, and one must consider the ability of the patient to tolerate a line placement complication. The internal jugular and femoral sites are more often preferred by providers due to ease of placement with ultrasound guidance. Depending upon body habitus, the internal jugular and femoral sites have similar risks of infection, but the femoral vein has

TABLE 1 Central Venous Catheter Insertion Bundle

Insertion Bundle Elements	Recommendations
Hand hygiene	Perform correct hand hygiene before and after each patient contact
Full patient barrier precautions	Use of maximal sterile barriers and aseptic technique including large sterile drape and sterile covers for equipment used during line insertion
Personal protective equipment	Use of sterile gown, sterile gloves, hat, and full face protection including mask and eye protection
Skin antisepsis	Aseptic technique maintained throughout CVC insertion Use of chlorhexidine skin antisepsis (or povidone-iodine for patients with chlorhexidine sensitivity)
Optimal catheter type selection	Select catheter with minimum number of ports necessary Aseptic lumen access Use antimicrobial impregnated catheter if likely prolonged duration of use (>7 days)
Optimal catheter site selection	Prioritize patient safety in evaluation risks/benefits of each site, including patient comfort and mobility, complication risks, infection risks, and operator experience
Ultrasound guidance	Use ultrasound guidance for placement of all central lines: internal jugular, femoral, subclavian and PICC lines
Sterile dressing	Apply sterile dressing immediately after placement
Safe disposal of sharps	Immediate disposal of sharps safely in accordance with local policy
Daily review of line necessity	Prompt removal of unnecessary CVCs
Healthcare personnel education	Routine education about CLABSI prevention
CVC insertion kits	Availability of CVC carts and kits with all necessary supplies
Insertion checklists	Provide checklists to ensure adherence to all proper evidence-based insertion practices
Evidence based practice adherence	Nonemergent procedures stopped if evidence-based practices are not followed
Review quality metrics and feedback	Feedback provided to healthcare providers regarding CLABSI/CRBSI episodes and overall unit/hospital CVC infection rates at routine intervals
Documentation	Details of CVC insertion clearly documented in records including insertion date, time, and inserting provider
Institutional investment	Obtain buy-in for CLABSI/CRBSI reduction initiatives from hospital leadership

CVC, Central venous catheter; *CLABSI*, central line-associated bloodstream infection; *CRBSI*, catheter-related bloodstream infection; *PICC*, peripheral inserted central catheter.

Adapted from The Joint Commission. Preventing Central Line–Associated Bloodstream Infections: Useful Tools, An International Perspective. Nov 20, 2013. Accessed August 23, 2021. http://www.jointcommission.org/CLABSIToolkit.

TABLE 2 Central Venous Catheter Maintenance Bundle

Maintenance Bundle Elements	Recommendations
Daily review of line necessity	Prompt removal of unnecessary CVCs with documentation
Accurate documentation	Details of CVC documented including location, date of insertion, duration, date of removal, any complications
Hand hygiene	Perform hand hygiene before IV system manipulation
Catheter injection ports	Cover open lumens with injection ports, sterile end-caps, or needleless connectors Access ports are appropriately sanitized before and after each use, "scrub the hub" protocol Caps are changed no more frequently than every 72 hours
Catheter site dressing monitoring	Change gauze dressing every 2 days, clear dressing every 7 days (or more often when soiled, damp, or loose)
Catheter access/manipulation	All access to central line with aseptic techniques Catheter site care with chlorhexidine at dressing changes (or povidone iodine) Ports/hubs cleaned with "scrub the hub" protocol before access
IV infusion set maintenance	Observe evidence-based institutional best practice guidelines
Infusate preparation	Use aseptic technique to prepare and transport infusate
Infusate administration	Prioritize infusions that require central venous access Minimize CVC use for infusions not needing central venous access
Personnel education	Standardize routine hands-on and competency-based training for all staff members manipulating CVCs

CVC, Central venous catheter; *IV*, intravenous.
Adapted from The Joint Commission. Preventing Central Line–Associated Bloodstream Infections: Useful Tools, An International Perspective. Nov 20, 2013. Accessed August 23, 2021. http://www.jointcommission.org/CLABSIToolkit.

a higher incidence of catheter-related deep vein thrombosis. Femoral vein cannulation is often chosen in emergency situations and in the face of coagulopathy because it is easily accessed and direct pressure can be applied to the site when necessary. The subclavian vein should be avoided in patients with kidney disease or who may require long-term dialysis because the risk of developing subclavian vein stenosis limits the outflow for future arteriovenous hemodialysis access. Catheters placed in situations where adherence to aseptic CVC insertion practices is not certain (such as emergent placement in the field or in a code situation) should be removed and replaced as soon as patient condition allows.

PICCs are widely used in patients who require intermediate and long-term access in outpatient and inpatient settings, as their use in these settings has shown a low infection rate profile of approximately 0.4 infections per 1000 catheter days. However, PICCs used in critically ill patients have a comparable rate of CRBSI when compared with conventional CVCs.

Catheter Selection

When a catheter is expected to be in place for a prolonged duration (>5 days), the use of an antiseptic- or antimicrobial-impregnated catheter can reduce infection risk and is recommended. A recent meta-analysis of chlorhexidine silver sulfadiazine or minocycline-rifampin impregnated catheters showed a reduction in CLABSI risk and CVC colonization, although there was no difference in sepsis or mortality.

Insertion

As in every patient encounter, proper hand hygiene must be practiced. Providers should also wear masks, eye protection, and caps for the protection of both the provider and patient. For insertion, maximum sterile barrier precautions should be employed including sterile gowns, gloves, and full draping. The skin should be disinfected using a chlorhexidine-alcohol solution, and the insertion site should be allowed to dry. For patients with chlorhexidine allergy or sensitivity, a tincture of iodine, an iodophor, or 70% alcohol can be used as an alternative. Aseptic sterile technique should be used throughout the procedure. The use of insertion checklists to ensure compliance with appropriate bedside insertion procedures can standardize the process and help reduce errors (Fig. 2).

Maintenance

The need for CVC should be assessed daily and removed when no longer necessary. The best way to prevent a CLABSI or a CRBSI is to not have a central line. Catheter dressings should be changed routinely as standardized maintenance of antimicrobial impregnated dressings reduces the rate of CRBSIs. Data support changing transparent dressings at weekly intervals and as needed for any soiled or leaking dressings. Proper hand hygiene should be used when accessing lines, changing the intravenous infusion tubing sets, or changing the dressing. There should be routine catheter hub and/or needleless connector disinfection with antiseptic solution. Appropriate IV administration tubing and set replacement should be changed based on the infusate, with set replacement after administration of parenteral nutrition every 24 hours and after every unit of blood product to minimize microbial growth.

SUMMARY

Catheter-associated bloodstream infections are a common clinical problem in the ICU that continue to have significant cost, morbidity, and mortality despite significant strides made over the past two decades in decreasing their incidence. Emphasis on standardized evidence-based insertion and management measures are the most effective prevention methods. Diagnosis and management of CRBSI relies on timely diagnosis, institution of early empiric treatment, catheter removal, and appropriate antimicrobial therapy.

Sample CVC Insertion Checklist

Patient's Name: _____

Medical Record Number: _____

Date of Insertion: _____

Site of insertion:
☐ Right ☐ Left ☐ IJ ☐ Subclavian ☐ Femoral

Pre-Procedure time out
- ☐ Identify patient
- ☐ Obtain informed consent
- ☐ Verify Side/site verified

Preparation
- ☐ Proceduralist and Assistants wear hat and mask, and perform hand hygiene
- ☐ Prep the site with Chloraprep (or Betadine if allergic)
- ☐ Proceduralist puts on sterile gown and sterile gloves
- ☐ Drape entire patient in a sterile fashion

Throughout the procedure:
- ☐ Maintain a sterile field
- ☐ Maintain aseptic technique
- ☐ Stop procedure if contamination of the sterile field CVC, or instruments occur

After the procedure:
- ☐ Attach caps or IV tubing to lumens before removing sterile drape
- ☐ Apply a sterile dressing
- ☐ Label dressing and IV tubing with date & time
- ☐ Remove drape and personal protective equipment
- ☐ Wash hands
- ☐ Dispose of all sharps in proper receptacles

FIG. 2 Sample central venous catheter insertion checklist. *CVC*, Central venous catheter; *IJ*, internal jugular; *IV*, intravenous.

Suggested Readings

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Septic Response and Management

Chris Cribari, MD, and Joel Elterman, MD

Sepsis continues to represent a significant challenge to healthcare providers both in the United States and throughout the world. Worldwide estimates report that sepsis contributes to 11 million deaths a year. Despite decades of research into sepsis and the establishment of best practices, the mortality rate for sepsis remains high, with rates increasing by severity of sepsis up to greater than 40%. Surgeons play an important role in the management of sepsis, both in the arena of critical care and in the management of the underlying causes.

DEFINITION

The first definitions for sepsis were developed by a consensus conference in 1991. These definitions have since been revised, once in 2001 and most recently by an international task force in 2016 resulting in The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Per the Sepsis-3 consensus, sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Box 1). Organ dysfunction is defined by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more (Table 1). Septic shock is defined as a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

BOX 1 Sepsis Definitions

- Sepsis: a life-threatening organ dysfunction caused by a dysregulated host response to infection
- Organ dysfunction: an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more
- Septic shock: a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia

TABLE 1 Sequential Organ Failure Assessment Score

	0	1	2	3	4
PaO_2/FiO_2 ratio	>400	301–400	<300	<200	<100
Platelets (xl0A3µL)	>150	101–150	51–100	21–50	<20
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6–11.9	>12
Mean arterial pressure (MAP)	MAP >70	MAP <70	Vasopressors	Vasopressors	Vasopressors
GCS	15	13–14	10–12	6–9	<6
Creatinine (mg/dL)	<1.2	1.2–1.9	2–3.4	3.5–4.9	>5

DIAGNOSIS

One of the significant challenges in the management of sepsis is identification and accurate diagnosis. Currently there is no single test that accurately predicts a diagnosis of sepsis. Traditionally, diagnosis was made by the findings of a systemic inflammatory response syndrome in the setting of infection. The systemic inflammatory response syndrome was considered when two or more of the following conditions existed: temperature >38°C or <36°C; heart rate >90 bpm; respiratory rate >20 or $PaCO_2$ <32; and a WBC >12,000 cells/mm^3 or <4000 cells/mm^3. A problem with using this criterion for the diagnosis of sepsis is that the systemic inflammatory response occurs in a number of noninfectious etiologies such as trauma, burns, and pancreatitis as well as a normal physiologic response to surgery. The diagnosis of sepsis requires a high index of suspicion and identification of a source of infection. The SOFA score is currently used to assist in the identification of organ dysfunction. The SOFA score includes the need for mechanical ventilation, FiO_2, PaO_2, GCS, serum creatinine, bilirubin, platelet count, and vasopressor support. Online calculators and smart phone apps are readily available to assist in the calculation of the patient's SOFA score. Additionally, a quick SOFA score has been developed to assist with screening that includes altered mental status, tachypnea, and hypotension. The presence of two conditions requires further consideration for the diagnosis of sepsis.

The use of serum biomarkers has also been studied in the diagnosis of sepsis. These include serum lactate, C-reactive protein (CRP), and procalcitonin (PCT). Lactic acid or lactate is a product of inadequate oxygen delivery and anaerobic metabolism, either as a result of inadequate tissue perfusion or hypoxia. It is included in the definition of sepsis as a marker of organ dysfunction and has been used to guide resuscitation in sepsis. However, there are noninfectious causes of an increased lactic acidosis, and the lactate can remain elevated if hepatic clearance is compromised. CRP is an acute phase protein released from the liver in response to inflammation and has also been used to identify infection. Although CRP is often elevated in sepsis, it has been shown to have a sensitivity of only 75% and a specificity of 67% when trying to differentiate between infectious and noninfectious causes of inflammation. Procalcitonin is the prohormone of calcitonin produced in the thyroid gland. Its regulation is affected by infection and has been proposed as a biomarker for sepsis. A meta-analysis has calculated the sensitivity of PCT for the identification of infection in sepsis to be 77% with a specificity of 79%. Although no single test has been identified to diagnose sepsis, these biomarkers have been used to evaluate response to treatment, and normalization has been associated with improved outcomes. Biomarkers are useful in identifying patients who are not responding to therapy because of inadequate antibiotics, bacterial resistance, or inadequate source control of infection. Therefore, serial measurements of these biomarkers should be considered to guide clinical decision making.

Accurate and timely identification of sepsis should start with a complete history, physical examination, and a high index of suspicion (Box 2). Imaging studies may be required to identify the source of infection. Cultures should be used to assist in the identification of infection as well as to guide antibiotic therapy. This should include blood, urine, and sputum, and may also include suspected sources such as peritoneal fluid, pleural fluid, or fluid from suspected abscesses as clinically appropriate. Obtaining culture data should be done before initiation of antibiotic therapy as able. This should be balanced with the risk of delaying the initiation of antibiotic therapy because we know that the timing of the initiation of antibiotic therapy affects outcomes.

BOX 2 Initial Approach to Suspected Sepsis

- Establish IV access
- Initiate infectious work-up
- Complete physical examination
- Obtain laboratory studies
  - CBC, BMP, LFT, ABG
  - Lactate, ±
  - Procalcitonin
  - Peripheral blood cultures × 2
- Targeted imaging
  - Chest x-ray, CT scan, ultrasound
- Fluid resuscitation
  - 30 mL/kg balanced crystalloid solution
- Vasopressor support
- Broad spectrum antibiotics
- Monitor response

Additional strategies to improve the early recognition of sepsis continue to be explored. Most recently, the use of artificial intelligence (AI) systems has been developed for this exact purpose. Researchers have developed AI algorithms to facilitate early detection and diagnosis, and studies in the literature purport an accuracy of up to 80%. Efforts to refine these algorithms are ongoing and may represent a significant improvement in our ability to detect and diagnose sepsis in the future.

TREATMENT

The basic principles of the management of sepsis have remained constant for decades. These include source control of the infection, restoration of end organ perfusion, and appropriate administration of antimicrobial therapy. In 2004, an international Surviving Sepsis Campaign published the first clinical practice guidelines for management of severe sepsis and septic shock. These guidelines were updated in 2008, 2012, and again in 2016, and they serve as an up-to-date reference for evidence-based practices. The recommendations have been included into a set of initial interventions and are referred to as sepsis "bundles." The bundle includes measuring lactate, obtaining blood cultures, initiation of broad-spectrum antibiotics, initial fluid resuscitation for patients with hypotension or a lactic acidosis, and initiation of vasopressor therapy for patients unresponsive to fluid

resuscitation. The initial goal was to complete the "bundle" within 3 hours of presentation, and some have advocated to complete the "bundle" in 1 hour as faster completion has been associated with lower in-hospital mortality. Criticism for completing the "bundle" in 1 hour for all patients who screen positive states that only a minority of patients who screen positive will obtain a confirmed diagnosis of sepsis. With this in mind, concern exists that some patients will be unnecessarily treated with antibiotics and the potential for overaggressive fluid resuscitation exists.

Fluid resuscitation should begin with a 30 mL/kg bolus of a balanced crystalloid solution for any patients with evidence of hypotension or an elevated lactate. The use of balanced crystalloid solutions has shown a decreased incidence of death, need for renal replacement therapy, or persistent real dysfunction when compared with normal saline. Colloid solutions such as albumin are not recommended in the initial resuscitation. Additionally, the use of hydroxyl ethyl starches in septic patients is associated with increased need for renal replacement therapy and should not be used in the resuscitation of septic patients. Following the initial resuscitation, ongoing fluid resuscitation should be guided by frequent reassessment of available hemodynamic variables and other endpoints of resuscitation. Fluid resuscitation beyond the initial resuscitation is critical as a sustained positive fluid balance in the ICU can have negative consequences.

Thorough initial assessment and frequent reevaluation is required during resuscitation. Sepsis and septic shock can exacerbate preexisting cardiac disease and may result in sepsis-related cardiac failure with both systolic and diastolic dysfunction (septic cardiomyopathy). It is important to discern the type of shock a patient may be experiencing (e.g., hypovolemic shock, distributive shock, cardiogenic shock vs. concurrent cardiogenic/septic shock) and subsequently choose the most appropriate treatment.

The variables for assessment of adequacy of resuscitation should include heart rate, blood pressure, urine output, and other dynamic variables to assess for fluid responsiveness. One of the simplest maneuvers is the passive leg raise. If the patient's systolic blood pressure increases within 60 seconds of raising the legs 45 degrees to a level above the heart, then they are likely to respond to further fluid resuscitation. This is more easily detected for patients with an intraarterial catheter and continuous blood pressure monitoring. If the patient is on mechanical ventilation, then pulse pressure variation (PPV) has also been associated with fluid responsiveness. During positive pressure ventilation, venous return can be decreased, resulting in a narrowing of the pulse pressure. Noninvasive monitors are available that can calculate the PPV. A PPV of >12% predicts fluid responsiveness, and a PPV <8% suggests euvolemia.

Additional noninvasive hemodynamic assessments include the use of bedside ultrasound. Variation in vena cava with respiration, ventricular size and function, and aortic flow variation can be assessed in real time on bedside point-of-care ultrasound. Additionally, the response to fluid challenge as well as with initiation of vasopressors and/or inotropes can be directly observed, providing a dynamic assessment of resuscitation. Echocardiography is useful to evaluate for cardiogenic shock and volume status as alternative causes for ongoing hypotension and to identify a need for inotropic support.

Following initial fluid resuscitation, patients with ongoing hypotension should be started on vasopressor support. The vasopressor of choice is norepinephrine with a goal mean arterial pressure (MAP) of 65 mm Hg. Vasopressin should not be used as first-line therapy. However, it has been suggested as an adjunct as it is associated with a decreased norepinephrine dose requirement and is thought to decrease sepsis-induced pulmonary inflammation. Dopamine has been shown to have increased rates of arrhythmias and should not be used routinely as a first-line vasopressor. In patients who demonstrate cardiac dysfunction, inotropic support may improve tissue perfusion. Dobutamine may be used in addition to norepinephrine in these select patients.

There has been research into maintaining a goal MAP of >85 mm Hg versus >65 mm Hg. Targeting a higher MAP was not associated with a mortality benefit; however, in patients with chronic systolic hypertension, it was associated with a lower incidence of organ failure and a decreased need for renal replacement therapy. The higher dose of vasopressors required to meet the MAP goal of 85 mm Hg was associated with increased arrhythmias, and this reinforces the point that treatment goals should be determined for each patient individually, but that a minimum baseline recommendation for a MAP goal of 65 mm Hg remains appropriate for most patients.

The next fundamental principle of the management of sepsis is the early administration of broad-spectrum antibiotics. The timing of antibiotics administration appears to be critically important as each hour delay in administration has been associated with an increase in mortality. Broad-spectrum coverage should include empiric treatment of gram-negative, gram-positive, and anaerobic organisms. The clinical history of the patient is essential in determining the appropriate empiric coverage as underlying diseases, chronic organ dysfunction, immunocompromise, and previous antibiotic exposure can be relevant in the selection of the appropriate agents. Moreover, indwelling medical devices and the underlying source of infection can also influence the choice of coverage. Antifungals should also be considered in certain high-risk situations. Once culture results are able to identify the organism and antibiotics sensitivities, therapy should be deescalated to limit the development of antibiotics resistance.

Source control represents the third crucial component in the management of sepsis. The importance of source control cannot be overstated, and many etiologies of sepsis cannot be managed without a surgeon. A focus on the rapid diagnosis of an infectious source that can be managed surgically must be a primary goal in the initial management of sepsis. Common infections that are amenable to surgical control include cholecystitis, cholangitis, intestinal ischemia, bowel perforation including perforated appendicitis, pyelonephritis with obstruction, abscess formation, necrotizing soft tissue infections, and bacterial contamination of any implanted medical device including catheters.

Guidelines from the surviving sepsis campaign recognize that despite adequate resuscitation and appropriate antibiotic therapy, severely ill patients will not stabilize or improve without adequate source control. Observation studies have demonstrated that when source control is achieved early, a lower mortality is seen even when adequate resuscitation and antimicrobial administration is delayed. Therefore, prolonged efforts at medical stabilization before source control are not advised. Paradoxically, patients who seem "too sick" to tolerate an operative intervention may in fact be "too sick" not to have an operative intervention. Clinical judgment as to the risks and benefits of surgical management in the setting of a critically ill patient will often fall on the surgeon. In general, the least invasive intervention that can adequately achieve source control should be exercised. If a patient does not improve clinically after intervention, it is imperative to evaluate if source control has been achieved. Patients may need reoperation if persistent source of infection has not been adequately addressed.

SUPPORTIVE TREATMENT ADJUNCTS

Ventilator Management

Patients with severe sepsis often require respiratory support with mechanical ventilation and are at higher risk for the development of acute respiratory distress syndrome (ARDS). Therefore, volume- and pressure-limited strategies of lung protective ventilation should be followed. Tidal volumes should be targeted at 6 mL/kg of ideal body weight, and respiratory acidosis can be safely tolerated as long as the pH is greater than 7.2. Higher positive end-expiratory pressure (PEEP) is recommended for patients who develop ARDS, whereas efforts to limit plateau pressures to less than 30 remains a strong recommendation.

The risk of ventilator-associated pneumonia is mitigated by elevating the head of the bed to 30 to 45 degrees, and the practice of oral

decontamination with agents such as chlorhexidine gluconate should also be included. Strategies that have been proven to decrease ventilator days such as sedation holidays and daily spontaneous breathing trials remain important as well.

Blood Products

The utilization of blood products in sepsis remains an important consideration as patients with severe sepsis often develop anemia, thrombocytopenia, and coagulopathy. With regard to anemia, several randomized controlled trials have evaluated transfusion thresholds during critical illness, and two trials have addressed transfusion thresholds in sepsis. In the absence of acute hemorrhage, myocardial ischemia, and severe anemia, current guidelines support transfusion of red blood cells for a hemoglobin below 7 g/dL. Earlier recommendations for early goal-directed therapy that included transfusion of red blood cells for a hemoglobin less than 10 g/dL when the $ScvO_2$ was less than 70% are no longer supported.

No randomized controlled trials for transfusion of fresh-frozen plasma (FFP) in the management of sepsis currently exist. The use of FFP is not recommended in the absence of bleeding or planned surgical procedures. However, source control in the management of sepsis often requires surgical intervention. Additionally, an increasing number of patients present with coagulopathy related to anticoagulation for chronic medical conditions. Although Coumadin was the mainstay of therapy in the past, there is an increasing use of direct oral anticoagulants (DOACs) with direct thrombin inhibitors that are not always readily reversible. Prothrombin complex concentrate (PCC) is widely used to reverse the action of DOACs in accordance with current guidelines because of a lack of specific reversal agents. Further, PCC are fast acting and can avoid complications related to the volume of FFP required to reverse coagulopathy in patients with underlying cardiomyopathy.

Thrombocytopenia is another common finding in sepsis and is thought to be related to increased platelet consumption as well as compromised production. Correction of thrombocytopenia with platelet transfusion is therefore often transient. For this reason, platelet transfusion recommendations are based on risk of bleeding. When active bleeding is present or surgical intervention is required, platelets should be transfused if platelet counts are less than 50,000/mm^3. In the absence of any bleeding risk, platelet counts as low as 20,000/mm^3 can be monitored.

Corticosteroids

It is well known that the response to critical illness requires cortisol production by the adrenal gland, and patients with severe sepsis can develop a relative adrenal insufficiency. Based on this, multiple investigators have studied the use of corticosteroids in the supportive care of patients with severe sepsis. Recently there has been an interest in including ascorbic acid and thiamine as part of a "metabolic resuscitation" termed HAT (hydrocortisone, ascorbic acid, thiamine) therapy. Early studies on this approach have had conflicting results, and a recent randomized controlled trial failed to show a mortality benefit; however, it did show a faster resolution of the shock state. Current recommendations do not support the routine use of corticosteroids for septic shock. Rather, corticosteroids should be reserved for patients who after adequate fluid resuscitation remain refractory to vasopressor therapy. In these patients, hydrocortisone should be started at a dose of 200 mg IV daily. The addition of ascorbic acid and thiamine requires additional study but does not appear to be harmful and can be considered.

Glycemic Control

Several randomized controlled trails and meta-analyses have been completed to study glycemic control and the use of insulin in critically ill patients. Hyperglycemia has been associated with worse outcomes in this patient population, and therefore insulin administration can be an important adjuvant therapy. Based on the currently available evidence, the goal should be to limit blood glucose levels to <180 mg/dL. Blood glucose levels should be monitored, and insulin therapy should be initiated for blood glucose levels over 180 on two consecutive measurements. If insulin therapy is required, monitoring of blood glucose levels every 1 or 2 hours is recommended, preferably with an arterial blood sample.

Renal Replacement Therapy

Acute kidney injury continues to be a common complication associated with severe sepsis. The indications for dialysis remain the same and should not be influenced by the presence of sepsis. Continuous renal replacement therapy may be preferred for patients with ongoing hemodynamic instability or a persistent vasopressor requirement, but otherwise there does not appear to be any benefit to continuous over intermittent renal replacement therapy.

Nutrition

Supportive care of patients with severe sepsis should include early initiation of enteral nutrition. Advantages of early enteral nutrition include maintenance of mucosal integrity in the gastrointestinal (GI) tract, modulation of metabolism with caloric support, and mitigation of the inflammatory response. Abdominal surgery and critical illness can limit the ability to provide full enteral nutritional support. In patients requiring vasopressors, initiation is generally not initiated until patient hemodynamics have improved as evidenced by modest or weaning vasopressor requirements. The use of postpyloric tube feedings and hypocaloric or "trophic" tube feedings has been shown to have benefit when patients are unable to tolerate calculated nutritional requirements. The use of parental nutrition should be limited to patients with contraindications to enteral nutrition after 7 days or in patients with preexisting severe malnutrition and an anticipated inability to receive enteral nutrition within 7 days of presentation. Nutritional supplements such as selenium, arginine, glutamine, and carnitine have been studied in the treatment of sepsis and severe sepsis as well, and while they have scientific justification for their use, clinical trials have not yet produced evidence to support routine use and they are not recommended.

Chemical Prophylaxis

Prophylaxis against deep vein thrombosis (DVT) and stress ulcer prophylaxis continues to be an important component of supportive care in sepsis management for critically ill patients.

DVT prophylaxis should include mechanical prophylaxis with sequential compression devices and delivery of subcutaneous low molecular weight heparin. When the creatinine clearance falls below 30 mL/min, then unfractionated heparin should be used.

Stress ulcer prophylaxis is recommended for any patients with risk of GI bleeding and should be discontinued when the risk is not present. Risk factors for GI bleeding include need for mechanical ventilation >48 hours, spinal cord injury, burns, or a history of upper GI bleeding. Proton pump inhibitors and histamine-2 receptor antagonists are both considered to be acceptable choices for stress ulcer prophylaxis.

GOALS OF CARE

Despite early identification and adherence to clinical practice guidelines, severe sepsis confers a high mortality rate, particularly in elderly patients and those with multiple comorbidities. Even when the patients survive, quality of life can be severely impacted, and prolonged rehabilitation may be required. While prognostication can be difficult early in the clinical course, the principles of palliative care and understanding the individual patients' beliefs surrounding

quality of life and end of life care is also extremely important. Goals of care and prognosis should be discussed with patients and their families when able and should take place within 72 hours of ICU admission. Frequent discussions with families as the clinical course progresses may be necessary, and when care is deemed futile, the goals of care should focus on the relief of pain and suffering for the patient and attention to spiritual and culture support of the family as appropriate.

Suggested Readings

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Multiple Organ Dysfunction and Failure

Alexandra B. Roginsky, MD

Critically ill patients are exceedingly complex and require a multisystem approach to care. It is, in fact, customary for daily documentation of such patients to be in a system-by-system format, acknowledging the importance of such an approach. Critically ill surgical patients require extreme attention to detail and organ system management. The underlying disease process in critically ill patients often affects other systems that were not initially involved in the pathologic process. It is the vital role of the surgeon to be diligent in the assessment and management of such situations.

This chapter is about multiple organ dysfunction and failure, and it is fitting that the term *multiple organ failure* (MOF) was first coined in 1975 by Arthur Baue, a thoracic surgeon. The current terminology is *multiple organ dysfunction syndrome* (MODS). The nomenclature signifies that organ dysfunction occurs without irreversible failure in critically ill patients. Without adequate treatment of underlying pathology, and at times even with such treatment, the dysfunction will progress to failure. As expected, the complexity of the entity is such that there is no one treatment that will correct MODS, and at times it will progress to *multiple organ system failure* as the final common pathway. The definition of MODS is a development of potentially reversible physiologic derangement that involves two or more systems in which homeostasis cannot be maintained without intervention. Primary MODS results from a well-defined insult in which dysfunction occurs early in the course and can be directly linked to the insulting event. Secondary MODS is organ failure not linked to insult itself, but rather the host's response.

Since the landmark publication, a multitude of studies have been published. There have been many attempts at scoring and predicting severity of multiple organ dysfunction. The Sequential Organ Failure Assessment (SOFA) is a scoring system that utilizes data points that combine physiologic parameters and treatment data points (Table 1). The original SOFA description was designed to assess severity of illness in sepsis and has later been expanded. The initial score is obtained 24 hours after admission and every 48 hours after (hence the term *sequential).* A 30% or more increase in score predicts a mortality of greater than 50%.

In addition, the Acute Physiologic and Chronic Health Evaluation (APACHE) is well known and utilized. There are multiple versions, APACHE I to IV. The calculator requires input of many variables, with over 120 variables in APACHE IV. The severity score derived from the multiple variables is used to calculate mortality and length of stay. It is a good predictive model, with the downside of large volume of variable entry for data.

TABLE 1 Sequential Organ Failure Assessment (SOFA) Score

Organ System	0	1	2	3	4
Respiratory: PaO_2/FiO_2	>400	<400	<300	<200 with ventilator support	<100 with ventilator support
Cardiovascular: hypotension	MAP >70, no pressors	MAO <70, no pressors	Dopamine <5	Dopamine >5 or epinephrine <0.1 or norepinephrine <0.1	Dopamine > 15 or epinephrine >0.1 or norepinephrine >0.1
Hepatic: bilirubin (mg/dL)	<1.2	1.2–1.9	2–3.4	3.5–4.9	>5.0
Coagulation: platelet count × 10^3	>150	<150	<100	<50	<20
Neurologic: GCS	15	13–14	10–12	6–9	<6
Renal: Cr (mg/dL) or UOP mL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or UOP <500	>5.0 or UOP <200

Cr, Creatinine; *GCS,* Glasgow Coma Scale; *MAO*, ; *MAP,* mean arterial pressure; *UOP,* urine output.
Vasopressor doses in micrograms/kg/min.

This chapter discusses multiple organ dysfunction on a system basis along with treatment and prognosis. Multiple organ dysfunction and ultimately failure is a disruption of the multiple system elegance that functions in all of us daily, which is often taken for granted.

DYSFUNCTION AND FAILURE BY ORGAN SYSTEM

Neurologic

Neurologic dysfunction is a term encompassing a broad range of diagnoses and physiologic processes. Mental status changes are very common in critically ill patients. The mental status changes are caused by both the underlying disease processes and treatments thereof. Changes in a patient's mental status can be caused by a primary central nervous system event, such as a traumatic brain injury or stroke, or a manifestation of sepsis, shock, sedating medications, and many other causes.

A change in a patient's mental status should prompt a detailed workup and evaluation for the underlying cause. Attributing mental status changes as purely pharmacologic should be a diagnosis of exclusion after a detailed workup has been completed. It is, however, necessary to review the patient's medications individually, especially in the context of the patient's age. Many medications can affect older adult patients with mental status changes that do not have such effects on younger patients. Neurologic changes can occur with sepsis, hypoxia, hypercapnia, hepatic insufficiency, hypoperfusion, and many other causes.

The easiest and fastest assessment of neurologic function is the Glasgow Coma Scale (GCS; Table 2). This scoring system is very familiar to surgeons, especially in the rapid evaluation of injured patients. The system attributes a point value to speech, motor function, and eye opening function, with the maximum (perfect) score of 15 and minimum of 3. A patient who scores 8 or less is considered at risk of being unable to protect his or her airway, and endotracheal intubation should be strongly considered.

TABLE 2 Glasgow Coma Scale

Component	Score
EYE OPENING	
Spontaneously	4
To voice	3
To pain	2
No response	1
VERBAL	
Oriented	5
Disoriented	4
Inappropriate	3
Incomprehensible sounds	2
No response	1
MOTOR	
Following commands	6
Localizing to pain	5
Withdrawing to pain	4
Abnormal flexion	3
Abnormal extension	2
No response	1

TABLE 3 Marshall Multiple Organ Dysfunction Score

Organ System	0	I	2	3	4
Respiratory: PaO_2/FiO_2	>300	226–300	151–225	76–150	≤75
Cardiovascular: HR × CVP/MAP	≤10	10.1–15	15.1–20	20.1–30	>30
Hepatic: bilirubin (mg/dL)	<1.2	1.2–3.5	3.5–7.0	7.0–14	>14
Hematologic: platelet count (× 10^3)	>120	81–120	51–80	21–50	≤20
Neurologic: GCS	15	13–14	10–12	7–9	≤6
Renal: Cr (mg/dL)	<1.1	1.1–2.3	2.3–4.0	4.0–5.7	>5.7

Cr, Creatinine; *CVP,* central venous pressure; *FiO_2,* fraction of inspired oxygen; *GCS,* Glasgow Coma Scale; *HR,* heart rate; *MAP,* mean arterial pressure; *PaO_2,* partial pressure of oxygen.

The GCS is also used as part of the Sequential Organ Failure Assessment (see Table 1) and the Marshall Multiple Organ Dysfunction Score (Table 3), key scoring systems in ICU populations. The SOFA score utilizes parameters both the patient's physiology and supportive means, and the Marshal Multiple Organ Dysfunction Score's parameters are physiologic data points.

Neurologic assessment is complex and includes assessment of pain as part of the evaluation for MODS. Neurologic changes, especially with pain out of proportion to expectation, should trigger an evaluation for a deeper underlying problem. Sepsis, bleeding, and contained abscesses are all potential sources and must be controlled. Pain control should be multimodal and effective and should limit contribution to delirium or confusion. Regional anesthetic approaches have grown in utilization to provide adequate analgesia and decreased need for opiate use. Many ICUs in the United States utilize continuous bedside scoring of delirium, pain, and agitation as part of nursing protocols and standardization of care.

The neurologic dysfunction of critically ill patients is highly complex and can persist for a long period after recovery from the index illness and hospitalization. There are known measures utilized to mitigate these long- term issues. ICUs should strive to maintain sleep-wake cycles, minimize sedation in ventilated patients (even providing sedation vacation), and make aggressive attempts at daily mobilization and physical therapy.

The ultimate central nervous system dysfunction and irreversible failure is brain death. Brain death can be caused by many pathologies, including trauma, shock, and sepsis. The underlying pathology causes global ischemia and ultimately absence of blood flow to the brain. The pathophysiologic process typically involves increased intracranial pressure and decreased cerebral perfusion pressure, and the brain ultimately dies. This is complete and irreversible biological death. The declaration of brain death is a legal process and varies from state to state. Usually, this process involves examination by two separate physicians with a defined separated time period. Other metabolic causes of brain dysfunction must be excluded to constitute a valid examination. The patient must be normothermic, have a documented normal toxicology assessment, and have a normal acid-base balance and electrolyte levels.

Cardiovascular

Cardiovascular dysfunction manifesting as hypotension and shock is likely the most frequent reason for ICU admission or transfer.

Multiple clinical entities can cause a cardiac insult and cardiovascular dysfunction, as opposed to a primary cardiac pathology. This is usually true in noncardiac surgical patients. Sepsis is an example of pathology that causes cardiovascular dysfunction but is a different primary pathology. Cardiovascular complications do occur in surgery and can be causes of cardiovascular collapse. Myocardial infarction, massive or submassive pulmonary embolism, or significant arrhythmias are all examples. Identifying the cause of cardiovascular dysfunction is critical to implementation of appropriate treatment. Echocardiography is one very helpful tool to identify pathology and can be useful to see wall motion abnormalities, valvular dysfunction, caval fullness, and atrial filling to assess volume status and resuscitation, as well as identifying thrombi.

Hypotension and hypoperfusion are present in all forms of shock. In distributive shock, such as shock resulting from sepsis or anaphylaxis, there is vasodilatation and capillary leak that causes hypotension. Septic shock is by far the most common form of distributive shock. Early treatment aimed at volume restoration is recommended with an infusion of 30 mL/kg actual body weight, started in the first hour and completed in 3 hours, with an occasional need for vasopressors. Response monitoring is generally geared toward a mean arterial pressure of 60 to 65 mm Hg and evidence of end organ perfusion. At times, the addition of vasopressor therapy is necessary, with norepinephrine as the first agent of choice. Source control, both in the form of broad-spectrum antibiotic therapy and possible surgical intervention, is critical to patient survival. Some surgical infections will necessitate more than one operation, requiring vigilance on the part of the surgeon to diagnose and time.

In hemorrhagic and hypovolemic shock, the body responds with vasoconstriction to compensate, but hypotension persists because of the low circulatory volume. In the surgical population, especially the trauma population, prompt recognition of hemorrhagic shock is vital, with measures taken to identify source of blood loss, repair, and restore volume. Volume restoration is accomplished with both crystalloid and blood products. In severe hemorrhage, a massive transfusion protocol should be employed.

True cardiogenic shock is caused by injury to the heart itself, such as myocardial infarction. The mainstay of therapy is addressing the underlying insult and providing inotropic support. Cardiac catheterization with intervention is indicated at times as well as intraaortic balloon pump placement or emergent pacing. The first-line agent for ionotropic support is epinephrine, and the second-line agent is dobutamine. Treatment of heart failure is very nuanced. The insult results in pump dysfunction, poor delivery of oxygenated blood to organs, compensatory vasoconstriction, and eventual hypotension, which may progress to end-organ dysfunction or failure.

Obstructive shock is caused by central cardiac outflow obstruction, such as with a massive pulmonary embolus, and with no adequate outflow, hypotension results. The presentation is acute and dramatic. There are overlapping signs such as tachycardia and hypotension with hypovolemic shock. The prompt treatment modalities involve anticoagulation, systemic or local thrombolytics, and even surgical embolectomy. Surgical decisions are influenced also by recent thrombolytic administration.

Neurogenic shock occurs when there is lack of central nervous system input into vascular tone. There is venodilation, reduced preload, vasodilation, and often bradycardia. Initial treatment of neurogenic shock involves volume reconstitution. Phenylephrine may be necessary to maintain appropriate mean arterial pressure, critical to support the central nervous system. With concurrent bradycardia, dopamine may be necessary to maintain adequate heart rate and cardiac output.

The diagnosis of shock type is often not obvious and requires nuanced evaluations. Recognition of type of shock is critical to treat appropriately before end-organ dysfunction and irreversible damage occurs. Especially for surgeons, more than one shock type can coexist in a trauma patient, such as neurogenic and hemorrhagic. Prompt recognition and aggressive measures are critical for both short-term survival and optimal long-term quality of life. If not treated adequately, the final pathway of cardiovascular system dysfunction is cardiovascular collapse and death.

Pulmonary

Pulmonary dysfunction and poor gas exchange are major components of critical illness and MOD. The main component of MODS in a critical care setting is acute respiratory distress syndrome (ARDS). ARDS may result from a primary injury to the lungs such as aspiration, traumatic injury, or pneumonia. It may be a consequence of a nonpulmonary primary insult such as sepsis, inflammation, hemorrhage, transfusion-related injury, or pancreatitis. Both primary and secondary ARDS are common in surgical intensive care settings.

ARDS was first recognized and described in the 1960s as a distinct type of hypoxemic respiratory failure affecting both lungs. There have been over 60 causes described, but most are caused by a few common etiologies. Sepsis is the most common, but even iatrogenic causes are well described, including medications such as amiodarone, chemotherapeutic agents, and radiation.

There are three well defined stages of ARDS: exudative, proliferative, and fibrotic. Early in the pathophysiology, there is a ventilation-perfusion mismatch. The process progresses to alveolar injury that produces diffuse alveolar damage. The initial injury produces toxic inflammatory cytokines that recruit neutrophils, and subsequently alveolar cell and capillary damage occur. The alveoli fill with proteinaceous debris and fluid, and the alveoli collapse. This initial stage lasts 7 to 10 days. If the patient survives, the above-described exudative stage may progress to the fibroproliferative stage and then ultimately to the fibrotic stage.

As with many medical pathologies, diagnostic criteria have been developed. The Berlin definition of ARDS was published in 2012. However, much of the data and evidence comes from earlier publications. To meet criteria, an insult must have occurred within 1 week of presentation, or a new or worsening symptom must have occurred within the week. Bilateral opacities must be present on chest radiograph or computed tomographic imaging. The respiratory failure cannot be explained by cardiac failure or fluid overload. There must be a moderate to severe oxygen exchange impairment. This is defined as fraction of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) (Table 4).

Respiratory support of patients with ARDS involves multiple strategies including minimizing further lung trauma. The ARDS Net Group data are recommended. Lung-protective ventilation, also known as *low tidal volume ventilation,* is utilized. This tidal volume is calculated at 4 to 8 mL/kg *predicted* weight. The plateau pressure goal is ≤30 cm H_2O. Collective evidence suggests that early utilization of low tidal volume ventilation improves mortality. The PaO_2 goal is 55 to 80 mm Hg, and the SpO_2 goal is 88% to 95%. Permissive hypercapnia is also utilized, accepting a pH <7.35 and $PaCO_2$ >45. PEEP is carefully applied to maximize alveolar recruitment. Early high PEEP is not recommended. Overresuscitation should be avoided.

In patients who fail to improve despite all of the aforementioned measures, other measures may be attempted. Prone ventilation has

TABLE 4 Acute Respiratory Distress Syndrome Categorization

Severity	PaO_2/FiO_2	Ventilatory Settings
Mild	≤200, ≤300	PEEP or CPAP >5 cm H_2O
Moderate	>100 and <200	PEEP ≥5 cm H_2O
Severe	<100	PEEP ≥5 cm H_2O

CPAP, Continuous positive airway pressure; *PEEP,* positive end-expiratory pressure.

been demonstrated to decrease mortality in patients refractory to initial ARDSNet strategies. Pulmonary vasodilators and neuromuscular blockers may be attempted as well. Ventilatory maneuvers such as recruitment maneuvers utilizing higher PEEP levels for some lengths of time may be helpful. In the past, high-frequency oscillatory ventilation was utilized as a rescue maneuver, but it has fallen out of favor because data demonstrates lack of benefit and possible harm.

Finally, if all measures have failed, extracorporeal membrane oxygenation may be considered and employed to provide adequate oxygen and allow the lungs to recover. With the best care, ARDS is associated with appreciable mortality, ranging from 35% in patients with mild ARDS to 46% in patients with severe ARDS. There have been many studies of predictors. There is also a lot of morbidity in survivors of ARDS, as with any critical illness, and those are complex outcomes that include physical and emotional issues, long-term return to work, and activity tolerance.

Renal

Acute kidney injury (AKI) is common in the surgical and ICU population. It is defined as an abrupt and usually reversible decline of glomerular filtration rate, urea and other waste product accumulation, and electrolyte dysregulation. The term *acute kidney insufficiency* has largely replaced *acute renal failure.* Acute insufficiency short of failure bears substantial clinical significance and warrants aggressive intervention. AKI has many causes, and surgery is a risk factor. Cardiac, vascular, and biliary operations are all risk factors, including the obvious factors of hypotension, shock, hemorrhage, and surgical reexploration. Nephrotoxic drug exposures, including iodinated contrast, and vasculitis are other risk factors. The incidence is difficult to know, as studies have had different definitions, making it difficult to compare studies. Estimates are that among hospitalized patients, up to 22% develop AKI, and in the intensive care population, up to 57%. The occurrence of AKI substantially increases perioperative mortality, up to 31%.

There are several consensus definitions of AKI. The most recent (from 2012) is the Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging system. There is also the Risk, Injury, Failure, Loss End-Stage Renal Disease (RIFLE) criteria and the Acute Kidney Injury Network (AKIN) criteria (Table 5). There are many overlapping factors among the three consensus definitions. The RIFLE criteria evaluate urine output and changes in serum creatinine. AKIN criteria are similar but utilize absolute changes in serum creatinine to define the injury. KDIGO combines both of the aforementioned criteria and allows for differences in short-term changes (48 hours) or longer-term course (7 days).

The classical teaching has been to divide AKI as caused by three broad categories: prerenal, renal, and postrenal. In renal patients, AKI is hardly ever that clean categorized and is multifactorial the vast majority of the time. Patients suffer from more than one pathophysiologic process. Prolonged prerenal pathology such as hypotension or postrenal pathology such as obstruction will cause intrinsic

TABLE 5 KDIGO, RIFLE, AKIN Classifications of Renal Failure

Stage	GFR/Serum Creatinine	Urine Output
KDIGO STAGING OF AKI		
1	Baseline × 1.5–1.9 Increase >0.3 mg/dL in 48 h	<0.5 mL/kg/h for 6–12 h
2	Baseline × 2–2.9	<0.5 mL/kg/h for >12 h
3	Baseline × 3 Increase > 4 mg/dL Initiation of renal replacement therapy <18 years of age decreased GFR <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for 24 h Anuria >12 h
RIFLE CLASSIFICATION OF RENAL FAILURE		
Risk for renal injury	Baseline Cr × 1.5 Decrease GFR >25%	<0.5 mL/kg/h × 6 h
Injury to kidney	Baseline Cr × 2	<0.5 mL/kg/h × 12 h
Renal failure	Baseline Cr × 3 Cr >4 mg/dL with increase of 0.0 mg/dL Decrease GFR >75%	<0.3 mL/kg/h × 24 h Anuria × 12 h
Loss of renal function	Persistent renal failure Loss of renal function >4 weeks	
ESRD	Renal failure >3 months	
AKIN CLASSIFICATION OF AKI		
1	Baseline × 1.5–1.9 Increase >0.3 mg/dL in 48 h	<0.5 mL/kg/h for 6 h
2	Baseline Cr × 2–3	<0.5 mL/kg/h × 12 h
3	Baseline Cr × 3 Cr >4 mg/dL with acute increase 0.5 mg/dL Renal replacement therapy	<0.3 mL/kg/h × 24 h Anuric × 12 h

AKI, Acute kidney injury; *AKIN,* Acute Kidney Injury Network; *Cr,* creatinine; *ESRD,* end-stage renal disease; *GFR,* glomerular filtration rate; *KDIGO,* Kidney Disease Improving Global Outcomes; *RIFLE,* Risk, Injury, Failure, Loss End-Stage Renal Disease.

renal damage. It is also important to differentiate the intrinsic renal injury by the type of insult and structure of the kidney affected, such as emboli to the vasculature, renal interstitial damage from allergic reactions or infections, or renal tubular damage from toxins such as contrast, antibiotics, myoglobin, and so on.

Operative patients have many factors that increase the risk of AKI. Multiple comorbidities such as obesity, diabetes, hypertension, cardiovascular disease, and smoking are extremely prevalent in modern US society. The nature and urgency of surgery also play a role. Specifically in surgical patients, hypovolemia and hypotension (either from hypovolemia or decreased vascular resistance caused by anesthetic administration) are critical factors. Direct injury to the kidneys can occur intraoperatively as well, even from positioning and retracting. It is critical that the surgeon maintain clear communication with the anesthesiologist regarding the patient's intraoperative hemodynamics to optimally manage going forward.

It is highly interesting to note that intraoperative urine output does not correlate well with AKI for elective surgeries. Reduction of a patient's risk of AKI involves addressing risk factors, attempting to minimize and optimize them, maintaining an intraoperative mean systemic pressure of 60 mm or more, and avoiding toxins when possible.

As with most organ system dysfunction, the main treatment of AKI is to address and fix the underlying cause (improve hypovolemia, treat sepsis, improve cardiac output) and provide supportive care. If renal failure does occur, renal replacement therapy should be initiated when indicated. The indicators may include volume overload, acidosis, hyperkalemia, and so on. In the ICU setting and in patients with hemodynamic compromise, renal replacement therapy is often performed via continuous venovenous filtration. In stabilized patients, intermittent hemodialysis is preferred.

Gastrointestinal and Hepatic

Gastrointestinal problems occur in critically ill patients often, and the gastrointestinal system is a critical component to develop MODS, both inside and outside the alimentary tract. Bacterial translocation is an important mechanism for the process. The bacterial translocation is believed to occur due to hypoperfusion and loss of cellular integrity. Bacterial entry into the systemic circulation and lymphatics causes a severe inflammatory response. Acute gastrointestinal injury is an important predictor of overall illness severity and outcomes. In 2012, the Working Group on Abdominal Problems, part of the Perioperative Intensive Care section of the European Society of Intensive Care Medicine, proposed a grading system of gastrointestinal dysfunction definitions to be used both clinically and in research, which has increased consistency (Table 6).

The complexity of patients and broad spectrum of severity is obvious in the summary of acute gastrointestinal insufficiency. The characteristics and presentation are all occurring in otherwise highly complex patients. Not surprisingly, higher acute gastrointestinal injury grades are associated with worsening mortality, and intervention is difficult.

Primary hepatic dysfunction can be the initiator in MODS, or it can occur secondarily. In situations of acute-on-chronic liver failure, it is usually a secondary event. At times of physiologic stress, splanchnic blood flow constriction occurs. This leads to a decreased perfusion of the liver and also shunting through other channels such as varices, worsening a preexisting hepatic insufficiency.

There are two types of hepatic dysfunction in MODS. Acute and sudden hepatic dysfunction is referred to as *shock liver,* which is ischemic. Hepatic ischemia occurs when the balance of oxygen supply and demand is not met. Progression leads to shock liver. The presentation is usually an acute and dramatic elevation of transaminases, then hyperbilirubinemia, and finally a loss of synthetic function, evidenced by an increase in international normalized ratio (INR), hypoglycemia, and hyperbilirubinemia. It is common for clinicians to refer to transaminase abnormality as a change in "liver function," or refer to levels as "liver function tests." The transaminases, alkaline phosphatase and bilirubin are biochemical markers of hepatic injury. The true synthetic *function* of the liver is measured by INR, albumin, and also bilirubin. The non– "shock liver" form of hepatic dysfunction is not as dramatic, a milder insufficiency, and usually resolves when MODS resolves. It manifests as an elevation in bilirubin, possibly transaminases, and no loss of synthetic function. The approach is treating the underlying cause of MODs, treating the hepatic dysfunction, avoiding hepatotoxins, and providing global supportive care including nutrition.

Severe shock liver is a major contributor to MODS. Reperfusion injury, not only initial compromise of perfusion due to sepsis or other cause, is a major factor. Most of the histologic damage is from reperfusion-reactive oxygen species. Under ischemic stress, Kupffer cells produce and release inflammatory cytokines such as tumor necrosis factor alpha into the systemic circulation, greatly affecting other organs' function. The loss of synthetic function and resultant rising INR portend a severe coagulopathy. Patients in this state cannot effectively clear lactate; they suffer from encephalopathy caused by hyperammonemia. The profound and progressing systemic inflammation causes cerebral edema, inflammation of microglial cells, and glutamine accumulation in astrocytes. This massive physiologic insult can also cause ARDS, AKI, progressive shock and MODS, ultimately MOF, and death.

Endocrine and Metabolic

Physiologic stress and insults result in many disturbances. The endocrine system and systemic patient metabolism are also affected,

TABLE 6 Acute Gastrointestinal Insufficiency

Grade	Characteristics	Examples	Management
1	Risk of developing dysfunction or failure	Postoperative nausea or vomiting	Supportive, avoiding drugs impairing motility, early enteral feeding
2	GI dysfunction, GI tract not able to perform digestion and absorption to satisfy all needs	Gastroparesis, high residuals to feeds, increased IAP (12–15 mm Hg)	Treat underlying condition, enteral challenges, prokinetic agents, postpyloric feedings
3	Gastrointestinal failure, restoration not achieved	Feeding intolerance, worsening bowel dilation, grade 2 IAP (15–20 mm Hg)	Measures to prevent worsening GI failure, treatment of IAP, evaluation for other intraabdominal pathology (e.g., cholecystitis)
4	GI failure with severe impact on distant organ function	Bowel ischemia with necrosis, GI bleed leading to shock, abdominal compartment syndrome	Laparotomy or other aggressive interventions (e.g., colonoscopy). No proven conservative approach

and it is an important component of multisystem dysfunction. The injury response begins in the central nervous system, with the hypothalamic-pituitary-adrenal axis. The process of glucose metabolism is affected, as is the hypothalamic-pituitary-thyroid axis.

At onset of insult, the initial response of the hypothalamic-pituitary-adrenal axis is increasing cortisol secretion. This occurs in proportion to severity of process. As the inflammatory process continues, the system cannot sustain and is exhausted, and relative adrenal insufficiency may be a result. Absolute adrenal insufficiency is rare in critically ill patients; rather, it is a relative insufficiency that occurs. Terms utilized are *functional adrenal insufficiency or relative adrenal insufficiency,* both with little consensus of diagnostic criteria. There is a high prevalence of hypothalamic-pituitary-adrenal axis dysfunction in the critically ill population, with the tern *critical illness corticosteroid insufficiency* utilized; however, there is no consensus criteria for diagnosis.

Cortisol is necessary for the arterial walls to respond to catecholamines to maintain tone. Historically, adrenal insufficiency was tested for with synthetic ACTH (cosyntropin) stimulation test to help guide administration of exogenous hydrocortisone. This has largely fallen out of favor as a result of several factors. The ACTH stimulation tests lack reliability in critically ill patients. There have been inconsistent results observed in the same patient given tests at different times; cortisol levels often increase in critically ill patients, even without exogenous stimulation. Additionally, some medications used in critically ill patients such as etomidate for intubation can suppress the hypothalamic-pituitary axis and lead to inaccuracies. The current recommendations are to use glucocorticoids selectively in patients who demonstrate refractory shock, defined as systolic blood pressure less than <90 mm Hg for over 1 hour after appropriate fluid and vasopressor administration. In the correct patient, hydrocortisone is administered, less than 400 mg a day in divided doses.

Adrenal glands also secrete mineralocorticoids, such as vasopressin. Vasopressin causes vascular constriction, acting on multiple receptors. Vasopressin also acts on the pituitary gland to secrete ACTH, leading to an increase in cortisol, as well as acting to increase water reabsorption. Similar to cortisol, vasopressin levels increase immediately after an injury and then can decrease. Endogenous vasopressin levels are not measured as most is platelet bound and has a short half-life. After adequate volume resuscitation, vasopressin can be exogenously administered, at fixed doses, although not as a first-line agent.

A hypermetabolic starter is present in critically ill patients, with the previously described surges in cortisol and catecholamines. These substances contribute to insulin resistance, hepatic gluconeogenesis, catabolism, and hyperglycemia. Uncontrolled hyperglycemia is associated with increased mortality, longer ICU stay, and increased infection risk. Hyperglycemia is also associated with poorer outcomes in subpopulations of stroke, myocardial infarction, and trauma patients. The mechanisms are multifold, including worsening inflammatory mediators, free radicals, and impaired immune function. Additionally, hypoglycemia, both in the presence and absence of insulin administration, is associated with poorer outcomes. It is important for the treating physician to be diligent in glucose management. In critically ill adult patients, the best evidence supports a glucose range target of 140 to 180 mg/dL. Multiple trials demonstrated conventional glucose control (target 140–180 mg/dL glucose) to have improved outcomes compared with intense insulin therapy (target 80–110 mg/dL glucose).

Thyroid function is also affected by critical illness in patients whose primary illness is not thyroid related and no preexisting thyroid pathology exists. The term is *sick euthyroid syndrome.* In these patients, there are low serum T3 and T4 concentrations, and serum thyroid stimulating hormone (TSH) may be low. This is likely acquired central hypothyroidism, thought to be driven by inflammatory cytokines, and protective such that excessive catabolism does not occur. Persistent hypothyroidism may be maladaptive. Usually this corrects when the critical illness resolves. Overall, thyroid function assays are not recommended in the critically inpatient population, and it is best to perform follow-up studies once the critical illness subsides.

Hematologic, Including Disseminated Intravascular Coagulation

Hematologic abnormalities are very common in critically ill patients with a multitude of causes and clinical manifestations. Anemia is often found in ICU patients. Anemia in the critical care setting is caused by anemia of inflammation (AI) or anemia of chronic disease (ACD). It is the second most common cause of anemia worldwide, with infection, malignancy, inflammatory disorders, COPD, and aging all contributing diagnoses. The pathophysiology of this entity is complex and multifactorial. One aspect is that there is reduced iron availability, which may be a defense mechanism to decrease iron available to invading organisms. Low iron levels decrease activity of erythroid progenitor cells in the bone marrow. The multiple inflammatory cytokines present in critical illness also suppress erythroid progenitor cell activity and can even induce apoptosis pathways. In the inflammatory state, there is less production of erythropoietin by renal cells and less response to erythropoietin in the bone marrow. With the high prevalence of anemia, transfusions are ubiquitous in critical care environments. Many trials have investigated the benefit of liberal or restrictive transfusion policies. Overwhelming evidence supports restrictive transfusion practices. Multiple societies have published transfusion guidelines since 2012. In hemodynamically stable and asymptomatic patients who are not bleeding, the transfusion threshold is at a hemoglobin level of 7 g/dL. In patients with acute coronary syndrome, transfusion is recommended at hemoglobin levels less than 8 g/dL. In an acutely bleeding patient, such as in the trauma population, transfusion is initiated independent of measured hemoglobin levels. Rapid bleeding may require activation of a massive transfusion protocol, with concomitant control of source of bleeding, usually operative in nature. Once the source has been controlled, restrictive transfusion practices should be implemented. All efforts should be utilized to decrease iatrogenic causes of anemia. Utilizing judicious phlebotomy, small-volume tubes, in-line blood conservation devices, and cell saver in the operating room are all helpful in decreasing the need for transfusions.

Thrombocytopenia is also common in critically ill patients and is generally defined as a platelet count less than 150,000/μL, further divided into mild (100,000–150,000/μL), moderate (50,000–99,000/μL), and severe (<50,000/μL). The prevalence of thrombocytopenia in acutely ill patents ranges from 8% to 68% at the time of ICU admission. Existence and severity of thrombocytopenia correlates with disease severity, organ dysfunction, and death. Notably, approximately 2.5% of the population lives with a platelet count below 150,000/μL and no pathology. Reduction in normal platelet levels has many causes. In critically ill patients, sepsis accounted for one-half of all cases, and 26% of cases were attributable to more than one cause. Other causes include immune etiology, liver disease, ethanol ingestion, consumption from mechanical devices, cytotoxic and noncytotoxic medications, and DIC. Platelet transfusion thresholds have been studied less than for red blood cells. In aggressive bleeding, platelets are administered in massive transfusion protocols. In the absence of bleeding, transfusion should be started with a platelet count less than 10,000/μL. If major procedures are planned, such as laparotomy, a platelet count greater than 50,000/μL is recommended, and at least 20,000/μL for central venous catheter placement. For intracranial bleeding or neurosurgical intervention, the target platelet level is above 150,000/μL. Obviously, measures should be taken to address the underlying reason for the thrombocytopenia. Hematologic expertise and bone marrow assessment may be necessary.

Coagulopathy in critically ill patients is very common, and like anemia and thrombocytopenia have numerous and overlapping etiologies. Liver failure and administration of anticoagulant medication are major causes of reduction in circulating coagulation factors.

Transfusion of plasma is indicated in rapidly bleeding patients with the massive transfusion protocols, DIC, liver failure coagulopathy. Plasma transfusion is also indicated to bring the INR below 1.5 for planned procedures. When there is a need to reverse supratherapeutic warfarin-induced coagulopathy or lower INR for procedures in such patients, it should be performed with prothrombin complex concentrate when available rather than with thawed fresh-frozen plasma.

The hematologic disturbances in MODS are multiple, and they reflect the severity of overall organism dysfunction and contribute to the driving process.

SPECIAL POPULATIONS

In the past 3 years, the world has experienced a pandemic as a result of a newly identified coronavirus. An unprecedented number of papers have been published about coronavirus disease 2019 (COVID-19). This chapter briefly describes the multiorgan dysfunction experienced by patients ill with the disease.

The estimates vary and have changed, but up to 20% of diagnosed patients require hospitalization, and of those hospitalized up to 25% require ICU–level care. The predominant feature is profound and acute respiratory insufficiency, with similar features and treatment of ARDS due to other causes. In the patients who progress to ARDS, dyspnea is often a late feature, over 6 days after symptoms onset, but progression to full ARDS is much faster, about 2 days after onset of dyspnea.

In critically ill patients with COVID-19, many of the aforementioned multiorgan dysfunction pathologies occur. There is a high prevalence of acute kidney insufficiency. Patients develop gastrointestinal and neurologic complications. Cardiac insults can occur, both early and delayed. COVID-19 also produces a hypercoagulable state, and has been the sole provoking factor for many pulmonary emboli. It is not surprising that the pandemic has strained the intensive care infrastructure, and the long-term effects are yet to be seen for survivors of all levels of illness, especially those who survived critical illness. There will be a whole body of literature about MODS and the pandemic and long-term survival.

PALLIATIVE CARE AND ETHICS

In this chapter, we discussed aggressive intensive care approaches to critically ill patients and best-evidence methods to improve survival. As with all illnesses, survival of MODS is more difficult to obtain in patients with more comorbidities, higher levels of frailty, and advancing age. Involvement of palliative care physicians and having multidisciplinary meaningful goal-of-care conversations are important in comprehensive patient management.

In patients with or without preexisting conditions and evidence of decline, palliative and goal-of-care discussions should be initiated. In surgical patients, it is vital that the surgeon be involved in both diagnostic and prognostic discussions and in short- and long-term outcomes. Part of the care surgeons provide is to discuss the realistic landscape of survival. The World Health Organization advocates for palliative care, and this should be considered in the treatment plan.

Eventually, patients may reach a point of futility. Futile interventions should not be performed. In situations in which there may be familial disagreement or difficulty discerning a patient's desires, ethics committees should be consulted. These pathways are also part of surgical practice, allowing families to gain an understanding of pathology in surgical patients.

SUMMARY

This chapter provides an overview of MODS as a whole and by individual system and discusses treatment approaches, especially for surgical patients. Ultimately, if the underlying causes cannot be reversed, multiple organ dysfunction progresses to MOF, and surgeons must be familiar with and understand this process.

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ANTIBIOTICS IN SURGICAL CRITICAL CARE

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Antibiotic therapy, source control, and resuscitation are the three primary strategies for combating sepsis, one of the most common reasons for patients to be treated in a surgical intensive care unit. Antibiotics, nearing the centennial of the creation and discovery of salvarsan, sulfonamides, and penicillin, are one of the few classes of medicines that are curative. During this time, many new classes and improvements on the originals have come along; however, bacteria have not been static, but have adapted and become resistant through a number of mechanisms: limiting uptake, modification of targets, inactivation, and active efflux. The current theory of antibiotic management includes broad-spectrum empiric therapy followed by deescalation to target the specific pathogens identified through culturing and polymerase chain reaction (PCR) techniques. Hospital- and unit-based antibiograms that identify local flora and resistance patterns are vital to proper antibiotic therapy. Antimicrobial stewardship is another mainstay to prevent further resistance from developing among bacteria. Pneumonia, peritonitis, soft tissue

infections, and catheter-based infections are the most common septic problems addressed the surgical intensive care unit.

HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA

Pneumonia is one of the most common infections encountered in the critical care arena. In the surgical intensive care unit, it can be divided into hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Community-acquired pneumonia, defined as a pneumonia present before admission, may be encountered, particularly in traumatic brain injury and stroke patients, and is caused by aspiration at the time of loss of control of the airway. HAP is defined as developing two or more days after admission to the hospital. In severe cases, it can lead to intubation and mechanical ventilation. VAP is defined as a pneumonia that occurs 3 days or longer after the onset of mechanical ventilation. The incidence of HAP and VAP is between 5 and 10 cases per 1000 hospital admissions, and they are the second most common cause of hospital-acquired infection. Thirty percent of HAP cases occur in the intensive care unit. Sixteen percent of patients ventilated longer than 1 day develop VAP, with an overall 13% mortality. The causative agents in VAP include *Staphylococcus aureus* (10%–20%), *Pseudomonas aeruginosa* (10%–20%), enteric gram-negative bacilli (20%–40%), and *Acinetobacter baumannii* (5%–10%). Resistance rates are high: 50% of *S. aureus* are multidrug-resistant *S. aureus* (MRSA), 28% to 35% of *Pseudomonas* spp. are resistant to cefepime, 19% to 29% of gram-negative bacilli are resistant to piperacillin-tazobactam, and 56% to 61% of *Acinetobacter* are resistant to carbapenems. HAP has a similar spectrum of organisms. HAP and VAP are different clinical entities, but they have many overlapping features.

The National Healthcare Safety Network (NHSN) of the Centers for Disease Control and Prevention have developed a surveillance algorithm that defines ventilator-associated events (VAE). The algorithm begins with a ventilator-associated condition (VAC). A VAC occurs after a period of ≥2 days of stability on the ventilator, when there is an increase in FiO_2 ≥0.20 or an increase in PEEP ≥3 cm H_2O that is sustained for ≥2 days. An infection-related ventilator-associated complication (IVAC) occurs after 3 days of mechanical ventilation and within 2 days before or after the onset of worsening oxygenation. The criteria for IVAC are temperature >38°C or <36°C or white blood cells (WBCs) ≥12 or ≤4 and a new antibiotic started and continued for ≥4 days. The algorithm then leads to possible and probable ventilator-associated pneumonia (Table 1).

It is notable that this algorithm uses only hypoxemia, temperature variability, WBCs, and the action of initiating antibiotic therapy as determinants. The VAC and IVAC are intended for use in public reporting, while VAP event rates are intended for internal quality

TABLE 1 Ventilator Associated Events

Ventilator-associated condition (VAC)	After ≥2 days of stability	FiO_2 increases ≥0.20 *or* PEEP ≥3 cm H_2O for ≥2 days
Infection-related ventilator-associated complication (IVAC)	After ≥3 days of mechanical ventilation and within 2 days before or after worsening oxygenation	Temperature >38°C or <36°C *or* WBCs ≥12 or ≤4 *and* New antibiotic started and continued for ≥4 days
Pneumonia before the 3rd day of mechanical ventilation is not ventilator associated.		
Possible ventilator-associated pneumonia	Purulent respiratory secretions (lungs, bronchi, trachea)	≥25 neutrophils *and* ≤10 squamous epithelial cells
	Or	
	Positive culture (any method) (Excluding normal or mixed respiratory/oral flora, *Candida* or other yeast, coagulase-negative *Staphylococcus,* and *Enterococcus*)	
Probable ventilator-associated pneumonia	Purulent respiratory secretions (lungs, bronchi, trachea)	≥25 neutrophils *and* ≤10 squamous epithelial cells
	And	
	Positive culture of endotracheal aspirate ≥10^5 CFU/mL Positive culture of bronchoalveolar lavage ≥10^4 CFU/mL Positive culture of lung tissue ≥10^4 CFU/g Positive culture of protected specimen brush ≥10^3 CFU/mL (Excluding normal or mixed respiratory/oral flora, *Candida* or other yeast, coagulase-negative *Staphylococcus*, and *Enterococcus,* except for lung tissue culture)	
	Or	
	Positive pleural fluid culture Positive lung histopathology Positive diagnostic test for *Legionella* spp. Positive diagnostic test for respiratory virus	

CFU, Colony-forming units; *WBC,* white blood cell.

improvement. Chest x-rays (and other radiographic evidence) for pneumonia are excluded from this algorithm because of the variability in reported findings on these studies. This does not preclude a clinician from using findings on chest x-ray to assist in decision making in reference to diagnosis and management of pneumonia.

The diagnosis of HAP and VAP is based on the clinical findings of hypoxemia, fever or hypothermia (temperature > 38°C or < 36°C), elevations or significant decreases in WBC count (WBC ≥12 or ≤4), purulent tracheobronchial secretions (or coughing up purulent sputum in the case of HAP), and new or progressive infiltrates on chest x-ray. Clinicians may observe all or some of these findings in the process of diagnosis of HAP or VAP. Procalcitonin is not recommended for diagnosis over clinical criteria as its sensitivity and specificity is not high enough to be an effective discriminator; a low procalcitonin in the setting of clinical criteria should not be the reason for withholding antibiotic therapy. Soluble triggering receptor expressed on myeloid cells (sTREM-1) and C-reactive protein (CRP) also do not improve diagnostic accuracy.

Once a diagnosis of HAP or VAP is considered, a culture of respiratory secretions should be obtained. For HAP, a sputum culture can be obtained by expectoration, sputum induction, nasotracheal suctioning, or endotracheal aspirate (ETA) in a patient who is intubated as a result of worsening HAP. For VAP, it is recommended to obtain an ETA for semiquantitative analysis. ETA is currently preferred over invasive sampling as these techniques do not lead to improved clinical outcomes. ETA can be performed more quickly and with fewer resources while bronchoalveolar lavage can worsen hypoxemia in patients with acute respiratory distress syndrome (ARDS). Quantitative results have not reliably led to decreases in antibiotic utilization. If invasive quantitative cultures are performed, then antibiotic therapy should be discontinued if the results are below the thresholds for the various tests (see Table 1). The decision to discontinue antibiotic therapy should be based on the clinical condition of the patient including whether there are other sites of infection, whether antibiotics had been initiated before obtaining the specimen, ongoing sepsis, and any other clinical concerns that the treating team may have. Gram stains have poor concordance with final culture results. The concordance improves with larger numbers of organisms viewed on the slide. MRSA screening tests can be helpful in determining the likelihood of MRSA infection. Thirty percent of positive MRSA PCR screens have MRSA pneumonia. In institutions and units with a low prevalence of MRSA, negative screens correlate with low likelihood of MRSA. As the prevalence increases, the correlation becomes less certain. Blood cultures should be drawn in all cases of suspected HAP or VAP; 15% of VAP patients have bacteremia. Twenty-five percent of positive blood cultures are from nonpulmonary sources and may point to additional nonpulmonary sources of infection.

Once HAP or VAP is considered, culture specimens should be obtained, and empiric antibiotic therapy should be initiated. The choice of antibiotics is based on the likelihood of resistant organisms and should target *S. aureus, P. aeruginosa,* and other gram-negative bacilli. Risk factors for multidrug-resistant (MDR) VAP include prior intravenous (IV) antibiotic use within 90 days, septic shock at the time of VAP, ARDS preceding VAP, ≥5 days in the hospital before VAP onset, and acute renal replacement therapy (RRT) before VAP onset. Prior IV antibiotic use within 90 days increases the risk for MDR HAP, MRSA HAP and VAP, and MDR *Pseudomonas* HAP and VAP (Table 2).

As each hospital and critical care unit has a different spectrum of pathogens with different resistance rates, a hospital-based antibiogram should be created and consulted to ensure optimal use of antibiotics. If the MRSA rate is >10% to 20% or the patient has risk factors for MRSA, one should use vancomycin or linezolid in the empiric therapy. Two antipseudomonal agents from different classes should be utilized if the patient has risk factors for MDR organisms, >10% of gram-negative organisms are resistant based on the antibiogram, or the rates are unknown. Dual antipseudomonal therapy improves the likelihood that at least one of the agents will be effective. Monotherapy for *Pseudomonas* and gram-negative bacilli is appropriate otherwise. Monotherapy should cover methicillin-sensitive *S. aureus* (MSSA) if not at risk of MRSA and vancomycin or linezolid will not be used. Delays in starting empiric treatment and inadequate empiric treatment lead to increased mortality.

TABLE 2 Risk Factors for Multidrug-Resistant Pathogens

Risk factors for MDR VAP	Prior IV antibiotic use within 90 days Septic shock at time of VAP ARDS preceding VAP ≥5 days in hospital before VAP onset Acute RRT before VAP onset
Risk factors for MDR HAP Risk factors for MRSA VAP/HAP	Prior IV antibiotic use within 90 days
Risk factors for MDR *Pseudomonas* VAP/HAP	

ARDS, Acute respiratory distress syndrome; *HAP,* hospital-acquired pneumonia; *IV,* intravenous; *MDR,* multidrug-resistant; *MRSA,* methicillin-resistant *Staphylococcus aureus; RRT,* renal replacement therapy; *VAP,* ventilator-associated pneumonia.

Table 3 outlines the typical treatment strategies. High risk of mortality in HAP includes septic shock and the need for mechanical ventilation. In VAP, high risk of mortality includes a mortality risk rate of 25% or septic shock. Piperacillin-tazobactam, cefepime, imipenem, meropenem, and levofloxacin cover MSSA. They are appropriate monotherapy for MSSA, *Pseudomonas*, and other gram-negative bacilli when resistance rates are low, and the patient does not have risk factors for resistance as noted in the Table 2.

Aztreonam (a monobactam antibiotic) may be used as a second-line agent in combination with other B-lactam antibiotics when no other agents are appropriate. Aztreonam binds preferentially to penicillin-binding protein 3 (PBP), but a more important mechanism may be a shielding mechanism whereby aztreonam binds to the bacteria's B-lactamase, sequesters the hydrolytic capacity of the B-lactamase, and allows the other B-lactam antibiotic to bind to its target PBP. Aztreonam may be used when there is a severe IgE-mediated allergy to penicillins or cephalosporins as there is no cross-allergenicity with B-lactam antibiotics, except for ceftazidime and cefiderocol with which it shares an identical R-1 side chain. Aztreonam has no activity against gram-positive organisms or anaerobes (see Table 3).

Once culture results and susceptibility testing are available, deescalation of initial empiric treatment should be undertaken. If the results confirm MSSA, oxacillin, nafcillin, or cefazolin are appropriate narrow-spectrum choices. MRSA should be treated with vancomycin or linezolid. *Pseudomonas,* other non-glucose-fermenting gram-negative bacilli, and enteric gram-negative bacilli can be treated with monotherapy based on the hospital antibiogram and the susceptibility results. Continuation of dual therapy is recommended in the setting of septic shock or high risk of mortality. Deescalation to monotherapy is appropriate once septic shock resolves.

Aminoglycosides should be avoided as monotherapy as they have poor lung penetration, carry the risk of nephrotoxicity and ototoxicity, and have a lower clinical response rate compared with other agents, unless there are no other appropriate choices because of resistance or patient factors such as allergic reactions. In two recent randomized trials, inhaled amikacin alone and in combination with fosfomycin showed no benefit.

TABLE 3 Empiric Therapy for Hospital-Acquired or Ventilator-Associated Pneumonia

Not at High Risk of Mortality Low Risk of MRSA	Not at High Risk of Mortality Risk of MRSA	High Risk of Mortality IV Abx in the prior 90 days
Piperacillin-tazobactam	Piperacillin-tazobactam	Piperacillin-tazobactam
Or	*or*	*or*
Cefepime	Cefepime Ceftazidime	Cefepime Ceftazidime
Or	*or*	*or*
Imipenem Meropenem	Imipenem Meropenem	Imipenem Meropenem
	or	*or*
	Aztreonam	Aztreonam (Can be used as a second-line agent if no other agents are appropriate)
Or	*or*	*plus*
Levofloxacin	Levofloxacin Ciprofloxacin	Levofloxacin Ciprofloxacin
		or
		Amikacin Gentamicin Tobramycin
		or
		Colistin Polymyxin B
	plus	*plus*
	Vancomycin	Vancomycin
	or	*or*
	Linezolid	Linezolid

MRSA, Methicillin-resistant *Staphylococcus aureus.*

Acinetobacter should be treated with ampicillin-sulbactam or a carbapenem (imipenem or meropenem; ertapenem has no activity against *Pseudomonas* or *Acinetobacter* spp.). If *Acinetobacter* or carbapenem-resistant gram-negative bacilli are only susceptible to polymyxins, inhaled colistin in addition to IV colistin (also known as *polymyxin E*) or IV polymyxin B is used. Inhaled colistin is preferred over inhaled polymyxin B as colistin has better pharmacokinetics and outcomes. Adding inhaled colistin to IV colistin or polymyxin B has been shown to reduce the duration of mechanical ventilation. It should be mixed in sterile water and used immediately, and one should avoid premixed products.

Ceftolozane-tazobactam, ceftazidime-avibactam, and meropenem-vaborbactam are newer agents that should be reserved for resistant organisms as part of antibiotic stewardship programs to minimize the development of resistance caused by overuse. Ceftaroline is a fifth-generation cephalosporin with activity against MRSA and can be an alternative when vancomycin and linezolid are not appropriate. Telavancin, a lipoglycopeptide derived from vancomycin, had increased mortality in HAP and VAP, especially in the setting of renal insufficiency. Daptomycin, a lipopeptide, avidly binds to pulmonary surfactant and is inactivated, thus becoming ineffective for pneumonia caused by MRSA, except for right-sided endocarditis with hematogenous pneumonia resulting from septic embolization.

Pharmacokinetic and pharmacodynamic dosing approaches are more efficacious for several categories of antibiotics. Vancomycin should be dosed to achieve trough levels of 15 to 20 μg/mL. A more recent approach is to determine the area under the serum concentration versus time curve for 0 to 24 hours (AUC_{24}). Calculators are available for utilizing this methodology. Aminoglycosides should be dosed using once-daily regimens, typically at 7 mg/kg. The activity of B-lactam antibiotics is improved by using extended duration or continuous infusions as their cell killing is enhanced by the time the drug exceeds the minimal inhibitory concentration (MIC). Many institutions have pharmacy-directed dosing and monitoring protocols to optimize the use and safety of these agents.

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) recommends that the overall duration of antibiotic therapy for HAP and VAP should be limited to 7 days. Limiting treatment to 7 days resulted in greater antibiotic-free days and decreased recurrent VAP caused by MDR organisms. In cases of VAP resulting from nonfermenting gram-negative bacilli, vigilance for recurrence of pneumonia should be undertaken when treatment is discontinued after 7 to 8 days. Prolonged treatment has been shown to result in more cases of MDR gram-negative bacilli. Early deescalation and discontinuation decrease the incidence of complications associated with antibiotic therapy. Procalcitonin levels in addition to clinical criteria are useful in the decision making for discontinuing antibiotic therapy, especially when durations exceed 7 days.

COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is not as common in a surgical critical care unit; however, CAP may be an associated condition, particularly in some trauma patients. Developing CAP or a UTI may

make an older adult patient more prone to a fall. Head injury and surgical stroke patients may aspirate during the loss of consciousness or loss of control of the airway and develop pneumonia more appropriately categorized as community-acquired than hospital-acquired.

The common pathogens in CAP are *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, S. aureus, Legionella* spp., *Chlamydia pneumoniae,* and *Moraxella catarrhalis*. MRSA and *P. aeruginosa* may also cause CAP in patients who have had MRSA or *Pseudomonas* infections in the past year, especially respiratory infections, those who have recently been hospitalized, or those who have received IV antibiotics in the previous 90 days. The IDSA/ATS have developed criteria to distinguish nonsevere from severe CAP (Table 4).

Sputum and blood cultures are currently recommended to help guide therapy, especially to deescalate from MRSA and *Pseudomonas* therapy. MRSA nasal PCR can also be helpful in determining whether to continue or start MRSA treatment. For severe CAP, it is recommended to obtain *Legionella* and pneumococcal urinary antigen testing and sputum culture or nucleic acid amplification for *Legionella*. Testing should also be performed for COVID-19 and for influenza when it is endemic. Clinical suspicion and chest x-rays should be used to make the diagnosis of CAP. Procalcitonin is not reliable enough to be used for the diagnosis of CAP; therefore, a low procalcitonin level in a patient with high clinical suspicion and radiographic evidence of CAP should not be used to withhold antibiotic therapy (Table 5).

Nonsevere CAP, without risk factors for MRSA or *P. aeruginosa,* should be treated with a B-lactam and a macrolide or doxycycline if macrolides and fluoroquinolones are contraindicated. Monotherapy with a fluoroquinolone is an alternative. If the patient had an infection with MRSA or *P. aeruginosa* in the previous year, vancomycin or linezolid or antipseudomonal treatment should be added. If the patient was hospitalized recently and received IV antibiotics in the previous 90 days, anti-MRSA or antipseudomonal treatment should be added if nasal PCR (for MRSA) or culture is positive.

Severe CAP without risk factors for MRSA or *P. aeruginosa* should be treated with a B-lactam and a macrolide or doxycycline if macrolides and fluoroquinolones are contraindicated. If the patient had an infection with MRSA or *P. aeruginosa* in the previous year, vancomycin or linezolid or antipseudomonal treatment should be added. If the patient was hospitalized recently and received IV antibiotics in the previous 90 days, anti-MRSA or antipseudomonal treatment should be started empirically and discontinued if nasal PCR (for MRSA) or culture is negative.

Deescalation from anti-MRSA or anti-pseudomonal treatment is appropriate at 48 hours if the patient is clinically improving and if nasal PCR (for MRSA) and culture results do not show MRSA or *P. aeruginosa*. Steroids should be avoided in the treatment of CAP. The typical recommended duration of therapy is 5 to 7 days depending on the patient's clinical improvement. Procalcitonin trending can be used to assist in termination of antibiotic treatment.

Five percent to 15% of pneumonia hospitalizations are associated with aspiration; however, several studies of acute aspiration events have suggested that anaerobic bacteria do not play a major role. Aspiration events are treated in this paradigm as community-acquired, hospital-acquired, or ventilator-associated depending on the timing of occurrence.

TABLE 4 Infectious Diseases Society of America/American Thoracic Society Criteria for Severe Community-Acquired Pneumonia

Three Minor Criteria or One Major Criterion Identify Severe CAP	
Minor Criteria	**Major Criteria**
Respiratory rate ≥30 breaths/min	Septic shock with need for vasopressors
PaO_2/FiO_2 ratio ≤250	Respiratory failure requiring mechanical ventilation
Multilobar infiltrates	
Confusion/disorientation	
BUN ≥20 mg/dL	
WBC <4	
Platelets <100	
Temperature <36°C	
Hypotension requiring aggressive fluid resuscitation	

BUN, Blood urea nitrogen; *CAP,* community-acquired pneumonia; *FiO_2,* fraction of inspired oxygen; *PaO_2,* partial pressure of oxygen in arterial blood; *WBC,* white blood cell.

ABDOMINAL SEPSIS

Gastrointestinal Tract

Infections in the abdominal cavity are caused by interruptions of the gastrointestinal tract secondary to infection, inflammation, ischemic changes, or perforation. The mainstays of treatment are source control via either operative or nonoperative management with proper antibiotic selection and duration of treatment. Infection arises from a disruption in the mucosal barrier that allows the intestinal flora to propagate into the intraabdominal cavity. Antibiotic selection should be targeted based on the suspected source given their distinct flora. A perforation of the upper gastrointestinal tract (UGI) will generally yield aerobic and anaerobic gram-positive bacteria or *Candida* spp. Colonic flora generally includes aerobic and anaerobic gram-negative bacilli (e.g., *Escherichia coli, Klebsiella* spp., *Proteus* spp., and *Enterobacter* spp.), streptococci, and enterococci. *Bacteroides fragilis* and *E. coli* are the most commonly isolated growths in cases of infection.

Treatment

Surgical treatment and/or percutaneous drainage still serve as the mainstay of treatment in intraabdominal infections. In addition to providing source control, this also allows for cultures and identifying resistant organisms. In cases of community-acquired mild to moderate infection severity, such as perforated appendicitis and diverticulitis in which there is no significant hemodynamic instability, empiric treatment with a combination regimen of a first-, second-, or third-generation cephalosporin or fluoroquinolone in addition to metronidazole or a single-agent regimen consisting of ertapenem or piperacillin-tazobactam is generally sufficient. The regimen does not require specific targeting of enterococci. Cefoxitin, moxifloxacin, and tigecycline are also options but have been falling out of favor given the considerable rates of resistance to cefoxitin and fluoroquinolones among *Bacteroides* and colonic flora and increased mortality that has been associated with tigecycline when compared with other antibiotics. Ampicillin-sulbactam should also not be used as empiric therapy given its high rates of resistance to *E. coli*. For patients who are at higher risk of morbidity and mortality (e.g., severe sepsis/illness, immunocompromised state) or antibiotic resistance, empiric therapy should be broadened to cover *P. aeruginosa*, extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, *Enterococcus*, and anaerobes. Antifungal therapy is not usually required but can be considered in severely ill patients with an upper gastrointestinal source of infection. Appropriate empiric therapy can be performed in combination with cefepime or ceftazidime in combination with metronidazole or a single agent with piperacillin-tazobactam, imipenem, meropenem, or doripenem. Vancomycin with aztreonam and metronidazole is an alternative when patients have true allergic reactions to beta-lactams or carbapenems. Vancomycin should be added on if MRSA is felt to be a factor. Duration of therapy depends on the sufficiency of source control and patient response. Generally,

TABLE 5 Infectious Diseases Society of America/American Thoracic Society Strategy for Treatment of Community-Acquired Pneumonia

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and IV Antibiotics and Risk Factors for MRSA	Recent Hospitalization and IV Antibiotics and Risk Factors for *Pseudomonas aeruginosa*
Nonsevere CAP	Ampicillin/sulbactam Cefotaxime Ceftriaxone Ceftaroline *plus* Azithromycin Clarithromycin Doxycycline (if macrolide or fluoroquinolone contraindicated) *or* Monotherapy: Levofloxacin Moxifloxacin	Add:Vancomycin Linezolid	Substitute for B-lactam:Piperacillin-tazobactam Cefepime Ceftazidime Imipenem Meropenem Aztreonam (use with gram-positive agent)	Add:Vancomycin Linezolid (if nasal PCR or culture positive)	Add coverage for *P. aeruginosa* if culture positive
Severe CAP	Ampicillin/sulbactam Cefotaxime Ceftriaxone Ceftaroline *plus* Azithromycin Clarithromycin Doxycycline (if macrolide or fluoroquinolone contraindicated)	Add:Vancomycin Linezolid	Substitute for B-lactam:Piperacillin-tazobactam Cefepime Ceftazidime Imipenem Meropenem Aztreonam (use with gram-positive agent)	Add:Vancomycin Linezolid (discontinue if nasal PCR or culture negative)	Add coverage for *P. aeruginosa;* discontinue if culture negative

MRSA, Methicillin-resistant *Staphylococcus aureus; PCR,* polymerase chain reaction.

if the contamination has been successfully removed or at least has a method for successful drainage (percutaneous catheter), a course of antibiotics for four to five days has been shown to be sufficient. A longer duration can be considered in cases in which the source control is felt to be inadequate or at least suboptimal, a patient with an intraabdominal source of infection will not undergo immediate surgery (e.g., appendicitis or diverticulitis with contained perforation), or cases of percutaneous drainage in which it is felt there may be ongoing drainage as the source of infection evolves (e.g., infected hematoma that is undergoing liquefaction).

Biliary

Infections of the biliary tree can either involve the gallbladder or the biliary ducts. These can either be primary infections of the actual ducts (cholangitis) or from stasis with or without obstruction (cholecystitis, acalculous cholecystitis, choledocholithiasis, biliary malignancy, periampullary mass, biliary stricture). Biliary infections will generally involve *Enterococci,* coliforms, and anaerobes. Treatment of mild to moderate infection includes a first-, second-, or third-generation cephalosporin or a fluoroquinolone in conjunction with metronidazole. Ertapenem or piperacillin-tazobactam can be considered for monotherapy. In cases of more severe infection (e.g., biliary obstruction, bilioenteric anastomosis in which the sphincter of Oddi is no longer present, risk of antibiotic resistance, or immunocompromised state), coverage should be broadened to include anaerobes and to account for antibiotic resistance. Combination therapy includes cefepime or ceftazidime in conjunction with metronidazole or single-agent therapy with imipenem, meropenem, doripenem, or piperacillin-tazobactam.

Treatment

The mainstay of treatment is source control with proper instrumentation (cholecystectomy, endoscopic retrograde cholangiopancreatography, percutaneous drainage).

Clostridioides difficile Colitis

Clostridioides (formerly *Clostridium*) *difficile (C. difficile)* has more recently become the most common cause of healthcare-associated infection in the United States and has an important community role, as well. The hallmark symptom is described as new-onset watery diarrhea with ≥3 stools in 24 hours. A leukocytosis commonly around 15,000 cells/mL is present. Signs and symptoms usually present after antibiotic therapy and may present during therapy or up to one month afterward. Common antibiotics that predispose a patient to *C. difficile* infection (CDI) include fluoroquinolones, clindamycin, cephalosporins, and penicillin, but any antibiotic has the ability to

cause CDI. Other risk factors include older age, recent hospitalization, and possibly proton pump inhibitor use. CDI can clinically present as mild diarrhea to severe/fulminant colitis leading to septic shock and multisystem organ failure. CDI may also present as an ileus in patients with a dilated, atonic colon secondary to the disease process. Diagnosis is established with either a positive nucleic acid amplification test (NAAT) for the toxin A and B gene or a positive stool test of *C. difficile* toxin antigens. It should be noted that liquid and not solid stool should be sent for testing.

Treatment

In addition to initiating antibiotic treatment, the patient should be isolated and placed on contact precautions. Hand hygiene with soap and water is key because it is able to kill off the *C. difficile* spores. The offending antibiotic agent should be discontinued. If the offending agent is necessary to treat a concomitant infection, it would be preferred to select an agent less commonly associated with CDI. Initial treatment involves either vancomycin or fidaxomicin for 10 days. In cases of fulminant disease, therapy could include either vancomycin orally and metronidazole intravenously or fecal microbiota transplantation (FMT) and vancomycin both administered rectally. Recurrence is treated with vancomycin or fidaxomicin in pulsed-tapered regimens. In severely ill patients with toxic megacolon or fulminant colitis causing septic shock or multisystem organ failure, a subtotal colectomy should be performed with sparing of the rectum. An alternative strategy would be a diverting loop ileostomy with intraoperative antegrade colonic lavage with polyethylene glycol solution followed by antegrade vancomycin flushes. FMT has been used in some patients with fulminant colitis as an alternative to surgery. Some retrospective studies have noted a mortality benefit when comparing FMT with surgery, but prospective randomized studies are still needed. In terms of treating recurrence when antibiotic therapy has failed, a new treatment, bezlotoxumab, was introduced on the market in 2016. Bezlotoxumab is a monoclonal antibody that binds to toxin B and prevents it from penetrating the cells of the GI tract. There are several clinical trials supporting recurrence rates, but the cost can be quite prohibitive at this time.

SURGICAL SITE INFECTIONS

Background

Surgical site infections (SSIs) are among the most common healthcare-associated complications following surgery. In the United States, it is estimated that approximately 2% to 4 % of patients will develop an SSI. There are various definitions for SSI. The CDC is widely used and defines an infection following a surgical procedure occurring on or near the surgical site within 30 days postoperatively or 90 days postoperatively if an implant or hardware is involved. SSI can then be further categorized by the depth of the infection as follows:

- Superficial: Skin and subcutaneous tissue
- Deep: Deep soft tissues of the incision (e.g., muscle and fascia)
- Organ/space: Any part of the body deeper than the fascia/muscle layers that was opened or manipulated during the procedure

Diagnosis can be made by purulent drainage from the specific level of infection (drainage via drain or catheter in the case of organ/space SSI), organisms identified by culture, radiographic findings of infection, diagnosis by an attending surgeon or physician based on expert opinion, or a deep incision that spontaneously dehisces. The degree of contamination is related to the wound classification of the procedure (clean, clean-contaminated, contaminated, and dirty). It should be noted that SSIs rarely occur during the first 48 hours of the postoperative period, and fevers during this period are caused by either non-infectious or idiopathic causes. SSIs that do occur during this period are almost always caused by *Streptococcus pyogenes* or *Clostridium* spp.

Treatment

The main focus on SSI is on prevention, which involves avoiding elective surgery in patients with active infection, proper timing of prophylactic antibiotics, proper skin preparation, and maintaining sterility during the procedure. Infected wounds should be opened and drained with tissue debridement if necessary. Prophylactic antibiotics should target the flora of the intended surgical site. The need for antibiotics is determined by the extent of infection, systemic findings, and patient comorbidities leading to an immunocompromised state (e.g., chronic steroid use, diabetes, active smoking history). Generally, antibiotics should be initiated in wounds with surrounding cellulitis, when an implant is present, when there are systemic signs of infection (fever, tachycardia, leukocytosis), or when septic shock occurs despite source control. When selecting antibiotics, the mindset should follow the choice of prophylactic antibiotics in terms of the involved surgical site flora. SSI after a clean case would usually involve skin flora, which mostly include gram-positive organisms such as *Staphylococcus* and *Streptococcus* spp. Mild infections can be treated with oral antibiotics, such as cephalexin or dicloxacillin. Trimethoprim/sulfamethoxazole (TMP/SMX), clindamycin, minocycline, or doxycycline can be used orally if MRSA is of concern. In more severe cases warranting IV antibiotics, cefazolin or vancomycin for MRSA can be used. In clean-contaminated, contaminated, and dirty cases that involved the GI or genitourinary tract, therapy should target gram-negative coliforms, anaerobes, as well as gram-positive skin flora. Antibiotics should include skin flora coverage, as mentioned earlier, in combination with gram-negative and anaerobic coverage, such as piperacillin-tazobactam, a carbapenem, or ceftriaxone with metronidazole. It should be noted that skin flora in the axilla and perineum have a higher incidence of gram-negative organisms, and the perineum also has a higher incidence of anaerobes, so empiric coverage in these areas should consider including the aforementioned antibiotics.

NECROTIZING SOFT TISSUE INFECTIONS

Necrotizing soft tissue infections, also known as *necrotizing fasciitis*, are rapidly progressing, life-threatening infections. Patients usually present with fever and severe pain in an extremity or in the perineal region or lower abdomen. Early on, it can be difficult to distinguish from non-necrotizing cellulitis or scrotal abscess. If the diagnosis is not made early, frequent reevaluation will reveal the rapid progression of the infection. Plain radiographs may be helpful by revealing gas in the soft tissues in gas-forming infections. CT scanning may also show gas in the soft tissues as well as tissue edema in the area of infection. The serum sodium is usually low, and C-reactive protein may be elevated. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score may aid in making the diagnosis in unclear cases. In some cases, an exploratory incision, with the expectation for wide surgical debridement, may be necessary to make the diagnosis. Early surgical exploration and resection of necrotic tissue along with antibiotic therapy is necessary to limit the high mortality that is associated with this disease.

Necrotizing soft tissue infections are divided into two types. Type 1 is a polymicrobial infection with aerobic and anaerobic bacteria. Diabetics with peripheral vascular disease and neuropathy develop polymicrobial infections in their feet and present with gangrene often necessitating guillotine amputation. Fournier gangrene of the male genitalia, necrotizing perineal infections in women, and necrotizing postoperative infections after gastrointestinal, gynecologic, or genitourinary tract surgery are often polymicrobial. Type 2 is a monomicrobial infection and can be caused by *S. pyogenes* (group A *Streptococcus*), *S. aureus* (usually community-acquired MRSA), *Clostridium perfringens* (gas gangrene) or other *Clostridium* spp., *Vibrio vulnificus*, or *Aeromonas hydrophila*. *S. pyogenes* can enter through a skin break or can be the pathogen in a cryptogenic deep soft tissue infection with no apparent portal of entry. *S. pyogenes* releases exotoxins such as streptolysin O, streptococcal pyrogenic

exotoxin A, and hyaluronidases, which cause vascular occlusion of venules and arterioles and subsequent tissue necrosis and allow the bacteria to migrate quickly through the tissue planes. *S. aureus* can enter through skin lacerations and is often community-acquired MRSA, which may have higher virulence than the hospital-acquired strains. *C. perfringens* is a causative pathogen in penetrating trauma and crush injuries. *C. septicum* infections are associated with occult colonic malignancies, and these should be investigated after the patient stabilizes from the septic episode. *V. vulnificus* usually infects wounds that occur in seawater or brackish water. It is also the most common infection after eating contaminated shellfish. *Aeromonas hydrophila*, on the other hand, is associated with wounds occurring in fresh water, but it may also be present in brackish water in estuaries.

Once the diagnosis is made, urgent surgery is the mainstay of treatment along with antibiotic therapy. Often it is not certain what the causative pathogen is, and broad-spectrum antibiotic therapy is warranted. Initial management includes vancomycin or linezolid or daptomycin plus piperacillin-tazobactam or a carbapenem or ceftriaxone with metronidazole. If a streptococcal infection is strongly suspected, a Gram stain with many gram-positive cocci in chains or, in the case of clostridial gas gangrene, many gram-positive rods, may be enough to change treatment to penicillin G. High-dose clindamycin is often added to the regimen for *Streptococcus, Staphylococcus,* and *Clostridium* infections. It is used to stop production of toxins and other virulence factors. In a murine model, clindamycin inhibited extracellular DNase Sda1 and streptolysin O (SLO), even when the *Streptococcus* was resistant to it. The activity of clindamycin and penicillin is also complementary as clindamycin acts on the stationary growth phase of bacteria, whereas penicillin G acts on rapidly growing bacteria and is less effective against the stationary growth phase.

Definitive treatment for *Vibrio* once culture results are available is doxycycline or minocycline plus ceftriaxone or ceftazidime. *Aeromonas* is treated with ciprofloxacin or levofloxacin. Susceptibility testing should always be reviewed to ensure that the antibiotics are effective against the organism. MRSA should be treated with vancomycin or linezolid. Linezolid, like clindamycin, is a protein synthesis inhibitor against exotoxins. Streptococcal toxic shock syndrome has been treated with intravenous immunoglobulin; however, a large study found that intravenous immunoglobulin had no effect on mortality or hospital length of stay. Hyperbaric oxygen therapy can be used as an adjunctive therapy for necrotizing soft tissue infections and gas gangrene, and it may be useful to decrease the extent of necrosis. Surgery should not be delayed for hyperbaric oxygen therapy, but it can be helpful as an adjunctive therapy in the postoperative period before subsequent debridements to decrease the extent of resection.

VASCULAR ACCESS DEVICE–RELATED INFECTIONS

Background

In the critical care setting, vascular access devices provide hemodynamic monitoring, fluid resuscitation, nutrition, and medications. Despite the benefits, these devices act as potential sources of localized and systemic bloodstream infections. Some studies have estimated between 84,000 to 204,000 central line–associated bloodstream infections (CLABSI) annually that result in a possibly 25,000 preventable deaths totaling nearly $21 billion dollars on an annual basis. Two terms have been used to describe bloodstream infections related to central venous catheters (CVCs): catheter-related bloodstream infection (CRBSI) and central line-associated bloodstream infection (CLABSI; Table 6). The terms are often used interchangeably but there are notable differences. CRBSI is a clinical definition based on certain criteria. This is the preferred term used by the Infectious Diseases Society of America (IDSA). It requires specialized techniques, not readily available at all hospitals, to test the catheter as the source of infection. CLABSI is a term based on criteria to recognize bloodstream infections in patients in the presence of a CVC without an obvious secondary source of bloodstream infection. This is the surveillance definition used by the CDC. Notable differences are listed in Table 6. Given the healthcare costs, morbidity, and mortality associated with these infections, several guidelines have been put in place to aid in prevention. These include educating and training healthcare personnel to insert and maintain catheters, taking maximal sterile precautions during catheter placement, ensuring proper sterilization of the skin, avoiding replacement of the catheter, avoiding changing the catheter over a wire, using antimicrobial-impregnated dressings, and selecting the proper site. Generally, femoral catheters have the highest rates of infection, followed by internal jugular and then subclavian.

Treatment

Treatment of CLABSI entails removal of the offending catheter and systemic antibiotics. With tunneled catheters, uncomplicated exit site infections can be treated with either a short course of topical antibiotics or systemic antibiotics. However, infections of the tunnel itself necessitate removal of the catheter. Initial antibiotic treatment should be curtailed to Gram stain results and eventually tailored to culture results and antibiotic sensitivities. The majority of catheter infections are caused by gram-positive organisms, with coagulase-negative staphylococci, enterococci, and *S. aureus* being the leading offenders. Common gram-negative bacteria include *Klebsiella, Enterobacter, Pseudomonas, E. coli,* and *Acinetobacter*

TABLE 6 Comparison of Catheter-Related Bloodstream Infection and Central Line–Associated Bloodstream Infection

CRBSI	Clinical signs of sepsis and positive peripheral blood cultures in absence of an obvious source other than CVC with one of the following: • Positive semiquantitative (>15 CFU) or quantitative (>10^3 CFU) culture from a catheter segment with the same organisms isolated peripherally • Simultaneous quantitative blood cultures with a ratio of ≥3:1 (CVC vs. peripheral) • Time to culture positivity difference no more than 2 hours between CVC cultures and peripheral cultures
CLABSI	Primary bloodstream infection in a patient who had a central line within the 48-hour period before development • Infection must not be related to an alternative cause

CFU, Colony-forming units; *CLABSI,* central line–associated bloodstream infection; *CRBSI,* catheter-related bloodstream infection; *CVC,* central venous catheter.

From Bell T, O'Grady NP. Prevention of Central Line-Associated Bloodstream Infections. *Infect Dis Clin North Am*. 2017;31(3):551–559.

spp. *Candida* spp. also account for a small percentage of infections. While awaiting culture results, empiric treatment should be initiated. This involves coverage for gram-positive and gram-negative organisms with consideration for the local prevalence and institutional antibiograms. Parenteral vancomycin should be considered if MRSA is common. Gram-negative coverage should be made on the risk of pseudomonal infection. If the risk is low, a third-generation cephalosporin such as ceftriaxone would be appropriate. In patients at higher risk for resistance or who are critically ill, a beta-lactam such as cefepime or a carbapenem with or without an aminoglycoside or a combination penicillin/β-lactamase inhibitor such as piperacillin-tazobactam should be considered. Generally, fluconazole would suffice for suspected candidemia. If azole resistance is suspected (either prior azole use or a non-*albicans* species such as *C. glabrata* or *C. krusei*), an echinocandin (micafungin, caspofungin, anidulafungin) is preferred. Candidemia should be suspected in patients who are on total parenteral nutrition (TPN) or prolonged broad-spectrum or empiric antibiotics, patients with malignancy, transplant patients, or those who have undergone femoral catheterization. For uncomplicated CLABSI patients who are not at risk for hematogenous spread (hardware or immunosuppression) with negative cultures for 72 hours after catheter removal, the duration is set depending on the organism isolated. *S. aureus* infections should be treated for 2 weeks. Coagulase-negative staphylococci should be treated for 7 days. Enterococci and gram-negative bacilli should be treated for 10 to 14 days. *Candida* should be treated for 14 days. Infectious disease consultation should be performed or at least considered in cases of *S. aureus, P. aeruginosa,* drug-resistant gram-negative bacilli, or *Candida* spp. It should also be considered in patients in whom catheter removal is not possible or at least not a preferable option in which salvage would be ideal. Consult should also be considered in cases of bloodstream infection complications, such as infective endocarditis, septic thrombophlebitis, distant musculoskeletal infection, mycotic aneurysms, or vascular graft infection.

CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

Catheter-associated urinary tract infections (CAUTIs) are the most common hospital-acquired infections, and many of these infections are associated with Foley catheters. The best prevention of CAUTI is avoidance of a Foley catheter: no Foley—no CAUTI. The NHSN has defined CAUTI as (1) positive culture for bacteria, (2) Foley catheter has been in place for >2 consecutive days and was still in place or removed that day or the day prior, and (3) ≥1 symptom of urinary tract infection. A group from the University of Michigan published a tiered approach to CAUTI prevention that includes four stages: Stage 0: avoid Foley catheter placement; stage 1: place Foley catheter with aseptic technique; stage 2: maintain awareness and proper care of catheters in use; stage 3: promptly remove catheters when they are no longer needed.

Another approach to avoiding the implication of infection is urine culture stewardship. Inappropriate culturing may lead to growth of bacteria but not in the clinical context of a true infection. This often leads to treatment with its attended complications including bacterial resistance, complications from unnecessary antibiotic use, and CDI. The IDSA recommends collecting urine cultures only if patients have signs and symptoms of urinary tract infection: new onset fever or rigors, altered mental status, malaise without other cause, flank pain, CVA tenderness, acute hematuria, or pelvic discomfort. If the catheter was recently removed, add dysuria, urgency, frequency, and suprapubic pain to the list of signs and symptoms (not included for indwelling Foley catheters because the catheter itself may be the cause of these signs and symptoms).

Alternatives to indwelling Foley catheters include intermittent catheterization and external urine-collection devices, such as condom catheters and female external catheters.

When a CAUTI does occur, the pathogens are the usual hospital spectrum including Enterobacteriaceae, *Pseudomonas, Enterococcus,* and *S. aureus*. Yeasts are generally colonizing organisms and rarely cause cystitis. Immunocompromised patients may be an exception.

Initial empiric treatment includes ciprofloxacin, levofloxacin, or TMP-SMX. Nitrofurantoin is a good option in patients with a creatinine clearance ≥30 mL/min and without signs and symptoms of systemic illness (only concentrates in the urinary tract; no systemic effects). If MDR organisms are likely piperacillin-tazobactam, cefepime, a carbapenem, ceftazidime-avibactam, or plazomicin may be better choices. Therapy is deescalated based on culture and sensitivity results. Typically recommended durations of treatment for CAUTI are 7 days with prompt resolution of symptoms or 10 to 14 days if there is a delayed response to treatment. In women younger than 65 years of age, treatment can be limited to 3 days with appropriate response.

ANTIBIOTIC RESISTANCE

Antibiotic resistance began in the 1940s, shortly after penicillin came into clinical usage when *S. aureus* developed resistance to it. Currently, 50% of *S. aureus* is methicillin resistant. Four main mechanisms of resistance are limiting uptake, modification of targets, inactivation, and active efflux.

MRSA has a variant of the penicillin-binding protein (PBP) 2 (PBP2a) that is encoded by the *mecA* gene. PBP2a confers resistance to B-lactams. The *mecA* gene is located in a staphylococcal chromosome cassette (SCC). Hospital-acquired MRSAs have larger SCC mec elements (type I, II, or III), which confer high antibiotic resistance but lower virulence. Community-acquired MRSAs have smaller SCC mec elements (type IV or V), which allow slightly more antibiotic susceptibility (usually susceptible to clindamycin and tetracycline) but have more virulence. The *van* gene is responsible for vancomycin resistance in *S. aureus,* but its penetrance is low.

Vancomycin resistance occurs in 40% of *Enterococci*. Vancomycin resistance is also conferred by the *van* gene and is more common in *E. faecium* than in *E. faecalis*. Linezolid is effective against vancomycin-resistant enterococcus. Nitrofurantoin is effective for cystitis, even with creatinine clearances down to 30 mL/min. It is usually available as a delayed-release formulation and generally cannot be administered via a feeding tube. Vancomycin-resistant enterococci have variable susceptibilities to ampicillin.

B-lactamases are becoming more prevalent and more difficult to treat. Some of them are inducible, so it is important to avoid certain antibiotics when there is a high suspicion of a particular bacterium. Some laboratories may test for these enzymes and report them on the susceptibility reports or provide guidance based on the organism and the susceptibility patterns. The Ambler classification is one way of organizing the various types of B-lactamases.

Class A B-lactamases include narrow-spectrum penicillinases (most commonly found in gram-positive cocci), ESBLs, and serine carbapenemases. ESBLs confer resistance to third- and fourth-generation cephalosporins and aztreonam. Carbapenems, ceftazidime-avibactam, and ceftolozane-tazobactam are active against ESBL producers. Plazomicin, fosfomycin IV, and eravacycline may also be used. Piperacillin-tazobactam may be less effective because of the inoculum effect (in which the MIC increases with inoculum size), suboptimal dosing, or another undetected resistance mechanism. High-inoculum infections include pneumonia and bacteremia. For uncomplicated cystitis caused by an ESBL organism, nitrofurantoin, TMP-SMX, amoxicillin-clavulanate, and fosfomycin PO can be used. In urinary tract infections, fluoroquinolones should be reserved for MDR organisms.

The serine carbapenemases are carbapenem-hydrolyzing enzymes notably found in *Klebsiella pneumoniae* (*K. pneumoniae* carbapenemase) and may be found in other Enterobacteriaceae, *Pseudomonas,* and *Acinetobacter*. They confer resistance to all B-lactams. Treatment options include ceftazidime-avibactam, meropenem-vaborbactam,

and imipenem-cilastatin-relebactam. Other agents that may be effective include plazomicin, fosfomycin, eravacycline, omadacycline, and polymyxins. Polymyxin B is preferred over colistin, except for in cystitis and as an inhalation agent. Ceftazidime-avibactam plus fosfomycin has been found to be synergistic.

Class B B-lactamases are the metallo-B-lactamases (zinc dependent) and include New Delhi metallo-B-lactamase, VIM-1, and IMP-1. They hydrolyze all B-lactams except for aztreonam; however, most metallo-B-lactamase producers also produce ESBLs, which inactivate aztreonam. A treatment strategy utilizes the knowledge of these mechanisms: aztreonam is added to ceftazidime-avibactam as avibactam inactivates the ESBL, preserving the activity of aztreonam. Notably, vaborbactam is ineffective against metallo-B-lactamases. Other treatment options include aminoglycosides, plazomicin, fosfomycin, cefiderocol, eravacycline, omadacycline, and polymyxins.

Class C B-lactamases are the ampC B-lactamases. There are three mechanisms of ampC resistance. Inducible chromosomal resistance can emerge when a B-lactam agent is used and is found in *Enterobacter cloacae, Serratia marcescens, Citrobacter freundii,* and *P. aeruginosa*. A second mechanism is non-inducible resistance caused by mutations in the ampC regulatory genes as seen in *E. coli*, *Shigella*, and *A. baumannii*. Another mechanism is plasmid-mediated ampC genes inserted into the organism, which can be found in *K. pneumoniae, E. coli,* and *Salmonella* spp. AmpC may be expressed alone or in combination with other mechanisms of resistance, such as efflux pump or permeability mutations, and confers resistance to cephalosporins, especially third generation. *E, cloacae* is the most common producer of inducible ampC, and avoiding the use of third-generation cephalosporins is important in preventing the induction of this enzyme. Treatment options include carbapenems, cefepime (which is able to avoid hydrolysis by ampC), fluoroquinolones, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam. Susceptibility to ceftolozane-tazobactam should be reviewed as tazobactam is often ineffective against ampC.

Class D B-lactamases are a large heterogeneous group including the oxacillinases (OXA-23-like, OXA-48, OXA-58-like, and others). They are expressed by Enterobacteriaceae, especially *Klebsiella*. Oxacillinase-48-like carbapenemases hydrolyze penicillins efficiently with lesser effects on carbapenems and cephalosporins. Some oxacillinases are inactivated by avibactam, but vaborbactam and relebactam are unreliable against OXA-48. Additionally, some OXA-enzymes have ESBL and ampC activity. Treatment options include ceftazidime-avibactam, cefiderocol, fosfomycin, eravacycline, and polymyxins.

Carbapenem resistance in some strains of *Pseudomonas* is caused by impaired permeability and active efflux pumps rather than by a carbapenemase. Pan-resistant Enterobacteriaceae can be encountered and are resistant to B-lactams (multiple mechanisms), aminoglycosides, fluoroquinolones, TMP-SMX, and polymyxins. Cefiderocol, which has a siderophore mechanism whereby it binds to iron and is actively transported into the bacterial cell, may be a treatment of last resort.

COVID-19

SARS-CoV-2 and COVID-19 pneumonia caused the great pandemic of 2020 and had a profound impact on the world and, especially, on medical care. Many surgical critical care units became COVID-19 ICUs as hospitals became overwhelmed with the number of patients and the severity of this illness. Our medical system, like many others around the United States and the world, worked hard on assessing the emerging information about this new virus and how to treat it. Our COVID-19 treatment algorithm went through frequent (sometimes within a week) updates to provide the medical teams across the health system with guidance. Patients with confirmed COVID-19 infection and hypoxemia are treated with remdesivir and dexamethasone. Remdesivir is a nucleotide prodrug that is metabolized to remdesivir triphosphate (RTP). RTP is incorporated into the viral RNA-dependent RNA polymerase, stalling further RNA synthesis. Dexamethasone decreased 28-day mortality among COVID-19 pneumonia patients who were on mechanical ventilation. It was also beneficial for those who were receiving supplemental oxygen. This was a novel breakthrough as steroids had been shown to increase mortality in cases of severe influenza, and the World Health Organization and the CDC recommended against steroids in early 2020. Additional coverage for CAP may be considered. Procalcitonin has been used to distinguish between isolated viral pneumonia and concomitant bacterial pneumonia on presentation and to help identify when secondary bacterial infection intervenes later in the treatment course.

COVID-19 is endemic in the population, and trauma and emergency surgical patients may present with active COVID-19 pneumonia or may be asymptomatic carriers. These patients will often be treated in surgical critical care units, and it is imperative that surgical intensivists be well versed in its diagnosis and treatment.

FUNGAL INFECTIONS

Background

Fungal infections contribute to considerable morbidity and mortality ranging from superficial infections (e.g., oral candidiasis, esophagitis, mastoiditis) to more severe infections (e.g., fungemia, funguria, endophthalmitis, meningitis, endocarditis, and other solid organ involvement). The incidence of these infections has been increasing, particularly with the increasing number of immunocompromised patients, such as those with neutropenia, HIV, indwelling catheters and prosthetic devices; patients on medical immunosuppression; and those with burns, diabetes mellitus, or requiring either long-term or broad-spectrum antibiotics. Infection with *Candida* spp. is a significant strain on the healthcare system. Although several species are known to cause human disease, greater than 90% of cases are caused by *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis,* and *C. krusei*. Although they all have unique virulence, susceptibility, and epidemiology, all species have the potential to cause all of the clinical syndromes. Aspergillus has been associated with burn wounds.

Treatment

Empiric treatment should be considered in critically ill patients who meet the risk factors listed earlier with no other known source of fevers or infection. In the ICU setting, empiric therapy for suspected candidiasis in nonneutropenic patients should include echinocandins, such as caspofungin, micafungin, or anidulafungin. Fluconazole is an alternative to echinocandins in patients unlikely to have azole resistance (*C. krusei* and *C. glabrata*) and have not had recent azole exposure. All non-neutropenic patients with candidemia should have a dilated ophthalmologic examination within 1 week of diagnosis. Given the minimal ophthalmologic findings of choroidal and vitreal infection until recovery from neutropenia, examinations should be held in neutropenic patients until the first week after recovery. When candidemia is confirmed in a nonneutropenic patient, indwelling catheters should be removed. However, in neutropenic patients, candidiasis is usually from a source other than a CVC (e.g., the GI tract), and catheter removal should be based on need for the catheter and clinical evaluation of the patient. Duration of empiric therapy in the ICU setting should be for 2 weeks in patients who improve. For those who have no clinical response after around 4 to 5 days and have no evidence of candidiasis, consideration should be given to discontinuing therapy. Candidemia without solid organ metastases should be treated for 2 weeks after clearance of *Candida* from the bloodstream. In patients with evidence of *Aspergillus* infection, voriconazole generally has good efficacy.

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Endocrine Changes with Critical Illness

Laura M. Adams, MD, and Jay J. Doucet, MD, MSc, FRCSC

Critical illness in surgical patients is associated with derangements in homeostasis and alteration in endocrine function, which may be parts of a stress response. Glucocorticoid levels, catecholamine levels, insulin hypersensitivity, and changes in thyroid hormone levels are some of the alterations that can be seen. Altered function in the hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-thyroid (HPT) axes lead to multiple endocrine changes. While some of these changes are probably adaptive to physiologic stress, there have been multiple studies with therapies intended to return the axes to their normal state and subsequent controversies over whether these efforts are beneficial or not. We will review the changes in the endocrine system resulting from critical illness and the evidence for interventions to return the system function to a state thought to be more normal.

ADRENAL INSUFFICIENCY

In critical illness, the hypothalamus produces corticotropic-releasing hormone and arginine vasopressin that stimulate the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH activates the adrenal cortex to produce and release glucocorticoids including cortisol into the circulation. The glucocorticoids act on the adrenal medulla to secrete epinephrine and norepinephrine, associated with the hypermetabolic and catabolic effects of the stress response ("fight or flight"). A feedback loop regulates the HPA via glucocorticoid suppression of ACTH secretion from the pituitary (Fig. 1). Cortisol mobilizes glucose for utilization for brain and heart via increased gluconeogenesis in the liver, decreases muscle utilization of glucose by increased resistance to insulin, improves blood pressure by maintaining sensitivity of vascular smooth muscle cells to catecholamines, suppresses immune response, and inhibits inflammatory response to injury.

The classical description of the stress response indicated that the HPA axis was activated, leading to increased ACTH secretion. However, clinically, ACTH levels are significantly lower in critically ill patients and particularly in septic shock patients. Current thought is that the increase in cortisol level seen in critical illness is mediated outside of the HPA axis. This may be to response to systemic inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6, which have a positive correlation with cortisol levels in critically ill patients. Critically ill patients typically have decreased cortisol response to exogenous ACTH, indicating that increased sensitivity of the adrenal is not the cause of increased cortisol levels. Decreased metabolism of cortisol by breaking down enzymes such as A-ring reductases in the liver and 11B-NHSD2 in the kidneys is a putative mechanism for the increased cortisol level.

The relative adrenal insufficiency (RAI) concept, also known as critical illness-related corticosteroid insufficiency (CIRCI) was based on the concept that cortisol levels are increased in response to physiologic stress. With greater stress, the greater the expected cortisol rise. Sepsis is a potent stressor, and it was also known that adrenalectomized animal models of sepsis die. There are no specific symptoms of adrenal insufficiency in critically ill patients; instead, suspicion is raised by refractory hypotension despite administration of sufficient intravascular fluid resuscitation and vasopressors. Currently there are no accurate clinical findings or laboratory tests to make a definitive diagnosis of RAI. Cortisol levels vary depending on the accuracy of the test. Measurement of total serum cortisol may not correlate with free biologically active cortisol. There is hourly variation in the secretion of cortisol.

The synthetic ACTH test was used to determine the presence of REI. In the low-dose version of the test, 1 μg of ACTH was administered, and cortisol levels were obtained at baseline and at 1 hour. An inadequate rise in serum cortisol in response to ACTH, defined as a rise less than 250 nM (9 mcg/dL), was used in the 2002 Ger-Inf-05 trial (also known as the Annane trial) of corticosteroids for septic shock to identify RAI. RAI patients were randomized to receive hydrocortisone 50 mg IV q6h and fludrocortisone 50 mcg daily for 7 days. This trial yielded a contradictory mortality benefit with supplemental corticosteroids in septic shock. This supported the RAI concept suggesting a role for "physiological" doses of corticosteroids. Two subsequent trials—the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) and Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock (CORTICUS)—reported modest (CORTICUS) or no (APROCCHSS) mortality benefit in septic shock patients (Table 1). However, both studies demonstrated decreased duration of shock physiology and decreased duration of weaning of vasopressors. A 2018 meta-analysis of 42 trials reported no or limited mortality benefit at 28 or 90 days

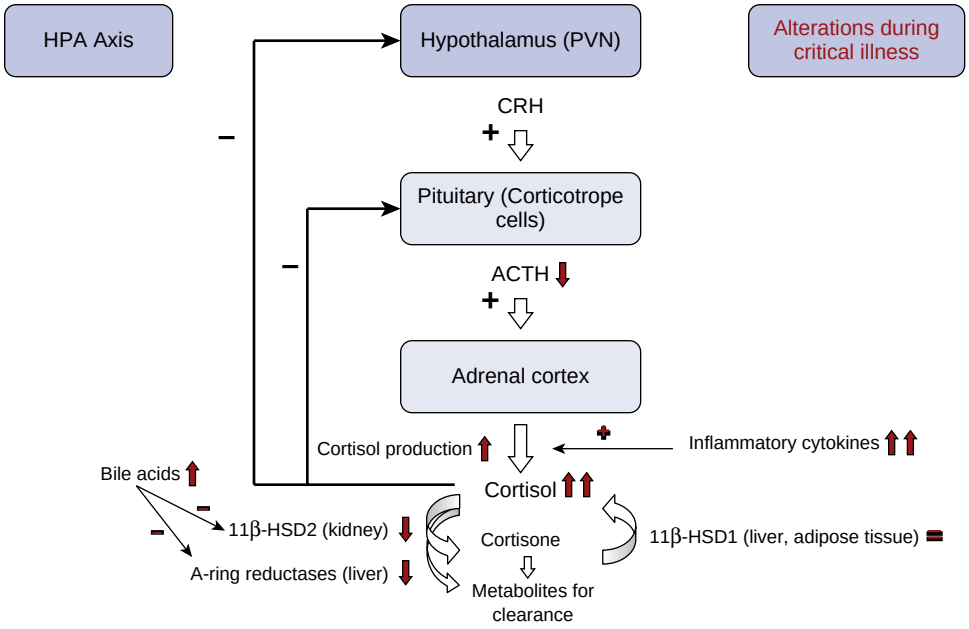


FIG. 1 Simplified overview of the regulation of the hypothalamus-pituitary-adrenal axis and cortisol metabolism during critical illness. ↑, Elevated plasma concentrations; ↓, decreased plasma concentrations; + stimulates; − inhibit; *ACTH,* adrenocorticotropic hormone; *PVN,* paraventricular nucleus. *(Modified from Peeters B, Boonen E, Langouche L, Van den Berghe G. The HPA axis response to critical illness: new study results with diagnostic and therapeutic implications.* Mol Cell Endocrinol. *2015;408:235–240.)*

with corticosteroid treatment of septic shock. A 2019 meta-analysis using random-effects modeling of 37 trials indicated steroid use in septic shock was associated with reduced 28-day mortality (RR, 0.90; 95% CI, 0.82–0.98; I2 = 27%), intensive care unit (ICU) mortality (RR, 0.85; 95% CI, 0.77–0.94; I2 = 0%), and in-hospital mortality (RR, 0.88; 95% CI, 0.79–0.99; I2 = 38%). Current Surviving Sepsis Campaign (SSC) guidelines for adults with septic shock and an ongoing requirement for vasopressor therapy recommend no further testing for RAI/CIRCI but starting administration of physiologic doses of hydrocortisone intravenously. Early tapering of the glucocorticoid dose is unnecessary and may be detrimental.

A search for adjuncts to hydrocortisone for septic shock led to a trial by Marik, which was a single-center, before-and-after trial of the "hydrocortisone, ascorbic acid, thiamine" (HAT) protocol that reported a mortality benefit in a small number of patients. However, a subsequent 2021 trial with 501 septic shock patients receiving HAT showed it did not significantly increase ventilator- and vasopressor-free days within 30 days. Five other randomized controlled trials of HAT cocktails between 2019 and 2021 showed no benefit in septic shock patients. HAT is not recommended by current SSC guidelines.

HYPERGLYCEMIA

Hyperglycemia, often associated with insulin resistance, is a frequent finding in critically ill patients. Euglycemia is maintained by the secretion of the peptide hormones insulin and glucagon from islet cells in the pancreas. Five different glucose transporter proteins (GLUT1-5) are responsible for the facilitated diffusion of glucose across cellular membranes. Insulin is known to be a strong antiinflammatory agent, but how it is regulated in critical illness is not yet clear. Insulin may potentiate the release of nitric oxide from the endothelium, which downregulates endothelial cell adhesion factors and proinflammatory cytokines.

Critical illness and sepsis are frequently accompanied by insulin resistance and dysregulation of glucose levels. Insulin-induced tyrosine phosphorylation of insulin resistance substrate 1 and subsequent activation of phosphoinositide 3-kinase is impaired in sepsis, resulting in defective GLUT4 function and decreased glucose uptake with insulin resistance in liver and skeletal muscle (Fig. 2). The resulting effect, called stress hyperglycemia, is associated with increased catabolism, including increased energy expenditure and negative nitrogen balance (Fig. 3).

Uncontrolled stress hypoglycemia in hospitalized patients has been associated in several studies with poor outcomes including increased mortality as well as increased surgical site and healthcare acquired infections. Neutrophil phagocytic activity and leukocyte oxidative bursts are decreased by hypoglycemia, which may be a cause of increased postoperative infection risk. The 2001 Leuven surgical trial reported that tight control of glucose with insulin drips to keep glucose levels between 80 to 110 mg/dL had reduced ICU mortality compared with conventional control of 180 to 200 mg/dL. Other benefits reported included decreased bloodstream infections, decreased acute need for dialysis or hemofiltration, reduced need for red cell transfusions, and less critical illness polyneuropathy. However, subsequent trials have not been able to substantiate the benefit of tight glucose control. This includes the 2009 Leuven medical trial that showed no significant difference in the primary outcome of total death from any cause in the hospital. The 2009 Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial was a multinational, multicenter pragmatic trial across medical and surgical ICUs with 6104 patients. NICE-SUGAR had the unexpected result of showing that the intensive glucose control group had a higher 90-day mortality and more hypoglycemic episodes in both medical and surgical ICU patients. There was no difference in length of stay, duration on the ventilator, or need for renal replacement therapy. A 2012 follow-up by the authors indicated that the mortality was associated with episodes of moderate to severe hypoglycemia, especially in patients with distributive shock. Initial enthusiasm for very tight glucose control has been replaced by guidelines suggesting more moderate glucose control targets. The 2021 SSC guideline recommends starting insulin therapy at a glucose level of ≥180 mg/dL (10 mmol/L) for adults with sepsis or septic shock. This is less stringent than the prior guideline, which recommended initiation of insulin therapy at a blood glucose of 150 mg/dL and maintenance of glucose levels below 180 mg/dL. Avoidance of hypoglycemia below 70 mg/dL (3.9 mmol/L) is important to avoid risk of mortality. ICUs need to carefully monitor insulin protocols to avoid hyper- and hypoglycemia, which can be associated with interruptions in tube feeding and use of inadequate sliding scale regimens or regimens that do not use long-acting insulins when transitioning off insulin drips.

Improved glycemic control can also be achieved via nutritional means such as using diabetic formulas that are low in carbohydrates, hypocaloric feeding, and supplementation with agents such

TABLE 1 Select Randomized, Controlled Trials Investigating Mortality Benefit with Corticosteroid Treatment for Septic Shock

					28-Day Mortality				
Trial	**N**	**Inclusion Criteria**	**Treatment***	**Shock Resolution**	**Control (%)**	**Treatment (%)**	**OR RR**	**Other Results**	**Conclusions**
Ger-Inf-05 (2002, Annane et al.)	299	Septic shock with hypotension resistant to ≥1	Hydrocortisone + fludrocortisone	Vasopressor withdrawal; median 7	61	55	Adjusted OR: 0.65	Effects enhanced in nonresponders	↓ 28-day mortality ↓ Duration of vasopressor administration
CORTICUS (2008, Sprung et al.)	499	Septic shock with hypotension resistant to ≥1 h vasopressors and fluid resuscitation	Hydrocortisone, 5 days, 6-day taper	Reversal of shock; median 3.3 days vs. 5.8 days	32	34	RR: 1.09 95% CI: 0.84–1.41		= 28-day mortality ↓ Duration of shock physiology
APROCCHSS (2018, Annane et al.)	1241	Septic shock ≤24 h and hypotension resistant to ≥6 h vasopressors and fluid resuscitation ≥2 dysfunctional organ systems	Hydrocortisone + fludrocortisone, 7 days, no taper	In 28 days after randomization, organ failure-free; mean 14 days vs. 12 days	33.7	38.9	RR:0.87 95% CI: 0.75–1.01	Primary outcome 90-day mortality 43 vs. 49% (RR: 0.88, 95% CI: 0.78–0.99)	↓ 90 days, ICU discharge, hospital discharge mortality ↓ Duration of vasopressor wean ↓ Duration of mechanical ventilation wean ↓ Duration of shock physiology
ADRENAL (2018, Venkatesh et al.)	3658	Septic shock and hypotension resistant to ≥4 h vasopressors and fluid resuscitation Mechanical ventilation	Hydrocortisone continuous infusion, 7 days, no taper	Resolution of shock; median 3 days vs. 4 days	23.4	22.3	OR 0.89 95% CI: 0.76–1.03	Primary outcome 90-day mortality No difference	=90-day mortality ↓ Duration of shock physiology ↓ Blood transfusion ↓ Time to ICU discharge
VICTUS (2021, Sevransky et al.)	501	Septic shock, P/F ratio of ≤300, SaO_2 FiO_2 of ≤315 + intubation and mechanical ventilation, or NIPPV, or HFNC, vasopressor > 1 h to keep MAP ≥65 mm Hg or higher despite 1 L IV crystalloid	IV vitamin C, thiamine, hydrocortisone or placebos within 4 hours of randomization and then every 6 hours thereafter up to 96 hours	Ventilator- and vasopressor-free days (VVFDs) in the first 30 days following randomization (day 0)	24	22	OR 0.9 95% CI: 0.594 –1.363	Primary outcome vasopressor and ventilator free days OR 1.030 95% CI: 0.755– 1.405	=30-day mortality

*Hydrocortisone given in 50-mg intravenous boluses every 6 h. The ADRENAL study used a continuous infusion of 200 mg daily. Fludrocortisone 50 μg was given by mouth daily where specified. *ADRENAL*, Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock; *APROCCHSS*, Activated Protein C and Corticosteroids for Human Septic Shock; *CI*, confidence interval; *CORTICUS*, Corticosteroid Therapy of Septic Shock; *ICU*, intensive care unit; *OR*, odds ratios; *RR*, risk ratio.

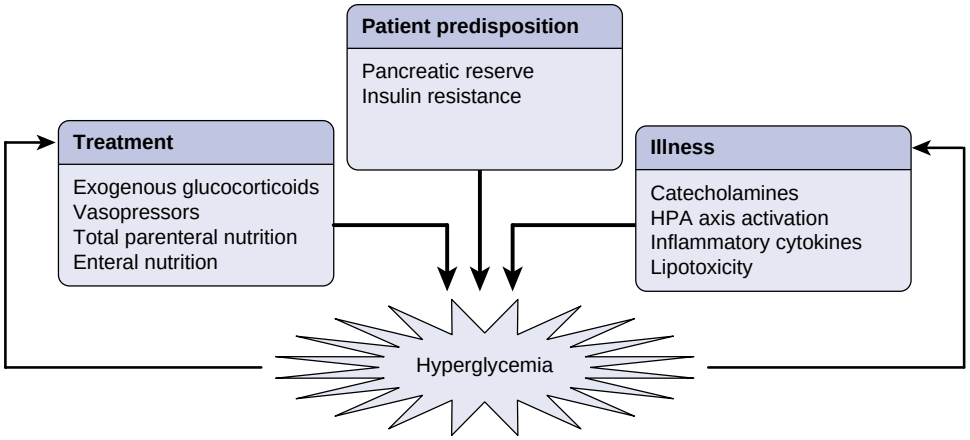


FIG. 2 Multifactorial causes of hospital-related hyperglycemia. *(From Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycemia.* Lancet. *2009;373[9677]:1798–1807.)*

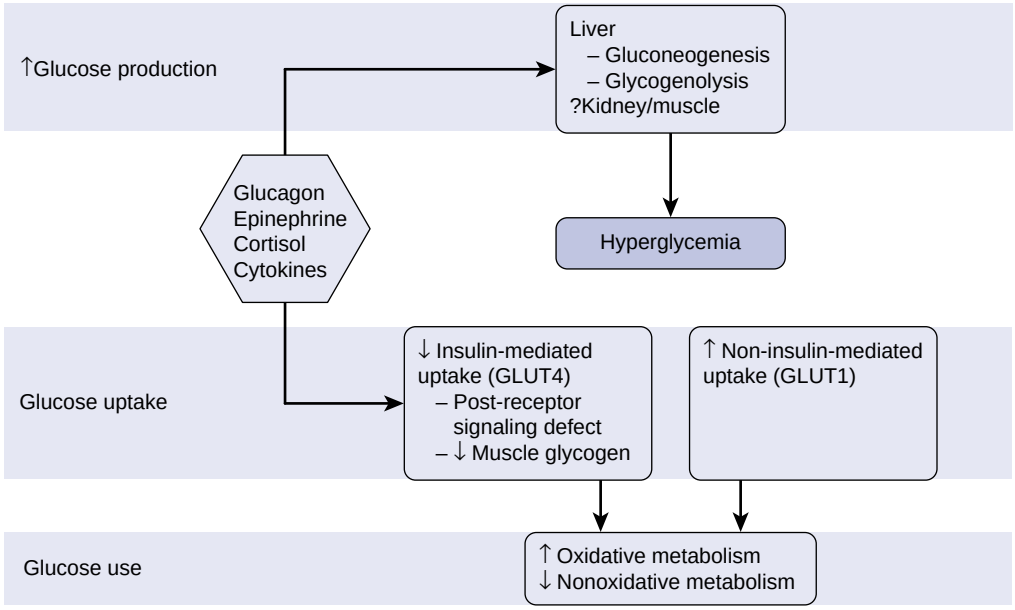


FIG. 3 Glucose metabolism in stress hyperglycemia. *(From Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycemia.* Lancet. *2009;373[9677]:1798–1807.)*

as glutamine. Although these reduce the rates of hypoglycemia and hyperglycemia, they have not been conclusively shown to improve clinical outcomes. Improved strategies for delivering insulin such as short-acting insulin infusions, continuous glucose monitoring, and closed-loop or robotic systems that can titrate continuous insulin based on continuous tissue glucose levels have also shown promise and are under study.

THYROIDAL DYSFUNCTION

Abnormal thyroid hormone levels are seen in a wide variety of critical illnesses including septic shock, myocardial infarction, burns, acute trauma, and after major surgery. Normally, serum levels of thyroid hormone are regulated through a feedback loop. Thyrotropin-releasing hormone (TSH) is secreted from the hypothalamus, which in turn stimulates the interior pituitary to synthesize and release TSH. TSH is released in a diurnal and cyclical fashion. It is the binding of TSH to thyroid physical or cell receptors that results in the release of thyroid hormones into the circulation. Thyroxine (T4) represents 90% of thyroid hormone, and 10% is triiodothyronine (T3). Free thyroid hormone comprises less than 1% of circulating hormone, and the rest is bound to proteins such as thyroxine-binding globulin, transthyretin, and albumin. The prohormone T4 is acted upon by deiodinases 1, 2, and 3, which convert it on uptake to target cells to the active form, T3, or to an inactive form, reverse T3 (RT3). A negative feedback loop is provided by the serum thyroid hormones to the hypothalamus and pituitary, which regulates TSH secretion (Fig. 4).

Patients with critical illnesses typically present with low or low normal T4, T3, and RT3 serum levels without elevated TSH. This serum laboratory picture is called nonthyroidal illness syndrome (NTIS), or euthyroid sick syndrome. Although it has been long known that NTIS severity is associated with poor outcomes of critical illness, the causes for this association have not been well studied. It is known that peripheral conversion of T4 to T3 is decreased due to decreased D1 activity and increased D3 activity. Meyer et al. found no significant difference between T3 and free T4 levels 2 days after admission to the ICU or on discharge from the ICU in critically ill patients. Free T4 levels were significantly decreased in nonsurvivors and increased in survivors. Furthermore, T3 levels on ICU admission were lower in septic patients as compared with those with systemic

inflammatory response syndrome. Decreased plasma thyroid hormone binding proteins and albumin, as well as inhibition of thyroid hormone binding transport and metabolism caused by increased bilirubin and free fatty acids, may be mechanisms for the acute decrease in T3 levels in critically ill patients.

T3 levels remain low and RT3 levels remain elevated as critical illness becomes prolonged. T4 and total thyroid hormone levels decline and TSH secretion loses its diurnal cycle. A possible reason may be a local increase in D2 activity in the hypothalamus, leading to higher local thyroid hormone levels, which alters the feedback set point. Peripheral tissues in prolonged critical illness may increase thyroid hormone transporters, activate more local thyroid hormone, and increase gene expression of active receptors. In organs such as kidney, liver, and muscle, the majority of T3 is produced by peripheral 5'-deiodination of T4 to T3 by the enzyme 5'-monodeiodinase, which has decreased activity when caloric intake is low and in lethal illness. T3 production is also inhibited by high concentrations of serum cortisol, interferon-α, nuclear factor-κB, interleukin-6, and free fatty acids as well as by medications such as amiodarone and propranolol. Inflammatory mediators also inhibit T4 binding to proteins, which results in a reduction in total serum T4. Decreased peripheral T4 deiodination by D1 or D2 may be responsible for reduced circulating T3 levels. Although a normal TSH level rules out primary hypothyroidism in healthy patients, the TSH level may be low or normal in patients with primary hypothyroidism and NTIS. Primary hypothyroidism is usually diagnosed by decreased T3 and T4 levels, but this can also be seen in patients with prolonged critical illness and during recovery from NTIS. High serum T3/T4 ratio, low serum RT3, and low thyroid hormone binding ratio may be more indicative of primary hypothyroidism, but the accuracy of these tests is limited. During recovery from prolonged critical illness, repeated testing over time may be necessary to confirm the diagnosis. In critically ill patients with elevated T3 and T4 levels, primary hyperparathyroidism should be considered, as this is a rare finding.

Management of known thyroid dysfunction in known or suspected underlying thyroid disease is different than that for NTIS. Patients with preexisting primary hypothyroidism receive a prior dose of thyroid replacement hormones. Patients with myxedema coma receive the replacement hormone, treatment of the underlying condition, and supportive care such as antibiotics, vasopressors, and passive rewarming. Intravenous glucocorticoids are also recommended because of the possibility of simultaneous adrenal insufficiency. Patients with thyroid storm are treated with propylthiouracil or methimazole, followed by iodine administration. Excess adrenergic response may be managed with β-blockers, and glucocorticoids are given if there is adrenal insufficiency.

Management of NTIS is controversial. There is no consensus in the literature regarding diagnosis and therapy. Studies have proposed thyroid hormones replacement therapy, either T4 alone or in combination with T3, but these were small, underpowered trials with heterogenous populations. In a study of severely burned patients given daily T3, no beneficial or detrimental effects were seen. In a study of coronary artery bypass graft patients, there was improved myocardial function and reduced need for vasopressors. However, there are no studies demonstrating a clear benefit in terms of long-term morbidity and mortality. Van den Berghe et al. studied patients with severe NTIS who were given TSH, growth hormone-releasing hormone, and growth hormone-releasing peptide 2, and reported protein catabolism was reduced with restored physiologic thyroid hormone levels. However, the lack of association of low T3/free T4 in this study fails to lend evidence to the potential usefulness of thyroid hormone treatment in critically ill patients. Secondary outcomes such as circulating thyroid hormone levels and markers of metabolism were improved. However, there was no impact on morbidity or mortality.

Use of thyroid hormones to treat NTIS has several challenges. High tissue levels of thyroid hormone may result from the large doses of thyroid hormone required to normalize serum levels.

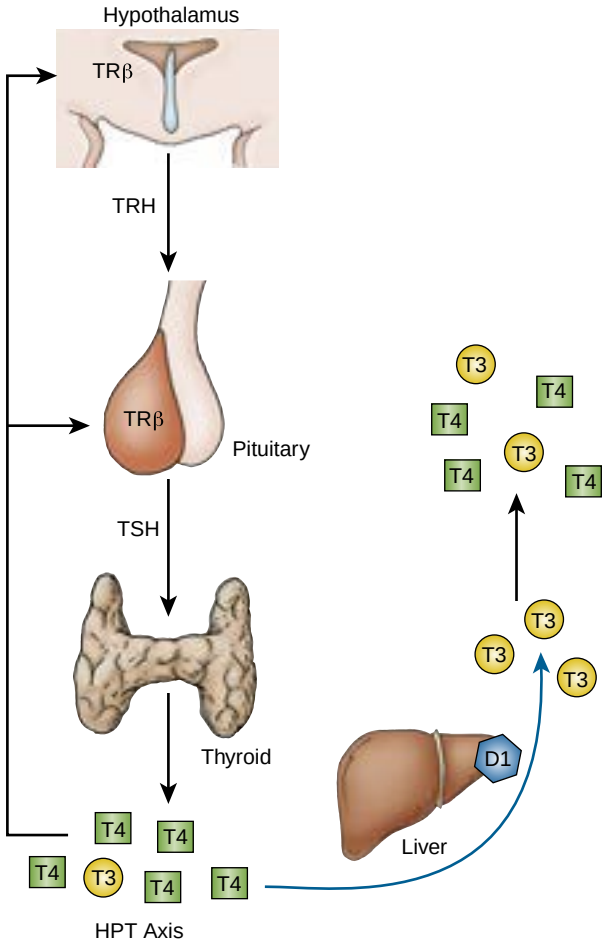


FIG. 4 Hypothalamic-pituitary-thyroid axis. *D1*, Deiodinase 1; *TRβ*, thyroid hormone receptor β; *TRH*, thyrotropin-releasing hormone; *TSH*, thyrotropin; *T3*, triiodothyronine; *T4*, thyroxine. *(From Waung JA, Bassett JH, Williams GR. Thyroid hormone metabolism in skeletal development and adult bone maintenance.* Trends Endocrinol Metab. *2012;23[4]:155–162.)*

Administration of thyroid hormone may also suppress the HPT axis, which may overutilize and deplete thyroid reserves. Administration of thyroid hormone to a patient recovering from NTIS may result in overtreatment and acute hypothyroidism.

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Nutrition Therapy in the Critically Ill Surgical Patient

Jason Sperry, MD

INTRODUCTION

Nutrition therapy has long been recognized as a critical component of medical care, both in patients with preexisting nutritional or metabolic deficiencies, as well as in healthy patients facing acute illness. More recently, the unique nutritional requirements and challenges presented by surgical patients relative to medical patients are increasingly recognized.

The correlation between nutritional status and postoperative recovery for the surgical patient was perhaps first quantified by Studley in 1936. In a series of 50 patients undergoing procedures for chronic peptic ulcers, postoperative mortality was close to tenfold higher in individuals who lost more than 20% of their body weight preoperatively. Metabolic and immune dysregulation triggered by the inflammatory insult of surgical trauma is thought to partly underlie the sensitivity to nutritional status seen among postsurgical patients. Some of the earliest published descriptions of metabolic changes after major trauma were by Cuthbertson in 1942, who characterized "ebb" and "flow" phases in metabolic alterations after trauma. Postsurgical changes to the metabolic landscape are often compounded by the inability to tolerate enteral feeding, particularly in those patients recovering from major trauma or gastrointestinal (GI) surgery.

Although the importance of nutritional optimization in recovery from major illness and surgical intervention has long been

recognized, it is arguable that it has historically been an underutilized adjunct in perioperative care. Growing awareness of this discrepancy in recent decades has led to increased interest in the crucial yet often neglected role of nutrition in the care of critically ill patients. The intent of this chapter is to review major metabolic changes triggered by surgical trauma or critical illness and to review the fundamentals of nutritional therapy in the critically ill surgical patient. In doing so, we aim to provide both a practical approach to current management of surgical nutrition and a framework for contextualizing future advances.

CHANGES IN METABOLISM IN THE ACUTELY ILL OR SURGICAL PATIENT

Critical illness and major surgery results in an initial period of stable or decreased energy requirements. Following resuscitation and stabilization, a unique hypermetabolic and catabolic state ensues to support vital organ function and repair of injured tissues. The classically described response includes activation of the stress response, resulting in increased circulation of cortisol, ACTH, catecholamines, glucagon, and inflammatory cytokines. The severe physiologic derangements are associated with a significant elevation in resting energy expenditure that can be 30% to 70% above baseline, peaks at 10 to 12 days, and can last for up to 3 weeks after resolution of acute illness.

While discrete energy requirements vary by patient factors and illness severity, patterns in energy utilization remain similar across patients. Liver synthetic activity increases, and glycogen is rapidly mobilized within the first 4 to 6 hours. Once glycogen stores are rapidly depleted, there is a shift to protein and lipid catabolism. Glutamine and alanine are released from metabolized muscle, with the latter shuttled to the liver as substrate for gluconeogenesis. These changes are summarized in Figure 1.

Prolonged protein catabolism with persistent illness or after major surgery results in peripheral insulin resistance secondary to accelerated gluconeogenesis and persistent hyperglycemia, as well as loss of lean body mass and serum albumin stores. Taken together, increased energy requirements and aberrant metabolism coupled with the challenges in providing nutrition to critically ill patients create a high risk for malnutrition.

MALNUTRITION

Although malnutrition globally impairs organ function, the GI tract is one of the first systems to be affected by malnutrition and with high consequence. Mucosal atrophy precludes the ability of enterocytes to effectively absorb and process nutrients, perpetuating a cycle of poor nutritional intake. Consequent breakdown of tight junctions of enterocytes creates deficiencies in the gut mucosal barrier and increases susceptibility to sepsis once the barrier to systemic translocation of both pathogenic and commensal bacteria is compromised. Malnutrition is directly linked to poor wound healing, immunosuppression, and perioperative morbidity and mortality.

Although malnutrition is highly prevalent in the critical care setting, approaching 50% by some estimates, variability in the definition of malnutrition creates wide variation in reported rates and limits the ability to propose subsequent interventions. Put most simply, malnutrition is any nutritional imbalance. However, this broad oversimplification lacks operative utility. By comparison, Jansen et al. defined malnutrition as a "decline in lean body mass with the potential for functional impairment at multiple levels: molecular, physiologic, and/or gross motor." The American Society for Parenteral and Enteral Nutrition (ASPEN) requires a patient to exhibit at least two of the six following criteria for a diagnosis of moderate or severe malnutrition: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation that may mask weight loss, and diminished functional status measured by hand grip strength. The Global Leadership Initiative on Malnutrition established a consensus definition of malnutrition that incorporates phenotypic and etiologic factors (Table 1).

Biochemical Markers of Nutrition

Since the inception of the field of nutrition science, the ability to accurately and swiftly determine a patient's baseline nutritive state and monitor their response to subsequent interventions has been of practical interest. The majority of biochemical markers of nutrition used in current practice are visceral serum proteins, facilitating easy serial measurement. However, as the majority of these markers are acute phase reactants, their utility in the setting of acute illness is limited.

Albumin is the most abundant protein in human serum. Its half-life of 20 days lends itself well to being used as a marker of chronic nutritional status but limits its applicability in acute critical illness. Interpretation of albumin levels can also be confounded in sustained proinflammatory states due to impaired synthesis and transcapillary leakage.

Transferrin is an acute phase reactant that acts as a transport protein for iron. While its half-life is approximately 10 days, its clinical application is limited given that values are influenced by iron status, liver disease, and inflammatory states.

Prealbumin is the most commonly utilized biochemical nutrition marker in the setting of acute illness. Also known as transthyretin, it is a transport protein for thyroid hormones. Synthesized by the liver and metabolized partially by the kidneys, the protein has a half-life of 2 days. Prealbumin levels are not affected by protein-losing enteropathies. However, values are modified by physiologic stress, infection, and liver dysfunction. Prealbumin is often obtained in conjunction with a C-reactive protein (CRP) to rule out an acute inflammatory state (defined as CRP>15 mg/L). Prealbumin and prealbumin-to-CRP ratios have been utilized as predictors of clinical outcomes, including overall survival, across a breadth of critical illnesses and surgical procedures.

Retinol binding protein has a very short half-life of 12 hours. It is more difficult to measure than prealbumin, and its levels are influenced by vitamin A levels. It is not commonly used in clinical practice.

Outside of serum proteins, several other markers of nutritional status have been studied. Urinary metabolites such as creatinine and 3-methylhistidine are proportional to muscle mass. Still, their levels are cumbersome to obtain, can be altered by renal function, and may not capture acute changes in protein stores. Other indicators of nutritional status such as delayed hypersensitivity reactions and insulin-like growth factor-1 (IGF-1) are not widely used in clinical practice given poor sensitivity and specificity in the setting of acute illness.

Anthropomorphic measurements of nutritional state include weight and body mass index. Such measurements can be misleading in assessing the nutritional status in obese patients, those with increased muscle mass, or in patients with significant edematous states. The derangements of protein metabolism in acute illness leads to sarcopenia: the loss of lean muscle mass, strength, and function. Hand grip has been verified in multiple studies as a reliable, easily measured marker of nutritional status. Other tests of sarcopenia include measurements of thigh and psoas muscle via ultrasound and computed tomography, respectively.

Scoring Systems of Malnutrition

Given that no single marker globally captures nutritional status in acute illness, numerous scoring systems have been developed to help practitioners identify patients who may benefit from aggressive

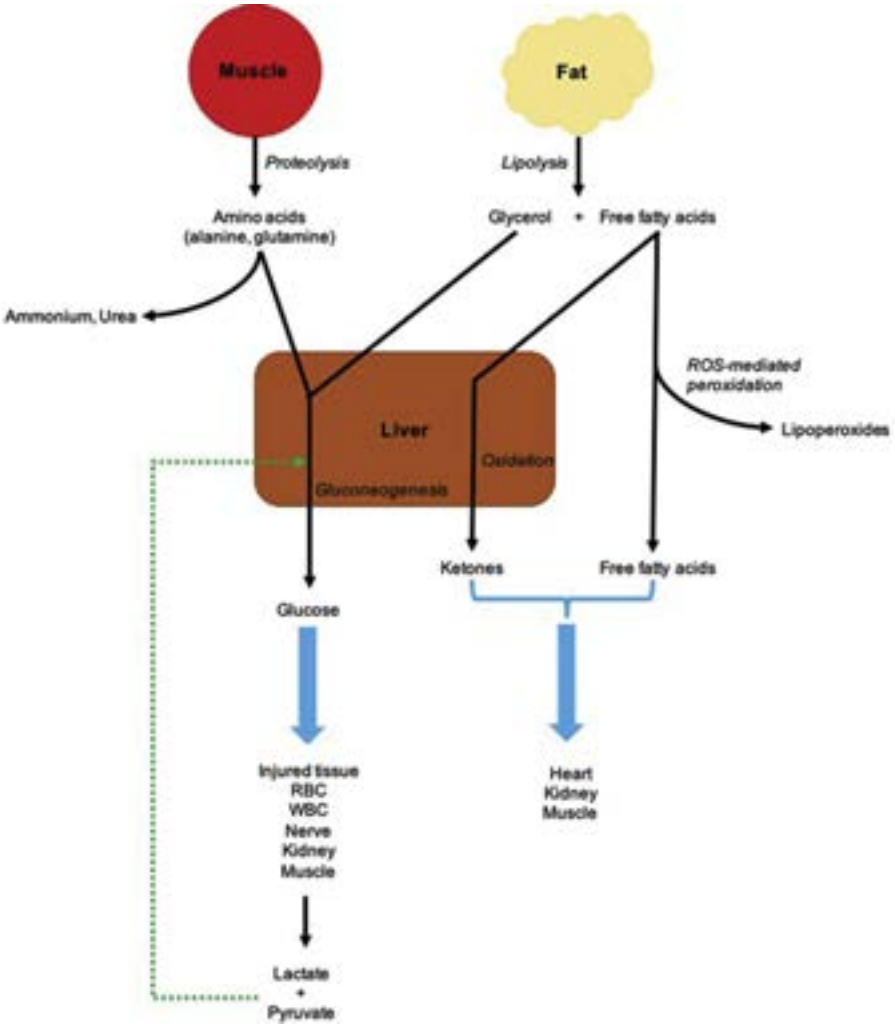


FIG. 1 Fuel utilization after major trauma. Traumatic injury alters patterns of fuel utilization. Downstream effectors of the stress response induce proteolysis of skeletal muscle and lipolysis of fat stores, releasing amino acids, glycerol, and fatty acids. Gluconeogenic amino acids (primarily alanine and glutamine) serve as substrate for hepatic gluconeogenesis, whereas fatty acids are oxidized to yield free ketones and fatty acids. Insulin resistance seen after major trauma or in critical illness results in primarily non–insulin-dependent tissues utilizing glucose for fuel. Ketones are used as a fuel source by select tissues as well. Excess amino acids are degraded into ammonium or urea. Fatty acids are prone to reactive oxygen species (ROS)-mediated peroxidation.

TABLE 1 Global Leadership Initiative on Malnutrition Diagnostic Criteria

PHENOTYPIC	
Unintended weight loss	>5% within past 6 months or >10% beyond 6 months
Low BMI	<20 if <70, <22 if ≥70
Reduced muscle mass	Reduced by validated body composition measuring techniques
ETIOLOGIC	
Reduced nutritional intake	≤50% of energy requirement >1 week, any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption
Inflammatory state/disease burden	Acute disease/injury or chronic disease-related

Requires at least 1 physiologic and 1 etiologic criterion to establish diagnosis of malnutrition. Severity of malnutrition is based upon physiologic criteria only.
Jensen, G. et al. GLIM Criteria for the Diagnosis of Malnutrition: A Consensus Report From the Global Clinical Nutrition Community. *JPEN*. 2019;43(1):32–40.

nutrition therapy. The Subjective Global Assessment, introduced in 1982, has historically been accepted as the gold standard for assessing nutritional status and need for intervention. Heyland et al. developed the Nutrition Risk in the Critically Ill score, which incorporates several measures of illness severity in additional to medical comorbidities. The Nutrition Risk Score is utilized in the ASPEN and Society of Critical Care Medicine (SCCM) guideline recommendations (Table 2).

Barriers to Nutrition

The surgical patient can present multiple barriers to nutrition, beginning with the condition for which surgery was performed. Acute and chronic illnesses can pose challenges in nutritional management by limiting use of enteral nutrition and altering metabolic demands resulting in aberrant energy expenditure.

Impairment of mental status—secondary to injury, sedation, acute illness, delirium, or chronic conditions—can preclude safe oral intake by prohibitively elevating aspiration risk. Collaboration with a speech language pathologist is vital in assessing swallowing function with the use of bedside intervention and imaging tests. Patients who cannot swallow may require placement of alternative routes to enteral access. Severe facial trauma presents similar barriers if it impairs oral intake while also prohibiting naso-oral feeding tubes and necessitating establishment of transabdominal feeding access.

A variety of GI tract injuries or dysfunctions can alter enteral nutrition tolerance and absorption. With the widespread adoption of damage control operations, clinicians are faced with patients with GI tract discontinuity for a period of time, making enteral feeding impractical. They must also be comfortable navigating the nutritional management of patients with an open abdomen, discussed later in this chapter. Motility issues such as ileus, obstruction, and gastroparesis, common after GI tract operations, also limit nutritional intake.

Adequate preoperative nutrition in the setting of elective operations can have a tremendous impact on outcomes. Patient access to adequate nutritive foods should not be neglected during preoperative planning. Socioeconomic barriers to adequate nutrition are well documented as a contributing factor to worse surgical outcomes in patients with low socioeconomic status.

DETERMINATION OF NUTRITIVE NEEDS

The metabolic demands of critical illness or the postoperative state impose highly variable nutritive requirements for optimal patient management. Caloric needs vary by gender, size, and magnitude of physiologic insult. Equations such as the Harris Benedict, used to calculate basal metabolic rate, cannot fully factor in variables altered in critically ill patients and are thus of limited use in this setting. The gold-standard method of determining caloric use, indirect calorimetry (IC), is associated with significant resource requirements and logistics that are impractical in the care of critically ill patients. New generation calorimeters incorporating smaller designs, rapid calibration, and increased ease of use may lend to more widespread utilization in the future. Interestingly, when IC has been compared with predictive equations, there does not appear to be a significant effect on mortality or certain markers of morbidity. Nevertheless, there does seem to be an improvement in nutritive intake in IC-guided nutrition plans.

Given the challenges of measuring discrete energy requirements in critically patients, the most-utilized strategy involves titration of caloric provisions with serial measurement of nutritional status. Critically ill patients may be started on a standard weight based 25 to 30 kcal/kg per day. Clinical indicators of nutritional status can direct changes in the nutrition plan as needed. Providing caloric content of 70% to 80% of the measured energy expenditure is an accepted practice; data suggests that lower and higher intakes are associated with increased mortality. Early overfeeding should thus be prevented. Interestingly, similar outcomes have been found with hypocaloric or normocaloric feeding so long as protein intake is equivalent.

Protein

Protein serves as the building block for every body system. Unlike lipids, protein is not stored for energy; loss of protein results in loss of function. The catabolic response of critical illness can rapidly deplete body protein stores. In critically ill patients with multiorgan dysfunction syndrome, muscle mass can decrease up to 20% in the first 10 days of ICU stay.

Multiple observational studies have demonstrated improvements in morbidity and mortality when higher quantities of protein are provided during nutrition therapy, although randomized controlled trial data has not demonstrated a consistent response. In the *post hoc* analysis of the RCT EPANIC trial and retrospective PROTINVENT study, early high protein intake was associated with worse outcomes, but overall low protein intake was similarly associated with higher mortality in the latter trial. ASPEN guidelines indicate protein intake should be at least 1.3 g/kg/day, which would be considered high protein intake in the aforementioned trials. Although there is no definitive consensus in the acutely ill patient, a reasonable approach to protein nutritional support is 0.8 g/kg/day for the first 5 days of critical illness with an increase to high dose after day 5.

For patients on tube feeds, protein can be provided in an intact or partially digested, hydrolyzed form. However, there is no conclusive data to suggest that hydrolyzed feeds offer any significant advantages over intact protein feeds in critically ill patients. Tube feed rate also presents challenges, with higher tube feed rates that are required to match the higher caloric and protein needs in critical illness often associated with discomfort, bloating, emesis, or diarrhea. Patients who are unable to achieve the protein goal secondary to intolerance of higher tube feed rates may benefit from modular protein supplementation. The Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol (PEP uP) is a new protocol for nutrition therapy in the critically ill with early utilization of modular supplementation. One provision of this protocol is to lessen the risk of protein debt. Patients are immediately initiated on protein supplements when enteral nutrition is started, and discontinuation does not occur until patients are receiving enough protein from tube feeds.

There is a large body of research focusing on the supplementation of specific amino acids in critically illness. Glutamine serves as a precursor for nucleotide synthesis and is a critical fuel source in cells with high turnover, including enterocytes. Despite evidence that glutamine is crucial in maintaining the gut mucosal barrier, additional supplementation of glutamine alone or in immunonutrition regimens have not demonstrated consistent improvements in morbidity or mortality.

Arginine is a conditionally essential amino acid involved in the synthesis of nitric oxide and lymphocyte differentiation and maturation. Prior concerns regarding arginine worsening the vasodilatory state in sepsis have been disproven. There has not been convincing evidence that routine arginine supplementation in addition to that already supplied in standard tube feed formulations is beneficial. Given the limited evidence that specific amino acid supplementation leads to improved outcomes, current guidelines emphasize the importance of overall protein content of feeding regimens.

Lipids

Lipids play critical roles in the maintaining the cell membrane, as precursors to steroid synthesis, and in fat-soluble vitamin metabolism, while providing the highest caloric content of any

TABLE 2 Commonly Used Scoring Systems of Malnutrition

NUTRIC Score		
Variable	**Range**	**Points**
Age	<50	0
	50–<75	1
	>75	2
APACHE II	<15	0
	15–<20	1
	20–28	2
	≥28	3
SOFA	<6	0
	6–<10	1
	≥18	2
Number of comorbidities	0–1	0
	≥2	1
Days from hospital to ICU admission	0–<1	0
	≥1	1
IL-6	0–<400	0
	≥400	1

NUTRITION RISK SCREENING 2002		
Variable	Description	Points
Nutritional impairment	None	0
	Mild: weight loss >5% in 3 months or food intake <50%–75% of normal requirement in the preceding week	1
	Moderate: weight loss >5% in 2 months or BMI 18.5–20.5 plus impaired general condition or food intake 25%–60% of normal requirement in preceding week	2
	Severe: weight loss >5% in 1 month (>15% in 3 months) or BMI <18.5 plus impaired general condition or food intake 0%–25% of normal requirement in preceding week	3
Severity of disease	Normal nutritional requirement	0
	Hip fracture, chronic illness (may have acute complications, e.g., cirrhosis or COPD), chronic dialysis, diabetes, cancer	1
	Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy	2
	Head injury, bone marrow transplant, ICU patient with APACHE >10	3
Age	<70	0
	≥70	1

APACHE, Acute Physiology and Chronic Health Evaluation.

The Nutrition Risk in the Critically Ill (NUTRIC Score) was created specifically for nutrition risk assessment in ICU patient. The original authors and further studies acknowledged that IL-6 values can be omitted from the model without a significant effect. Score totaling 6 to 10 (5–9 without IL-6) are deemed high risk for mortality and malnutrition and outcomes can be modified by nutritional intervention. The Nutrition Risk Screening 2002 (NRS2002) was designed to distinguish a positive effect in nutrition trials and is used to identify patients likely to benefit from nutrition support. All ICU patients meet initial screening criteria for an NRS 2002 score calculation. Scores range from 0 to 7 selecting the patient factors that result in the highest score. It is used in conjunction with the ASPEN SCCM 2016 Nutrition Guidelines. For example, ≤3 is low risk and applies to withholding parental nutrition for first week in patients who cannot tolerate enteral nutrition in ASPEN guidelines, recommend rescreening weekly. A score ≥5 is high risk, and it is considered criteria for faster escalation of enteral nutrition or institution of parental nutrition in 24 to 48 hours to meet caloric needs in the guidelines.

NUTRIC score adapted from Heyland et al. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care.* 2011;15(6):R268. doi:10.1186/cc10546. NRS 2002 score based upon Kondrup et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr.* 2003;22(3):321–336. doi:10.1016/s0261-5614(02)00214-5.

macronutrient per gram. Lipids of interest include omega-6 and omega-3 fatty acids. These essential fatty acids are involved in the synthesis of the inflammatory mediators eicosapentaenoic acid and arachidonic acid, respectively. While there is some inconsistent data to suggest that omega-3 fatty acid supplementation may lessen ICU length of stay, no mortality benefit has been demonstrated. In critically ill patients requiring total parenteral nutrition (TPN), there have been some weak data to support withholding the addition of intravenous fat emulsions (IVFE) for the first 7 to 10 days, as earlier initiation may increase infectious complications. Current ASPEN SCCM guidelines recommend limiting IVFE to 100 g/week for the first week.

Carbohydrates

Carbohydrates are the primary energy source in the human diet. As mentioned in earlier sections, derangements of carbohydrate metabolism in critical illness or the postoperative state can lead to relative insulin resistance and resulting hyperglycemia. Targeting a blood glucose between 140 and 180 is acceptable for most ICU patients, as studies of more stringent glucose goals resulted in worse outcomes. Certain populations have lower glucose goals, such as postcardiac surgery patients, where stricter glycemic targets have been associated with lower sternal wound infection rates.

ROUTES OF NUTRITION

When possible, enteral nutrition is the preferred route of nutritional support. Enteral nutrition has the advantages of preserving the gut mucosal barrier and reduces infectious complications when compared with parenteral nutrition. Stimulation of the gut associated lymphoid tissue and maintenance of the gut microbiome by enteral feeding may alter immune function and the inflammatory state. Early initiation, occurring within 48 hours of admission, lessens the risk of malnutrition compared with later feed initiation. Some data also suggest that it may lower infection risk.

While continuing to be topics of debate, enteral nutrition is generally withheld in uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper GI bleeding, bowel ischemia, bowel obstruction, abdominal compartment syndrome, high GI residual volume (>500 mL per 6 h), and high-output fistula without distal feeding access. It should be noted that enteral nutrition in patients on stable doses of pressors is safe despite prior practice patterns of holding nutrition due to concerns of exacerbating gut ischemia.

Routes of enteral feeding vary from physiologic oral intake to surgically placed routes of enteral access. In patients who cannot tolerate oral intake, nasoenteric tubes are a convenient option. If prolonged access is needed, surgically placed tubes often provide reliable and more comfortable options for the patient.

When comparing gastric to duodenal or jejunal tubes, there are a few noted advantages of more distal access. Jejunal tubes decrease risk of aspiration and pneumonia compared with gastric tubes. Distal tubes are also beneficial in the setting of proximal obstruction, proximal dysmotility or severe esophagitis. Postpyloric tubes may improve feeding tolerance, increasing the probability of patients receiving adequate nutrition.

Frequency and Formula of Tube Feeds

Studies on continuous versus bolus tube feeds have not demonstrated superiority of one strategy over the other. Continuous or cycled tube feeds are preferentially used with critically ill patients to mitigate their increased risk of aspiration.

Traditional practice targets a goal hourly rate of tube feeds to meet the desired caloric goal for the patient. Tube feeds are started at a slow rate that is increased slowly while monitoring tolerance with clinical evaluations of nausea and objective evaluation of gastric residual volume. The PEP uP changes this paradigm by focusing on a 24-hour total volume instead of an hourly rate and aims for goal volume immediately instead of the slow uptitration used in traditional practice. Use of a 24-hour goal volume rather than an hourly rate may be particularly beneficial in critically ill patients, who often face frequent interruptions of tube feeds.

Most patients can be initiated on a polymeric or semielemental isotonic tube feed formula, as specialty formulas have not demonstrated consistent benefits, with subsequent adjustments based on tolerance of standard formulas. One such reason to adjust formula is diarrhea. Before changing tube feed formula, the first step is to evaluate and consider discontinuing medications that could be compounding tube feed-induced diarrhea, including laxatives, prokinetics, or magnesium supplements. If there is clinical suspicion, testing for infectious causes such as *Clostridioides difficile* should also be considered. Once this is done, tube feed formula osmolality, delivery rate, formula type, and fiber content can be modified. Switching to a mixed fiber (soluble and insoluble fiber) formulation or adding a soluble fiber supplement may improve persistent diarrhea, although this must be done carefully in critically ill patients, in whom insoluble fiber can worsen dysmotility and bowel ischemia. Other adjustments to consider including switching to a formula with reduced fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPS), altering osmolality of feeds, protein composition, rate of feeds, and using antimotility medications.

For patients who have volume restrictions or cannot tolerate high volumes of tube feeds, energy-dense formulas should be considered. Motility adjuncts can also be considered for patients who continue to have difficulty reaching tube feed goals. Metoclopramide and erythromycin are the most commonly studied and most commonly prescribed prokinetic agents. Prokinetics have not demonstrated any consistent benefit with mortality, length of stay, infectious complications, or ventilator duration in critically ill patients There are data to suggest a benefit with decreasing gastric residual volumes and improve patient comfort with metoclopramide, leading to increased overall volumes of tube feeds received. As such, in the PEP uP protocol, patients are started routinely on metoclopramide unless medically contraindicated.

Total Parenteral Nutrition

When introduced in the 1960s, TPN presented a new frontier for nutritional therapy. Although our understanding of the importance of enteral feeding in maintaining the gut mucosal barrier leads to preference for enteral feeding when possible, a multitude of situations remain in which TPN is necessary. Examples include patients with severe obstruction or ileus, severe shock, a high output enteric fistula without distal feeding access, or severe GI hemorrhage. Parenteral nutrition is also necessary for patients with severe short gut syndrome or those in GI discontinuity. In patients with low nutrition risk, TPN should not be initiated for 7 days. Patients at high risk for malnutrition or already chronically malnourished should be started on parenteral nutrition as soon as feasible. In patients receiving enteral nutrition, supplemental parenteral nutrition should be initiated if they are unable to consistently obtain 60% of goal caloric needs enterally after 7 to 10 days. TPN is not without risks. Given that is most commonly infused through central access, there is an associated risk of line infections. Patients exclusively on TPN may also be at higher risk of infection due to impairment of the gut mucosal barrier in the absence of enteric feeds. TPN is also associated with metabolic derangements, including hyperglycemia, hypertriglyceridemia, and steatotic liver disease. Patients on TPN are closely monitored for these conditions with routine serum testing.

SPECIAL CONSIDERATIONS

Refeeding Syndrome

Refeeding syndrome is a potentially fatal phenomenon that occurs when nutrition is reintroduced to patients who have undergone a period of starvation (>5 days), with magnified risk in those with prolonged malnutrition. The syndrome is characterized by severe fluid and electrolyte derangements that generally occur within 72 hours of nutrition reintroduction. The underlying mechanism involves the metabolic and hormonal changes involved with refeeding after starvation as the body switch back to glucose metabolism. Notably, feeding results in increased insulin, stimulation of anabolic processes, increase in the basal metabolic rate, and the rapid intracellular migration of already depleted serum electrolytes. The hallmark electrolyte abnormality is hypophosphatemia, which results from influx of phosphate into cells to synthesize adenosine triphosphate. Hypokalemia and hypomagnesemia are also common. Refeeding syndrome can be seen in both enteral and parenteral nutrition. Management involves close monitoring of electrolyte levels, aggressive intravenous electrolyte repletion, and decreasing the caloric intake.

Pancreatitis

Feeding in acute pancreatitis has been vigorously researched without establishment of a clear consensus. Contrary to prior beliefs, earlier initiation of feeding within 24 to 48 hours is beneficial in patients with pancreatitis of any severity. Feeding should be reassessed if it increases patient discomfort. For patients requiring enteral access, nasojejunal tubes have historically been regarded as beneficial in this subset of patients to decrease pancreatic secretion by delivering postpancreatic feeds. However, several studies demonstrate noninferiority of nasogastric tubes. Immunomodulating formulas have some potential benefits in this subset of patients, but data is relatively insufficient.

Trauma/Burns

As in most critically ill patients, trauma and burn patients should receive enteral nutrition when feasible and tolerated. Burn patients have exceptionally high caloric needs due to the catabolic response to burn injuries. The increased energy requirements are proportional to burn surface area (BSA). Although the Curreri formula (25 kcal/per kg body weight/day + 40 kcal/day × % BSA burned) is the traditional estimate for caloric requirements, IC may be of benefit in these patients. Protein is critical in the burn patient with a goal 1.5 to 2 g/kg/day with a positive nitrogen balance. Ideally, enteral nutrition should be initiated within 4 to 6 hours of admission.

Nutrition therapy of trauma patients follows the standard guidelines for the critically ill patient. Immune-modulating formulas in these patients is promising, but strong evidence is lacking. Patients with traumatic brain injuries (TBI)s may benefit from postpyloric feeding tubes to lower rates of ventilator associated pneumonia. The Brain Trauma Foundation recommends that TBI patients attain basal caloric replacement by the fifth to seventh day of admission at the latest. These patients may also benefit from supplementation of arginine and omega-3 fatty acids, with data indicating lower rates of bacteremia with immune enhancing nutrition.

Open Abdomen

With the advent of damage control surgery, practitioners must be comfortable managing patients with open abdomens. Despite initial hesitancy to start enteral feeding in patients with exposed viscera, there is evidence that early enteral feeding is beneficial in the absence of bowel injury. Patients started on at least trophic enteral feeds within 48 hours have demonstrated improved rates of fascial closure and decreased incidence of fistula formation. The speculated benefits of enteral feeding are increased splanchnic blood flow and decreased bacterial translocation, which may decrease bowel wall edema, facilitating closure.

GI Surgery

Our knowledge of nutrition for patients undergoing GI surgery has evolved tremendously over the last several decades. Much of this research has emerged from the colorectal field. Enhanced recovery after surgery (ERAS) protocols have changed nutrition practices for patients undergoing GI procedures, and includes early feeding, pharmacologic strategies for prevention ileus, and a new focus on beginning nutritional therapy in the preoperative setting.

Early feeding within 24 hours after bowel resections and anastomosis has not been shown to increase anastomotic leaks or fistula formation and has been shown to reduce overall complications while decreasing length of stay. There is an increased rate of emesis in patients who undergo early feeding. Patient-controlled nutrition, in which patients advance their diet at their own request, and avoid clear liquid diets altogether, are currently being advocated in clinical practice.

Postoperative ileus is a major impediment to initiating enteral nutrition after major abdominal surgery. Sham feeding with sugar-free gum has been shown to decrease length of postoperative ileus and may lessen hospital stay. It is incorporated into many ERAS pathways. Alvimopan, a mu-opioid receptor antagonist has been demonstrated to accelerate GI function after abdominal surgery and has become a standard postoperative practice in some institutions.

Preoperative nutrition therapy is a cornerstone of ERAS protocols and is being adopted into general preoperative care for elective GI surgeries. Patients' nutritional status is closely tied to surgical morbidity and should not be neglected in the preoperative evaluation of surgical patients. Studies on preoperative nutritional supplementation have demonstrated improved outcomes after a variety of procedures.

Chyle Leaks

Chyle leaks present a challenging problem to nutrition therapy in postoperative patients. In patients with low volume leaks, low-fat, high-protein enteral diets are generally adequate. Exclusion of long chain fatty acids is advocated. If there is concern for essential fatty acid deficiency, IV fat emulsions can be given. Medium chain fatty acids are not taken into the lymphatic system in large quantity and thus can be incorporated slowly into a diet after chyle leak. For patients who do not improve on a low- or no-fat diet, TPN is appropriate. Early initiation of TPN is used in patients with high volume leaks >1 L/day, as the reduction in chyle flow may promote healing and prevent nutritional derangements. Somatostatin analogues such as octreotide can be used to reduce chyle production and improve rates of healing.

Enterocutaneous Fistula

In patients with enterocutaneous fistula (ECF) and low output (<500 mL/day), enteral nutrition may be feasible. With proximal fistulae, establishment of distal feeding access should be attempted when possible. High output fistulae (>500 mL/day) may require parenteral nutrition to meet the fluid, electrolyte, and caloric requirements required for healing. Patients with fistulae should receive protein in the range of 1.5 to 2.0 g/kg/day and possibly more with higher fistula output or enteroatmospheric fistula. Fistuloclysis, feeding through a fistula, can be used if the ECF site does close spontaneously. Tube feeds, fluids, and fistula secretion can be reinfused through the fistula in the absence of distal obstruction. Somatostatin analogues such as octreotide can be used in high-output fistulae to reduce drainage and enhance closure rates.

Morbidly Obese

The incidence of obesity continues to increase in the United States and other Western countries. Nutrition therapy in the obese patient presents unique challenges. ASPEN SCCM guidelines outline nutritional goals for obese patients, which allow permissive underfeeding, weight-based formulas for specific BMI ranges, and increased protein supplementation. Obese patients should still be started on early enteral nutrition. Although easily forgotten, obese patients are often malnourished and require the same nutritional care as patients who are cachectic.

CONCLUSION

Nutritional care in patients undergoing major surgery or critical illness poses many challenges but is inseparably tied to patient outcomes. The team approach—including nurses, dieticians, speech pathologists, and physicians—is crucial for optimal patient care. Enteral feeding should be used in most circumstances and earlier feeding of patients is generally safe. Novel technologies, protocols, and feeding formulations present new opportunities for research and nutritional interventions.

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Coagulation Issues and the Trauma Patient

Nadia Ijaz, MD, and Michael B. Streiff, MD

INTRODUCTION

More than 5 million people die worldwide each year as a result of major trauma. Trauma is the fifth leading cause of death worldwide and the number one cause of death in individuals 5 to 44 years of age. Among trauma-related deaths, hemorrhage is responsible for 30% to 40% of fatalities. Over the last decade, numerous advances have been made in the understanding of trauma-induced bleeding and hypercoagulability. In this chapter, we will review the current theories on the pathogenesis of traumatic hemorrhage and the approach to its diagnosis and management.

OVERVIEW OF NORMAL HEMOSTASIS

Normal hemostasis involves the coordinated, synergistic, and balanced interactions of the vascular system, platelets, procoagulant and anticoagulant proteins, and the fibrinolytic system. In the absence of vascular injury, each component exists in a quiescent state such that the blood remains fluid but with the potential to rapidly form an insoluble coagulum or platelet plug. In the event of an injury, the exposed subendothelial collagen binds to platelets via von Willebrand factor while tissue factor activates the coagulation cascade to form a fibrin clot. Simultaneously, the vessel wall contracts to reduce blood loss and shunts blood to intact vessels.

The prothrombotic potential of platelets and the coagulation proteins is tempered by platelet inhibitors such as prostacyclin, nitric oxide, and endogenous anticoagulants such as antithrombin, protein C, and protein S that downregulate thrombin generation and fibrin formation. In addition, the fibrinolytic system digests the fibrin clot preventing its propagation beyond the breached vessel (Fig. 1).

In major trauma, severe tissue injury and hypoperfusion precipitate the massive activation of hemostatic and inflammatory responses that are maladaptive and can lead to a fatal hemorrhagic diathesis. The following section describes the current theories on the pathogenesis of trauma-induced coagulopathy (TIC)

TRAUMA-INDUCED COAGULOPATHY

The term *trauma-induced coagulopathy* was coined at a workshop conducted by the National Institute of Health (NIH) in April 2010 to understand and address the factors involved in the diagnosis and management of hemostasis and coagulation related to severe injury and the spectrum of its presentation.

TIC can manifest itself as several different phenotypes ranging from ineffective hemostasis to hypercoagulation and states in-between. There is considerable overlap in the manifestation of these phenotypes, where initial TIC (within the first few hours) is usually due to extensive hemorrhage and shock, whereas later stage TIC (after 24 hours or so) account for a hypercoagulable state leading to thromboembolic events.

Historically, coagulopathy associated with trauma has been attributed to massive tissue factor release triggering widespread intravascular coagulation with consumption of platelets and coagulation factors leading to a bleeding diathesis. A dilutional coagulopathy from intravenous fluids used in resuscitation and the negative impact of acidosis, hypothermia, and hypocalcemia on coagulation protein function also play a role. Brohi and colleagues have demonstrated that the coagulopathy of trauma is not an iatrogenic insult caused by resuscitation but rather a consequence of the traumatic injury itself and have called this entity *acute traumatic coagulopathy*. They have also noted that acute tissue injury and hypoperfusion activate protein C lead to the degradation of factors V, Va (activated factor V), and VIIIa (activated factor VIII). The autoanticoagulant features of TIC may also result from endothelial damage and degradation of endothelial glycocalyx, which has anticoagulant properties similar to heparin. This phenomenon, called endotheliopathy of trauma (EOT), has yet to be fully explained but is considered the cause of capillary leakage. Thrombocytopenia and platelet dysfunction also contribute to the pathogenesis of TIC and are strong predictors of mortality. Hyperfibrinolysis has also been demonstrated in patients with TIC, which Brohi et al. attribute to degradation of plasminogen activator inhibitor 1 (PAI-1) by activated protein C. PAI-1 is the principal endogenous negative regulator of tissue plasminogen

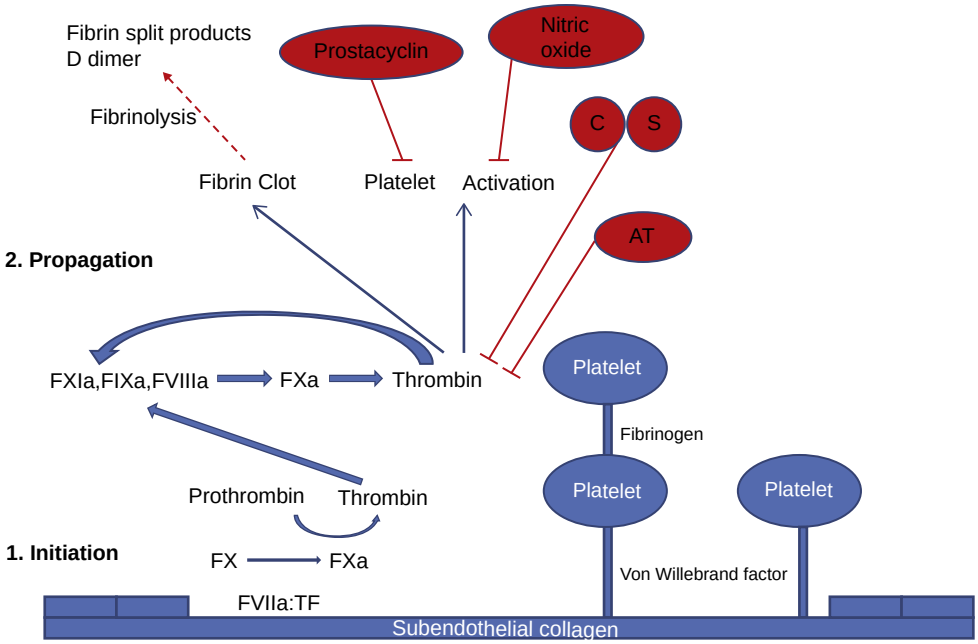


FIG. 1 Diagram of normal hemostasis. Hemostasis is initiated by the exposure of subendothelial collage which initiates activation of the coagulation cascade through tissue factor and factor VIIa. Subsequent production of small amounts of thrombin results in propagation/amplification of the coagulation response leading to fibrin clot formation and platelet activation. Collagen exposure also triggers platelet adhesion and aggregation through interactions with von Willebrand factor (adhesion) and fibrinogen (aggregation). The endogenous anticoagulant proteins, antithrombin and the protein C/protein S complex inhibit thrombin activity/generation while prostacyclin and nitric oxide inhibit platelet function. The fibrinolytic system degrades fibrin clot into fibrin degradation products such as D dimers.

activator (TPA), which activates plasminogen, the primary fibrinolytic enzyme. Gando et al. have attributed TIC to disproportionate thrombin activation and factor and platelet consumption, which is accentuated by secondary fibrinolysis (Fig. 2).

The acute coagulopathy of trauma can be further compounded by hypothermia, acidosis hemodilution, and hypocalcemia. The coagulation cascade is a series of enzymatic reactions that are temperature-sensitive. Hypothermia can be classified as mild (internal body temperature <36°C), moderate (32–36°C) or severe (<32°C). There is a 10% reduction in coagulation factor activity for each 1°C drop in body temperature. Body temperatures below 33°C have been shown to reduce coagulation factor activity to below 33% and alter fibrin kinetics. Hypothermia also affects platelet function by reducing the rate of thromboxane B2 production and the interaction of platelet surface glycoproteins with von Willebrand factor. Hypothermia may also cause hepatic sequestration of platelets. Core body temperatures above 34°C adjusted for other variables have a mortality rate of 7%, which increases to 40% with core body temperatures below 34°C. To reduce iatrogenic hypothermia, cold, wet clothing should be removed patients should be covered with warming blankets warm intravenous fluids and blood products should be administered; and operating rooms should be kept warm.

Massive injury and prolonged hypotension can cause acidosis, which in conjunction with hypothermia and excessive crystalloid resuscitation fluid can significantly affect hemostasis. Acidosis significantly impairs coagulation protease function at a pH below 7.1. Activation of thrombin is reduced by 50% at a pH of 7.2 and 90% at pH 6.8. Acidosis impairs the propagation phase of clot formation and promotes accelerated degradation of fibrin by nearly twofold. Platelet aggregation is also impaired by 50% at a pH of 7.1 or less due to changes in platelet structure.

After traumatic injury, the body attempts to correct hypotension by shifting extravascular fluid into the intravascular space. This adaptive response is compounded by administration of crystalloids during routine resuscitation. The result can be a dilutional coagulopathy that reduces coagulation factor concentrations and platelet counts. Among trauma patients who receive more than 2 liters of fluid, about 40% develop a coagulopathy. The incidence of coagulopathy increases to more than 50% among patients receiving more than 3 liters of fluid and greater than 70% among patients receiving more than 4 liters of fluid. Crystalloids also lead to tissue edema, cause compartment syndrome, and promote inflammation. Therefore, current trauma resuscitation guidelines recommend permissive hypotension with a mean arterial pressure (MAP) of 50 mm Hg. Hypotensive resuscitation (MAP ≥50 mm Hg) is associated with lower blood product utilization, a decreased incidence of coagulopathy, and lower mortality compared with standard resuscitation goals (mean MAP of 65 mm Hg). An exception is made for patients with severe traumatic brain injury (TBI) (GCS ≤8) or spinal injury where a MAP of ≥80 mm Hg is recommended to maintain tissue perfusion.

Calcium is essential for normal coagulation. About 55% of calcium is bound to albumin, and the rest is ionized calcium. Calcium ions are essential for the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X to bind to the phospholipid-rich membranes of activated platelets. Calcium is also necessary for fibrin polymerization, clot stabilization, and platelet aggregation and activity. For optimal functioning of the hemostatic system, ionized calcium concentration should be maintained above 0.9 mmol/L. Infusion of intravenous fluids and citrated blood products, such as plasma and packed red cells (pRBCs), compounded by decreased clearance of citrate due to inadequate perfusion of the liver can cause hypocalcemia.

The incidence of TIC is also influenced by the type of traumatic injury. Patients with severe blunt force trauma experience more widespread tissue damage than those with penetrating trauma where damage is more localized. Blunt force trauma victims are therefore

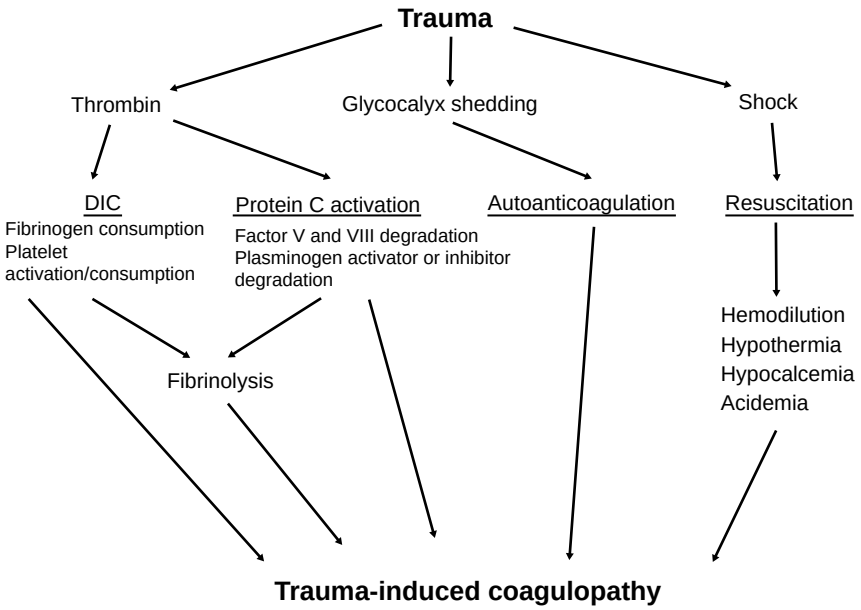


FIG. 2 The pathogenesis of trauma-induced coagulopathy. Trauma-induced coagulopathy is multifactorial. Trauma results in thrombin generation which may induced a coagulopathy by activation of the coagulation cascade and fibrinogen as well as platelets leading to a consumptive coagulopathy akin to disseminated intravascular coagulation. Secondary fibrinolysis can result in clot lysis and microvascular bleeding. Alternatively, the coagulopathy of trauma may result from the formation of thrombin-thrombomodulin complexes that activate protein C and degrade factors V and VIII and plasminogen activator inhibitor I. Some evidence suggests that endothelial injury may trigger shedding of the endothelial glycocalyx, which contains endogenous glycosaminoglycan anticoagulants that lead to a coagulopathic state. Hypotension and fluid resuscitation contribute to the coagulopathy of trauma by leading to hypothermia, hypocalcemia, acidosis, and a dilutional coagulopathy.

more prone to TIC. In patients with TBI, local release of tissue factor due to increased permeability of the blood-brain barrier and cerebral edema activates the coagulation cascade, which in turn potentiates TIC and causes greater coagulation abnormalities. Nonetheless, hypotension and decreased tissue perfusion appear to be the biggest drivers of TIC.

The presence of concomitant disease states and drug therapy can also adversely influence TIC. Patients with diseases of the bone marrow, kidney, and liver can have hemostatic aberrations due to decreased blood counts, platelet function, and coagulation factor activity, respectively. Hypertension, diabetes, and tobacco use result in endothelial dysfunction that can be compounded by acute traumatic injury. Patients on antiplatelet medications such as aspirin, clopidogrel, prasugrel, and anticoagulants such as warfarin, LMWH, and direct oral anticoagulants will present additional challenges to hemostatic management in trauma.

CLINICAL ASSESSMENT OF TIC

The clinical examination of the trauma patient focuses on vital signs and their trends, as well as signs and symptoms of bleeding including changes in mental status, urine output, abdominal distention, evidence of penetrating wounds, and intraabdominal hemorrhage including Cullen's sign (ecchymosis around the umbilicus or over the left upper quadrant reflecting intraabdominal bleeding or splenic rupture) and Grey Turner's sign (flank bruising reflecting retroperitoneal hemorrhage) (Tables 1 and 2). Thoracic trauma should prompt investigation for pneumothorax and hemothorax as well as rib/sternal fracture and rupture of the thoracic aorta. Clinical exam is supplemented with imaging techniques including chest and abdominal radiographs, ultrasonography (including point-of-care FAST ultrasound at the bedside), computed tomography, and angiography.

Laboratory testing in the diagnosis of TIC relies on standard laboratory studies including complete blood count (CBC), activated partial thromboplastin time (aPTT), prothrombin time/International Normalized Ratio (PT/INR) (Note: It is important to point out that INR is designed specifically for monitoring vitamin K antagonists), functional fibrinogen level (as measured by Clauss assay), arterial blood gas analysis, base deficit, and lactate levels. In addition, point-of-care testing with thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are increasingly being used to assess hemostasis. Serial monitoring of these tests is essential to monitor the patient for ongoing bleeding and progressive coagulopathy. Standard laboratory testing has a number of limitations. The CBC only measures platelet numbers but not platelet function. Similarly, the PT, aPTT, and fibrinogen may not provide the most accurate picture of hemostasis. These tests are performed at 37°C and at a normal pH and thus do not reflect the true extent of the coagulopathy in vivo. The PT and aPTT are relatively insensitive to reduced clotting factor levels until they decline below 30%. In addition, conventional laboratory tests take a median of 80 minutes to perform and do not provide information on clot strength and fibrinolysis.

The shortcomings of conventional laboratory testing, particularly the time taken to perform these tests, has stimulated interest in point-of-care tests. The iStat critical care analyzer (Abbott Diagnostics Point-of-Care Inc., Princeton, NJ) is a handheld point-of-care hemoglobin analyzer that can provide results within minutes. Although excellent agreement with the central laboratory CBC was obtained in cardiac surgery patients, moderate concordance with the CBC was noted in trauma patients. A meta-analysis of 32 studies of

TABLE 1 ATLS Classification of Blood Loss Based on Initial Patient Presentation

Parameter	Class I	Class II	Class III	Class IV
Estimated blood loss	Up to 750 mL	750 to 1500 mL	1500 to 2000 mL	More than 2000 mL
Estimated blood loss	Up to 15% blood volume	15% to 30% blood volume	30% to 40% blood volume	More than 40% blood volume
Pulse rate	<100	100 to 120	120 to 140	More than 140
Systolic blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14 to 20	20 to 30	30 to 40	More than 35
Urine output	More than 30 mL/h	20 to 30 mL/h	5 to 15 mL/h	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Initial fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Adapted from Spahn DR, Bouillon B, Cerny V, Duranteau J, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care.* 2019;23(1):98.

TABLE 2 ATLS Responses to Initial Fluid Resuscitation

Parameter	Rapid Response	Transient Response	Minimal or No Response
Vital signs	Return to normal	Transient improvement-recurrence of hypotension, tachycardia	Remain abnormal
Estimated blood loss	Minimal (10% to 20% blood volume)	Moderate and ongoing (20% to 40% blood volume)	Severe (More than 40% blood volume)
Need for more crystalloid	Low	Low to moderate	Moderate as bridge to blood transfusion
Need for blood	Low	Moderate to high	Immediate
Blood preparation	Type and crossmatch	Type-specific	Emergency blood release
Need for surgery	Possible	Likely	Highly likely
Early presence of surgeon	Yes	Yes	Yes

Adapted from Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care.* 2019;23(1):98.

noninvasive hemoglobin testing in 4425 patients using co-oximetry and spectroscopy devices recommended caution when using these devices for decision making regarding transfusions. More positive results have been noted with point-of-care viscoelastic hemostatic test platforms such as thromboelastography (TEG; Haemonetics Corporation, Boston, MA) and rotational thromboelastometry (ROTEM; Werfen, Bedford, MA). Unlike central laboratory coagulation tests, these viscoelastic point-of-care test systems provide a rapid assessment of whole blood (WB) coagulation as well as platelet and fibrinogen function and fibrinolysis. In the TEG system, a 0.36 mL WB sample is placed in a sample cup in which a pin is suspended. The cup rotates back and forth through an arc of 4°45′ every 5 seconds, which recreates the low-shear environment of venous blood flow. As fibrin strands are formed, they cause the pin to deviate toward the side of the sample cup. With the onset of fibrinolysis, the pin deviates back toward the center of the sample cup. The process of clot formation, contraction, and fibrinolysis is measured and graphically displayed by a transducer or electromagnetic sensing system attached to the pin, which in turn sends the information to a computer for analysis and graphing. The TEG 6s is the latest generation TEG that uses a resonance technique instead of the cup rotation, where the blood sample undergoes vibration, and the vertical movement of the blood meniscus is measured using LED illumination. In ROTEM, the pin rather than the cup oscillates 4°75′ every 6 seconds, and clot formation is detected by an optical transducer.

TEG and ROTEM measure the various phases of clot formation and dissolution using a series of parameters. The time to initial clot formation is the R time for reaction time in the TEG system and the clotting time CT on the ROTEM platform. The coagulation time or K time (TEG) or clot formation time CFT (ROTEM) represent the kinetics of fibrin formation. In both TEG and ROTEM, the alpha angle represents the burst of thrombin generation that results in rapid fibrin formation and pin deviation. The maximal amplitude (MA; TEG) or the maximal clot firmness (MCF; ROTEM) represents

the maximal strength of the clot reflecting the joint contribution of fibrin and platelets. Fibrinolysis is measured as percentage of clot lysed at 30 minutes (LY_{30} or A_{30}) in the TEG platform and the clot lysis index (the percentage of maximal clot firmness present at 30 minutes, CLI_{30}) in the ROTEM system. Measurements can also be conducted at 60 minutes on both platforms (LY_{60} and CLI_{60}).

Use of additional test reagents allows for further dissection of the hemostatic system. On the TEG platform, tissue factor can be substituted for kaolin to perform the rapid TEG or r-TEG test, which measures activation of the extrinsic pathway and normally provides results in 1 to 3 minutes instead of 3 to 8 minutes with standard kaolin TEG. In the functional fibrinogen TEG assay, abciximab is added to the reaction mix to inhibit platelet function, providing a selective view of fibrinogen function and contribution to hemostasis. The TEG platelet mapping assay evaluates platelet aggregation in the presence of adenosine diphosphate or arachidonic acid. It is used to assess the inhibitory effect of antiplatelet therapy with medications like aspirin and clopidogrel. On the ROTEM platform, EXTEM allows for interrogation of the extrinsic pathway, INTEM focuses on the intrinsic pathway, and FIBTEM selectively measures fibrinogen function. APTEM includes aprotinin in the reaction mix to eliminate the influence of fibrinolysis on hemostasis. Additional description of the standard and specialized TEG and ROTEM test parameters and their interpretation can be found in Tables 3 and 4. The FIBTEM has been demonstrated to be a predictive parameter of coagulopathic bleeding in trauma, cardiac surgery, and massive postpartum hemorrhage. Excessive fibrinolysis or hyperfibrinolysis measured with TEG and ROTEM has shown to be associated with increased mortality in trauma patients. FIBTEM and MCF have shown to predict the need for massive transfusion more accurately than the PT. Transfusion therapy based on point-of-care ROTEM testing protocols have shown to be associated with reduction in the need for blood products. However, a Cochrane systematic review found that while TEG- or ROTEM-guided transfusion protocols were associated with reduced bleeding, they had no impact on morbidity or mortality. Therefore, prospective management trials assessing the benefits of point-of-care viscoelastic testing protocols are needed.

The limitations of TEG and ROTEM include long testing times (clotting time within 5 minutes but full hemostatic analysis with fibrinolysis requires 30–40 minutes) and the need for testing at 37°C (although testing algorithms can be adjusted to 32°C and 39°C). Normal results have been seen in patients with von Willebrand disease and anticoagulants such as warfarin. In addition, POC testing requires daily calibration to ensure quality control and ongoing training to ensure testing is performed correctly.

The 2019 update of the European practice guideline on management of trauma-associated coagulopathy recommended early and repeated measurement of PT, aPTT fibrinogen, platelet counts, and point-of-care viscoelastic testing (TEG, ROTEM) be used to characterize TIC and guide hemostatic therapy. The guidelines now also consider standard parameters and viscoelastic test results as equivalent in the evaluation of bleeding in the trauma patient.

MANAGEMENT OF TRAUMA-INDUCED COAGULOPATHY

The evolution of the understanding of TIC has led to a shift in clinical management geared towards "damage control resuscitation" (Fig. 3). This approach involves hemostatic management of the lethal triad by addressing its components including preventing hypothermia, correcting acidosis, restricting resuscitative fluids to avoid dilutional coagulopathy with permissive hypotension, and early correction of coagulopathy. The damage control strategy involves a "grab and run" approach in the field to avoid prolonged transport time to the hospital. This is achieved by temporary cessation of bleeding by either direct pressure or use of tourniquets and bandaging. There is minimal fluid resuscitation en route followed by in-hospital control of bleeding or damage control strategies to control hemorrhage. This is followed by further stabilization of the patient in the ICU and finally plans for definitive surgery.

Permissive Hypotension

Instead of the traditional approach of restoring near normal blood pressure, permissive hypotension aims to maintain a MAP of 50 mm Hg, limiting systolic blood pressure to 80 to 100 mm Hg. This strategy is supported by animal trauma models that demonstrated that restoration of systolic blood pressure above 90 mm Hg was associated with disruption of hemostatic plugs, rebleeding, and worse outcomes. These results have been confirmed in trauma patients. Patients whose MAP was maintained above 50 mm Hg required less IV fluids, fewer blood products, and had lower mortality than patients with a MAP target of 65 mm Hg. One exception to this rule is a patient with TBI, where maintenance of intracranial perfusion pressure is of paramount importance to limit neurologic injury. Therefore, maintenance of a MAP of 80 mm Hg is recommended for TBI patients.

Targeting a lower mean arterial blood pressure limits administration of intravenous crystalloid reducing the likelihood of dilutional coagulopathy. Randomized controlled trials (RCTs) found no advantage of colloid (albumin) versus crystalloid administration in ICU patients. Albumin was associated with worse survival outcome in patients with TBI. Use of hypertonic saline is not associated with any benefit in TBI or hypovolemic shock. Hypotonic solutions should be avoided in TBI as they can increase cerebral edema.

Hypothermia, Acidosis, and Hypocalcemia

Hypothermia is a key component of the lethal triad. Passive (warm ambient temperature, blankets, removal of wet or cold clothing) and active warming (forced hot air warming devices, warmed IV fluids and blood products) techniques should be employed. Acidosis can contribute to TIC. Although bicarbonate and tris-hydroxymethyl amino methane (THAM) can increase pH, there is no evidence that these interventions can significantly affect hemostasis in trauma patients Instead, aggressive blood product support and surgical control of bleeding should be emphasized. If reversal of severe acidosis is necessary, experts have recommended THAM over bicarbonate since it does not result in excess sodium administration or CO_2 production.

Calcium is necessary for normal function of vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X. Therefore, maintenance of normal calcium concentrations is necessary for normal hemostasis. As mentioned earlier, citrated blood products along with hypoperfusion of the liver to remove citrate can lead to hypocalcemia. Hypocalcemia has been associated with increased mortality. Therefore, the 2019 European Trauma Guideline recommends regular monitoring of ionized calcium during massive transfusion and calcium supplementation as needed to maintain calcium levels in the normal range.

BLOOD PRODUCT MANAGEMENT

Massive blood component transfusions are undertaken in severe traumatic injury to account for the acute loss of blood. Most hospitals now have massive transfusion protocols (MTP) in place. Once these protocols are activated early on in trauma, they allow for rapid initiation of blood component delivery leading to lower overall total blood component use, decreased organ failure, and lower mortality in trauma patients.

Management of transfusions in traumatic injuries has been profoundly influenced by advances made in the treatment of combat injuries. Experience in the Iraq War suggested that a transfusion ratio of 1:1:1 for red blood cells, platelets, and plasma was associated with improved outcomes for patients with massive bleeding.

TABLE 3 TEG and ROTEM Test Parameters and Interpretation

Physiologic Event	Hemostatic Variable Measured	Test Threshold	TEG Test Parameter	ROTEM Test Parameter	Hemostatic Therapy
Clot initiation time to initial fibrin formation	Reflects concentration of coagulation factors upstream of fibrinogen	Time from test initiation to deviation of pin 2 mm from center	R Time (Reaction time) Normal range 3–8 minutes (citrate or kaolin activation)	Clot time (CT) EXTEM: 42–74 sec INTEM: 137–246 sec	Plasma
Clot formation kinetics	Reflects functional fibrinogen concentration/rate of fibrin formation	Time required to deviate pin from 2–20 mm	K time Normal Range 1–3 minutes (citrate or kaolin activation)	Clot Formation Time (CFT) EXTEM: 46–148 sec INTEM: 40–100 sec	Cryoprecipitate/fibrinogen concentrate
α angle	Reflects functional fibrinogen concentration/rate of fibrin clot formation	Angle in degrees formed by line from horizontal to line at 2 and 20 mm of pin deviation	α angle Normal range 55–78 degrees (citrate/kaolin)	α angle EXTEM: 63–81 degrees INTEM: 71–82 degrees	Cryoprecipitate/fibrinogen concentrate
Maximal clot strength	Measures interaction between fibrin and platelets and platelet function	The maximal distance of pin deviation	Maximal Amplitude (MA) Normal Range 51–69 mm	Maximal Clot Firmness (MCF) EXTEM: 49–71 mm INTEM: 52–72 mm FIBTEM: 9–25 mm	Platelets/cryoprecipitate/fibrinogen concentrate
Fibrinolysis	Measures activity of the fibrinolytic system	TEG: Percent decrease in MA deviation at 30/60 min ROTEM: Residual clot measured as percentage of MCF remaining at 30/60 minutes	Lysis at 30 minutes (LY30) Normal range: 3%–7.7%	Clot Lysis Index at 30 min (CLI30) Normal range: 94%–100%	Tranexamic acid

Legend: EXTEM refers to ROTEM test parameter that looks at the extrinsic pathway, INTEM refers to the ROTEM test parameter that looks at the intrinsic pathway, and FIBTEM is a ROTEM test parameter that focuses exclusively on the contribution of fibrinogen to clot.

TABLE 4 Specialized TEG and ROTEM Tests

Test	Additives	Mechanism	Indication
Kaolin TEG	Kaolin (highly charged aluminum silicate)-cephalin (phospholipid phosphatidylethanolamine)	Kaolin-cephalin activates contact factors in the intrinsic pathway	Evaluates function of intrinsic and common pathways
Rapid TEG	Tissue factor	Tissue factor activates factor VII in the extrinsic pathway	Evaluates function of the extrinsic and common pathways
Functional Fibrinogen TEG	Abciximab- monoclonal antibody against glycoprotein IIb/IIIa blocks platelet aggregation	Abciximab blocks platelet aggregation	Measures fibrinogen function/contribution to hemostasis
ROTEM EXTEM	Tissue factor/polybrene (polybrene inhibits heparin)	Tissue factor activates factor VII in extrinsic pathway	Measures function of extrinsic and common pathways
ROTEM INTEM	Ellagic acid	Ellagic acid activates contact factors in the intrinsic pathway	Evaluates function of intrinsic and common pathways
ROTEM FIBTEM	Tissue factor/polybrene/cytochalasin D	Tissue factor activates extrinsic pathway. Cytochalasin D blocks actin to prevent platelet function	Evaluates the fibrinogen function and its contribution to hemostasis exclusive of platelet function
ROTEM APTEM	Aprotinin	Aprotinin inhibits plasmin blocking fibrinolysis	Evaluates fibrinolysis

A meta-analysis demonstrated that a plasma-to-red cell ratio of 1:1 to 1:2.5 was associated with a 62% reduction in the risk of death, although the authors underscored that the level of supporting evidence was low. A prospective study that measured hemostatic parameters after every 4 units of blood found that plasma-to-red cell ratios of 1:2 or 3:4 was associated with optimal hemostasis by laboratory testing. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial published in 2015 was a multicenter that showed no difference in mortality at 24 hours and 30 days in patients transfused with plasma, platelets, and pRBCs in the ratio of 1:1:1 or 1:1:2. More patients in the group receiving blood products in the ratio of 1:1:1 achieved hemostasis at 24 hours, with fewer deaths due to bleeding. The safety profile and complications in both groups were similar. The current 2019 European Trauma Guideline recommends plasma be administered in a ratio of at least 1:2 with red cells in patients with massive hemorrhage. Fibrinogen concentrate and pRBCs can also be used early on, but further management should be based on coagulation parameters or results of viscoelastic testing.

Fresh Whole Blood

The military has been using fresh whole blood (FWB) since World War I. A single 500 mL unit of FWB has a hematocrit of 38% to 50%, 15 to 40 $\times$ 10^5 platelets per microliter, and 100% clotting factor activity. This makes FWB an attractive replacement product, especially in combat settings where there is a large ready supply of available donors. The use of WB in civilian trauma patients is uncommon; however, it has started to gain traction. A civilian trial conducted by Cotton et al. in 2013 reported that use of WB was not superior to use of individual blood components in severely injured patients predicted to receive massive transfusion. However cold-stored low-titer group O blood (LTOWB) is being used in civilian settings without evidence of hemolysis in nongroup O patients and without increased transfusion reactions. There appears to be a 50% reduction in post-ED blood product use when compared with component therapy after controlling for variables such as severity of trauma. Compared with component therapy, WB has less volume and can be stored in a single medium. However, certain questions remain unanswered regarding large volume transfusion, definition of low titer, and the issue of leukoreduction, which can affect platelet functions and duration of storage.

Packed Red Blood Cells

Most patients who are actively bleeding receive pRBCs instead of WB. Red blood cells not only improve tissue perfusion and oxygenation, RBC also express phosphatidylserine on their surface, which actively participates in thrombin generation and hence assists in coagulation. RBC also augment hemostasis via a phenomenon called "margination" where RBC cause platelets to shift toward the periphery, increasing their proximity to injured vessel walls and facilitating adhesion during trauma. Anemia is associated with a reduction in platelet aggregation and activation. A drop in the hematocrit from 40% to 10% decreases platelet function fivefold. The loss of as little as 2 units of blood is associated with a 60% increase in the bleeding time.

A unit of pRBCs has an average volume of 250 mL and hematocrit of about 70%. It can raise the hemoglobin by 1g/dL and the hematocrit by 3%. The shelf life is about 42 days. However, cryopreserved RBCs have a shelf life of 10 years.

Packed RBC transfusions are not without risks. Acute reactions to pRBC transfusion can occur including acute febrile or hemolytic transfusion reactions and hypocalcemia due to the acid citrate dextrose used as an anticoagulant in RBC units. The delayed effects of pRBC include transfusion transmitted infections, delayed immunologic transfusion reactions, multiorgan failure, systemic inflammatory response syndrome, and sepsis. Mortality is increased in trauma patients transfused RBC with a predicted low risk of death. Strategies to minimize the need for RBC include intraoperative salvage of spent RBC, permissive hypotension, and ICU protocols with lower transfusion triggers. Regarding the logistics, group O pRBC and AB plasma are used as universal donor products, and they are immediately available for transfusion. Type-specific blood is usually available in 5 to 10 minutes, and crossmatched blood usually takes 40 minutes to an hour to prepare.

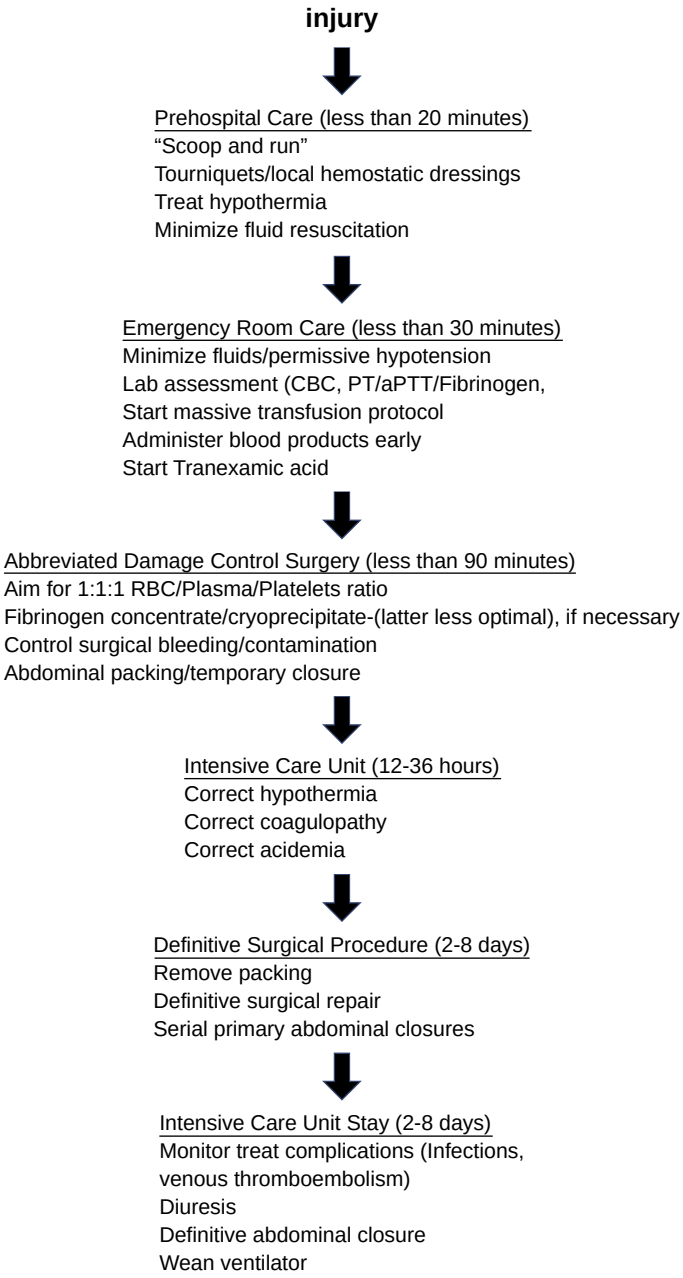


FIG. 3 Contemporary approach to traumatic injury management. *(Adapted from Duque P, Mora L, Levy JH, Schöchl H. Pathophysiological Response to Trauma-Induced Coagulopathy: A Comprehensive Review.* Anesth Analg. *2020; I 30:654–664.)*

Plasma

Plasma is an excellent source of albumin and all the coagulation factors including fibrinogen. Plasma is collected from WB or by apheresis and is termed fresh-frozen plasma (FFP) if it is frozen within 8 hours of collection or called FP24 if frozen within 24 hours. FFP is stored at −25°C and keeps for 1 year. It requires thawing before use and should be compatible with the recipient ABO type. Rh compatibility and crossmatching are not needed. As FFP must be thawed before use and thawing plasma can take time, major trauma centers usually have thawed plasma on hand. In addition, they have rapid thawing devices that can thaw 2 units of plasma in about 2 minutes. Once thawed, plasma should be transfused within 24 hours. Thawed plasma can be kept refrigerated for 5 days. A unit of FFP is given over 30 minutes and requires a standard 170 to 200-micron filter. A 250 mL unit of plasma provides about 500 mg of fibrinogen. There is some loss of factors V and VIII, but most coagulation factors are still available at satisfactory levels.

Another type of plasma called liquid plasma or never frozen plasma keeps for 26 days and can be used in settings where availability of thawed plasma may be problematic. Lyophilized, freeze-dried, or spray-dried plasma (solvent/detergent treated) was initially used by the US Army in World War II for rapid resuscitation of war casualties. This plasma (LyoPlas N-w) is compatible with all blood groups and does not contain ABO antibodies. It is leukodepleted and attenuated to reduce the risk of infection and transfusion-related reactions. It can be stored at room temperature for 2 years and reconstituted within minutes with sterile water (200 mL) provided in the kit. Storage at 2°C to 8°C causes only a 10% reduction in factors V, VIII, and wWF, whereas storage at room temperature reduces fibrinogen and wWF by 54%. It should be used within 6 hours of reconstitution. Due to ease of transport, quick reconstitution, and admission, freeze-dried plasma appears to be a promising agent in trauma-induced bleeding. So far, it is not routinely used in civilian practice.

Disadvantages of plasma include greater product volume (although this can be an advantage during resuscitation), transfusion-associated infectious diseases (less for solvent-detergent plasma), transfusion-related lung injury (TRALI), and allergic reactions.

Fibrinogen Replacement

Fibrinogen is the precursor to fibrin clot formation and the principal mediator of platelet aggregation. Fibrinogen is the first coagulation factor to be depleted in severe bleeding. Hypofibrinogenemia is common in patients with massive blood loss and independently associated with severe bleeding in patients. In a multicenter trial, fibrinogen values below 229 mg/dL were associated with significantly increased mortality. Fibrinogen function can be monitored using conventional laboratory assays such as the Clauss fibrinogen assay or with point-of-care tests such as TEG or ROTEM. Retrospective studies suggest that early use of fibrinogen for hemorrhage control is associated with effective bleeding control and may provide a mortality benefit, but confirmatory prospective studies are needed.

Fibrinogen can be administered as FFP, cryoprecipitate, or fibrinogen concentrate (Table 5). Administration of FFP alone is unable to provide clinically significant increases in fibrinogen and bleeding control as evidenced by a single RCT comparing coagulation factor concentrates and FFP, which had to be terminated early due to treatment failure in the FFP arm. Cryoprecipitate, the precipitate harvested after thawing FFP slowly at 4°C, contains 150 to 250 mg of fibrinogen per 15 to 20 mL unit. In an average size adult (80 kg), each unit of cryoprecipitate should raise the fibrinogen level 10 mg/dL. An advantage of cryoprecipitate is that it allows infusion of larger amounts of fibrinogen (1000–2500 mg in one 10-unit transfusion) in a smaller fluid volume (200 mL), avoiding the larger volumes required for FFP and allowing for more rapid administration of fibrinogen. Disadvantages of cryoprecipitate include the risk for transfusion-associated infectious diseases (10 donor exposures for one 10-unit cryoprecipitate transfusion), TRALI, and allergic reactions. Due to the risk of infection, several countries in Europe no longer use cryoprecipitate.

Fibrinogen concentrates such as RiaSTAP (CSL Behring, King of Prussia, PA) are virally inactivate concentrates of human fibrinogen that have been FDA approved for the treatment of congenital afibrinogenemia and hypofibrinogenemia. Fibrinogen concentrates afford the advantage of a more rapid preparation time, larger fibrinogen concentrations in smaller infusion volumes, and lower risks for transfusion-related infectious diseases. Fibrinogen concentrates provide a consistent dose of fibrinogen with administration compared with FFP

and cryoprecipitate, but they are more expensive as well. The European Trauma Guideline recommends close monitoring of fibrinogen levels with TEG or ROTEM and replacement with fibrinogen concentrate (3–4 g for a 70-kg adult) or cryoprecipitate (15–20 units for a 70-kg adult). Repeat doses should be guided by serial TEG or ROTEM monitoring. If viscoelastic testing is unavailable, fibrinogen supplementation should be undertaken when fibrinogen concentration drops below ≤1.5 to 2 g/L with the Clauss fibrinogen assay. A recent systematic review/meta-analysis of 26 studies including 5 RCTs (N = 258) found there was no difference in transfusion requirements, thromboembolic events, or mortality between fibrinogen concentrates and comparator. The authors noted that the quality of evidence was judged low to moderate due to concerns regarding bias imprecision and inconsistency. Several large RCTs comparing fibrinogen concentrate to alternative plasma products are currently in planning or underway.

Platelets

Platelets are a critical component of the hemostatic plug. Platelet counts less than 100,000/μL and 50,000/μL have been identified as thresholds below which diffuse bleeding and microvascular bleeding ensue, respectively. Therefore, expert panels have recommended that platelet counts should not be allowed to decline below 50,000/μL in traumatic injured patients and maintained above 100,000/μL for patients with massive bleeding or TBI. The standard dose of platelets is 1 platelet concentrate ($60–80 \times 10^9$ platelets) per 10 kg body weight. This dose should increase the platelet count by 30,000 to 50,000/μL (see Table 5).

Antiplatelet Medications

It is important to note that platelet count does not measure platelet function, and severe injury is associated with platelet dysfunction. In addition, use of antiplatelet medications is common in the general public. Pretrauma use of antiplatelet medications has been associated with an increased risk of intracranial hemorrhage in patients with head trauma. Development of viscoelastic tests (TEG platelet mapping, ROTEM Platelet) useful for measuring platelet dysfunction in trauma patients is an active area of clinical investigation. At present, WB platelet aggregometry is the gold standard, although it is not useful as a real-time test for transfusion management. For reversing platelet dysfunction associated with aspirin, transfusion of 5 random donor units of platelets is recommended. For patients on dual antiplatelet regimens (i.e., aspirin and clopidogrel), 10 to 25 random donor units of platelets are recommended (see Table 5).

Anticoagulant Medications

Use of anticoagulant medications is widespread in the general public given the prevalence of thromboembolic disorders such as atrial fibrillation and venous thromboembolism. In patients taking warfarin, a four-factor prothrombin complex concentrate (Kcentra, CSL Behring, King of Prussia, PA) that contains all the vitamin K–dependent factors is superior to FFP for rapid reversal of warfarin. Intravenous vitamin K (infused no faster than 1 mg per minute) should be administered to ensure sustained reversal. Protamine should be used for reversal of unfractionated heparin and low-molecular-weight heparin, although protamine only partially reverses low-molecular-weight heparin (dalteparin 80% reversal, enoxaparin 60% reversal). There is growing use of direct oral anticoagulants such as the oral direct thrombin inhibitor, dabigatran, and the oral direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban. Idarucizumab (Praxbind, Boehringer-Ingelheim Ridgefield CN), a humanized mouse monoclonal antibody against dabigatran, has been demonstrated to rapidly reverse dabigatran and should be administered in any trauma patient on dabigatran. Andexanet alfa, a recombinant modified inactive form of factor Xa, has been licensed to rapidly reverse the anticoagulant effects of apixaban and rivaroxaban in patients with uncontrolled and life-threatening bleeding. Dosing recommendations are also available for edoxaban. Prothrombin complex concentrates in varying doses have also been used for reversal of oral factor Xa inhibitors (see Table 5).

Recombinant-Activated Factor VII

Recombinant human-activated factor rFVII (Novoseven, Novo Nordisk, Plainsboro, NJ) is a recombinant concentrate of activated factor VII that was developed initially for the treatment of hemophilia patients with factor inhibitors. It has since been applied to a broad array of patients with refractory bleeding including trauma patients. In two parallel placebo-controlled RCTs of 301 severely injured trauma patients (blunt and penetrating trauma), Boffard et al. found that rFVIIa reduced RBC transfusion and the need for massive transfusion in patients with blunt trauma with similar trends in penetrating trauma. In the CONTROL trial, Hauser et al. randomized major trauma patients who had bled 4 to 8 units of blood within 12 hours of surgery and were still bleeding despite damage control resuscitation and operative management. The trial was terminated early due to futility after enrolling 573 of 1502 patients. They found that rFVIIa reduced blood product use but did not improve mortality. A case-control study of rFVIIa in patients with TBI was associated with higher mortality. Retrospective analysis indicated a higher incidence of thromboembolic episodes in patients with penetrating trauma. In light of these results, the European guidelines suggest that rFVIIa be considered only if major bleeding and traumatic coagulopathy persist despite conventional therapy. The recommended dose is 200 μg/kg for the first dose and 100 μg/kg for doses 2 and 3 administered 1 and 3 hours after the first dose (see Table 3). Studies have suggested that rFVIIa is ineffective in patients with a pH of 7.2 or less, platelet counts less than 100,000/μL, or with hypothermia and hypocalcemia. These conditions should be corrected before initiating therapy. The guidelines do not support its use in patients with TBI.

Tranexamic Acid

Tranexamic acid (TXA; Cyklokapron Pfizer, New York, NY) is a lysine analog that inhibits fibrinolysis due to its activity as a competitive inhibitor of plasminogen activation and at high doses as a noncompetitive inhibitor of plasmin. In the CRASH-2 trial, TXA (1 g loading dose over 10 minutes followed by 1 g over 8 hours) significantly reduced all-cause mortality (14.5% vs. 16%; relative risk [RR] 0.91 [95% CI 0.85 to 0.97]) and the risk of death due to bleeding (4.9% vs. 5.7%; RR 0.85 [95% CI 0.76 to 0.96]). Further analysis found that early administration of TXA (within 1 hour and 1–3 hours of trauma) was associated with reduced death due to bleeding, but administration after 3 hours increased the risk of death due to bleeding (4.4% vs. 3.1%; RR 1.44 [95% CI 1.12 to 1.84]). The European Trauma Guidelines recommend TXA administration as early as possible (within 3 hours) after injury for patients with significant hemorrhage. CRASH 2 has renewed the interest in the use of TXA as it is easy to administer and relatively inexpensive. The recent CRASH 3 trial showed that early administration of TXA (within 3 hours) in mild to moderate TBI (GCS score of 9–15) reduced 28-day mortality. This benefit was not seen in patients with severe TBI. The risk of thromboembolic events and seizures were similar in both placebo and TXA groups. Studies on out of hospital TXA use in moderate to severe TBI showed no clear benefit on 6-month functional neurologic outcomes. There may be some questionable benefit of using prehospital TXA during transport of the trauma patient especially in those with severe shock (systolic BP <70 mm Hg), but large powered studies are needed to justify its use. Studies have also investigated intramuscular administration of TXA use after the 1 g IV bolus dose, and besides transient injections site erythema, no other side effects were seen. Studies looking into the

TABLE 5 Hemostatic Agents for Management of Traumatic Bleeding

Hemostatic Agent	Indication	Mechanism of Action	Dose
Tranexamic acid	Active bleeding or significant risk of bleeding	Inhibits plasmin-mediated fibrinolysis	1 g IV over 10 minutes followed by 1 g over 8 hours
Cryoprecipitate	Fibrinogen deficit (fibrinogen <150–200 mg/dL or fibrinogen threshold defined by TEG or ROTEM)	Corrects fibrinogen deficit	15–20 single donor units in 70-kg adult
Fibrinogen concentrate	Fibrinogen deficit (fibrinogen <150-200 mg/dL or fibrinogen threshold defined by TEG or ROTEM)	Corrects fibrinogen deficit	3–4 g in 70-kg adult
Recombinant human factor VIIa	Persistent major bleeding despite conventional hemostatic measures	Induces burst of thrombin generation, triggering platelet activation, fibrin clot formation	Initial dose of 200 μg/kg IV followed by 100 μg/kg at 1 and 3 hours later
Platelets	Thrombocytopenia	Restores adequate functional platelet mass for hemostasis	1 platelet concentrate per 10 kg (increases platelets 30,000–50,000/μL
Platelets	Reversal of antiplatelet medications	Restores adequate functional platelet mass for hemostasis	For reversal of aspirin: 5–10 platelet concentrates For reversal of dual antiplatelet agents: 10–25 platelet concentrates
Vitamin K	Warfarin Reversal	Bypass warfarin inhibition of vitamin K-dependent coagulation factor synthesis	10 mg of vitamin K IV (slow infusion no faster than 1 mg per minute)
Prothrombin complex Concentrate	Warfarin or Factor Xa Inhibitor Reversal	Replaces vitamin K-dependent coagulation factors	INR 2–3.9: Dose 25 units/kg (not to exceed 2500 units) INR 4–6: Dose 35 units/kg (not to exceed 3500 units) INR >6: Dose 50 units/kg (not to exceed 5000 units) Factor Xa inhibitor reversal: 25 Units/kg (or 1500–2000 units) IV X 1
Idarucizumab	Dabigatran reversal	Antibody binds and inactivates dabigatran	5 g IV (administered as two 2.5 g IV 50 mL infusions)
Andexanet-alfa	Apixaban, edoxaban, or rivaroxaban reversal in uncontrolled and severe bleeding	Binds and sequesters factor Xa inhibitor and restores thrombin generation; inhibits tissue pathway factor inhibitor	400–800 mg IV followed by 4–8 mg/min IV infusion depending on time and dose of factor Xa inhibitor used

pharmacokinetics of the intramuscular dose showed noninferiority to the intravenous route. Clinical data regarding the use of other antifibrinolytic agents such as aminocaproic acid and aprotinin are still lacking (see Table 3).

Desmopressin

Desmopressin (DDAVP; 1-deamino-8-D-arginine vasopressin) is a vasopressin analog that induces the release of preformed stores of von Willebrand factor and factor VIII from the endothelium. Desmopressin is used in the treatment of mild von Willebrand disease, and hemophilia A and platelet dysfunction disorders. There are no studies documenting the efficacy of desmopressin in trauma patients.

Local Hemostatic Agents and Dressings

Local hemostatic agents/dressings are important adjuncts to blood products in achieving hemostasis in trauma patients. Collagen-based hemostatic agents induce platelet aggregation. They are often combined with thrombin to activate fibrin clot formation. Cellulose-based hemostatic agents do not have any coagulation factors and are used with local packing. Gelatin-based products swell when in contact with blood resulting in local compression of bleeding vessels. These products often contain thrombin to activate the coagulation cascade. Fibrin sealants have been used extensively in cardiac and vascular surgery, neurosurgery, and orthopedic surgery for local hemostasis. They appear to be effective even in the presence of coagulation disorders. Zeolite, a mineral that absorbs fluid-concentrating

coagulation factors and platelets at the site of injury, also has been used for control of hemorrhage from external wounds. Zeolite generates significant heat so it should only be used for hemostasis of external injuries. Newer versions have been developed that are less exothermic. Chitosan is a chemically modified form of chitin, the structural constituent of the exoskeleton of crustaceans. It is thought to augment platelet aggregation and adhesion. Poly-N-acetyl glucosamine is a polysaccharide derived from marine algae that triggers vasoconstriction and platelet activation. It has been FDA approved as a hemostatic agent (Rapid Deployment Hemostat [RDH]; Marine Polymer Technologies, Inc., Danvers, MA) and a bandage (mRDH bandage) for the treatment of trauma patients. XStat (Remedx, Wilson, OR) can be injected into the wound where it quickly expands to provide compression and achieve hemostasis. Several agents are in development. The European Trauma guideline has recommended the use of local hemostatic agents in combination with conventional surgical management in the treatment of traumatic injury-associated bleeding.

RECOMMENDED APPROACH TO TRAUMA-ASSOCIATED BLEEDING

In the field, trauma patients should be quickly stabilized for rapid transport to the nearest trauma center. Bleeding should be controlled with local hemostatic measures such as hemostatic dressings and tourniquets (see Fig. 3). Hypothermia should be treated. Intravenous crystalloid resuscitation should be minimized consistent with paired goals of permissive hypotension and limit dilutional coagulopathy. Upon arrival in the emergency department, the initial clinical trauma evaluation should proceed while laboratory studies including screening coagulation studies, viscoelastic testing, CBCs, and a type and crossmatch are being drawn and radiographic studies are ordered. Until a type and crossmatch are available, type O blood and AB plasma can be used for replacement. Maintenance of a ready pool of thawed plasma in the blood bank facilitates rapid replacement therapy. Satellite blood banks in the emergency department can also speed blood product transfusion. To limit dilution of coagulation factors and platelets, PRBC, FFP, and platelets should be transfused in a 1:1:1 ratio while damage control surgery proceeds. TXA should be administered as early as possible (within 3 hours) in trauma patients who are actively bleeding or at risk for significant hemorrhage. Hypothermia should be limited by administering warm fluids and blood products and keeping the patient in a warm environment. Acidemia should be kept in check and reference calcium levels should be maintained. Serial laboratory testing can assist in tailoring blood product component therapy to the patient's clinical situation. Laboratory testing should include PT, aPTT, fibrinogen, and base deficit. Viscoelastic testing such as TEG and ROTEM are used to complement conventional laboratory testing, although prospective studies demonstrating improved clinical outcomes are needed. Fibrinogen concentrates or cryoprecipitate should be considered for patients with hypofibrinogenemia (fibrinogen less than 2 g/dL). Additional transfusions should be based on serial fibrinogen, TEG, or ROTEM testing. rhFVIIa should be considered in patients with bleeding unresponsive to conventional blood product support. For trauma patients taking antiplatelet agents or anticoagulants, reversal strategies including platelet transfusions (for antiplatelet agents), intravenous vitamin K, and prothrombin complex concentrates (for warfarin or oral factor Xa inhibitors apixaban, edoxaban, and rivaroxaban) should be employed early in treatment. Andexanet alfa should be used in patients taking oral factor Xa inhibitors with intracranial or spinal hemorrhage or life-threatening uncontrolled bleeding despite conventional measures. Idarucizumab should be used for reversal of dabigatran. Local hemostatic therapies (fibrin sealants, collagen hemostats, etc.) can be used to complement damage control surgery. A target of 7 to 9 g/L for hemoglobin and platelet counts of 50 to 100 $\times$ 10^9 is appropriate for a goal-directed approach to TIC.

TRAUMA-INDUCED COAGULOPATHY IN CHILDREN

In children, especially neonates and infants, the hemostatic processes are not fully developed. As a result, despite similarities in the pathogenies, diagnosis, and management of TIC compared with adults, there are certain differences.

TBI and physical abuse tend to be more prevalent in children. There is a greater incidence of TIC in these patients. Venous thromboembolic events occur less frequently in children compared with adults but remain high in TBI and abusive head trauma patients.

Children have a greater circulatory reserve and higher circulatory blood volume compared with adults, especially children less than 50 kg. So, the signs and symptoms of blood loss may not be as apparent as in adults. Coagulation tests such as the PT and aPTT are prolonged in neonates and infants less than 6 months of age reflecting the reduced synthetic function of the immature liver. Antithrombin, protein C, and protein S levels are also lower in infants. Administration of blood products in children is based on body weight. Blood products are usually administered as 1:1:1, but there may be a mortality benefit with higher ratios of plasma to pRBCs. However, robust studies in children with TIC are still lacking.

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Post–Intensive Care Syndrome

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INTRODUCTION

With an aging population and advancements in critical care, more patients are surviving their admitting diagnosis and becoming intensive care unit (ICU) survivors. Patients whose critical illness is prolonged (more than 7–14 days) are an especially high-risk group of patients who may experience problems after discharge from the ICU. Once the patient is discharged from the hospital, the sequelae of prolonged ICU hospitalization continue to have an impact on their daily lives. Post–intensive care syndrome (PICS) is a relatively new syndrome intended to describe the constellation of the chronic disabilities that occur in the period following critical illness. Although there is no official definition of this syndrome and it is not listed in ICD-11, ICU stakeholders first came together in 2010 to discuss the long-term outcomes after discharge from ICUs. Most experts agree that the syndrome includes new or aggravated dysfunction(s) in physical, cognitive, and/or psychological domains; it is not only limited to the patient but also, to some extent, their caregivers. These limitations may resolve over a period of months or years, or they may persist. A multicenter cohort study published in 2018 found that at 3 and 12 months, one or more PICS problems were present in 64% and 56%, respectively, of ICU survivors. The most frequently reported impairment is altered cognition, with more than 25% of all ICU survivors suffering from some form of cognitive impairment after hospital discharge. Depression and physical disabilities are also quite common (up to one-third of all patients). Onset of these disabilities can start to occur within 24 to 48 hours after admission, and the aftereffects can be seen in ICU survivors up to 5 years and beyond after hospital discharge. This newfound syndrome is associated with increased healthcare costs and use, reductions in quality of life, and prolonged unemployment. Because of this, PICS is now being recognized as a public health burden. Certainly, the COVID pandemic has magnified the numbers of patients with problems after a prolonged ICU stay. In a recently published study of the top 10 research priorities in surgical critical care, interventions to mitigate PICS (#3), identifying predictors and strategies to prevent PICS (#5), and long-term cognitive and functional outcomes following PICS (#8) were of the top 10 topics identified by leaders in surgical critical care.

PHYSICAL IMPAIRMENT

ICU-acquired weakness (ICUAW) in patients who are critically ill commonly manifests as muscle weakness in three ways: polyneuropathy, myopathy, and/or muscle atrophy. These are clinically indistinguishable and more commonly affect proximal muscle groups. These problems affect a patient's ability to use both their arms and legs, with simple activities such as getting up from a chair (quadriceps) or lifting one's arms to get dressed becoming challenging. Up to 80% of patients admitted to the ICU develop some form of neuromuscular dysfunction. Muscular weakness is associated with longer durations of mechanical ventilation and hospitalization, along with greater functional impairment for survivors. One-third of surviving patients after emergency surgery and critical illness will have problems with activities of daily living (ADLs) at 3 months and up to 20% at 1 year.

Critical illness polyneuropathy (CIP) is characterized by a symmetric, distal, sensory-motor axonal polyneuropathy affecting limbs and respiratory muscles, as well as sensory and autonomic nerves. Electrophysiology studies demonstrate abnormal sensory and motor responses, and histologic analysis of sensory nerves generally appear normal early in the course of illness, with axonal degeneration evident only late in the course. Muscle stimulation with a stimulating needle electrode demonstrates preserved motor action potential amplitude differentiating neuropathy from myopathy. Theories regarding the etiology of CIP include loss of the blood-nerve barrier, inexcitability of the endoneurial membrane, and direct toxic effects from ICU therapies including hyperglycemia or lipids in parenteral nutrition.

Critical illness myopathy (CIM) is characterized by limb and respiratory muscle weakness with retained sensory function. Muscle biopsy specimens demonstrate atrophy with preferential loss of thick filaments reflecting myosin loss and muscle necrosis. Proposed causes include chemokine-induced autophagy of muscle, muscle membrane inexcitability, acquisition of channelopathies, or direct toxic effects of ICU care including corticosteroids or neuromuscular blockade.

The most consistently implicated risk factors in developing ICUAW are those associated with severity of illness, including prolonged mechanical ventilation, sepsis, multisystem organ failure, prolonged bedrest, deep sedation, and duration of ICU stay. Age and preadmission health and functional status also appear to be important risk prognosticators for resilience and long-term functional outcomes. There is marked variability in the recovery potential of skeletal muscle following critical illness resolution—a proportion of survivors will suffer long-term weakness, while others may expect full to near-complete recovery.

The finding of generalized weakness is extremely common in critically ill patients and warrants an accurate differential diagnosis; ICUAW should be a diagnosis of exclusion. ICUAW is usually excluded in the presence of the following: the neurologic assessment indicates a brain disease; facial muscle involvement; weakness is asymmetric, descending/ascending, or fluctuating; the presence of fasciculations; or suspicion of a pharmacologic side effect. These findings suggest a structural problem, and a specific neurologic diagnosis should be established.

Currently there are no consistently effective therapies that prevent these problems from occurring. Champions of early mobility/exercise and neuromuscular stimulation have promoted their use in the critically ill with some success. If initiated early and combined with an effort to minimize sedation and paralysis, short-term physical functional outcomes can potentially be improved. Although this is an active area of clinical trials, a recent prospective cohort study that examined mobilization during critical illness found that achieving higher levels of mobilization in the ICU had a positive influence on health status at 6 months from ICU admission. Given that early mobilization is among the only straightforward preventive measures, we recommend mobilizing surgical patients with critical illness as a routine practice for ICUAW. This requires a dedicated multidisciplinary group of providers who will limit sedation and therapists who will get patients out of bed when intubated, on pressors, even if they have many lines and tubes in place. Patients who are on bed rest should be relatively few but can use in-bed devices (bike) to maintain strength of the lower body.

COGNITIVE IMPAIRMENT

The reported incidence of cognitive impairment after critical illness varies widely from 4% to 64%. This dementia is a progressive, irreversible clinical syndrome that is a result of widespread impairment of mental function. Incidence rates rise following an ICU admission, as critical illness is seen as a trigger resulting in cognitive impairment. *The Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) elaborates on the diagnosis of dementia as having problems with seven domains: complex attention, executive function, learning, memory, language, perceptual-motor function, and

social cognition. The diagnosis is made by history taking, physical examination, cognitive and mental state examination, and review of medications. The Global Deterioration Scale, Clinical Dementia Rating, and Mini Mental State Examination are the most well-known screening and ranking of severity scales. Of note, reversible medical problems as well as delirium should be ruled out before the diagnosis of dementia. Because delirium is so common in the ICU, the diagnosis of dementia following a prolonged ICU stay may take some time to become clear as the patient experiences less waxing and waning (delirium resolves) and a more prolonged change in mental capabilities is noted.

ICU delirium, defined as a neurobehavioral syndrome resulting from an imbalance in neurotransmitter synthesis, function, or availability, is observed as a range of clinical features, from increased agitation and hyperactivity to somnolence and withdrawal. The presence of delirium, which is often missed, and its duration are associated with neurocognitive dysfunction and mortality over the first year after critical illness. The average length of a delirium episode ranges between 2 and 7 days; however, in some cases, delirium can last for weeks. With an incidence of 15% to 25% following elective surgery, and upwards of 50% following major surgery, it is one of the most common postoperative complications in older adults. After age 65 years, the risk of delirium increases 2% with each additional year of life and approaches 90% when older adults progress to palliative care settings. The duration and degree of delirium is strongly linked with development of dementia.

Other major risk factors associated with cognitive impairment are acute brain dysfunction (stroke, alcoholism), hypoxia, hypotension, glucose dysregulation, respiratory failure requiring prolonged mechanical ventilation, severe sepsis, use of renal replacement therapy, acute respiratory distress syndrome, age, and prior cognitive impairment.

PSYCHOLOGICAL IMPAIRMENT

Psychological impairment after discharge from the ICU commonly manifests in the form of depression, anxiety, and posttraumatic stress disorder (PTSD). Up to one-third of ICU survivors report symptoms of depression, and almost one-tenth of patients have symptoms consistent with PTSD, which is characterized by intrusive memories that arise from a combination of true events after ICU discharge. Greater than 50% of patients report anxiety. Given the high incidence of psychological impairment, patients with suspected PICS should undergo formal mental assessment if feasible. However, it is important to address all underlying medical problems that may be associated with or mimic depression. Anemia, neuromuscular disorders, electrolyte imbalance, and endocrine pathology can all cause potentially reversible depressive symptoms. Therefore, a thorough history, physical examination, and laboratory workup is imperative before a diagnosis and referral is made.

Risk factors associated with the development of psychological impairment include female gender, low socioeconomic status, unemployment, preexisting psychiatric illness, and personality disorders. Management strategies used in the ICU such as the choice of analgesia, sedation, and use of antipsychotics and restraints are all considered as risk factors for the development of psychological impairment and delirium.

An interesting, yet debatable, prevention strategy to target ICU-related psychological impairment is the use of ICU diaries. Diaries are a written daily account done by the hospital staff or patient's family outlining procedures and progress of the disease/recovery. Because patients often suffer significant memory loss during the time in the ICU, a journal may help to supplement the disorientation associated with a prolonged ICU stay. A recent systematic review and meta-analysis found that ICU diaries decrease anxiety and depression and improve health-related quality of life among ICU survivors and potentially result in less PTSD among ICU patients' families and caregivers.

PREVENTION OF PICS

Prevention strategies utilized in the ICU are the most important way to inhibit the development of physical, cognitive, or psychological impairment. In 2018, The American College of Critical Care Medicine and the Society of Critical Care Medicine (SCCM) updated the Clinical Practice Guidelines for the Management of Pain, Agitation/Sedation, Delirium (PAD) to include Immobility and Sleep disturbance (now PADIS) in adult patients in the ICU. These guidelines have been integrated into the ABCDEF bundle to help treat and prevent the development of PICS:

A — Assess, Prevent, and Manage Pain
B — Both Spontaneous Awakening Trials and Spontaneous Breathing Trials
C — Choice of Analgesia and Sedation
D — Daily Delirium Monitoring
E — Early Mobility and Exercise
F — Family Engagement and Empowerment

This bundle has also been shown to decrease the rate of hospital death within 7 days, decrease delirium days, decrease physical restraint use, and decrease ICU admissions and discharge to nursing homes and rehabilitation facilities.

Assess, Prevent, and Manage Pain

Pain treatment should be guided by a reliable, valid, and routine pain assessment. The SCCM recommends assessment in the following order: obtaining the patient's self-reported pain, looking for behavioral changes, eliciting the family to help identify pain behaviors, and assuming pain is present. For patients who are not able to communicate their pain level, bedside assessment tools such as the Behavioral Pain Scale (BPS) for Pain Assessment in Intubated Patients and Critical Care Pain Observation Tool (CPOT) should be used. Pain should be treated in a multimodal fashion, and pain should be well managed before a sedative is added.

Both Spontaneous Awakening Trials and Spontaneous Breathing Trials

This component focuses on setting a time(s) each day to stop sedative medications, orient the patient to time and day, and conduct a SBT with a goal to liberate the patient from the ventilator as soon as possible. Prolonged ventilation and deep sedation have been shown to lead to worse patient outcomes. Studies have shown that using SAT and SBT synergistically helps decrease mechanical ventilation days, hospital lengths of stay, and delirium. Combining these management plans is the focus of the Wake Up and Breathe Protocol, a two-step process that starts with a SAT safety screen followed by a SAT if criteria are met. If a patient passes the SAT, they move onto the SBT safety screen followed by a SBT. Unless absolutely contraindicated, every patient should undergo this process every day. ICUs should have well-established protocols to ensure this happens to all patients every day, excepting the very few patients in whom it is contraindicated.

While a patient may require sedation, the depth and quality of sedation should be routinely assessed. The Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) are the most valid and reliable scales for assessing quality and depth of sedation in ICU patients. Although it is a conditional recommendation, in mechanically ventilated patients a target of light sedation compared with deep sedation should be routine. There is no clear definition for light vs. moderate sedation; however, in most studies, a RASS of -2 or higher (toward zero) is considered light sedation.

Choice of Analgesia and Sedation

This component focuses on developing a safe yet effective regimen to control pain and agitation. As previously stated, pain should be

treated in a multimodal fashion. Nonopioid analgesia (i.e., acetaminophen, ketamine, nonsteroidal antiinflammatory drugs) should be used as adjuncts with the aim of sparing opioid use and thereby opioid-induced adverse side effects and improving analgesic effectiveness. Nonpharmacologic strategies, such as massage, cold therapy, and relaxation techniques should also be incorporated into the conceptual management of pain and sedation. Again, lighter sedation should be targeted, and unless a patient is suffering from agitation/delirium secondary to alcohol or benzodiazepine withdrawal, benzodiazepines should be avoided. Benzodiazepines modulate gamma-aminobutyric acid (GABA)-A receptors, the most common inhibitory neurotransmitter in the central nervous system. GABA-A receptors are found abundantly in the limbic system, which modulates mood. Benzodiazepines have been associated with depression and increased incidence of delirium. Lastly, sedation goals should be obtained using propofol or dexmedetomidine in mechanically ventilated patients.

Daily Delirium Monitoring

This element focuses on assessing, preventing, and managing delirium. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools for adult ICU patients. Nonpharmacologic strategies have an early and important role in preventing and managing delirium. These include identifying and treating reversible medical conditions like hypoxia and infection. Discontinuing or decreasing medications that may increase delirium risk (i.e., benzodiazepines) should be routine. Ensuring appropriate sleep-wake cycle, providing hearing and vision aids when appropriate, mobilizing patients early, limiting noise, and involving family members in helping to orient patients are simple cost-effective strategies that should be incorporated into ICU patient care. Pharmacologic strategies should be administered only in certain situations. Typical antipsychotic agents such as haloperidol or an atypical antipsychotic (e.g., quetiapine, ziprasidone) should only be administered when a patient is experiencing distressing symptoms of delirium like anxiety, hallucinations, or agitation that is putting themselves or others at harm. A recently published, randomized, double-blind, placebo-controlled study of delirious ICU patients with acute respiratory failure or shock examined whether the administration of haloperidol or ziprasidone decreased the duration of delirium compared with placebo. The use of either antipsychotic had no effect on duration of delirium or mortality, ventilator liberation, or length of stay. It is also important to remember that these agents should only be used in a short-term manner and immediately discontinued once these distressing symptoms have resolved. Studies have found that patients started on an antipsychotic for delirium in the ICU often remain on these medications unnecessarily after discharge, which can result in significant morbidity and financial cost. Hypoactive delirium and prophylactic use of antipsychotic agents are not currently recommended.

Early Mobility and Exercise

This element focuses on assessing patients frequently and implementing activity early on, with the goal of patients reaching their maximum mobility daily. Assessment consists of four steps. Step 1 is patient selection. Contrary to popular and historical belief, most patients in the ICU can be mobilized in some way every day. Observational studies and small randomized controlled trials have shown that it is a safe and feasible strategy in the ICU to mobilize patients. Early mobilization may potentially reduce delirium and duration of mechanical ventilation, while also improving long-term functional outcomes. Although there are exclusion criteria as to who should remain at bedrest, local guidelines should be developed as to which patient populations should be/not be routinely mobilized. Patients on a ventilator can be mobilized out of bed and can walk with assistance (Fig. 1). While a great deal of institutional variation exists, even patients who have loss of abdominal domain can participate in physical activity. Each day, the clinician team should review the patient's activity history and make note of what the patient's maximum participation should be (step 2). The team should be specifically aware of muscle strength (see prior description of muscle weakness) (step 3) and the patient's ability to participate in physical therapy (step 4). Clinicians should encourage patient participation in physical therapy daily. Even when they are unable to get out of bed, patients can do exercises in bed (beyond range of motion). Most ICUs now have exercise bicycles that can help to maintain proximal muscle strength in both the arms and legs. The close collaboration with physical therapists, nurses, providers, and family members is the key to safe and effective mobility.

Family Engagement and Empowerment

Finally, the ABCDE bundle has evolved to include family engagement and empowerment. Critical illness not only affects the patient but their entire support system. ICU care should be patient- and family-centered care. This focuses on keeping patients and families informed and involved in decision making. Providing physical and emotional support and maintaining a clear understanding of patient's comprehension of their illness, goals of care, and cultural beliefs is essential to the best outcomes of prolonged ICU care. Through this partnership and family presence, anxiety of the families and patients can be reduced, patient satisfaction and safety increased, and ICU length of stay reduced.



FIG. 1 Intubated patient ambulating.

CAREGIVER BURDEN

Family members and caregivers of critically ill patients can be affected physically and psychologically during and after the ICU stay of their loved one. This is referred to as Post-ICU Care Syndrome Family (PICS-F). Major risk factors for its development are poor communication between staff and caregivers, being in a decision-maker role (surrogate), lower educational level, and having a loved one who died or was close to death. Sleep deprivation, depression, anxiety, and PTSD are the most common problems experienced by family members, and these frequently persist beyond hospitalization. Approximately 50% of families have to make major adjustments to their work life, often limiting salaries. Requiring family members to move to less-expensive homes, lose their savings, or delay medical care or educational plans for other family members are all shockingly common.

POST-ICU CLINICS

Post-ICU clinics, which started in 1985 in the United Kingdom, were designed to evaluate and treat ICU survivors. Their goal is to aid in the diagnosis of physical, cognitive, and psychological impairments, symptom management, medication reconciliation, discussion of prognosis, and implementation of rehabilitation. These impairments have a profound impact on patients' lives. Approximately one-third of patients never go back to work, whereas another third of patients do not go back to their pre-ICU job or at the same pre-ICU salary. Many patients experience financial constraints and lack the resources to help get them back to their pre-ICU state. ICU survivors are at high risk for readmission to the hospital and ICU, with one-quarter of patients requiring assistance with ADLs a year after ICU admission.

The 6-minute walk test (6MWT) is a validated and widely used assessment of cardiopulmonary and musculoskeletal function that is relevant to ADLs. This test is commonly employed in post-ICU clinics to assess and follow physical impairment. A recent meta-analysis of the 6MWT and critical illness found that literature fails to show consistent negative associations between ICU factors, such as severity of illness, duration of mechanical ventilation, and length of stay, on postdischarge 6MWT results. However, there are some data to support that female sex and the diagnosis acute respiratory distress syndrome (ARDS) compared with control groups have lower 6MWT results, even years after discharge from the hospital.

Given this lack of definitive association based on ICU factors alone, it is difficult to predict which ICU survivors will have the greatest impairments in physical function; nevertheless, using measures such as the 6MWT allows for patient's progress to be followed in a standardized way following discharge.

Finally, these clinics usually consist of physicians, nurses, social workers, physical and occupational therapists, pharmacists, and psychologists who not only provide treatment for the patients but also provide support for family members and caregivers. Unfortunately, due to many barriers, including a lack of funding, staffing, referrals, and a standardized concept, as well as patient barriers like lack of transportation, severity of illness, ongoing institutionalization, feeling overwhelmed, or fear of return to an ICU-associated environment, these clinics have not been found to improve health-related quality of life more than the standard of care. However, these barriers should not reduce the importance of the long-term follow-up of patients, family members, and caregivers. Our challenge is to standardize and implement longitudinal models of care that start the day a patient enters the ICU and continues for the rest of the hospitalization and after discharge.

ONGOING CLINICAL TRIALS

Given the infancy of PICS, there are many ongoing clinical trials to help better define preventive and treatment strategies for ICU survivors. One multicenter observational study is examining the relationship between early unmet needs after discharge and subsequent outcomes in acute respiratory failure survivors, with the hypothesis that early unmet needs are associated with worse outcomes. Another prospective randomized controlled trial aims to determine the feasibility and potential benefit of PICS support group for ICU survivors compared with standard of care. Finally, considering the impact COVID has had on critical care, many studies aim to describe the clinical manifestations of PICS in COVID patients and their rehabilitation following discharge.

CONCLUSION

Although mortality of ICU patients has declined significantly, morbidity after discharge remains a significant issue. PICS is a frequent but likely underrecognized entity that signifies the constellation of physical, cognitive, and psychological impairments arising during critical illness and persisting long afterward. This syndrome also has an effect on patient's family members and caregivers. Studies have shown that many patients and their loved ones fail to get back to their pre-ICU state, even years after discharge. Preventive measures like the PADIS guidelines and ABCDEF bundle show promise in reducing these impairments in ICU survivors. However, further work is needed to highlight the long-term sequelae of the ICU and standardize follow-up approaches, including post-ICU clinics to help diagnose, treat, and support ICU survivors and their families.

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